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Breathing: The Art of Living

Focus on: Optimizing Respiratory Function

VIRTUAL WORKSHOP
June 16th 2022

HYBRID WORKSHOP
Shangri-La Jakarta
June 17th 2022

VIRTUAL SYMPOSIUM
June 18th - 19th 2022

The 23rd International Meeting on Respiratory Care Indonesia (Respina) 2022

Volume 10, 2022

Proceeding

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The 23rd International Meeting on Respiratory Care
"Breathing : The Art of Living, Focus on Optimizing Respiratory Function"
Volume 10, 2022

Breathing : The Art of Living
"Focus on Optimizing Respiratory Function"

▶ THE VENUE

Shangri-La Hotel
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Jakarta Pusat 10220

▶ DATE

Workshop: June 16th,17th, 20th, and 21st, 2022
Symposium: June 18th - 19th, 2022
Exhibition: June 18th - 19th, 2022

The Society of Respiratory Care Indonesia
2022

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Preface

On behalf of the 23rd Respina 2022 organizing committee, | extend a warm welcome to all participants to attend **The International Meeting of Respiratory Care Indonesia (Respina) Hybrid Conference** which will be held on June 16th – 21st, 2022. Respina has been organized since 1998 as one of the largest respiratory care events in Southeast Asia.

As the global pandemic continue to bring extraordinary life to us moreover inevitably affect the health, social and economic sector of many countries in the world. A huge number of studies to tackle the COVID-19 problem has been produced, however, challenges in the respiratory field are still remain exist and must be comprehensively solved.

This year, Respina will carry on 13 tremendous workshops and a spectacular virtual conference that presents many distinguished national and international speakers. We do strongly hope to bring you such an interactive, attractive, and outstanding experience into the event including the remarkable RespiQuizz for medical students, scientific poster and free paper presentation, Case Report Forum, Studium Generale, and Lessons Learned session.

I am so grateful to everyone supporting and participating in the 23rd Respina. I am looking forward to meeting you virtually and together feeling the excitement of this scientific meeting.
Welcome to Respina Hybrid Conference 2022!

Warm regards,
Dian Yulianti, MD
Chairperson

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First, we would like to express our gratitude, Alhamdulillah, for successfully producing this Respina Proceeding Book titled Breathing: The Art of Living, Focus on Optimizing Respiratory Function.

This Proceeding Book, which was compiled from various works of experts presented in The 23rd International Meeting on Respiratory Care Indonesia (Respina) 2022, is expected to be a reference for the public, academics, and practitioners in the field of respiratory diseases and related topics.

For this reason, we extend our appreciation to the committee and the expert community who jointly played a role in collecting these scientific materials, which were packaged in a beautiful book and marked with the distinctive Respina logo.

We hope that this book can become a guide for academics and practitioners in the future, both on their activities in campus and in the realm of health services, especially in respiratory-related diseases.

For the works of all teams, we are thankful, and God will bless us all.
Thank you very much

Kind regards,
Prof. Kuntaman, MD

About Respina 2022

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Respiratory Care Indonesia (Respina) is an annual international meeting in Indonesia on respiratory care. Respina is a result of collaboration of five pillars, which are Department of Pulmonology and Respiratory Medicine Faculty of Medicine University of Indonesia, American College of Chest Physician – Indonesia Chapter, Asian Pacific Society of Respirology, Indonesia Society of Bronchoscopy and Indonesian Society of Respirology, in answering the global problem of respiratory care. The mission of the meeting is to bring the up-to-date and latest information of respiratory care and as media of collaboration to each respiratory care practitioners in cooperative spirit.

Starting on 2006, Respina is proudly joined by societies that shared the same interest particularly in respiratory care, and they are as follows:

- Indonesian Society of Respirology
- Indonesian Association of Thoracic and Cardiovascular Surgeons
- Indonesian Society of Radiology
- Indonesian Neurological Association
- Indonesian Heart Association
- The Indonesian Society of Anesthesiology and Intensive Therapy
- The Indonesian of Physical Medicine and Rehabilitation Association
- Indonesian Pediatric Society
- The Indonesian Otorhinolaryngological Head and Neck Surgery Society

Four other professional organizations joined Respina in 2011, they are:

- Indonesian Association of Clinical Pathologists
- The Indonesian Physician of community medicine and Public Health Association
- Indonesian Sports Medicine Association
- Indonesian Society for Clinical Microbiology

One professional organization joined Respina 2021 is:

- Indonesian Association of Obstetrics and Gynecology

Respina 23rd meeting we have been conducting and during the years, Respina has become one of the major respiratory events in Indonesia and gained greater and still growing interest from physicians across the regions, particularly from our colleagues in Southeast Asia.

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HOW TO MAKE PRONE POSITION FEASIBLE OUTSIDE ICU SETTINGS

Nicolino Ambrosino
ICS Maugeri, IRCCS, Institute of Montescano Pavia, Italy

ABSTRACT
Mechanical ventilation in the prone position (PP) is a validated strategy of invasive ventilator support in the treatment of acute respiratory distress syndrome (ARDS). The physiologic rationale for PP is: a) redistribution of V/Q ratio; b) lung recruitment of previously dependent regions occurs as oedema flows away from antigravitational alveoli.

There has been use of PP also in non-intubated patients with ARDS and in patients with COVID-19 outside the ICU. This strategy is feasible and a useful option in the management of acute respiratory failure due to COVID-19. Prone position was associated with a significant improvement in oxygenation and breathing pattern, with good tolerance.

COVID-19 may result in lung injury with two phenotypes and it might be helpful to categorize patients as having one phenotype or another. Different ventilatory approaches are needed, depending on the underlying physiology [1]. The COVID-19 pandemic, has led to a rapid increase in individuals requiring critical care pushing clinicians to use new approaches to save resources for invasive mechanical ventilation. Before COVID-19 pandemic, there was limited research on prone positioning (PP) in non-intubated patients suffering from acute respiratory distress syndrome (ARDS). A few physiological and clinical studies have evaluated the effects of PP in non-intubated patients with COVID-19 under non invasive respiratory support (NRS) or spontaneously breathing.

Pathophysiological rationale of PP. Pleural pressure is not homogeneous across the lung surface. It is less negative in dependent than in non-dependent parts of the lung. In supine position, transpulmonary pressure is greater in the ventral (non-dependent) lung than in the dorsal (dependent) lung. In ARDS, this difference is intensified by the increased weight of oedematous, injured tissues and consequent dorsal alveolar derecruitment. At the same time, the aerated ventral lung preferentially receives greater airflow and is at risk for overdistension

Mechanical ventilation in PP is a validated strategy in the treatment of ARDS[2] with several beneficial effects on pulmonary physiology. In supine position, pulmonary oedema accumulates in basal regions, leading to increased air volume delivered to apical and anterior lung units, which also receive less pulmonary circulation. Prone positioning leads to more homogeneous distribution of ventilation, decreasing the shunt fraction and improving ventilation/perfusion matching. [2]

Clinical studies. Early application of PP with high flow nasal cannula (HFNC), especially in individuals with moderate ARDS and mild hypoxaemia, may help to avoid intubation [3]. Studies have reported improvement in oxygenation during PP in non-intubated awake patients with COVID-19 during spontaneous breathing and NRS[4-10,12].

In a prospective study, more than one thousand adults requiring respiratory support with HFNC for acute hypoxaemic respiratory failure due to COVID-19, were randomly assigned to awake PP or standard care[9]. Treatment failure occurred in 40% of patients in awake PP and in 46% of those in standard care. The incidence of adverse events was low and similar in both groups. Authors concluded that awake PP of patients with hypoxaemic respiratory failure due to COVID-19 reduces the incidence of treatment failure and the need for intubation without any signal of harm[9].

In another study[10], patients with PaO2/FiO2 >150, in spontaneous breathing with ultrasound and chest x-ray assessed lung posterior consolidations[13] were evaluated. Under continuous pulse oximetry (SpO2) monitoring, patients maintained active PP. Three out of 16 (18.7%) patients did not tolerate the procedure. Three more patients showed a worsening in PaO2/FiO2 to < 150 and required NRS, two of whom finally needing endotracheal intubation. After 72 hours, 10 out of 16 (62.5%) patients improved oxygenation and were discharged home. The conclusion was that In non-intubated spontaneously breathing COVID-19 patients with PaO2/FiO2 > 150, active prolonged PP was feasible and tolerated with significant improvement in oxygenation.

A retrospective cohort study [12] in two teaching hospitals over a 3-month period compared severe and critical COVID-19 patients admitted for NRS and subjected to awake PP with those receiving standard care. There was a greater effect of PP compared to standard care on endotracheal intubation rate with greater benefit for patients on HFNC. Compared to standard care, PP patients also showed a favorable difference in days free from respiratory support. However mortality and tracheostomy rate were not significantly different [12].
"Negative" studies are also reported[14,15].

Open questions. We need more information on:
- The effects on patient outcomes
- The optimal frequency and duration
- The criteria for stopping prone positioning
- Target population (which patients are most likely to benefit and which ones should be excluded?)
- The potential adverse events

Conclusion
Mechanical ventilation in the PP is a validated strategy of invasive ventilator support in the treatment of ARDS patients. There is a physiologic rationale for PP and lateral decubitus also in non-intubated patients. More studies are required to answer questions still unclear.

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POST-COVID 19 SYNDROME: AN INSIGHT ON ITS PATHOGENESIS

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According to the published data from WHO in December 2021, the prevalence of post COVID-19 syndrome range from 10 to 20%.[1] Likewise, a recent 2022 retrospective study by the United States Centre for Disease Control and Prevention (CDC) showed that 1 in 5 adult COVID-19 survivors aged 18-64 years old would experience post COVID-19 syndrome, while it was 1 in 4 in the older COVID19 survivor population.[2] There is no minimum number of symptoms required to diagnose post COVID-19 syndrome, as, like acute COVID-19 episodes, a variety of symptoms from different organ systems may occur together. These symptoms may be new onset following initial recovery from acute COVID-19 episode or persisting from initial illness.[3] Furthermore, individuals with post COVID-19 syndrome seemed to be stratified into two main subsets.[4]

First are the survivors recovering from severe acute COVID-19 episodes. In this group, many individuals may have severe lung or other organ damage directly related to the high viral burden and inflammation during the acute COVID-19 episode. It made them at risk of having lingering symptoms due to the prolonged or incomplete discovery at follow-up.[4] The first type of survivors was characterized by old-aged or individuals with comorbidities, which were also known factors for severe acute COVID19 episodes.[4-6] In contrast, the second type of survivors were usually females that experienced mild to moderate or even asymptomatic SARS-CoV-2 infection.[4,7] The symptoms they experienced are usually new onset and may not be linked to the severity of their acute COVID-19 episode.[4,5] Several studies have been conducted to delineate the pathogenesis of post COVID-19 syndrome.

Cheon et al.[8] analyzed and compared the immunology profile between 10 severe COVID-19 survivors aged > 60 years old and five healthy age-matched controls using flow cytometry and RNA sequencing procedures. This study demonstrated that three months after the severe COVID-19 episode, survivors with respiratory symptoms had higher CD8+ T and specific RBD memory B cell populations in their lungs than healthy controls. These inflammatory cells had higher cytotoxic molecules and expressed tissue destructing gene programs that were positively correlated with decreased lung function and the extent of lung lesions.[8] Interestingly, the ongoing and sustained inflammatory response was not only documented in severe COVID-19 survivors but also in survivors of the mild-to-moderate episode.[9] In 2022, Phetsouphanh et al. reported that the peripheral blood samples from mild-to-moderate COVID-19 survivors still showed persistently high inflammatory cytokines and the continued absence of naïve immune cells at eight months compared to the healthy controls. Therefore, post COVID-19 syndrome may also result from an interplay between virus and host factors.[9,11]

The virus could cause tissue damage directly by entering the host's cells or indirectly by inducing the production of inflammatory cytokines from the activated host's immune response. Endothelial injury and platelet activation are driven directly and indirectly by immune cell activation by the virus could also cause a prothrombotic state that further increase tissue injury. However, the host could also have a genetic or physiological predisposition for immunologic aberration so that the immune response to the infectious threats may be overblown, persist longer, or have delay or defect in the resolution of inflammation.[5,9,11] Currently, several published hypothetical mechanisms were being associated with the persistently elevated hosts' inflammatory response in post COVID-19 syndromes, such as undetected pathogen reservoir deep in the host body, autoimmunity from molecular mimicry or impaired regulatory T cell function, reactivation of human herpesvirus, and alterations in the gut microbiome-brain axis following an initial immune response.[4,9,11] Persistent respiratory symptoms had been correlated with the increase in opportunistic gut pathogens, such as Streptococcus anginosus, *Streptococcus vestibularis, Streptococcus gordonii,* and *Clostridium disporicum.*12

With a prevalence of 20-35%, dyspnea is one of the most common respiratory symptoms in post COVID-19 syndrome.[13] Dyspnea was assumed to be the outcome of direct viral toxicity and inflammatory cytokines sequelae on the lung parenchyma.[14] However, the association between dyspnea, decreased lung function, and abnormal lung lesions were rare.[15] Furthermore, 30% of COVID19 survivors who experienced new onset dyspnea had normal lung function and scans. Moreover, they had a positive Nijmegen questionnaire score of >22/64, associated with functional respiratory complaints.[15,16] Therefore, clinicians should also consider nonorganic factors in the pathogenesis of post COVID-19 syndrome.[14,16] Nevertheless, much is still unknown about the pathogenesis of post COVID-19 syndrome.

In conclusion, post COVID-19 syndrome resulted from the interaction between direct viral toxicity and host-specific response to acute infection.[9,11] Hence, it would not be restricted to those recovering from severe COVID-19. Current evidence also showed that COVID-19 vaccines only provide partial protection against the risk of developing post COVID-19 syndrome.[17] Furthermore, although most patients with post COVID19 syndrome would recover within one year as the inflammation subsided, the symptoms might persist for some patients.[18] Therefore, the implementation of COVID-19 prevention strategies is still relevant.[17] Clinicians should also perform routine assessments to detect post-COVID-19 syndrome among COVID-19 survivors, particularly for survivors with previous severe acute COVID-19 episodes, females, older aged individuals, or survivors with comorbidities. [5,6]

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REHABILITATION POST COVID-19 IN CERTAIN COMORBIDITIES

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ABSTRACT
Post COVID-19 symptoms were remain existing after eradication of the coronavirus infection and its relation to its disease severity and multiple clinical conditions. A substantial portion of people with COVID-19 subsequently experience lasting symptoms including fatigue, shortness of breath, and neurological complaints such as cognitive dysfunction many months after acute infection. Emerging evidence suggests that this condition, commonly referred to as *long COVID* but also known as *post-acute sequelae of SARS-CoV-2 infection (PASC)* or *post-COVID-19 condition,* could become a significant global health burden.[1,2] Post-COVID-19 condition extends beyond the cardio-respiratory system to affect most other bodily systems both anatomically and physiologically. Although causes of post-COVID-19 condition are unclear, persistent immune activation may be involved.[3–5] It is necessary to formulate rehabilitation programs for these patients, to help them restore physical and respiratory function and to reduce anxiety and depression, particularly patients with comorbidities and those who live alone or in rural settings, to restore a good quality of life.[6] Comprehensive medical approaches include the rehabilitation aspect for post COVID survivor were needed in handling post COVID-19 condition and comorbidities to conservate and optimize their functional ability outcome in the future.

Keyword: Rehabilitation, Post COVID-19, comorbidities

BACKGROUND

After WHO declared COVID-19 Pandemic on 2020 than continued by wave after wave in COVID peak, the post-COVID-19 symptoms and diseases appeared on many survivors from COVID-19 which are similar to that of the post-severe acute respiratory syndrome (SARS) fatigue. Many studies aim to investigate and characterise the manifestations which appear after eradication of the coronavirus infection and its relation to disease severity.7

POST COVID-19 CONDITION AND COMORBIDITIES

Many studies had done on post COVID-19 and established several clinical conditions that persist after the infection disappeared. PubMed Clinical queries found 864 results refine the post COVID-19 conditions. The post-COVID-19 manifestations are largely similar to the post-SARS clinical syndrome.[6,8,9]

Marwa Kamal et al studied 287 survivors to collect data about the COVID-19 status and other comorbidities of the subject, and finally data about post-COVID-19 manifestations. Only 10.8% of all subjects have no manifestation after recovery from the disease while a large percentage of subjects suffered from several symptoms and diseases. The most common symptom reported was fatigue (72.8%), more critical manifestations like stroke, renal failure, myocarditis and pulmonary fibrosis were reported by a few percent of the subjects. There was a relationship between the presence of other comorbidities and severity of the disease. This study said that there was correlation between severity of COVID-19 was related to the severity of post-COVID-19 manifestations.[7,8,10]

Post-COVID-19 condition extends beyond the cardio-respiratory system to affect most other bodily systems both anatomically and physiologically. Although causes of post-COVID-19 condition are unclear, persistent immune activation may be involved. Risk factors for different syndromes of post-acute SARS-CoV-2 sequela have not been characterised, but it has been hypothesised that several post-COVID-19 condition phenotypes may exist, although pathophysiology, management, and outcomes are currently unknown.[11]

Hannah et al identified 205 symptoms in 10 organ systems among patients with long covid and comorbidities. The survey, which was published as a preprint at the end of December included 3762 respondents from 56 countries. Most patients (91.6%)had not been admitted to hospital. The most frequent symptoms reported after six months were fatigue, post-exertional malaise, and cognitive dysfunction. The survey found that 21% of patients were still experiencing severe symptoms after six months. Two thirds required a reduced work schedule or were no longer working owing to their illness.[12–14]

The condition is was not clear that it would last for months or years and that there was a “large hidden iceberg” of people who self-isolated while unwell at home but had no formal health record evidence of covid-19, as they became ill before widespread testing. Around 10-20% of the globe's covid-19 infections lead to long covid, we have a legacy of 10-20 million long term cases to manage. This has massive ramifications for the lives of the affected, direct affect to survivors and families, also for healthcare planning.[1,6]

Long-term health consequences of COVID-19 remain unknown, but reports suggest that prolonged symptom duration and limitations in functioning are common among hospitalised as well as non-hospitalised adults and children. The spectrum of long-lasting symptoms is wide and varies from mild discomfort to severe adverse effects on physical, cognitive, and psychosocial health with important wider implications on functioning, including employment and school attendance.[15–17]

REHABILITATION IN POST COVID-19 AND CERTAIN COMORBIDITIES

The World Health Organization has urged countries to prioritise rehabilitation for the medium and long-term consequences of covid-19 and to gather information on “long covid” more systematically.[1] PubMed Clinical queries refine 239 results in search of rehabilitation in post

COVID-19 and comorbidities. The complexity of the clinical setting and the speed of spread of the severe acute respiratory syndrome coronavirus 2, which leads to rapid occupation of beds in the intensive care unit, make it necessary to discharge patients with COVID-19 who have mild symptoms as soon as possible. For these reasons, it is necessary to formulate rehabilitation programs for these patients, to help them restore physical and respiratory function and to reduce anxiety and depression, particularly patients with comorbidities and those who live alone or in rural settings, to restore a good quality of life.[6,18]

Many questions were frequently asked about the kind of rehabilitation services requires for survivor of COVID-19 and related researches were trying to provide answer to that questions. Identification of survivor comorbidities, complications from an intensive care unit stay with or without intubation, and the effects of the virus on multiple body systems, including those pertaining to cardiac, neurological, cognitive, and mental health were needed.[19]

The following post COVID-19 rehabilitation have been proposed with respect to recovery of the respiratory system as well as recovery of mobility and function. A thorough assessment and an individualized, progressive treatment plan which focuses on function, disability, and return to participation in society will help each patient to maximize their function and quality of life. Careful consideration of the rehabilitation environment will ensure that all patients recover as completely as possible.[6,14]

CONCLUSION

All survivors recovered from COVID-19 should undergo long-term monitoring for evaluation and treatment of symptoms and conditions that might be precipitated with the new coronavirus infection.[6] Comprehensive medical approaches include the rehabilitation aspect for post COVID survivor were needed in handling post COVID-19 condition and comorbidities to conservate and optimize their functional ability outcome in the future.

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SAFE RETURN TO WORK AFTER COVID-19 IN PATIENTS WITH CARDIOVASCULAR DISEASES

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INTRODUCTION

Acute respiratory disease due to a new corona virus infection, later known as COVID-19, began to spread in Wuhan, China and then spread throughout the world. In Indonesia, the first case was detected me in March 2020, and so far 6.05 million Indonesians have been infected and have caused 157,000 deaths.[1]

Symptoms arising from this viral infection may include fever, weakness, cough, shortness of breath, sore throat, headache, anosmia, hypogeusia, ageusia, asthenia, conjunctivitis, gastrointestinal disturbances such as loss of appetite, nausea and vomiting, in addition to non-specific symptoms.[2]

Infected individuals can show variations in the severity of the disease from asymptomatic, mild, moderate, severe and even critical symptoms to death. Cardiovascular disease is one of the comorbidities that exacerbates the appearance of this COVID-19 disease, and often causes a higher risk of death. On the other hand, COVID-19 can also cause cardiovascular disorders from mild to severe and cause death as well.[3]

Individuals who have suffered from COVID-19 after undergoing treatment, care or self-isolation may appear asymptomatic, still show symptoms of weakness, short-term shortness of breath, or long-term sequelae, even with other symptoms due to complications such as cardiovascular diseases, impaired function kidney, lung function and others. This will affect a person to return to work, in addition to fears of transmitting or contracting again, also as a result of the long-lasting complications of COVID-19 which interfere the ability to work as before.[4]

In this paper, we will discuss how to prepare a post-COVID-19 person with cardiovascular disease either previously as a comorbid or due to COVID-19 to return to work safely.

CARDIOVASCULAR DISEASES AS COMORBID AND AS THE EFFECT OF COVID-19

The presence of comorbidities such as hypertension, diabetes, coronary heart disease, heart failure, dyslipidemia in patients suffering from COVID-19 can cause a 1.4 times higher severity, and even lead to higher mortality.[5] Although this virus causes infections of the respiratory tract, its systemic effects can cause different appearances in each individual depending on comorbidities and physical conditions.

In addition, systemic inflammation due to COVID-19 can cause cardiovascular complications such as:[2]

- Acute cardiac injury, which is characterized by increased troponin enzymes, symptoms of acute heart failure or myocardial infarction.
- Myocarditis
- Acute coronary syndrome, due to the occurrence of acute thrombosis in the coronary arteries
- Arrhythmias, in the form of ventricular fibrillation, ventricular tachycardia, atrial fibrillation and prolongation of the QT interval which can cause recurrent arrhythmias.
- Thromboembolism that can occur in various places, both central and peripheral.

The reciprocal relationship between COVID-19 and cardiovascular disease can be seen in the following figure, (figure 1)

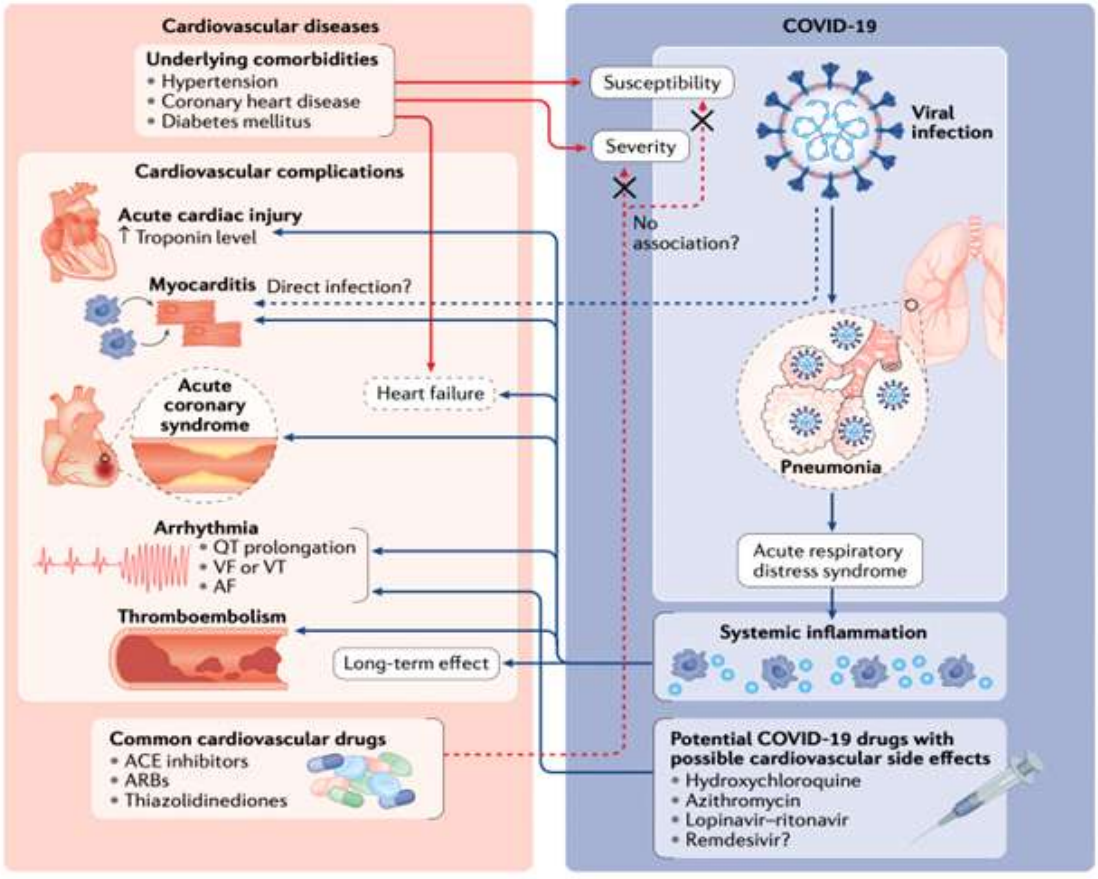

Figure 1: Interrelationships between COVID-19 and cardiovascular comorbidities. Taken from Nishiga et al, 2020.

Due to this causal and reciprocal relationship, in patients with COVID-19, the following cardiovascular diseases may arise during or after treatment:

- Cerebrovascular disease (stroke, TIA)
- Dysrhythmias (sinus tachycardia, atrial fibrillation, sinus bradycardia, ventricular arrhythmias, atrial flutter)
- Ischemic heart disease (acute coronary syndrome, myocardial infarction, ischemic cardiomyopathy, angina)
- Non-ischemic heart disease
- Pericarditis
- Myocarditis
- Heart failure, cardiogenic shock
- Thromboembolic disease

The presence of cardiovascular disease as a comorbid and the emergence of cardiovascular disease disorders after COVID-19 disease can increase the risk and death. The risks and consequences of each cardiovascular disorder in COVID-19 and its additional burden can be seen in the following figure (figure 2 and figure 3):[6,7]

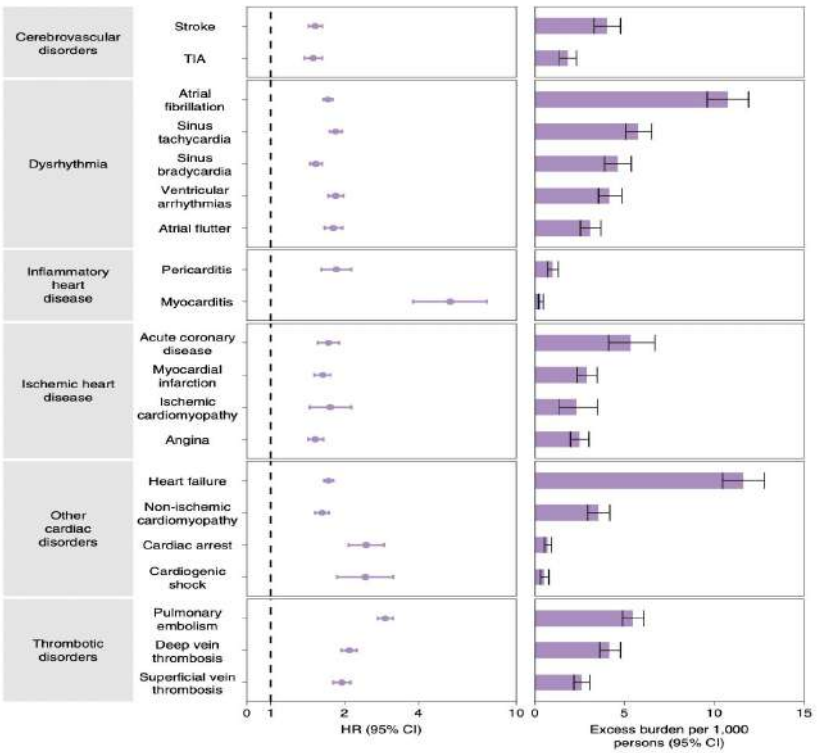

Figure 2. Hazard ratio and excess burden per 1000 patients due to Covid-19 within 12 month. Taken from Xie Y, et al, Nature Medicine, 2022.

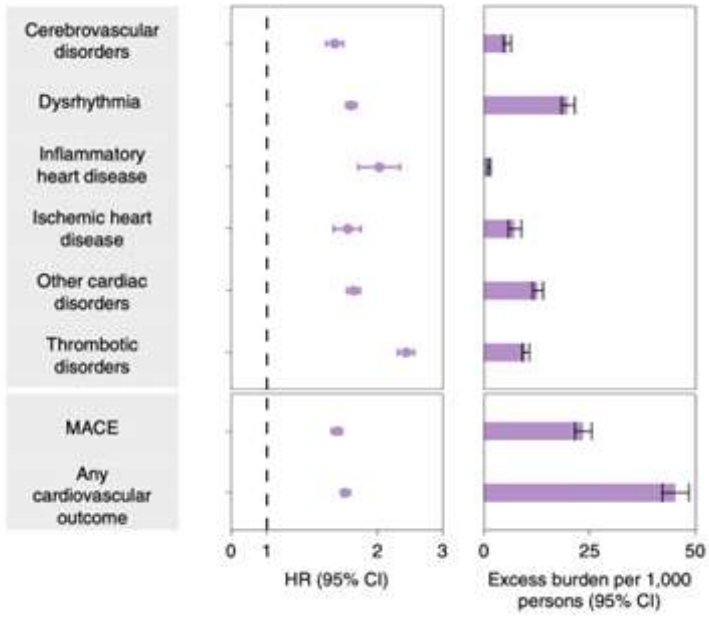

Figure 3: Post-COVID-19 cardiovascular disease outcomes in 12 months. Taken from Xie Y, et al. 2022.

Each of these risks and their outcomes are different for each COVID-19 disease condition, the highest being in Intensive Care, followed by usual care, and the lowest in untreated COVID-19 patients.[6]

Steps to return to work after COVID-19

The specific approach of patients returning to work after Covid-19 treatment is not clearly defined, but several assessment steps are needed to ensure their safety, the safety of their co-workers and the safety of their work environment. It is also necessary to consider the conditions of transmission in the community or in the workplace.

The steps required during the assessment are: (1) Assessing the level of transmission in the community, (2) assessing the level of individual risk, (3) assessing the level of risk due to work and in the workplace, (4) Establishing medical treatment for each case. [8]

From Nabeel et al, the steps can be imitated from the return-to-work approach in high-risk workers, namely:[9]

- Assess the risk of transmission in the workplace, depending on the level of interaction between workers and the nature of the work.
- Identify individual risk levels and stratify disease control levels
- Establish preventive measures in the workplace
- Provide advice to employees and company regarding modified risk control strategies.

For patients with COVID-19 with cardiovascular disease as comorbid or as the effect of COVID-19 infection, an individual risk assessment is required, based on:[10]

- Symptom
- Electrocardiogram or Holter ECG monitoring 24 hours, to determine the risk of arrhythmia, myocardial infarction, myocarditis, or myocardial ischemia.
- Echocardiography, to assess pump function, heart structure, which may be disturbed due to myocarditis, pericarditis, ischemia, myocardial infarction, heart failure.
- Functional capacity measurement can be done with simple cardiac exercise tests such as 6- minute walk test, or treadmill/leg ergocycle test, and measurement of oxygen saturation
- Pulmonary function tests may also be required, depending on clinical analysis and needs.
- Psychological examination or mental status is also necessary to determine the person's readiness to return to work

In addition to individual risks, it is also necessary to carry out risk assessments to and from other workers, for example, there is a possibility that the patient can transmit or be re-infected from his co-workers. Work arrangements and conditions must be determined by the company, such as the provision of personal protective equipment, hand washing facilities, preventive information, and arrangements for post-infectious examination, treatment or self-isolation. [11]

Next is a risk assessment to and from the work environment, concerning the equipment that must be operated, the gathering place environment, room temperature controller, dining area and others.

SETTING A RETURN-TO-WORK STRATEGY

It is very important to carry out a comprehensive assessment to return patients back to work not only from the clinical perspective of the disease. In this case, it is necessary to involve an occupational medicine specialist to be able to conduct a comprehensive assessment and make steps to approach returning to work for employees in a company or place of work.

The specialist can discuss with management the overall recommendations for the company and each employee, and create a return-to-work program for each employee suffering from COVID-19 with or without cardiovascular disease. It must be determined whether to return to the previous job, or be given another job, another place, retraining is required, or modification of the way of working is required.

From the position statement of the cardiopulmonary assessment prior to returning to high-hazard occupation post-symptomatic Covid-19, it is possible to imitate the examination steps and actions that can be taken for sufferers. [10] This can be seen in Figure 4 and Figure 5:

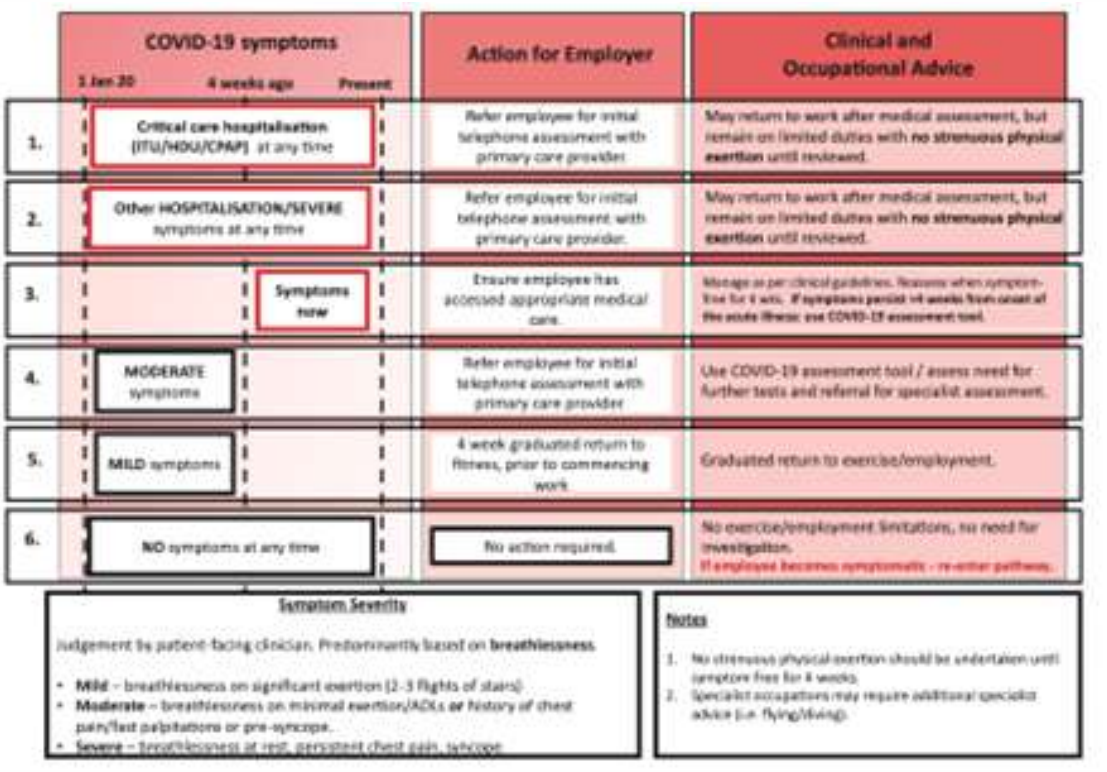

Figure 3: Example of risk assessment flowchart for COVID-19 patients in highrisk places. Taken from Rienks e al, 2022.

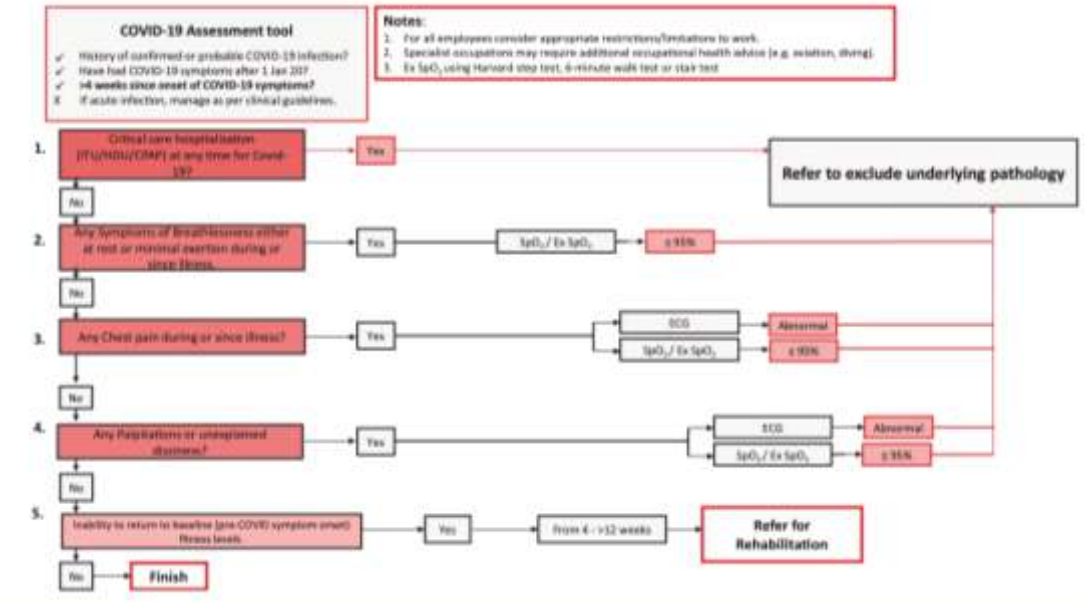

Figure 4: An example of an examination and action flow, quoted from Rienks, 2022.

CONCLUSION

Cardiovascular disease can be a comorbid that exacerbates the manifestations of COVID-19 and can be a result of COVID-19. The appearance and risk of those who have cardiovascular comorbidities or have cardiovascular disease as a result of COVID-19 may be more severe. The level of risk and consequences is highest if it causes treatment in the ICU.

A comprehensive special cardiovascular assessment needs to be carried out if there is a history of cardiovascular complications or there are cardiovascular comorbidities during COVID-19, taking into account the symptoms that still exist.

It is necessary to involve a specialist in occupational medicine, to be able to make an assessment and create a comprehensive program to return to work in a company.

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DEVELOPING A REGULAR WRITING HABIT

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ABSTRACT
Regular medical writing means to contribute to evedence based medicine and is a scientific responsibility. Some suggestions may be followed but nothing can substitute the passion for science. At the same time we must avoid to fall into the Publish or Perish hole.

The optimal patient management depends on a combination of clinical expertise, research evidence and patient preference. Using EBM can reduce mistakes, the costs and optimise the care [1,2]

Regular writing:
· Should not be just a mean to delvelop an academic career.
· Contributes to EBM and scientific knowledge.
· Is a big scientific and medical responsibility
· Lack of writing may vanish any potential innovation in our work

Daily accessing medical literature is the corner stone of any researcher or practitioner. No research, writing or good medical practice is possible without a solid possession of literature. At the same time, always look at you work as a potential source of scientific information, measure what you do. A regular writing habit should result from personal solid medical practice or active research work or both.

Papers can be poorly written, some researchers are poor writers, or do not enjoy to write, remember that bad writing has consequences for the reader, logical connections may be neglected, rationale of the research may be not described, papers may be cluttered with jargon.

Writing papers is important for academic career leading to competition with emotional pressure, shortening the appropriate and thoughtful interval between research work and reporting The competition may lead to inappropriate if not illegal behaviours. Researchers should be accurate when submitting data for publication, avoiding the problems related to data analysis or ethical issues, such as lack of authorization by the Ethical Committees. Below simple examples:
Plagiarism is the "wrongful appropriation" and "stealing and publication" of another author's "language, thoughts, ideas, or expressions" and the representation of them as one's own original work. Duplicate publication, multiple publication, or redundant publication refers to publishing the same intellectual material more than once, by the author or publisher. These flaws should be

avoided using available tools such as plagiarism identification by computational softwares.

Another point is the topic of our research. An example of these issues is COVID-19 pandemic which deserves special attention by the scientific community. However, several other diseases might be neglected, which can also compromise the health worldwide as the COVID-19. The COVID-19 pandemic has been associated with a storm of information by social media (infodemic) and with increase in publications (paperdemic) resulting in high percentages of retractions.[3-5].
In conclusion regular writing is not the aim of research but a mean to spread scientific knowledge to care better our patients.

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THE ART OF PERFORMING EXERCISE TESTS IN POST COVID-19 SYNDROME

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INTRODUCTION

In order to assess survivors' long-term health comprehensively and provide rehabilitation, all aspects of health that influence recovery, including organ impairments, functional limitations and personal circumstances, should be assessed.[1] Based on covid.go.id (access on 30 May 2022) Indonesian positive case 6.054.633, cured 5.895.176 and death 156.586.

The World Health Organization's International Classification of Functioning, Disability and Health (WHO ICF) model put forward in 2001 provides a coherent view of different aspects of health from biological, individual and social perspectives. This framework has been extensively researched and validated for describing health state, epidemiology and public health, classifying outcome measures and planning interventions. The interplay between these factors in COVID-19 survivors is important to recognize in order to characterize their multi-systemic problems and disability and improve "functioning" by targeted interventions.[1]

Physical medicine and rehabilitation is known as a medical specialty that studies about physical medicine and comprehensive rehabilitation services based on functional assessment to functional diagnosis and prescribes therapy in the form of biomedical and technical interventions that aim to optimizing the function of individuals with or without disabilities.[2]

This paper focuses on exercise testing, which relates to the three main domains of ICF. Mainly on functional capacity, as mentioned before, focusing on individual aspects as of we can make a specific exercise based on patient.

FUNCTIONAL ASSESSMENT

Functional assessment measures an individual's level of function and ability to perform specific tasks on a safe and dependable basis over a defined period. A detailed assessment should include a pertinent clinical history; a neurologic and musculoskeletal evaluation, a physical effort determination, and a comprehensive evaluation of behaviors that might impact physical performance. Assessments must be valid, reliable, and reproducible. They can be self-administered questionnaires or clinician administered.[3]

Exercise capacity refers to one's physiological maximal response to exercise (e.g., maximal oxygen consumption or heart rate) or the body structure's maximal ability to fulfill its own function (e.g., maximal voluntary contraction of a skeletal muscle). Functional capacity is defined as one's

maximal potential to realize a functional activity in a standardized environment (e.g., walking distance during the 6-minute-walk test).[4]

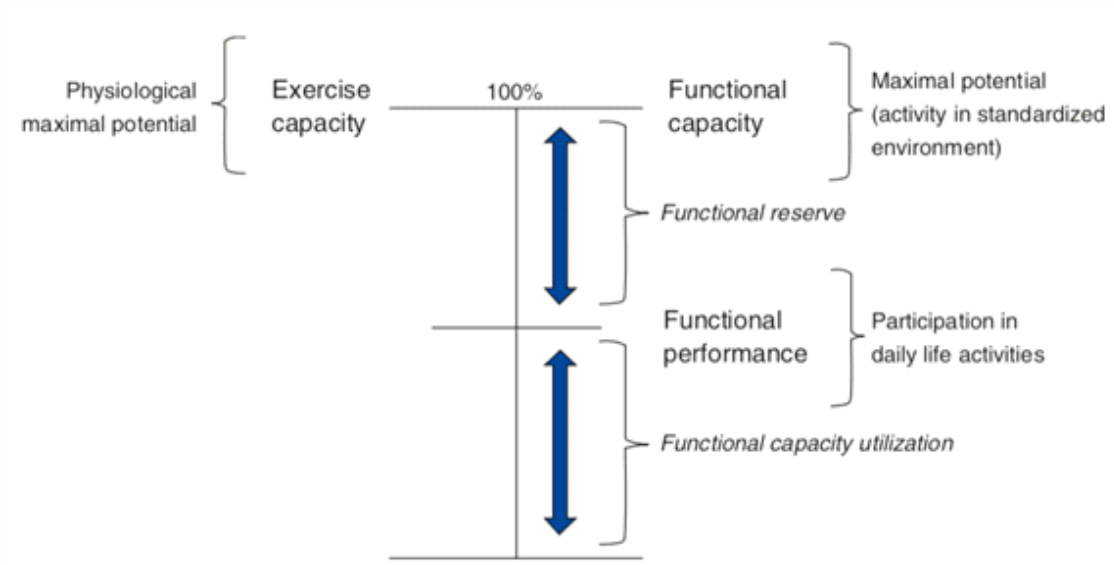

Figure 1[4]

Functional performance refers to the ability to complete "the physical, psychological, social, occupational, and spiritual activities that people actually do in he normal course [and context] of their lives to meet basic needs, fulfill usual roles, and maintain their health and well-being" (e.g., ability to get dressed without help). Functional performance thus refers to participation in daily life activities and is usually performed at a level that does not require nor meet maximal exercise capacity. Examples of commonly used outcomes and associated tests hinged on the ICF components and categorized according to the different key concepts to which they refer are presented in Table 1. A greater physiological exercise capacity will likely result in a greater maximal potential ability to realize functional activities, and thus patients should perform a daily functional task more easily (e.g., in a lesser time, with less dyspnea [better functional performance]).

INTERNATIONAL CLASSIFICATION OF FUNCTION

The International Classification of Function (ICF) was developed by the World Health Organization to provide a comprehensive framework of definitions and structures for rehabilitation, allowing a patient- centered outcome assessment, including not only body structures and functions but also patient functioning in activities and participation.

The Five Domains of Function and Disability As illustrated in Figure 1, the ICF framework presents functioning and disability of an individual with a given health condition as the interaction between five different domains: body functions and structures, activities, participation, environmental, and personal factors.[4]

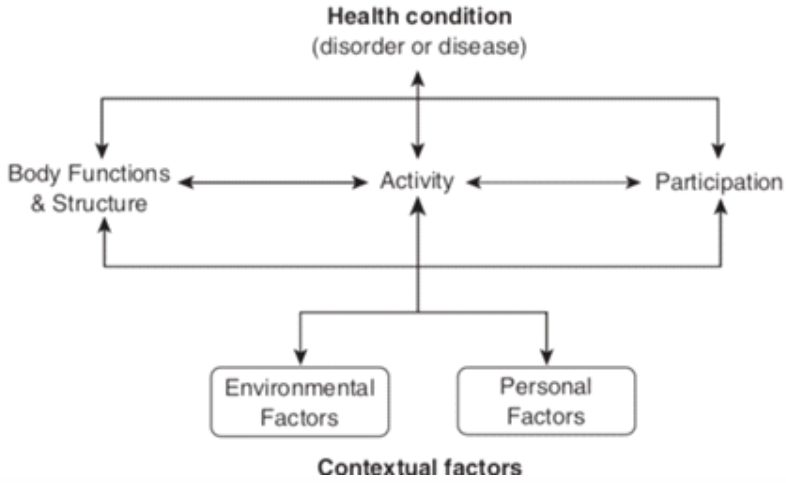

Figure 2 [4]

Based on the spread of these meaningful concepts, each outcome measure was classified into one of the main individual ICF components, defined as follows:

Body structure and body function refers to anatomical structure or physiological function such as those required for cognition, cardiovascular function, motor functions, pain or emotion. Activities: refers to the execution of tasks at an individual level. Participation: refers to the individual's involvement in everyday life situations. Environmental factors: refer to physical, social and attitudinal factors in the person's life and society which hinder or facilitate the functioning of the individual. Personal factors: refers to characteristics that are unique to each individual such as age, gender, ethnicity, personality, resilience or experiences.

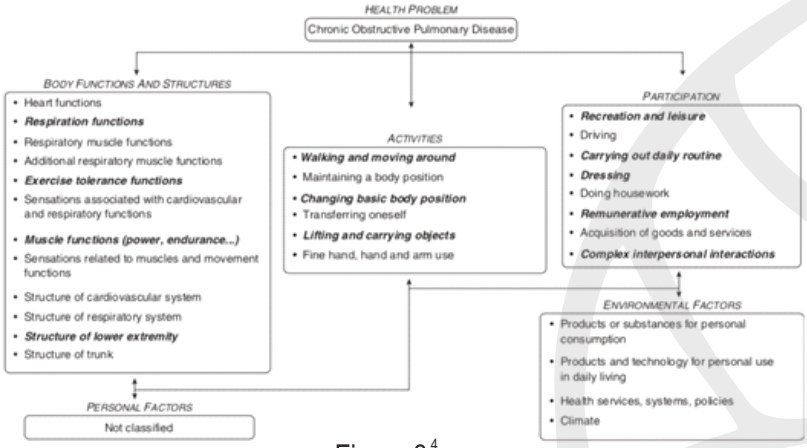

Figure 3 [4]

Table 1. Examples of commonly used outcomes in chronic obstructive pulmonary disease and associated tests hinged on the ICF components

Exercise Capacity			Functional Capacity			Functional Performance		
Body Structures and Functions	**Tests**	**Outcomes**	**Activities**	**Tests**	**Outcomes**	**Participation**	**Tests and Questionnaires**	**Outcome(s)**
Respiration function	Spirometry, plethysmography (lung volumes)	FEV_1, FVC, TLC, IC	Walking	6MWT, ESWT	Maximal distance walked, time walked at the given speed	Recreation and leisure	Pedometer	Number of daily steps (physical activity quantification)
Exercise tolerance function	Incremental and endurance CPET	$V_O$$_2$max, time at a constant work rate	Moving around (climbing)	Glittre ADL test, 3MST, SCPT	Time to complete five laps, number of steps ascended and descended, time and velocity during the ascension	Carrying out daily routine	Pulmonary Functional Status and Dyspnea Questionnaire	Level of dyspnea during daily activities
Muscle function (power, endurance)	Isometric, isotonic, or isokinetic measurements of voluntary/nonvoluntary contractions, surface electromyography	Peak muscle torque, total amount of work performed, time to exhaustion, twitch force	Changing basic body position	5STS, GST, TUG	Test duration	Dressing, remunerative employment, recreation, and leisure	Canadian Occupational Performance Measure	Ability (score on a 1–10 scale) to perform significant problematic activities
Structure of lower extremity: muscles of the thigh	Computed tomography, bioelectrical impedance, biopsy	Muscle mass, midthigh cross-sectional area	Lifting and carrying objects	6PBRT, UULEX	Number of rings moved, test duration, and weight of the heaviest bar lifted	Complex interpersonal interactions, remunerative employment	London Chest Activity of Daily Living	Ability (score on a 1–5 scale) to perform without help daily activities

Definition of abbreviations: 3MST = 3-minute constant rate step test; 5STS = five-repetition sit-to-stand; 6MWT = 6-minute-walk test; 6PBRT = 6-minute pegboard and ring test; CPET = cardiopulmonary exercise test; ESWT = endurance shuttle walk test; Glittre ADL test = Glittre Activities of Daily Life test; GST = grocery shelving test; IC = inspiratory capacity; SCPT = stair climb power test; TLC = total lung capacity; TUG = timed up and go; UULEX = unsupported upper limb exercise test; $V_O$$_2$max = maximal oxygen consumption.

Table 1[4]

The used of COPD ICF model based on expert consensus protocol of rehabilitation COVID-19 patients.[5]

Exercise Capacity

Table 1 presents examples of exercise capacity tests for various body structures and functions. Field walking tests are, however, primarily considered to assess functional capacity, as explained in the next section. Often used as a surrogate to determine functional capacity, maximal exercise tests, such as incremental and constant cycling and walking tests, are usually performed with comprehensive monitoring of cardiopulmonary variables, providing precise indications of maximal and submaximal exercise capacity and of the physiological responses to exercise, in addition to being useful for prognostication of patients with respiratory diseases. [4]

Functional Capacity

Field walking tests are low cost, require little equipment, and are considered to be more reflective of daily life than laboratory-based treadmill or cycle ergometer tests. Although these tests were developed to evaluate functional capacity and indicate one's maximal ability to conduct a functional activity (in that case walking), they can also measure exercise capacity by providing physiological measures when cardiopulmonary variables are monitored (body functions).[4]

The most recognized test is the self- paced 6-minute-walk test, which has been used in many clinical trials of pulmonary rehabilitation in COPD. The incremental shuttle walk test and the endurance shuttle walk test are externally paced field walking tests.

FUNCTIONAL PERFORMANCE

Functional performance should be considered as a whole with context (which includes physical and social environments), no laboratory-based tests are fully representative of patients' true ability to fulfill their social roles, as laboratory and often clinical contexts obviously differ on several aspects (e.g., distractions, physical environment, direct or indirect pressure from evaluators) from the real-life situations in which patients usually perform their activities.

Functional performance could be assessed using both direct observation of daily life activities in patients' real environment and/or questionnaires such as the Pulmonary Functional Status and Dyspnea Questionnaire, the Pulmonary Functional Status Scale (short form), the London Chest Activity of Daily Living, and the Canadian Occupational Performance Measure.[4]

Table 2. Functional tests commonly used in chronic obstructive pulmonary disease and further described in the second part of this seminar series

Abbreviation	Name
3MST	3-minute constant rate step test
4MGS	4-m gait speed
5STS	Five-repetition sit-to-stand
6MST	6-minute step test of free cadence
6MWT	6-minute walk test
6PBRT	6-minute pegboard and ring test
BBS	Berg Balance Scale
ESTW	Endurance shuttle walk test
Glittre ADL test	Glittre Activities of Daily Life test
GST	Grocery shelving task
SCPT	Stair climb power test
SPPB	Short physical performance battery
TUG	Timed up and go
UULEX	Unsupported upper limb exercise test

RESEARCH

Kajal Patel, et all made a systematic review about post covid syndrome. In the 36 studies included in this review, there were 33 different outcome measures used at follow-up. The commonly used outcome measures included Pulmonary Function Tests (PFT; 20 studies), Impact of Event Scale (IES-R; seven studies), Short-Form 36 (SF-36; six studies), 6-Minute Walking Distance (6MWD; five studies), Hospital Anxiety and Depression Scale (HADS; three studies) and St George's Respiratory Questionnaire (SQRG; Anxiety and Depression Scale (HADS; three studies) and St George's Respiratory Questionnaire three studies).[1]

Many centers have temporarily suspended face-to-face activity and assessments have largely ceased; this has posed a challenge to rehabilitation providers, who have been unable to individually assess and prescribe the essential exercise component of the programme. Added to this, rehabilitation staff may have been redeployed to acute areas, COVID research teams or to work from home due to shielding.

Centers have risen to this challenge and turned to providing remote programmes in the form of home-based manuals, phone calls and virtual classes (tele-rehabilitation) However, there is a worry from the rehabilitation community that the effectiveness of rehabilitation may be diluted, particularly if no measure of exercise tolerance is completed at baseline.

Many functional exercise tests lend themselves to being conducted virtually in the home with minimal equipment. A rapid narrative review was carried out by Linzy Houchen-Wolloff et all.6 The study had the following features. Participants: adults, all with long-term conditions; intervention: any/none; outcome: Duke activity status index (DASI), sit to stand (STS, 30 s, 1 min and 5 repetitions), short physical performance battery (SPPB), 4-metre gait speed (4MGS) or step test (Chester/others) AND directly compared to one of the recommended exercise tests for cardiopulmonary rehabilitation: 6-min walk test (6MWT), incremental shuttle walk test (ISWT) or cardiopulmonary exercise test (CPET) in terms of reporting agreement/correlation; Study design: primary research only, controlled trials or observational studies. Results: Sixteen articles out of 249 screened were included (n=2271 patients). Overall, there were weak–strong correlations for the included tests with a recommended exercise test (r=0.38–0.85). There were few reported issues with feasibility or safety of the tests. However, all tests were supervised in a clinical setting. The test that had the highest correlation with the field walking test was the 4MGS with the ISWT (r=0.78) and with the 6MWT (r=0.85). Discussion: The 4MGS has the highest correlation with routine measures of exercise tolerance. However, it may be difficult to standarize in a remote assessment or to prescribe exercise from. Clinicians should strive for face-to-face standarize exercise tests where possible to be able to guide exercise prescription

For reference in Indonesia we have 6 minute track to 4-meter gait speed and cut off point Indonesian adults.[7] Although Four meter gait speed is closest to the standard test (6 MWT and ISWT), other short tests such as sit-to-stand, or step tests still can be used.

Rachmawati et all , performing the bedside m30STS in their recently studies, may be simpler than the 6MWT for COVID-19 patients treated in an isolation ward because it only requires a small space.[8]

Time up and go test (TUG) is a tool to determine fall risk and measure the progress of balance, sit to stand and walking. It is a Simple screening test that is a sensitive and specific measure of probability for falls among older adults. In ICF for COPD, TUG for measure basic activity. Nathan Morelli el all reported using TUG as a functional assessment and cognitive measurement.[9]
Objective: The purpose was to examine Dual Task (DT) performance in patients surviving severe and critical COVID-19 com- pared to patients with chronic lung disease (CLD). Secondarily, we aimed to determine the psychometric properties of the Timed Up and Go (TUG) test in patients surviving COVID-19. Design: Prospective, cross-sectional, observational study. Setting: Academic medical center within United States. Patients: Ninety-two patients including 36 survivors of critical COVID-19 that required mechanical ventilation (critical-COVID), 20 patients recovering from COVID-19 that required supple- mental oxygen with hospitalization (severe-COVID), and 36 patients with CLD serving as a control group. Measurements and Main Results: Patients completed the TUG, DT-TUG, Short Physical Performance Battery (SPPB), and Six Minute Walk Test (6MWT) 1-month after hospital discharge. A subset of patients returned at 3-months and repeated testing to determine the minimal detectable change (MDC). Critical-COVID group (16.8 ± 7.3) performed the DT-TUG in significantly slower than CLD group (13.9 ± 4.8 s; P = .024) and Severe-COVID group (13.1 ± 5.1 s; P = .025). Within-subject difference between TUG and DT-TUG was also sig- nificantly worse in critical-COVID group (−21%) compared to CLD

(−10%; P = .012), even despite CLD patients having a higher comorbid burden (P<.003) and older age (P<.001). TUG and DT-TUG demonstrated strong to excellent construct validity to the chair rise test, gait speed, and 6MWT for both COVID-19 groups (r = −0.84to 0.73, P < .05). One- and 3-months after hospital dis- charge there was a floor effect of 14% (n = 5/36) and 5.2% (n = 1/19), respectively for patients in the critical-COVID group. Ceiling effects were noted in four (11%) critical-COVID, six (30%) severe-COVID patients for the TUG and DT-TUG at 1-month. Conclusion: The ability to maintain mobility performance in the presence of a cognitive DT is grossly impaired in patients sur- viving critical COVID-19. DT performance may subserve the understanding of impairments related to Post-intensive care syndrome (PICS) for survivors of critical illness.

CONCLUSION

The ICF for COVID-19 may refer to Chronic Lung disease ICF. The application test still based on evidence based medicine but has an art in itself, especially for functional performance tests which included in health related quality of life questions (HRQL).

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COMPREHENSIVE EXERCISE PRESCRIPTION TO OPTIMIZE FUNCTIONAL CAPACITY RESTORATION FOR POST COVID-19 SYNDROME

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ABSTRACT

Post COVID-19 Syndrome or "Long COVID", are long-term symptoms that some people experience after they had COVID-19. The most functional problem impact of post covid syndrome are restrictive lung disease and severe fatigue syndrome. This condition can affect a person's ability to perform daily activities and work. The aim of comprehensive exercise prescription is to optimize functional capacity restoration for post COVID-19 syndrome patients.

From exercise testing, on clinical experiences is useful to guide recommendations for return to activity & work. For safety reasons, the test can be terminated prior to the subject reaching a measured or estimated O2max, volitional fatigue, or a predetermined endpoint (i.e., 50%–70% heart rate reserve [HRR] or 70%–85% age-predicted HRmax). We recomendate Submaximal exercise testing walk test 4 meter and 6-min walk test that is easily to do. The advantages of this test are easy to administer with large numbers of individuals at one time, and little equipment is needed. 6-min walk test has been used to evaluate Cardiorespiratory Endurance Capacity in populations such as elderly and some clinical patient populations (individuals with pulmonary disease, Cardiac problems, other Comorbid). During testing, measuring variables HR, BP, workload, rating of perceived exertion (RPE), and other subjective indices as valuable information regarding functional response to exercise, and before that, needed skrining about absolute contraindication of exercise testing.[2]

After exercise testing, Exercise Prescription is given. An therapeutic exercise program ideally is designed to meet individual physical health and fitness goals within the context of individual health status, function, and the respective physical and social environment. The FITT-principle of therapeutic exercise prescription is recommendations on build exercise pattern. We also must periodically monitor the exercise programs that we have provided, both hospital-based and home-based programs. The clinician should also monitor the patient sign and untoward symptoms.

FITT principles are **Frequency** (how often), a number days per week dedicated to an (exercise program), important contributor to get benefits resulted from Therapeutic Exercise. Cardiorespiratory endurance is recommended on 3–5 times/week (most adults), with the frequency varying with the intensity of exercise, walking, static/cycling, or using different muscle groups (swimming, jogging), with/or daily intensity Physical Activity for some individuals. **Intensity** (how hard), start with Moderate (40%–59% heart rate reserve [HRR] or O2R) intensity aerobic

exercise is recommended for most adults, or start mild (30%–39% HRR or O2R) intensity aerobic exercise for individuals with deconditioned. **Time** (duration or how long), average 30–60 min/session (day) (with ≥150 min/week) of moderate intensity exercise. This recommended amount of exercise may be accumulated in continuous exercise session or +/- ≥10 min over of a day. In addition, it is also recommended that short duration of therapeutic exercise with mild intensity, start from 10-20 min/session (day) for some individual with deconditioning to help back their Functional ADL All base on Exercise Testing results and Tailored Made. **Type** (mode / kind) rhythmic, endurance type exercises with involving large muscle groups are recommended to optimize cardiorespiratory endurance. [3]

Program adjustments, made by increasing exercise time/duration per session 5-10 minutes every 1-2 weeks during the first 4-6 weeks of an exercise program are appropriate for most adults. After a regular exercise program of 1 month, FITT is gradually adjusted upwards over the next 4-8 months - or longer for older adults and deconditioned individuals. Avoid large increases in FITT components to minimize the risk of muscle soreness, injury, undue fatigue, and the long-term risk of overtraining. These are our clinical recommendations that clinicians can do in dealing with functional problem of Long COVID.

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PEARLS OF IMPROVING RESPIRATORY DYSFUNCTION POST COVID-19

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ABSTRACT
Medical concerns during the pandemic era have revolved around improving respiratory dysfunction, both during and after COVID-19 infection. It is then expected that this literature review would assist clinicians in choosing the right modality to further improve respiratory dysfunction in the post COVID condition. Identifying the respiratory dysfunction could begin by using the International Classification of Functioning, Disability and Health (ICF) concept, and stratifying the dyspnea or cough problem in post COVID syndrome. Afterwards, analysing the breathing pattern and the postural control could then illustrate what component is disturbed in the current respiratory function. Administering breathing retraining seems empirical to be given to almost all patients, enforcing the fact that expiration should be longer than inspiratory time. Chest expansion exercises could then follow to further improve lung recruitment and gas exchange. Several devices could also be used to manually hyperinflate lungs or strengthen both inspiratory or expiratory muscles. Monitoring assessed problems are essential aspects of providing effective rehabilitation program, thus should be performed in this situation as well. Lung auscultation, inferior chest expansion, breathing pattern and cardiorespiratory endurance are the evaluations that should be done before and after.

BACKGROUND
Medical concerns during the pandemic era have revolved around improving respiratory dysfunction, both during and after COVID-19 infection.[1] Despite having the same vector of COVID-19, respiratory dysfunction presents different functional disorders during acute COVID-19 infection and after the viruses have resolved, a condition commonly known as long COVID, or post-COVID syndrome.[2] Acute COVID-19 infection generally presents with breathing difficulties due to airway clearance function, whereas post-COVID syndrome naturally comes from the oxygen diffusion disorder, which eventually leads to muscle fatigue, and chest expansion disorder. The dual presentation of both obstructive and restrictive respiratory disorder has then piqued many interests from the medical research field,[2] especially the functional aspects of individuals as approached through physical medicine and rehabilitation. Concerns arise as studies show possibilities of irreversible respiratory dysfunction from previous studies, as the long-term sequelae of COVID-19 is still understudied.[1] It is then expected that this literature review would assist clinicians in choosing the right modality to further improve respiratory dysfunction in the post COVID condition.

IDENTIFICATION

During initial presentation, an individual with this condition should then be differentiated if it comes from the disease itself or from prolonged immobilization.[1,3] Epidemiologically, three of the most common symptoms of post COVID syndrome found are fatigue, dyspnea, and cough, each being present in >34% of patients.[4] Similarly all these three symptoms could originally be the result of infection and prolonged immobilization, with both dyspnea and cough being the underlying symptoms behind fatigue. Among the management that could be provided for these groups of individuals, chest physiotherapy seemed to be a general therapy being prescribed frequently.[5] It was however less known how chest physiotherapy is an umbrella term for a set of therapies being provided for the respiratory function. This particular topic will then be discussed further to provide better understanding and thus more accurate therapies towards the addressed respiratory dysfunction.

The functional disorder should then be further outlined on dyspnea and cough as they cover different aspects of respiratory function. Analyzing the problem could be initiated from the International Classification of Functioning, Disability, and Health (ICF) concept, stratifying problems of body function, structure, and activities and participation before approaching each of these with specific therapies.[6] Simply put, the Both dyspnea and cough would cause problems in low cardiorespiratory endurance, thus leading to limited functional capacity, being classified in the group of activity and participation.[7]

In the level of body function, breathlessness seems to be a problem that could both be an inspiratory or expiratory problem. Although there is a lot of body structure involved in breathing, it could be focused more on the chest wall anatomy, involving ribcage, intercostal muscles, and diaphragm. After prolonged immobilization or during tachypneic episodes of COVID, there are chances that it disturbs the oxygen uptake of respiratory muscles, causing fatigue in these short structure muscles, and nonphysiologic muscle recruitment persists. All in all these would cause inaccurate muscle recruitment, leading to ineffective muscle contraction, hence causing persistent dyspnea.

On the other hand, sputum retention could be caused by difficulties in expulsion, or excessive production of sputum, this then becomes disability as addressed in airway clearance function. Respective body structures involved are the ciliary structures in lung parenchyma. It is rather uncommon to have a productive cough during post COVID, therefore hypersensitivity of cilia membranes are the most likely culprit of post COVID dry cough.

PHYSICAL EXAMINATION

A recent meta-analysis has published that epidemiologically post COVID spirometric assessment revealed obstruction (7%), restrictive (15%), with the most being altered diffusion capacity (39%).[2] Interestingly, these studies were not examined at similar timings, some of which was 1 month after COVID, and the others could be anytime ranging up to 3 month. Therefore, the British Thoracic Society has recommended that these tests should be done 3 months after the infection.[2]

Correlating post COVID condition to the body function disorder into the common presenting symptoms, it could be seen that initially the localized lung tissue damage would result in desaturation, and thus would trigger a pontine response to cause tachypnea.[8] The apparent tachypnea will then cause increased inspiratory effort with reduced expiratory recoil, which further would eventually lead to muscle fatigue. It should be remembered that prolonged muscle fatigue would cause ineffective respiratory muscle recruitment, and these would cause changes in muscle mass, beginning from those accessory respiratory muscles with abundant type 2 muscle fibers.[9] The vicious cycle must then be unchained through several efforts, and these could be identified step by step through chest therapy.

Initially physical examination would mainly involve postural assessment and breathing pattern assessment, through which muscular action could be examined based on problems of breathing pattern.[5,10] Assessing the correct posture is highly related to assessing chest expansion, as mainly the ribs that encloses the lung tissues are all attached to the thoracic spine and sternum. These attachments would then ensure any changes to the spinal alignment would then result in a restrictive lung disorder. One of the most common and simplest postural problem is the forward head posture, in which due to anterior translation of the head position, it would cause pathologic stretches on the neck accessory inspiratory muscles, such as the upper trapezius, scalenes, and sternocleidomastoids.[11] Similarly, observing breathing pattern, it normally should go in the ratio of 1:2 for inspiration to expiration respectively. Therefore, when inspiratory time is short, and expiratory is even shorter, there should be further assessments done on the primary muscles of inspiration, namely diaphragm and external intercostals, accessory muscles of inspiration, and expiratory muscles such as the rectus abdominis.[11]

REHABILITATIVE INTERVENTION

Although there are several modes of respiratory rehabilitation intervention during the acute phase, only some of these are relevant to most cases of post COVID syndrome. Four of the modalities include breathing exercises, incentive spirometry, peak expiratory pressure devices, and manual hyperinflation.[10] These modalities will then be further discussed in the following paragraphs, and some of the other unexplained components could be used too in specific situations as required.

Breathing exercises as popularly known breathing retraining should always be enforced to patients. The fact that expiratory process is passive is less known by the general community, and when patient is asked to initiate breathing, often they will extend their head instead of expanding their chest. This is often the case as patients inspire and activate their upper trapezius to extend, rather than it should elevate their posterior ribs, anchoring its superior attachment on the cervical spine.[11] Another important aspect is the ratio of 1:2, that during the cases of tachypnea, patient tends to force their inspiration, and their expiration time is significantly shorter. An effective strategy to tackle this is to educate, or retrain their breathing action to a newer method that they rarely use, such as the abdominal breathing technique. Abdominal breathing reinforces the expansion of abdominal cavity during inspiration, in order to improve diaphragmatic excursion, and oppositely pushes air out by contracting abdomen during expiration. The method could also be combined with

pursed lip breathing when patients gain significant control over their breathing technique. There are no specific consensus regarding dose of the exercise, however patients could be instructed to repeat this for one minute per session, 3 sessions per day minimum to help them habituate the method in overcoming tachypnea.[5]

Chest expansion have been touched upon several times in the previous paragraphs, there is however a method to further expand the chest using a simple device, namely the ambulatory bag commonly found in resuscitation kit. The concept remains that chest should expand at its highest during inspiration, and if the lung is filled with more air during inspiration, supposedly the chest would expand further.[5] Similar to the previous exercise, that the patient should be able to control their breathing technique well, that is to inhale air naturally, in addition to the manually hyperinflated volume of air for two to three times before coughing. When they gain significant control over this technique would allow patients to perform this even without utilizing the device, and learn to hyperinflate before fully expiring air. This method could also be used to improve cough efficacy. The chest expansion itself could be trained by asking patients to inflate their lower chest instead of their upper. Several movements could be given as they practice breathing retraining, this includes bending their thorax backwards instead of the lumbar spine in order to expose more of the ribs and expand it to improve lung recruitment.[5]

It should also be remembered that both inspiratory and expiratory muscles are all skeletal muscles, which mean that they could be controlled voluntarily, and could be strengthened with correct loading. In the case of inspiratory muscles, there are two main devices available to strengthen, that is resistive (volume) type device and threshold (pressure) type devices. Both of these devices could be differentiated by observing the numbers as shown on the devices, those with millilitre unit represent resistive inspiratory devices, and function to achieve longer duration of inspiration. On the other hand, threshold devices have mmHg measurements, indicating pressures that needs to be overcome in order to complete one cycle. Similarly, expiratory muscle exercise device also utilizes pressure. By repeating the movement through specific loading, these muscles will undergo the overload principle of exercise, thus increases its muscle bulk, and neuromuscular recruitment, both of which would be summed into respiratory muscle strength. Therefore the correlated muscle strength parameter that could be measured (in mmHg) are the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP).[1,12–14]

Last but not least, monitoring and evaluation fills a crucial role in providing effective respiratory training. Lung auscultation could be done to assess symmetry between lungs, and evaluate how the airway is cleared. Breathing pattern as priorly discussed should have longer expiratory time. Chest expansion should be symmetric, with expansion of lower rib to indicate adequate expansion. Ultimately, endurance should improve as the patient is less fatigued during daily living activity performance.[1,5]

CONCLUSION

To conclude, the respiratory training involves several steps, as it begins with identification of problems, preferably utilizing the international classification of functioning, disability, and health (ICF) for better stratification of disabilities and its extent. Analysing the problematic component of breathing may take time to master, but for ease, it could be differentiated into postural problem or breathing pattern disorder. After knowing the specific muscles, they could then be trained in regards to their pathology, ergo tightness should be stretched, and weakness shall be strengthened. Finally, evaluation should be done beginning from the organ level, up to the functional activity performance, in order to show a streamlined respiratory training regimen in improving Post COVID Syndrome.

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PATHOGENESIS AND EARLY RECOGNITION OF SEPSIS IN RESPIRATORY SYSTEM

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Sepsis is a complex syndrome that results from infection. It is a life-threatening clinical condition with extensive physiological and biochemical abnormalities. According to the Third International Consensus Definition for Sepsis and Septic Shock, sepsis is a life-threatening organ dysfunction resulting from dysregulated host responses to infection, emphasizing for the first time the crucial role of the innate and adaptive immune host response in the development of the clinical syndrome. Epidemiological data about sepsis from the 2017 Global Burden of Diseases, Injuries and Risk Factor Study showed that the global burden of sepsis was greater than previously estimated. Approximately 49 million people are affected by sepsis every year and it is estimated that 11 million deaths are caused by this syndrome, accounting for up to 19.7% of all deaths worldwide. Bacteria have been shown to be the predominant pathogen of sepsis among patients with pathogens detected, while sepsis caused by viruses is underdiagnosed worldwide. The coronavirus disease that emerged in 2019 in China and now in many other countries has brought viral sepsis back into the vision of physicians and researchers worldwide. Although the current understanding of the pathophysiology of sepsis has improved, the differences between viral and bacterial sepsis at the level of pathophysiology are not well understood. Diagnosis methods that can broadly differentiate between bacterial and viral sepsis at the initial stage after the development of sepsis are limited. New treatments that can be applied at clinics for sepsis are scarce and this situation is not consistent with the growing understanding of pathophysiology. Only timely fluid resuscitation and early administration of broad-spectrum antibiotics have been shown to reduce mortality. A decisive factor is the time of correct diagnosis and the initiation of causal, supportive and adjunctive measures.

Recent studies showed that respiratory viral infections were underdiagnosed in patients with sepsis or septic shock. In both these studies, conducted in three middle-income countries from Southeast Asia and in a rural area of a high-income country (Sweden), viruses were detected in around one-third of adult patients with sepsis. The viruses, which can cause severe disease, included influenza A and B, respiratory syncytial virus, coronavirus, human metapneumovirus, parainfluenza virus types 1–3, adenovirus, enteroviruses, and rhinovirus. The CAP-China study, which was conducted in 34 hospitals from 10 provinces of mainland China, showed that the proportions of patients with community-acquired pneumonia (CAP) who developed sepsis during hospitals were 40.1 and 39.6% among those with influenza and non-influenza viral infections, respectively. As well as for commonly detected viruses, emerging novel virus infections can also result in sepsis and have raised global health concerns, these include: severe acute respiratory

syndrome-coronavirus (SARS-CoV) ; Middle East Respiratory Syndrome-coronavirus (MERS-CoV); and SARS-CoV-2 which caused the recent outbreak of the coronavirus disease 2019 (COVID-19) in China and in many other countries all over the world.

According to the Surviving Sepsis Campaign, intravenous antibiotics within 1 h after recognition of both sepsis and septic shock is strongly recommended. Apart from the benefit of empirical antibiotic use for patients with sepsis, a more precise prescription of antimicrobial therapy, including antiviral therapy for patients without bacterial infection, should be further explored. It is urgent to pay more attention to the role a virus plays in sepsis. The most common sites of infection among patients with sepsis are the respiratory tract (64–68%), followed by the abdominal tract, bloodstream, and renal and urinary tract. Viral sepsis has been defined as life-threatening organ dysfunction due to a dysregulated host response to viral infection.

PATHOPHYSIOLOGY OF RESPIRATORY VIRAL SEPSIS

Respiratory viral sepsis is a highly heterogeneous and multifaceted syndrome characterized by an overwhelming and systemic dysregulated host immune response to respiratory viral infection, with organ dysfunction including, but not limited to, the lung. Previous studies provided evidence for extrapulmonary organ dysfunction caused by respiratory viral infection: e.g. acute kidney injury and cardiac injury among cases with influenza infection; acute kidney injury and thrombocytopenia reported for MERS-CoV infection; high viral loads in the gut and liver and moderate viral loads in the kidney among fatal cases with SARS-CoV infection; and liver dysfunction reported for respiratory syncytial virus infection. Studies have showed that around half of the COVID-19 fatalities developed acute kidney injury, heart failure or coagulopathy.

In another recent study that included 183 COVID-19 patients, disseminated intravascular coagulation was observed in 71.4% of fatal cases, and in 0.6% of non-fatal cases. The multi-organ dysfunction determines that viral sepsis is a more complicated clinical status than severe viral pneumonia, with inflammation in the lung which is the primary and specific target organ of the respiratory virus. The type of infection and host response to the specific pathogen are determinants of sepsis and closely related to prognosis after the development of sepsis. The pathophysiology of sepsis includes that the immune response initiated by an invading pathogen fails to return to homeostasis, and thus culminating in a pathological syndrome that is characterized by sustained excessive inflammation and immune suppression.

The initial sensing of the host innate system after infection is to recognize pathogen-associated molecular patterns mediated by innate pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), retinoic acid-inducible gene-1 like receptors, NOD-like receptors, and C-type lectin receptors. For most of the infections, the host innate immune system can eliminate the pathogen through pro-inflammatory responses, including the release of cytokines and chemokines (tumor necrosis factor (TNF), interleukin (IL)-1β, IL-12 and IL-18), the recruitment of phagocytes, and the local activation of the complement and coagulation systems. Among patients with sepsis, pathogens cannot be eliminated by the host immune system and the homeostasis of the host immune system is disturbed, resulting in both an excessive inflammation and immune

suppression. The excessive inflammation of sepsis is mediated through the release of pro-inflammatory mediators by leukocytes and parenchymal cells, endothelium and platelets. Leukocyte and parenchymal cell injury results in the release of damage-associated molecular patterns, further disrupting the host response by activating many of the PRRs. These PRRs can also recognize pathogen-associated molecular patterns, leading to a vicious cycle that also involves organ damage and dysfunction. The coagulation system, complement system, neutrophils and vascular endothelium are also activated in this stage. In the immune suppression stage, both adaptive and innate immune systems are involved. This stage is characterized by the apoptosis of T-cells, B-cells and dendritic cells, the exhaustion of T-cells, and the expansion of regulatory T-cell and myeloid-derived suppressor cell populations. Patients with sepsis have increased numbers of myeloid-derived suppressor cells, which are immature myeloid cells that can impede immune responses, particularly T-cell function. Reprogramming of antigen-presenting cells leads to a reduced HLA-DR expression and a diminished capacity to produce pro-inflammatory cytokines. The most important findings in sepsis are the delayed apoptosis of neutrophils and the appearance of immature band-like neutrophils in peripheral blood that have deficits in antimicrobial effector functions.

HOST IMMUNE RESPONSE TO RESPIRATORY VIRUS

The causes and characteristics of sepsis can be highly heterogeneous . Current knowledge of the pathophysiology of respiratory viral sepsis is limited to the specific immune responses to viral infection. For the influenza virus, haemagglutinins of different strains determine attachment to the epithelial of which specific part of the airway, and the viral polymerase complex is associated with different levels of viral replication and cytokine production in the infected epithelial cells. Seasonal influenza, such as H3N2 and H1N1, targets preferential epithelium in the large airways (trachea, bronchi and bronchioles) by binding to α2,6-sialylated glycans, while H1N1pdm09 and H5N1 tend to infect both large airways and alveoli by binding to α2,3-sialylated glycans of pneumocytes.

Different to bacteria, an influenza virus invades the alveolar epithelial cells first but not alveolar endothelial cells. Pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8 are produced by the infected epithelial cells and can damage the epithelial–endothelial barrier. Endothelial cells can also be damaged through remodelling of the cellular cytoskeleton, loss of intercellular junctional integrity and cellular apoptosis. These processes lead to pulmonary oedema and respiratory insufficiency, which could further develop into severe pneumonia, acute respiratory distress syndrome and sepsis.

Viral reactivation may also play a role in the prognosis of sepsis. Immune exhaustion during sepsis provides the probability for some latent infections to escape immunological control, and replicate under this more forgiving environment. Some reactivated viral infections, such as the Epstein–Barr virus, were reported to be associated with clinical outcomes among patients with sepsis. The potential mechanism is that reactivated viral microRNAs might be involved in sepsis by functional mimicry mechanisms with cellular microRNAs produced by the human genome, sharing the regulation of the same signaling pathways and regulating the same spectrum of microRNAs.

DIAGNOSIS OF RESPIRATORY VIRAL SEPSIS

The diagnosis of respiratory viral sepsis depends on two steps: one step is the diagnosis of sepsis using the SOFA score, and the other important and challenging step is identifying the cause of the sepsis as a respiratory virus. The differentiation between bacterial and viral sepsis, especially at the initial stage after the development of sepsis, is important for the treatment of sepsis and prevention of mortality from sepsis. However, no golden standard was identified to broadly and efficiently determine and differentiate the presence and type of infection. Pathogen detection is the most important step of differential diagnosis between respiratory viral and bacterial sepsis. Point-of-care testing and next-generation sequencing provide the possibility for a quick and accurate identification of the potential pathogen that is causing the sepsis. Next-generation sequencing is especially important for confirmation of infection by novel viruses. The role next-generation sequencing played in the laboratory confirmation of SARS-CoV-2 infection is important. Testing multiple pathogens in one test and saving time are the advantages of point-of-care testing, which are especially important for sepsis. Furthermore, the use of point-of-care testing for sepsis was not limited to pathogen detection, but was also used for blood plasma protein quantification (e.g. C-reactive protein and procalcitonin) and leukocyte monitoring (through antibody capture or intrinsic property characterization). Clinical characteristics, blood biomarkers including C-reactive protein and procalcitonin, were not fully demonstrated to clearly discern viral and bacterial infection among patients with pneumonia, while the discrimination ability among patients with sepsis needs to be further demonstrated.

Early Recognition

The earliest clinical sign of sepsis is often a rapid respiratory rate. This may be driven by pyrecia, lactic acidosis, local lung pathology, pulmonary edema, cytokine-mediated effects on the respiratory control center or a combination of several of these factors. Hypoxemia occurs as a result of pulmonary pathology, shunting of deoxygenated blood through the lungs (cytokine mediated) or pulmonary edema secondary to capillary leak.

TREATMENT OF RESPIRATORY VIRAL SEPSIS

Timely intervention is the key to effective treatment among patients with sepsis. These include an initial fluid resuscitation and antibiotic therapy within the first hour. In patients with hemodynamic instability after the initial fluid resuscitation, further hemodynamic stabilization and assessment of fluid responsiveness should be continued. During the disease progression of COVID-19, some patients with viral sepsis have clinical features including cold extremities, weak peripheral pulses and severe metabolic acidosis, while the blood pressure levels remain normal. These clinical features indicate the continuing internal environmental disorders and microcirculation dysfunction among these patients. Thus, hemodynamic stabilization is necessary and important throughout the progress of treatment for patients with viral sepsis. The recommendation of antibiotic therapy is for all patients with sepsis. A previous study showed that the proportion of sepsis cases with a negative culture was around 42%. Future studies to evaluate effectiveness of antibiotic use and potential antibiotic resistance among these patients are needed, as inappropriate prescription can increase antibiotic resistance. Pathogen-directed therapy should be the emphasis during treatment for patients with sepsis. For patients with suspected or confirmed respiratory viral

sepsis, the early initiation of antiviral drugs with inhibiting viral replication and decreasing viral load is the most important step. Around 90 antiviral drugs have been formally approved for the treatment of human infectious diseases over the past 50 years, covering viruses that could cause viral sepsis, such as the influenza virus, human cytomegalovirus and respiratory syncytial virus. However, studies with these antiviral drugs were rarely conducted to evaluate the effectiveness for respiratory viral sepsis, which should be the focus of future research. Current findings indicate the potential effect of baloxavir, oseltamivir, peramivir and zanamivir for influenza infections and cidofovir for adenovirus infections in immunocompromised patients. Furthermore, the broad-spectrum antiviral drug ribavirin for the treatment of immunosuppressed patients with rhinovirus and respiratory syncytial virus infections, and arbidol for rhinovirus, respiratory syncytial virus, adenovirus and parainfluenza virus infections were also suggested. The broad-spectrum antiviral drugs, which refer to antivirals targeting viral entry and replication or modulating cellular defense systems, should be distinguished from broad-spectrum antibiotics which act against both gram-positive and gram-negative bacteria. The potential effectiveness of ribavirin for rhinovirus infection and cidofovir for adenovirus infection were only indicated by several case reports, and need to be further demonstrated.

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PEDIATRIC SEVERE PNEUMONIA: PROMPT MANAGEMENT TO PREVENT SEPSIS

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ABSTRACT
Pneumonia is still major health problem and the main cause of mortality among children under-5-years old. Sepsis is the most common cause of death in children with community acquired pneumonia. Severe sepsis, which are sepsis-related organ dysfunction and septic shock, require intensive treatment and monitoring in the PICU. Despite intensive intervention and empirical antibiotics, the mortality is quite high. Pneumonia is the most common underlying cause of sepsis. Younger age (< 2 months old), malnutrition and severely ill are the predominant risk factors in children with pneumonia to develop severe sepsis and its consequence of death.

Prevention of sepsis should be started at community level to prevent children suffered from severe pneumonia. Fulfill child's nutritional needs, mother's well-being to prevent low birth weight infant, and prevention of HIV vertical transmission are importance program to protect children from pneumonia. Pneumococcus and HIB vaccination should widely be scaled up as it has been demonstrated to decrease incidence of severe pneumonia.

Timely referral of severe cases of pneumonia to the hospital, along with proper oxygenation and early antibiotics given in the health care facility, would expectedly prevent clinical deterioration before they admit to the hospital. Upon admission, sepsis screening should be performed as early as possible and periodically continued later during hospitalization. Starting empiric antibiotics within 1 hour of recognition is a must in children with septic shock, and so is that within 3 hours in sepsis-associated organ dysfunction in the absence of shock.

Furthermore, implementation of other optimal aspects of sepsis care, such as initial adequate fluid resuscitation, and also reliable and frequent source control are mandatory to prevent sepsis in children with severe pneumonia.

Keywords: severe pneumonia, sepsis, sepsis-associated organ dysfunction, septic shock, empiric antibiotics

BACKGROUND

Globally, pneumonia is still number one killer in children under-5-years old. Approximately 101.8 million pneumonia episodes were estimated in children under-5-years in 2015, despite of 37% reduction of mortality.[1] Although children hospitalized with community acquired pneumonia have a

low rate of bacteremia, pneumonia is the leading cause of sepsis in children.[2,3] Mortality for children with sepsis ranges from 4% to 50%, depending on disease severity, risk factors, and geographic location.[4] Neonates with positive blood culture pneumonia have twice and a half higher risk of death compare to those with negative blood culture.[5] More cases are caused by viral pathogens than to bacterial.[6]

The etiology is not identifiable in most cases of pediatric sepsis, confirming that microorganisms other than bacteria might also be the causative agent (Table 1). However, Staphylococcus aureus, Pseudomonas and other gram-negative bacteria are the most common pathogens in pediatric pneumonia with sepsis.[7]

Table 1. Common pathogens isolated from blood culture in children with pneumonia

Organism	Percentage
Staphylococcus aureus	15
Pseudomonas	13
Other Gram-negatives	10
Candida	7
Other Gram-positives	6
Escherichia coli	5
Streptococcus pneumoniae	4
Haemophilus influenzae	4
No identifiable pathogens	31

source: Cruz *et al.* J Am Coll Emerg Physicians Open. 2020

HOW DOES PNEUMONIA LEAD TO SEPSIS IN CHILDREN?

The initial immune response to infection is recognition by the innate immune system. When organisms enter the respiratory tract, the pathogen-associated molecular patterns (PAMPs) of microorganisms will be recognized by pattern recognition receptors (PRRs), such as TLRs, NOD receptors and C-type lectin receptors. Together with later-activated adaptive immunity, most infections can be overcome by the innate immune system with its competent cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1β, IL-12 and IL-18. Phagocyte recruitment, complement activation and involvement of coagulation system are also of important mechanism in microbial defense. When the immune system is unable to completely eliminate the pathogen and the homeostasis of the host's immune system is disturbed, dysregulation of excessive inflammation occurs.[8]

Pro-inflammatory mediators are released by leukocytes, phagocytes, as well as by parenchymal cells, endothelium and platelets. Damage-associated molecular patterns (DAMPs) released by damaged leukocytes and parenchymal cells trigger more activation of many other PRRs and further exacerbate the inflammatory reaction. These chain events of hyperinflammation will lead to severe tissue damage and, in turn, multi-organ dysfunction. In this setting, vascular endothelial damage and dysfunction occur together with activation of the complement and coagulation system. Myeloid-derived suppressor cells which are immature myeloid cells increase to suppress

T-cell function, in response to suppress the occurring hyper-inflammation. The apoptosis of neutrophils is delayed in patients with sepsis. Besides, increase neutrophil production, resulting in immature band-like neutrophils that have lower phagocytic ability and antimicrobial effector function (Figure 1).[8]

Although most sepsis is associated with bacterial infections, viral respiratory infections can also cause sepsis. In contrast to bacterial infections, viruses invade alveolar epithelial cells and not alveolar endothelial cells, although endothelial damage is also later involved. In SARS-CoV2 infection, an increase in Th2 cytokines occurs early, in contrast to the general setting of sepsis in which the increase occurs after excessive inflammation.[8]

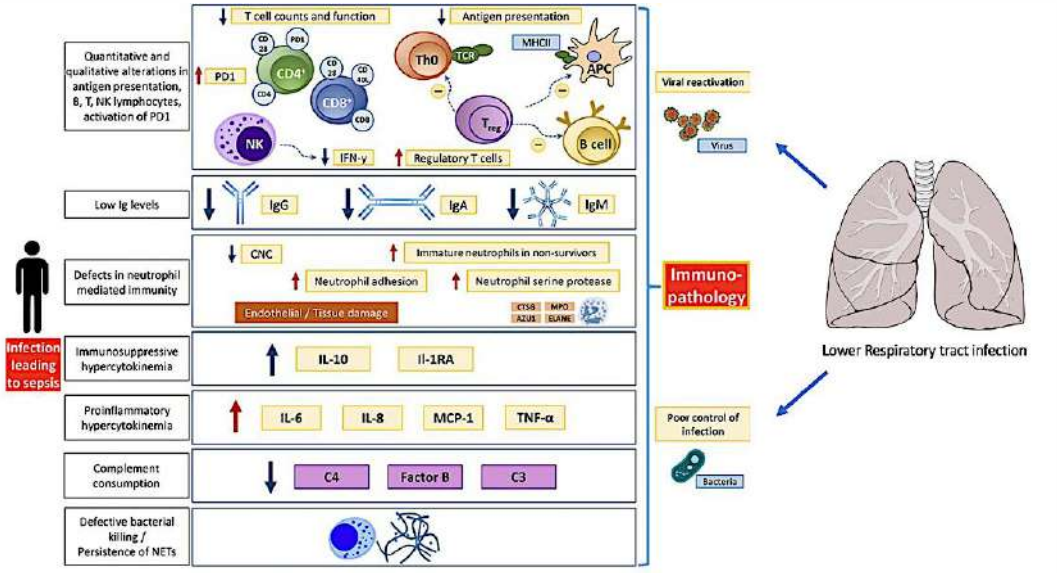

Figure 1. Dysregulation of immune respons to viral and bacterial pathogen in pneumonia. APC, antigen presenting cell; AZU1, azurocidine 1; CNC, circulating neutrophils count; CTSG, cathepsin G; ELANE, elastase; IFN-y, interferon y; Ig, immunoglobulin; MHCII, major histocompatibility complex II; MPO, myeloperoxidase; PD1, programmed death protein 1; TCR, T cell receptor.

Source: Jarczak D, et al. Front Med. 2021; 8; 628302

Diagnosis and treatment of severe pneumonia in children

The clinical manifestations of pneumonia are generally persistent fever (>38.5°C) and increased work of breathing, tachypnea and chest indrawing. The severity of pneumonia is clinically related to hypoxemia. Respiratory distress with grunting, nasal flaring, or severe lower chest wall indrawing indicate severe pneumonia requiring hospitalization. Clinical danger signs in infants and children include inability to drink/breastfeed, decreased consciousness, seizures, persistent vomiting, dehydration, and severe malnutrition. 10-12

Examination with pulse oximetry is very useful for indirectly assessing hypoxemia, oxygen saturation below 90% indicates significant hypoxia that occurs in severe pneumonia. This examination is inexpensive and very helpful in primary health care facilities in making the decision to refer a patient or not.[10] Complete blood counts and markers of infection such as C-reactive protein (CRP) are usually helpful in the diagnosis of pneumonia, although they are not related to the severity of the disease or the etiology of the pneumonia. Generally, they are not useful in the management of uncomplicated pneumonia.[11,13] However, CRP concentrations ≥40 mg/L with radiological confirmation of pneumonia suggests bacterial pneumonia.[12] Chest X-ray in severe pneumonia may include infiltrates and consolidation of the lungs. In addition, complicated pneumonia such as parapneumonic effusion, empyema, lung abscess and necrotizing pneumonia can be seen on chest radiographs.[11,12] Other radiological examinations such as CT scan are rarely routinely performed in severe pneumonia, unless local complication is suspected.[12]

In patients with very severe pneumonia, bacterial cultures from sputum or blood samples are performed to determine the etiology of pneumonia. This is especially true in patients who are clinically suggestive of sepsis, to determine the appropriate antibiotics. Blood cultures are not recommended routinely, but may be considered in hospitalized patients and should be done in complicated pneumonia. Positive blood cultures are obtained only in less than 10% of patients. Sputum cultures may be considered in adolescents, but their interpretation must be careful because of respiratory tract commensals.[12]

Studies have confirmed previous evidence that there is no way of reliably distinguishing clinically (or radiologically) between etiological agents. Some bacteria, such as Staphylococcus aureus, can complicate influenza in infants and older children. However, bacterial pneumonia should be considered in children when there is persistent or repetitive fever >38.5oC together with chest recession and a raised respiratory rate.[13]

Management of severe pneumonia is to ensure oxygen support, empirical antibiotics and supportive therapy. Patients with oxygen saturation <90% on room air should be treated with oxygen given by nasal cannula, high-flow delivery device, head box or face mask to maintain oxygen saturation >90%. Patients with severe respiratory distress clinically showing signs of respiratory failure should be admitted to the pediatric intensive care unit (PICU) for ventilator support (Figure 2). PICU admission is also indicated for patients with unstable cardiovascular conditions (hypotension, poor perfusion) who require cardiovascular monitoring and those with decreased level of consciousness need to be admitted to the PICU. The first-line antibiotic ampicillin 200 mg/kg (4 divided doses) in combination with gentamicin 7.5 mg/kg IM/IV once daily is given for at least five days. Ceftriaxone 80 mg/kg/day dose every 24 hours (max 2 g/day) or cefotaxime 50 mg/kg/dose every 8 hours (max 2 g/day) can be given as second-line antibiotics (if after 48-72 hours with first-line AB does not show clinical improvement).[14]

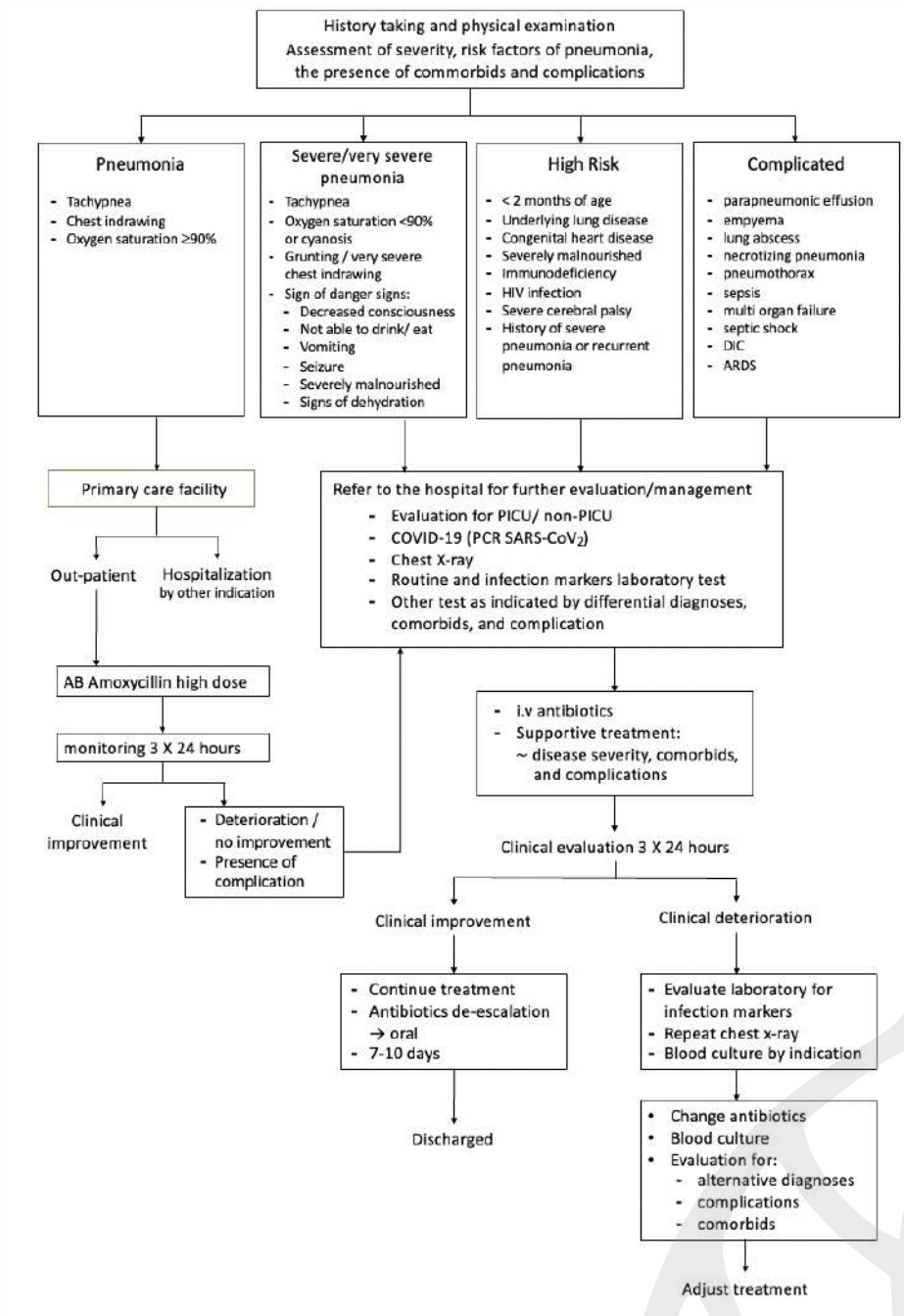

Figure 2. Management of severe pneumonia and complicated pneumonia in children. Children with severe/very severe or complicated pneumonia or have high risk of poor outcomes should be referred to the hospital for further management. Early antibiotics and supportive measures should be followed by close clinical monitoring. Clinical deterioration requires thorough laboratory and radiology evaluation, as well as consideration of antibiotics switching.

How to identify sepsis in severe pneumonia children?

Sepsis is systemic inflammatory response in the presence of infection with life-threatening organ dysfunction. Septic shock occurs when there is cardiovascular dysfunction, usually requires PICU admission for inotropic support.[7] Identifying children meeting criteria for systemic inflammation response syndrome (SIRS) is challenging. Age-related variation of vital signs range, various condition causing abnormal vital sign and late manifestation of hypotension in paediatric patients are ones of the obstacles compared to adults. Poor peripheral perfusion, tachycardia, temperature instability and altered mental status in children with severe pneumonia indicate the presence of sepsis. The screening of these signs should be initiated at the first presentation of acutely unwell children in emergency department, as well as to those who had hospitalized with severe pneumonia.[4,7]

Elevated WBC count is no longer recommended to identify higher risk of bacteremia in young children, as it has poor sensitivity and specificity for clinical practice. Although CRP has moderate sensitivity to identify febrile children with bacterial infections, it has low positive predictive value for predicting sepsis. Several studies have demonstrated an association of elevated blood lactate levels with adverse outcomes in children with septic shock. Blood lactate greater than 2 mmol/L indicating higher mortality in children with hypotension requiring vasopressors.[4]

The Surviving Sepsis Campaign (SSC) has recommended to obtained blood culture before initiating empiric antibiotics in children with sepsis, whenever this does not substantially delay the administration of antibiotics. When sepsis is suspected children with pneumonia, sputum specimen should also be obtained for culture.

Sepsis prevention in pediatric severe pneumonia

It is essential to prevent serious systemic complications of pneumonia, i.e. sepsis and septic shock, by promptly manage all children with pneumonia. Provision of healthy environment and fulfillment of proper nutritional needs are measures to protect children getting serious ill. Preventing pneumonia by scaling up vaccination program and particular intervention for those who has higher risk of developing pneumonia are expectedly reducing its morbidity and mortality, including that due to sepsis (Figure 3).

Protection and prevention of pneumonia should be started in community scale, before children being ill from pneumonia. Risk factors of pneumonia in children, such as HIV infection, low birth weight, malnutrition, lack of exclusive breastfeeding, overcrowding, indoor air pollution, and maternal cigarette smoking, should be reduced to decrease the incidence of pneumonia in children.[15] Vaccination against *Haemophilus influenzae* type-B and *Streptococcus pneumonia* could substantially decrease the prevalence of pneumonia and sepsis.15

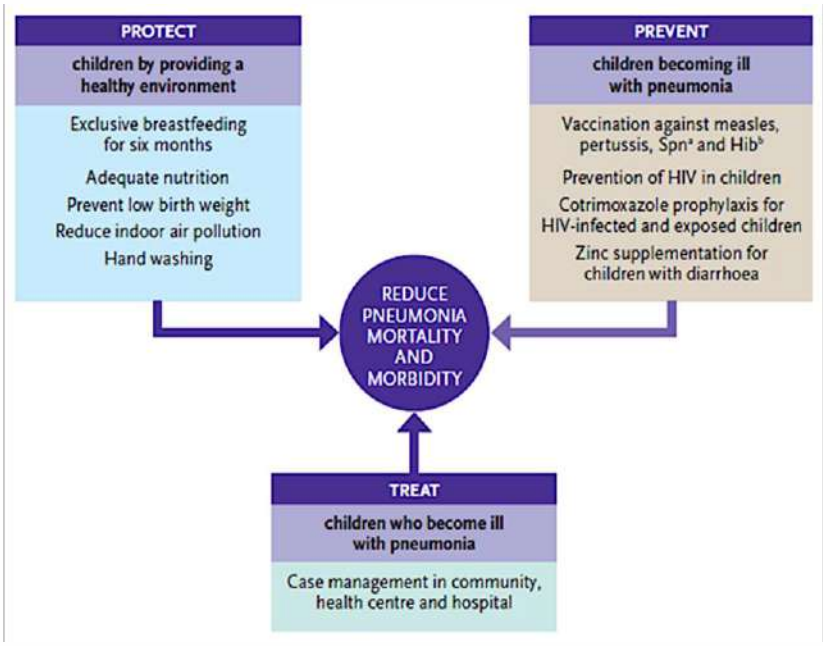

Figure 3. The protection and prevention to reduce mortality and morbidity of pneumonia in children. Protection by providing healthy environment and prevention of children from becoming ill, integrated with prompt treatment of severe pneumonia, expectedly will reduce the morbidity and mortality of children with pneumonia.
Source: WHO. Global action Plan for Prevention and Control of Pneumonia (GAPP), 2009

When a child diagnosed as pneumonia, prevention of sepsis in these children have to be even more important. Decision to refer patients with pneumonia should be based on the level of severity, which classified based on presence of profound respiratory distress, e.g. grunting or cyanosis, and the presence of danger signs, such as decreased consciousness, seizure or malnutrition. First parenteral empiric antibiotics should be given in health care facility during patient stabilization before referral to the hospital. This early antibiotic is important and expectedly would prevent patient further deterioration, in addition to oxygen therapy during stabilization and transport to the hospital.[10] However, it is difficult to differentiate severe pneumonia with other severe/very severe disease or sepsis in infant less than 2 months of age, demanding more attention and timely management of this age group in health care facility. The presence of comorbid, such as congenital heart disease, underlying lung disease, neuromuscular problem, or immunodeficiency, should be identified and anticipated accordingly.[12]

Upon hospital admission, signs of sepsis should be screened in children with severe pneumonia since the first presentation at emergency department.[4] More attention should be concerned to infants (especially those <2 months old), those with more severe illness and with comorbidity, as they have higher risk for mortality.[5,12,16] The use of mechanical ventilation and inotropic support independently associated with bacteriemia in children with lung infection (Table 2).[17] Procalcitonin

(PCT) has the most favourable test characteristics for the identification of children with bacterial infections, particularly for invasive bacterial infection. However it needs further research to determine its role in children with sepsis.[7]

Table 2. Treatment supports that increases the risk of developing sepsis in children with severe pneumonia*

Inotropic support
Central line >7 days
Urinary catheter
Conventional mechanical ventilation
Endotracheal mucolytic
Extracorporeal Membrane Oxygenation (ECMO)

*The table is arranged in order of higher risk
Source: Guitart C, *et al.* BMC Pediatrics. 2022

The choice of first antibiotics used for children with severe pneumonia is important. World Health Organization had revised the recommendation for the first-line antibiotics for children with severe pneumonia.10,[14] Studies showed that patients less than five years of age receiving combination of ampicillin and gentamycin has shorter time to recovery compared to other.[18] Moreover, early antibiotic administration within first six hour since patient presentation could prevent mortality of severe pneumonia. In children with sepsis in PICU, antibiotic administration delay of more than 3 hours would increase the risk of death by almost 4-folds.[7] This implies that the early recognition of signs of sepsis in children with severe pneumonia must be of equal importance to empirical antibiotic administration. The Surviving Sepsis Campaign recommends starting antibiotics as soon as possible. Antibiotics should be started within 1 hour of recognition in children with septic shock, and within 3 hours in sepsis-associated organ dysfunction but without shock, given appropriate evaluation after recognition.[4,7]

The empiric antimicrobial therapy should cover broad range of pathogens and is based on the prediction of most-likely causative bacterial pathogens. And this could be comprised of single or multiple antimicrobials agents.[4] The absence of clinical improvement within 48-72 hours of therapy initiation indicates a forementioned thorough evaluation and consideration of antibiotics with broader coverage. Ceftriaxone is preferred as second-line antibiotics for a such condition. However, it is important to consider local pattern of microbial resistance for antibiotics de-excalation.[12,13]

Implementation of optimal aspects of sepsis care, such as the timely administration of empirical broad-spectrum antibiotics, initial adequate fluid resuscitation, reliable and frequent source control is important to prevent sepsis in health care facility, as well as maintaining strict hygiene standards such as hand washing.[19] Time to recovery in children with pneumonia is associated with body weight, highlighting the importance of nutritional management to prevent disease progression to sepsis.[18] Since clinical signs are often inadequate to detect hypoxia, continuous monitoring using pulse oximetry is required.[12]

In conclusion, sepsis is the most common cause of mortality in children severe pneumonia. Prevention of sepsis in children with severe pneumonia should be started at community intervention level to reduce all risk factors. Once children with severe pneumonia are hospitalized, sepsis signs screening should be performed as early as the first presentation. Early administration of empirical antibiotics and close clinical monitoring should always be carried out to prevent patients from developing sepsis.

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OPTIMIZING LUNG FUNCTION AND FUNCTIONAL ABILITY IN PATIENTS WITH PLEURAL EFFUSION

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ABSTRACT

Background: There is an association between pleural effusion (PE) with restrictive ventilatory limitation and inspiratory muscle dysfunction. The removal of fluid from the pleural space improves dyspnea, lung function, and functional capacity, but the functional improvements achieved at rest cannot be assumed to exercise conditions, even with moderate exercises.

Methods: Literature was searched using PubMed and Google Scholar databases using specific keywords related to rehabilitation of PE. References and their citation were explored to find out the relevant topic.

Results: Pulmonary rehabilitation (PR) has been proposed as part of the management of PE. The lung expansion technique is a group of interventions that can be used to accelerate pleural fluid drainage to reduce the possibility of complications from tube drainage. In patients with PE, the PR program can improve dyspnea as a result of a mobilization program and lung expansion techniques through deep breathing, incentive spirometry, and positive airway pressure. Data about the role of IMT and aerobic exercise specific for PE was very limited.

Conclusion: Based on the functional impairments found in PE, both before and after the removal of pleural fluid, a PR program is needed to improve symptoms and enhance pulmonary functions and functional ability.

Keywords: Dyspnea, functional level, lung function, pleural effusion, respiratory muscles

Background

Pleural effusion (PE), defined by abnormal accumulation of fluid in the pleural space is related to restrictive ventilatory limitation and impairment of inspiratory muscle to create pressure. Patients with PE experience respiratory symptoms such as dyspnea, pain, and cough which impair quality of life (QoL) and daily activities.[1,2] In extreme cases, PE can progress to respiratory failure and death.[2] Kookoolis et al. found that 14% of patients were admitted with chest radiograph marking PE. The mortality rate of PE was 15% of patients dying within 30 days and 32% dead within one year of hospital admission.[3]

One type of PE is malignant PE (MPE), which is a common complication of advanced malignancy. The yearly hospitalization of MPE in the United State is close to 125.000, with the incidence being

more than 150,000 cases per year. Lung cancer is the most frequent etiology in males and breast cancer in females.[4]

Before drainage of unilateral PE, there is impairment of daily activity due to dyspnea, further caused by restricted lung inflation. Restricted lung inflation may also predict greater improvement in dyspnea after sustained control of effusion.[1] Drainage of fluid in a substantial amount from the pleural space results in improvement of dyspnea, lung function, and functional capacity. PE drainage results in increased oxygen delivery with subsequent increased functional residual capacity and oxygenation.[1,2]

In mechanically ventilated patients, drainage of a large volume of PE (>500 ml) also improves oxygenation and end-expiratory lung volume. An increase in oxygenation is correlated with an increase in lung volume and a decrease in trans-pulmonary pressure.[5] As mentioned by earlier research, there is an improvement in spirometric 24 hours after drainage of pleural fluid. The functional improvements achieved at rest cannot be assumed to exercise conditions, even with moderate exercises, such as daily activities.[2]

Pulmonary rehabilitation (PR) is a comprehensive management that consists of exercise training, education, and behavioral modification aimed at improving the physical and psychological state of patients with respiratory illness and promoting long-term adherence to health-promoting behaviors.[6] PR is applied not only to patients with chronic obstructive pulmonary disease (COPD), but also to patients with asthma, bronchiectasis, interstitial lung disease, and other restrictive lung diseases. It is known to improve the quality of life.[7]

Methods

Literature was searched using PubMed and Google Scholar databases. Keywords used were functional impairment, dyspnea, respiratory function, lung function, pulmonary function, activity, exercise, pulmonary rehabilitation, respiratory rehabilitation, physical therapy, functional ability, PE, restrictive lung disease, and pleural procedure. References and their citation were explored to find out the relevant topic.

Results Functional Impairments in PE Respiratory Symptoms

Dyspnea, or a subjective experience of respiratory discomfort, is a severe symptom that includes a sense of work/effort, chest tightness, and air hunger. It affects up to 80% of individuals with malignant pleurisy, and even more so in patients with heart failure-related effusions. A large effusion in a patient with normal lungs, a moderate effusion with an underlying heart or lung disease, or a tiny effusion with severe cardiopulmonary diseases can all produce dyspnea.[8]

Approximately 25% of patients with MPE are asymptomatic and incidentally found on examination or radiography. In symptomatic patients, dyspnea is the most common presentation, sometimes accompanied by chest pain and cough. Dyspnea is caused by a combination of decreased chest wall compliance, diaphragmatic depression, mediastinal shift, and reduced lung volume that

enhances neurogenic reflexes. The effusion compresses the lung parenchyma, resulting in decreased chest wall compliance. Chest pain is usually associated with the involvement of the parietal pleura, ribs, and other intercostal structures. Instead of only fluid volume removal, improvement in these mechanics is leading to post-thoracentesis symptoms alleviation. Constitutional symptoms such as cachexia and weight loss, which are frequently related with the underlying malignancy, are also associated.4

There is an imbalance between defective ventilatory mechanics (decreased respiratory system compliance) and deficient inspiratory muscle performance in restrictive lung disease. The thoracic cage is displaced by a greater fluid accumulation, which compromises inspiratory muscle function. Respiratory compliance and inspiratory muscle performance may be impaired in different ways depending on the effusion volume and the disease underlying the effusion. Dyspnea is usually determined by the amount of the effusion, the patient's underlying cardiopulmonary reserve, and, potentially, the presence of anemia (whether inflammatory or secondary to chemotherapy). Dyspnea was more strongly linked to restricted lung inflation than effusion volume. [1,8]

After the pleural cavity was emptied, the dyspnea sensation improved. At rest, dyspnea is mild and well-tolerated, but exerting even a modest amount of effort exacerbates the symptoms, resulting in a sensation of discomfort that makes even the most common daily activities difficult.2 Larger PE may push the diaphragm inferiorly, impairing its ability to generate pressure and causing neuro-mechanical uncoupling. It has been proposed that the effect of a larger effusion on diaphragm function is a more important cause of dyspnea than restricted lung expansion. [1,9]

Decreased Lung Compliance

A restrictive ventilatory defect was induced by PE, which resulted in a decrease in vital capacity (VC), functional residual capacity (FRC), and total lung capacity (TLC). When the amount of fluid in the pleural space increases, the pleural pressure rises, causing the distending pressure on the chest wall and lung to change. Assuming that the compliance of the chest wall and lung remain constant, the chest wall volume grows while the lung volume declines.[10]

The volume of the lung and the chest wall were uncoupled and are no longer equal as a result of the PE. In addition to preventing full expansion of the ipsilateral lung, the contralateral lung may be affected, and the ipsilateral chest wall is usually distended. The decrease in lung volume is outweighed by the small changes in airway function, causing the lungs to empty more quickly. [10,11]

Respiratory Muscle Dysfunction

The association between restricted lung inflation and reduced diaphragm movement could be explained in several potential explanations. The diaphragmatic contribution to lung expansion may be directly affected by the bulk effect of effusion on diaphragm movement. An enhanced mass effect of the effusion could possibly be the cause of both restricted diaphragm movement and diminished TLC.[1,10,12,13] Because pleural fluid rests between the diaphragm and the lung, it is unable to expand it effectively.8 One study indicated that when diaphragm movement was impeded, PE was 86% larger on average than when diaphragm movement was normal.[1]

Breathing at a volume greater than normal for the chest wall resulted in shortened inspiratory muscles, which act on an unfavorable section of their length-tension curve. After the pleural fluid is removed, the volume of the chest wall shrinks dramatically, especially in individuals with extensive pleural fluid accumulations and parenchymal pulmonary involvement, causing the lungs to become unnaturally stiff. The lengthening of the inspiratory muscles towards the conclusion of exhalation is associated with a decrease in chest wall volume.[12]

Exercise and Activity Limitations

Dyspnea on exertion rather than rest is often the first complaint of a patient with PE.[13] Along with the presence of PE, several factors need to be investigated to explain physical limitations due to the underlying disorder. The main cause is cancer, which causes systemic changes that can reduce exercise capacity, as well as tuberculosis and liver damage. The distance traveled before thoracentesis was about 27% shorter than expected in a healthy population with the same characteristics.2 PE can also affect sleep quality and efficiency.[13]

Removing an average of 1.5 L of pleural fluid increased walking distance by 11%. After the procedure, the patient had improved exercise capacity, but did not reach the predicted levels and maintained a 16% reduction. Patients with PE mainly report an inability to perform their normal routine tasks.[2] Research by Murganandan et al. shows the level of pre-drainage functional impairment was similar to that of very severe and stable COPD patients, and the 6-minute walking distance (6MWD) was similar to that of COPD patients hospitalized for acute exacerbations. The average post-drainage improvement in their study was 30 m, which corresponds to the minimum clinically important difference of 25 m commonly used in COPD studies. Fluid drainage not only improved 6MWD but also improved the post-drainage Borg score both before and after 6MWD. The improvement in 6MWD did not correlate with the improvement in symptoms. This suggests that other individual factors (such as comorbidity) may play a role in determining benefits. [14]

Optimizing Lung Function and Functional Ability in Patients with PE

Physical therapy has been suggested as part of the treatment of a PE and have to be included as soon as possible in a management program. Enhancing functional capacity and reducing the hazards associated with intensive care and bed rest are two of the most significant goals of physical therapy in the context of hospitalization due to respiratory diseases, including PE. Inclusion of mobilization and breathing exercises can reduce the musculoskeletal complications and improve respiratory function. Physical therapy interventions that induce intrathoracic pressure, such as deep breathing and incentive spirometry, may aid drainage and shorten the length of hospital stay. [15]

Mobilization

Walking on the first day following lung surgery appeared to have certain advantages, such as allowing the thoracic drainage tube to be removed sooner. Mobilization of patients after thoracic surgery appears to have a positive impact on their functional recovery.[16] A randomized controlled trial involving 104 inpatients with PE with or without an intercostal drainage tube found that adding breathing exercises and mobilization to other standard care reduced the severity of the PE, as

measured by blinded chest radiograph assessment, and cut the length of stay by an average of 12 days.17

Breathing Exercise and Incentive Spirometry

Lung expansion techniques have been recommended as one group of intervention that could be utilized to speed up the drainage of a pleural fluid collection, reducing the risk of tube drainage problems. Lung expansion procedures such as deep breathing, incentive spirometry, and positive airway pressure (PAP) exercises are routinely used in patients with drained or non-drained PE. One study found that most of the chest physiotherapists applied deep breathing exercise. Combination of lung expansion techniques and walking were also applied.[16]

Exercise combined with deep breathing is a low-cost and simple intervention. Deep breathing appears to have better effect in individuals with cardiac surgeries and higher adherence to treatment than incentive spirometry.[15] Valenza et al. found a greater improvement in spirometric parameters, chest radiographs, and length of hospital stay in patients with PE given respiratory physical therapy compared to control. In addition to standard physical therapy, they were given pursed-lip breathing, active expiration, and incentive spirometry. [15]

Positive Airway Pressure

PAP is a lung expansion technique that can help to expand the lungs and facilitate drainage. PAP may be administered non-invasively through a face mask via non-invasive ventilation (NIV). Increased intra-pleural pressure would induce drainage and reabsorption of the pleural fluid collection, hastening the recovery of respiratory function, allowing earlier chest drainage removal, and shortening the hospital length of stay.[17]

Oliveira et al. found a significant improvement in PE size in the intervention group (83.5%) compared with the control group after 4 weeks of treatment with continues PAP (CPAP). One year following therapy with anti-TB medications, 50% of patients with pleural TB develop pleural thickening, and preventing pleural fibrosis is one of the goals of TB treatment. Pleural fibrosis is thought to be associated with a faster reduction in PE volume.[18]

The use of intermittent 15 cmH2O CPAP in combination with mobilization and respiratory care reduces the duration of chest drainage, hospital stay, pulmonary problems, antibiotic use, and treatment expenses. When compared to CPAP of 4 cmH2O, using 15 cmH2O did not result in a higher rate of adverse events or lower tolerance (without therapeutic effect).[17]

CPAP is typically thought of as a high-tech, hospital-based intervention, yet its application requires low-cost equipment. In addition, CPAP is widely available in outpatient health care units and in home care settings. Complication associated with the use of NIV are rare. Gastric inflation at less than 30 cmH2O, aspiration of gastric contents, and local complications such as skin abrasions from contact with the mask and conjunctivitis have all been documented in previous investigations. These complications are preventable and curable.20 Other limitations in the used of PAP are the lack of familiarity of technique and the risk of broncho-pleural fistula.[16]

Inspiratory Muscle Training

Although there is diaphragmatic dysfunction due to the fluid accumulation in the pleural cavity, evidence of use of inspiratory muscle training in patients before and after pleural procedure is very limited. There was improvement in ventilation and respiratory volume on the side with PE in a study that used diaphragm exercises in addition to pharmacological treatment twice a day for two weeks.[18]

Aerobic Conditioning

There is no study found related to the role of aerobic exercise specifically in patients with PE. However, there may be a developing frame of proof supporting aerobic exercise of PR as an essential intervention for patients with restrictive lung disease due to lung fibrosis. Patients with lung fibrosis must be early in receiving tailored exercise-based PR program. Based on their research, Tonelli et al. recommended that PR must be a primary management in patients with interstitial lung disease of different severity.[19]

A systematic review and meta-analyses by Hanada et al studied that PR by aerobic training alone or using breathing exercises or IMT led to significant improvements in exercise capacity, dyspnea, and health-related QoL. Aerobic and breathing exercise combined have a complementary impact on improving score of dyspnea. Aerobic exercise combined with IMT can be useful due to the fact that elevated inspiratory muscle strength can enhance the performance of the breathing muscle tissue required for ventilation. An increase in exercise endurance can further result in an increase in aerobic capacity, and therefore a reduced ventilation load during exercise.[20]

Dyspnea scores improved after giving breathing exercises combined with aerobic exercise. Improvement in symptoms was noted in response to repeated stimulation of high ventilation demands during exercise sessions, chest expansion during deep breathing exercises, and stretching of the chest muscles. These ventilation stimulation can contribute to more efficient breathing patterns and increased respiratory muscles strength, pleural elasticity as well as compliance of lung tissue. This mechanism also decreased perception of dyspnea after an exercise program. Aerobic combined with breathing exercises also showed greater benefits in improving HRQL scores. [20]

CONCLUSION

In patients with PE, PR program can improve symptom of dyspnea as a result of mobilization program and lung expansion techniques through deep breathing, incentive spirometry, as well as PAP. Data about the role of IMT and aerobic exercise specific for PE was very limited. Based on the functional impairments found in PE, both before and after removal of pleural fluid, PR program is needed to improve symptoms and to enhance pulmonary functions as well as functional ability.

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CIRCADIAN RHYTHM AND HEALTH EFFECTS OF SLEEP DISRUPTION

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Circadian comes from Latin words, circa (Approximate) and dies (day), so its meaning "approximately one day". The circadian rhythm refers to behavioral, physiological, and molecular changes with a cycle length of about 24 hours.[1] This rhythm averages around 24 hours, according to the conditions of day and night on earth, but not always the same for each individual.[2] The suprachiasmatic nuclei (SCN), a bilateral structure located in the anterior part of the hypothalamus, is the central pacemaker of the circadian timing system.[3] The mechanism in biological clock on SCN cells is like a moving clock mechanism, which determines the time accurately within 24 hours.[3] Cells in the SCN produce two protein called Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1).[3,4] At the beginning of the cycle, CLOCK and BMAL1 bind together to promote transcription of genes called Period (PER 1-3) and Cryptochrome (CRY 1-2) to produce protein.[5,6] PER and CRY Protein then bind together and inhibit the CLOCK and BMAL1 to transcript of their own genes.5,6 Gradually after PER and CRY protein break down fully, CLOCK and BMAL1 back to promote transcription of PER and CRY again, to begin the new cycle.5,6 This process takes about 24 hours until it is repeated again.[5,6]

Melatonin, a hormone secreted by the Pineal Gland, is one of the major signaling molecules used by the circadian oscillator to maintain and also adjust circadian rhythms. Its secretion is affected mostly by light to the eyes, and also by other factors such as age, environmental and physiological factors.[4] Photosensitive retinal ganglion cells in the inner retina relay photic information to the SCN via retinohypothalamic tract. In response to photic stimuli, a multisynaptic pathway from the SCN to adrenergic fibers innervating the pineal gland regulates norepinephrine release from these fibers, to halt Melatonin synthesis.[3] Synthesis and release of melatonin is stimulated in the dark usually at night, while it is suppressed by light during the day. Exposure to light at night directly causes the plasma melatonin levels to fall and disrupt the circadian rhythm, because the SCN also have the melatonin receptors MT1 and MT2.[1,3]

The locations that melatonin receptors MT1 and MT2 are found in almost all organ in the body such as: brain, retina, cells of immune system, cardiovascular system, gastrointestinal system, pancreas, liver, kidney, skin and many more.[7,8] Many research found that there are many effect of melatonin throughout the body such as: neuroprotective, anti-inflammatory, pain-modulating, blood pressure-reducing, retinal, vascular, seasonal reproductive, ovarian physiology, osteoblast differentiation, anti-tumor and antioxidant.[7] Therefore if there is a sleep disturbance or an

increased amount of light into the eye at night, it causes a decrease in melatonin levels, and the impact will be suffered on many organs.[8]

Health effects of Circadian Rhythm Disturbances and Sleep Disruption

Many studies have found that circadian rhythm disturbances may be associated with diseases and health disorders such as: sleep disorders, cancer, susceptibility to infection, metabolic syndrome, Alzheimer's disease, and aging.[9] Specific to respiratory function, abnormal circadian rhythms are associated with Airway diseases, reflected in daily changes of airway caliber, airway resistance, respiratory symptoms, and abnormal immune-inflammatory responses. Patients with chronic obstructive pulmonary disease (COPD) and asthma develop more frequent and severe exacerbations, with an increased rate of emergency room visits and hospitalization, mostly at night and in the early morning hours.[11] Evidence also demonstrated a negative effect of short sleep, induced by partial sleep restriction, on asthma symptoms and health-related quality of life.[12] Among older adults, short and long sleep duration is associated with an increased risk for hospitalizations and emergency department visits in asthma patients.[12] Sleep abnormalities affect immune function in a reciprocal manner, leading to changes in proinflammatory cytokines, such as tumor necrosis factor, interleukins 1 and 6, and C-reactive protein, which can increase the risk of lung infection.[10]

Sleep deprivation increases sleepiness, impairs mood states and emotional processing and contributes to altered risk-taking and decision-making behavior. Long-term sleep restriction may lead to a reduced sense of sleepiness despite continuing reductions in cognitive performance capabilities.[13] Important negative health outcome measures such as weight gain, obesity, type 2 diabetes, cardiovascular disease, hypertension and inflammation have been associated with insufficient sleep.[13] Several immune-related transcripts and markers of infection are altered after sleep restriction, providing a possible pathophysiological basis for the elevated risk of falling sick after sleep loss. Insufficient sleep has been associated with elevated mortality, enhanced accident risk and a generally increased incidence of errors.[13]

Mutations in circadian clocks have been associated with Circadian Rhythm Sleep Disorders (CRSD). The International Classification of Sleep Disorders (ICSD-2) suggests classification of CRSD into six distinct types. These include: delayed sleep phase type (DSPT), advanced sleep phase type (ASPT), irregular sleep wake phase type, free-running type, jet lag type, and shift work type.[1,9] There are 100 sleep disorder classifications; however, they are typically manifested in one of the following three ways: failure to obtain the necessary amount or quality of sleep (sleep deprivation), an inability to maintain sleep continuity (disrupted sleep, also called sleep fragmentation, difficulty maintaining sleep, and middle insomnia), and events that occur during sleep (eg, sleep apnea, restless legs syndrome).[10]

Sleep and/or time-in-bed duration represents a major dimension for measuring sleep, but other indices do exist. Sleep's health properties also depend on sleep quality, sleep architecture, and the timing of sleep within the day.[14] The National Sleep Foundation convened an 18-member multidisciplinary expert panel, evaluate scientific literature concerning sleep duration

recommendations. The panel agreed that, for healthy individuals with normal sleep, the appropriate sleep duration for newborns is between 14 and 17 hours, infants between 12 and 15 hours, toddlers between 11 and 14 hours, preschoolers between 10 and 13 hours, and school-aged children between 9 and 11 hours. For teenagers, 8 to 10 hours was considered appropriate, 7 to 9 hours for young adults and adults, and 7 to 8 hours of sleep for older adults.[14]

Risk factors for sleep disruption are vast and involve a combination of biologic, psychologic, genetic, and social factors. Lifestyle factors include consuming excessive amounts of caffeine and drinking alcohol. Performing shift work or being a college student is also a risk factor for sleep disruption. Exposure to excessive nighttime light pollution and underexposure to daytime sunlight can lead to disruption of circadian rhythms. Stressful life circumstances, such as being the parent of a young infant or serving as a caregiver for a family member with a chronic, life-threatening, or terminal illness, are also contributors to sleep problems. In addition to the stress and worry associated with caregiving, caregivers of patients with complex medication schedules may experience sleep disruption due to the requirement to wake themselves during the night to administer medication.[10] Sleep disruption is frequently attributable to a sleep disorder, such as obstructive sleep apnea and restless legs syndrome.[10]

Treatments for Circadian Rhythm Sleep Disorders and Sleep Disruption

In patients with sleep disorders, it is necessary to search and treat for other possible diseases that underlie the occurrence of these disorders such as: asthma, COPD, neurologic disease, psychiatric disorder, or any disease which can cause body discomfort. Finding out on the patient's lifestyle, day night activity, stress level, and occupation is also important. Because most of the times, the best solution for dealing with sleep disorders is to change your lifestyle, activity, and stress management. One of the most popular, cultural and widely available lifestyles is drinking coffee. Research conducted by Drake et al stated that drinking coffee less than 6 hours before bedtime can have a sleep-disrupting effect. Therefore, it is advisable not to consume coffee 6 hours before bedtime.[15] Relaxation techniques, such as meditation can be alternative treatment of insomnia. Techniques of slow, deep breathing in adjunct to sleep hygiene (quiet, dark, relaxing, and at a comfortable temperature) and relaxation therapies may be highly effective in initiating sleep as well as facilitating falling back asleep.[16]

There are several treatment modalities specifically for CRSD that are designed to address the underlying mismatch between the desired timing of sleep and the ability to fall asleep and remain asleep that characterizes CRSD, including chronotherapy, phototherapy, and melatonin administration. Chronotherapy involves modifying the scheduling of sleep to resynchronizing the underlying circadian rhythm so that it is at a normally entrained clock time. Phototherapy takes an advantage of this by timing bright light exposure at strategic times in designed to advance (in the case of DSPT) or delay (in the case of ASPT) the circadian system to a time that will allow sleep to occur at the desired time. In DSPT, morning exposure to bright light is used to advance circadian rhythmicity and sleep time while in ASPT, conversely, evening exposure to bright light is used to delay circadian rhythmicity and sleep time.[2] The hormone melatonin is produced by the pineal gland at night, and its secretion is closely regulated by the circadian timing system. Melatonin

administration in the evening has been shown to benefit patients with DSPS by producing advances of circadian rhythms and sleep timing. Doses of 0.5-5 mg are administered in the late afternoon or evening (1-6 hours before desired bedtime) for days or weeks, but the optimal dose and administration schedule have not been standardized.[2]

Conclusions

The circadian rhythm refers to behavioral, physiological, and molecular changes with a cycle length of about 24 hours. The suprachiasmatic nuclei (SCN), a bilateral structure located in the anterior part of the hypothalamus, is the central pacemaker of the circadian timing system. Melatonin, a hormone secreted by the Pineal Gland, is one of the major signaling molecules used by the circadian oscillator to maintain and also adjust circadian rhythms. Circadian rhythm disturbances and sleep disruption may be associated with diseases and health disorders such as: sleep disorders, cancer, susceptibility to infection, metabolic syndrome, Alzheimer's disease, and aging. Treatments for CRSD and Sleep Disorders are primarily lifestyle changes. Chronotherapy, phototherapy, and melatonin administration are several treatment modalities specifically for CRSD.

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DRUG INDUCED SLEEP ENDOSCOPY (DISE) AS A TOOL TO DIAGNOSE SLEEP DISORDER BREATHING (SDB) / OBSTRUCTIVE SLEEP APNEA (OSA)

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INTRODUCTION

Sleeping is essential for humans, where one-third of their time is spent sleeping to maintain quality of life and productivity and minimize the possibility of having non-communicable diseases. Sleep is also vital to reduce the risk of having a work accident.[1]

Sleep Disordered Breathing (SDB) is a spectrum of sleeping disturbance, which usually happens at the age of 30 to 60. The spectrum of SDB consists of snoring, Upper Airway Resistance Syndrome (UARS), Obstructive Sleep Apnea (OSA), and Obesity-Hypoventilation Syndrome (OHS); which is characterized by a period of apnea during sleep. Even though they were experiencing apnea during their sleep, the patients usually did not realize the sign and symptoms, as well as the long-term aftereffect of this disorder. Hence, early diagnosis is crucial to hinder disease progression.[2]

The prevalence of SDB increased as they got older and reached its peak at the age of 30-60 years, comprising 28-67% of elderly men and 20-54% of elderly women in the population. As the terminal phase of SDB, OSA is strongly correlated with other comorbidities, such as laryngopharyngeal reflux (LPR), lingual tonsil hypertrophy (LTH), obesity, hypertension, diabetes mellitus type 2, cardiovascular, and metabolic events frequently present with OSA.[2]

Along with the anatomical factors such as oropharynx and hypopharynx which are easily collapsed due to the physiological absence of bones and cartilage, a deficit in the sensory pathway of the airway mucosa which lessens the airway muscular control to dilate also contributes to causing the imbalance between negative intraluminal pressure and pharynx dilator muscle as the compensatory mechanism. In consequence, there is an increased airway resistance at the upper airway which may develop an airway collapse, hence obstruction. As a result, apnea occurs during sleep.[3]

Two theoretical principles underlie the pathophysiology of OSA. The first one is the Starling Resistor model in which the pharynx is represented as an airway tube that collapses and isrestricted by two structures, i.e. nasopharynx at the top, trachea at the bottom, and a rigid lateral wall. However, if there is a nasal obstruction in the upper airway, then it may cause the intraluminal negative pressure which can lead to a sucking effect, hence causing a narrow oropharynx.[3]

The following figure illustrates the mechanism of the effect of the intraluminal collapse (represented by Pcrit or critical pressure). While the P upstream (P us) represents upstream pressure; and P downstream (Pds) represents downstream pressure, both within rigid airway tubes.[3,4] pressure; and P downstream (Pds) represents downstream pressure, both within rigid airway tubes.[3,4]

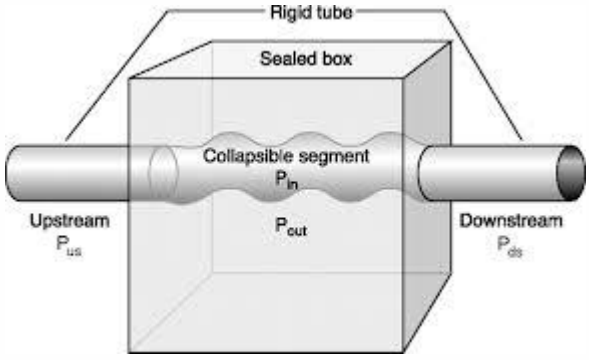

Figure 1. Starling Model [3]

Each finding has a different interpretation as follows [4]

- P us > P ds > P crit: no flow limitation due to lower downstream luminal pressure (P ds) compared to transmural pressure of the collapse (P crit). Hence, the patency is preserved.
- P us > P crit > P ds: upstream luminal pressure is lower but the downstream pressure is higher than the collapsible segment. But due to loss of flow, the collapsed segment is exposed to upstream pressure hence the airway reopens, causing flutter or snoring.
- P crit > P us, P ds: The critical pressure is greater than the transmural pressure, hence the collapse/apnea occurs.

In compensating the negative pressure built inside the tube or the airway, the pharyngeal dilator muscle plays an important role. However, in patients with SDB, this compensatory mechanism fails, hence resulting in upper airway obstruction.[5]

The second mechanism of upper airway resistance syndrome as one of the SDB spectrum is the Bernoulli equation that explains the increase of flow velocity within two points as it passes through a smaller diameter, hence decreasing the pressure. Similar to the aforementioned statement which emphasizes the role of the dilator muscle for compensating the negative pressure to prevent the collapse.[6]

To prevent the progression of the disease, early diagnosis is very essential through history taking, physical examination, and further examination using DISE and PSG.

DIAGNOSIS

Diagnosing SDB begins with anamnesis using several questionnaires, such as Epworth Sleepiness Scale (ESS) and STOP-BANG, followed by physical examinations. There are several factors, both internal and external that contribute to the occurrence of SDB, such as age, gender, body mass index, and the anatomical airway structures (lingual tonsil, palate mole, and durum, as well as conchae), i.e. Friedman Tongue Position (shown in Figure 2) and the presence of lingual tonsil hypertrophy or LTH (shown in Figure 3).

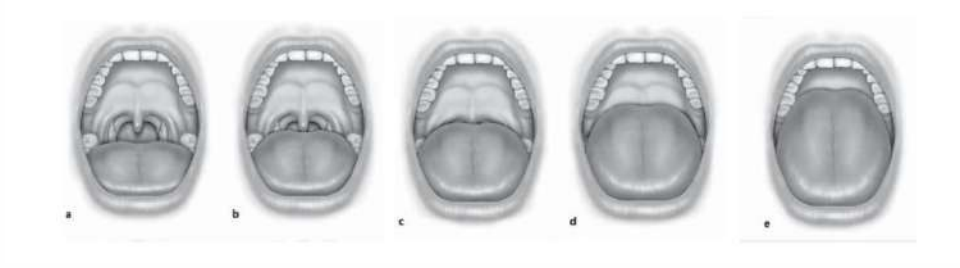

Figure 2. Friedman Tongue Position (FTP)[7]

(a) FTP 1 where the tonsil and uvula are visible; (b) FTP IIa tonsil is invisible, most of the uvula is still visible; (c) FTP IIb base of the uvula is visible and all part of mole palate; (d) FTP III distal part of mole palate is visible; (e) FTP IV palatum durum is the only part that is visible

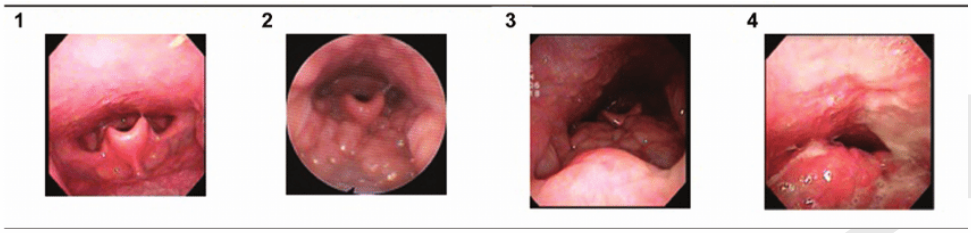

Figure 3. Lingual Tonsil Hypertrophy (LTH) Grading[8]

(1) Grade I: None to minimal; (2) Grade II: Mild (<50% filling up the vallecula); (3) Grade III: Moderate (>50% effacement of vallecula); Grade IV: Severe (epiglottis is unvisualized)

Polysomnography (PSG) is the gold standard examination that has to be conducted for SDB. Several parameters that can be evaluated are apnea and hypopnea during stages of sleep with different sleep positions, as well as displaying saturation and heart rate during sleep. Then, the examination is continued by conducting DISE to ameliorate findings and diagnosis by determining the size and configuration of the collapse.

DISE

A dynamic examination called Drug-Induced Sleep Endoscopy (DISE) depicts a real-time illustration of the airway collapse during sleep. This procedure resembles or mimics natural sleep (non-rapid-eye movement / NREM) by giving anesthesia with a certain depth of sedation to exhibit the identical effect of sleep apnea due to upper airway collapse. DISE improves the diagnosis process and gives specific locations of the airway obstruction as well as the morphology and configuration.[9]

Procedure

There are several steps in conducting DISE, (1) positioning, (2) sedating and monitoring (3) inserting a flexible rhinolaryngoscope, and (4) evaluating using VOTE classification. Firstly, patients' preparation begins by positioning the patient supine, then giving topical anesthesia ontothe nasal cavity. Vital signs, as well as cardiac activities, are monitored. Secondly, sedation is done by using either midazolam (0.07 mg/kg with low titration)10, propofol (1 mg/kg bolus)11, or dexmedetomidine (initiated with bolus 1.5 mcg/kg and followed with maintenance dose 1.5 mcg/kg/hour)12 using *Target Computerized Infusion* (TCI) and its sedation depth is monitored and controlled by using qCON or Bispectral Index Score (BIS) with the value of 40-60 (deep sedation) or 60-80 (light sedation). Thirdly, after achieving the depth of sedation, a flexible rhinolaryngoscope is used to evaluate the upper airway structural components. Finally, evaluation using VOTE classification.[13]

Figure 4. DISE Procedure

(a) Flexible rhinolaryngoscope; (b) qCon to monitor the depth of sedation

Component and Configuration

The DISE procedure evaluates the upper airway collapse based on the VOTE classification that was established by Eric Kezirian.9 Several components are assessed during the procedure, such as Velum / V (palatum mole, lateral wall of pharynx, velopharynx), Oropharynx / O (tonsil and lateral wall of pharynx), Tongue Base / T, and Epiglottis / E. The configuration of V, O, and T components may present in the form of concentric, laterolateral, or anteroposterior, however, the E component can be presented as anteroposterior (trap door or pushed types) or lateral configuration (open book).[14]

WHAT TO LOOK FOR: THE VOTE CLASSIFICATION				
STRUCTURE	DEGREE OF OBSTRUCTION	CONFIGURATION		
		A-P	LATERAL	CONCENTRIC
Velum				
Oropharynx lateral walls				
Tongue base				
Epiglottis				

Figure 5. VOTE Classification[9]

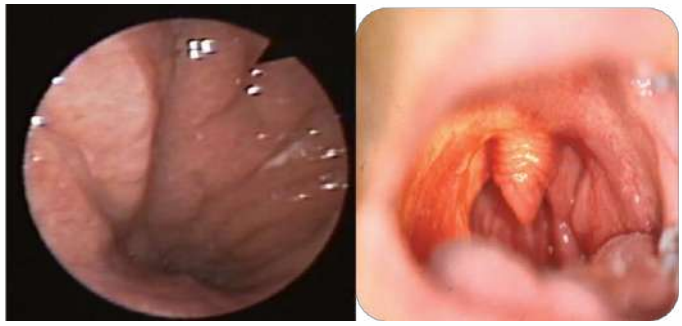

Figure 6. Velum Structure

Comprises of soft palate, uvula, lateral pharyngeal wall tissue at the level of oropharynx

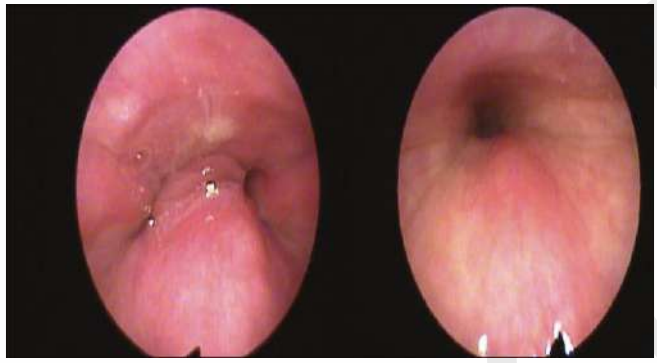

Figure 7. Velum Components and Morphology[15]

(a) Anteroposterior configuration; (b) Laterolateral configuration

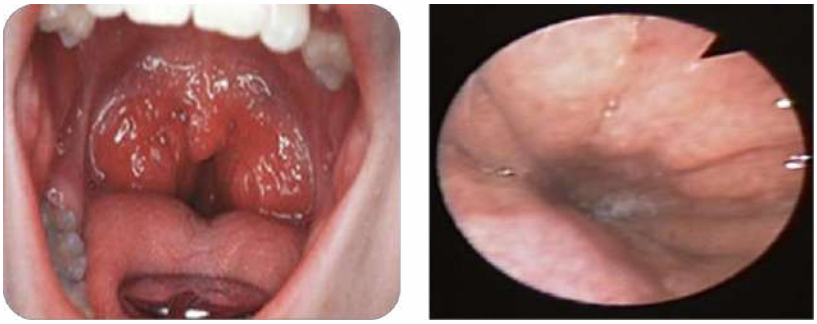

Figure 8. The Structure and Morphology of Oropharynx
(b) Palatine tonsils; (b) Lateral pharyngeal wall tissues

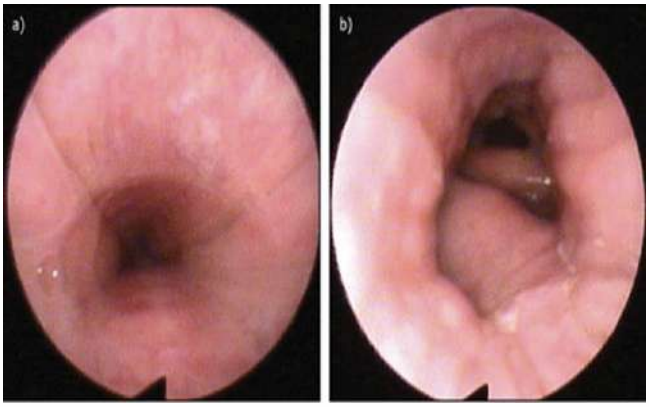

Figure 9. The Collapse Configuration in Oropharynx[16]
(a) Concentric collapse; (b) Laterolateral collapse

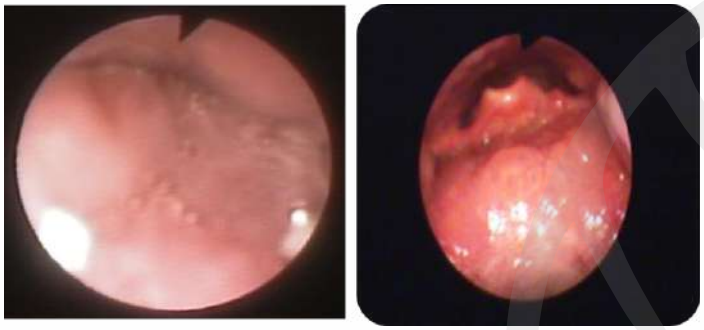

Figure10. Tongue Base Structure
Comprises of soft palate, uvula, lateral pharyngeal wall tissue at the level of oropharynx

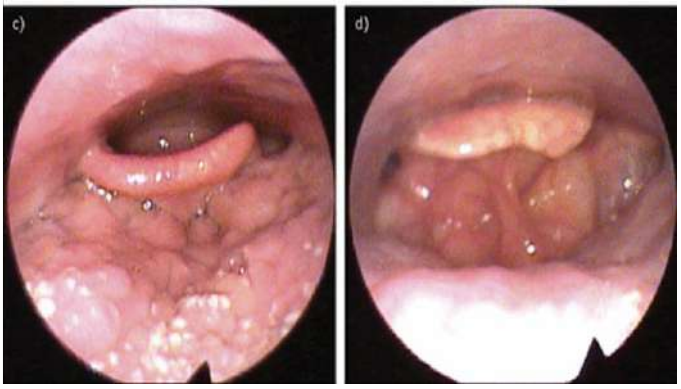

Figure 11. Tongue Base Collapse with Anteroposterior Configuration[16]

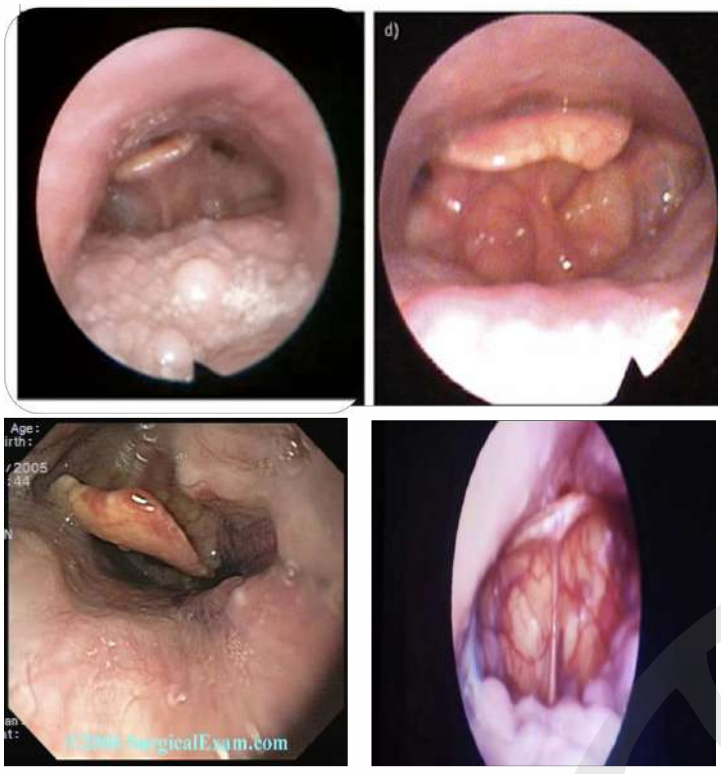

Figure 12. Epiglottic Collapse with Anteroposterior Configuration[9]

Anteroposterior prolapse can result in the folding of the epiglottis with decreased structural rigidity of the epiglottis or An apparent posterior pharyngeal wall, with normal epiglottic structural integrity. [9]

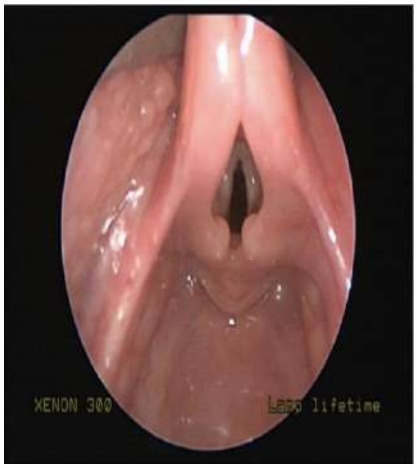

Figure 13. Epiglottic Collapse with Lateral Configuration

A center vertically oriented crease of decreased rigidity enables this folding to occur in the same location. A substantial proportion of OSA subjects demonstrate a significant epiglottic contribution during DISE.[9]

The degree of airway collapse at each structure is divided into 3 degrees, which are (1) No collapse; (2) Partial collapse, between 25 - 75% of the total area; and (3) Complete collapse, >75% of the total area. To be simplified, no collapse and partial collapse are grouped into non-severe collapse (<75%) and complete collapse as severe collapse (>75%).

DISE Interpretation

The recommendation of the treatment and management is decided after determining the location, morphology, and configuration of the structural collapse based on the VOTE classification through the DISE procedure. Velum collapse is treated with nasal surgery; oropharyngeal collapse is treated with uvulopalatopharyngoplasty (UPPP); tongue base collapses with genioglossus advancement; epiglottic collapse is treated with positioning based on the best lowest saturation during DISE.[17]

CONCLUSION

To conclude, as one of the most severe forms in the SDB spectrum, OSA is prevalent in both males and females, resulting in decreased quality of life, hence intervening activities in daily living. Thus, early diagnosis is crucial to prevent the disease progression from worsening. History taking, physical examination to assess the FTP and LTH, then followed by the gold standard examination, which is PSG. DISE is used to illustrate the location, morphology, and configuration of the airway collapse for determining the most appropriate treatment for the patients. Structural collapse should be observed based on the VOTE classification, comprised of Velum, Oropharynx, Tongue base, and epiglottis. Each of them may be presented as anteroposterior , laterolateral, or concentric configuration. Then further described with the degree of severity, i.e. no, partial, and complete collapse.

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CPAP THERAPY FOR OBSTRUCTIVE SLEEP APNEA

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Obstructive sleep apnea (OSA) is associated with significant morbidity and mortality. Continuous positive airway pressure (CPAP) has become first choice for therapy, normalising breathing during sleep and improving daytime sleepiness and quality of life. The technology for delivering CPAP to patients with OSA has undergone considerable advances since the initial description of this therapy by Sullivan in 1981.[1] The development of autotitrating devices has enabled newer models of patient care to evolve, providing similar outcomes to more traditional and time consuming in-lab polysomnography diagnostic and treatment approaches.[2]

Ongoing follow up and troubleshooting remains a key aspect of care to ensure the efficacy of therapy. With the challenges of following up patients experience over the past two years, there is increasing interest in the role of remote monitoring in ensuring adequacy and efficacy of therapy.

Despite improvements in technology, acceptance and adherence to CPAP therapy remain a challenge.[3] While it is widely thought that OSA may be a modifiable risk factor for cardiovascular events backed up by observational studies,[4] several recent large randomised CPAP trials have failed to show any such benefit. A number of reasons have been put forward to explain this, including poor patient adherence to therapy and selection of patients who may not be representative of the usual patient population seen by sleep clinics.[5] It is now increasingly recognised that OSA is a heterogeneous disorder, and that metrics beyond simple apnea-hypopnea index are needed to better characterise the severity of disease and identify patient subgroups who are at higher risk for cardiovascular disease due to coexistent OSA.

Measures such as symptom subtypes and hypoxic burden are now being investigated to determine if these better classify patients who may be at higher cardiovascular risk and responsive to therapy.[6-7] In addition, recognising the importance of a more personalised approach to prognosis and intervention based on specific OSA pathophysiology is being increasingly seen as a way forward to optimise treatment effectiveness and outcomes.[8] Advances in technology and changes in models of care for patients with OSA are providing exciting opportunities to review and improve our management of this common and disruptive disorder.

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SLEEP DISORDERS IN NEUROLOGY

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ABSTRACT
Sleep is essential for a person's health and wellbeing. Disturbed sleep reduces the quality of life and restfulness of sleep, is a risk factor for secondary diseases and may be caused by other medical conditions. Sleep medicine is relevant in neurology. A disordered sleep–wake cycle can have major effects on many common neurological complaints. In recent years, evidence has emerged for a bidirectional relationship between sleep and neurological disorders. Patients reporting sleeping problems describe the following 3 cardinal symptoms: the inability to fall asleep or sleep through the night, excessive daytime sleepiness; or sleep-related movement phenomena. The diversity of sleep-related disorders is reflected in the variety of specialties involved in the care of these patients—ranging from respiratory medicine to otorhinolaryngology to neurology. In this review only sleep disturbances pertaining neurology will be discussed.

Keywords: sleep disorder, neurology, cardinal symptoms, bidirectional relationship

INTRODUCTION

Sleep is essential for a person's health and wellbeing. Disturbed sleep reduces the quality of life and restfulness of sleep, is a risk factor for secondary diseases and may be caused by other medical conditions. Sleep is a dynamic and complex behavioral process. In recent years, evidence has emerged for a bidirectional relationship between sleep and neurological disorders. Sleep−wake disorders (SWDs) are very common and may be the first/main manifestation of underlying neurological disorders. SWDs may represent an independent risk factor for neurologic morbidities. Sleep−wake function may influence the course and outcome of neurological disorders.[1] Patients reporting sleeping problems describe the following 3 cardinal symptoms: the inability to fall asleep or sleep through the night, excessive daytime sleepiness; or sleep-related movement phenomena.[2]

The diversity of sleep-related disorders is reflected in the variety of specialties involved in the care of these patients—ranging from respiratory medicine to otorhinolaryngology to neurology.[2] In this review only sleep disturbances pertaining neurology will be discussed.

DISORDERS OF INITIATING AND MAINTAINING SLEEP

Difficulties in initiating and maintaining sleep is mainly caused by insomnia, however, circadian rhythm sleep disorders may also cause this complaint. Insomnia is characterized by difficulty in

either initiating sleep, maintaining sleep continuity, or poor sleep quality. These symptoms occur despite the presence of adequate opportunity and circumstance for sleep and result in daytime dysfunction. There are 3 categories of insomnia: chronic insomnia disorder, short term insomnia disorder and other insomnia disorder. Chronic Insomnia Disorder when the sleep disturbances occur at least 3 times a week and have been present for the last 3 months. Short-Term Insomnia Disorder when the sleep disturbances have been present for less than 3 months. Other Insomnia Disorder should be assigned to cases that fail to meet the criteria for short term insomnia disorder.3

Insomnia may be caused by other medical conditions. With more than 50% of disorders of initiating and maintaining sleep being caused by psychiatric illnesses (including addiction), psychiatric examination plays a key role in the assessment of insomnia. Similarly, diseases of the central and peripheral nervous system, such as restless legs syndrome (RLS), are among the most common causes of insomnia; thus, neurological evaluation is conducive to diagnosing important underlying problems. In patients with abnormal breathing during sleep, the chief complaint of excessive daytime tiredness is very prominent; therefore, disorder of initiating and maintaining sleep should be explicitly addressed during history taking.3

A distinct cause of insomnia are disturbances of the internal ("body") clock. Circadian rhythm abnormalities are characterized by deviation of the internal body rhythm (e.g. sleep, digestion) from the external time of the day. A broad spectrum of related disorders illustrates the effect of the internal clock, influencing the activity of every system of the body throughout the day.2 Humans, like most other organisms, have near-24-hour rhythms in many aspects of physiology and behaviour, including the daily cycle of sleep and wakefulness. These circadian rhythms are not a simple response to environmental changes associated with day and night, but are intrinsic to the organism. One of the many daily rhythms generated by the circadian timing system includes a rhythm in sleep-wake propensity. This rhythm is timed such that the greatest drive for wakefulness occurs just before usual bedtime, and the greatest drive for sleep occurs in the latter part of the night, around the time of usual awakening. This circadian rhythm in sleep-wake propensity interacts with a sleep-wake homeostatic process, a process that reflects recent sleep-wake history and produces greater sleep drive with longer wake durations. When these two sleep regulatory systems are in balance, they allow for a consolidated sleep episode at night and a long and consolidated wake episode during the day.4

Circadian rhythm sleep wake disorder is defined as a disorder caused by alterations of the circadian time-keeping system, its entrainment mechanism, or a misalignment of the endogenous circadian rhythm and the external environment. The most common presenting symptoms are difficulty initiating and maintaining sleep, and excessive sleepiness.3

Classification of Circadian Rhythm Sleep Wake disorder:
- Disorders that occur after a voluntary or imposed shift in the timing of sleep:
- shift work disorder (SWD)
- jet lag disorder (JLD)

Disorders that involve mechanisms intrinsic to the circadian system:
- advanced sleep-wake phase disorder (ASWPD)
- delayed sleep-wake phase disorder (DSWPD)
- non 24 hour sleep wake rhythm disorder (N24HSWD)
- irregular sleep-wake rhythm disorder (ISWRD)

EXCESSIVE DAYTIME SLEEPINESS

Sleepiness and sudden sleep attacks during the daytime have a negative impact on performance and may be indicative of abnormal sleep regulation or disturbed sleep at night.[2] Hypersomnia can be caused by Central Disorders of Hypersomnolence or other secondary hypersomnias. Figure 1 showed the diagnostic flowchart for hypersomnia.

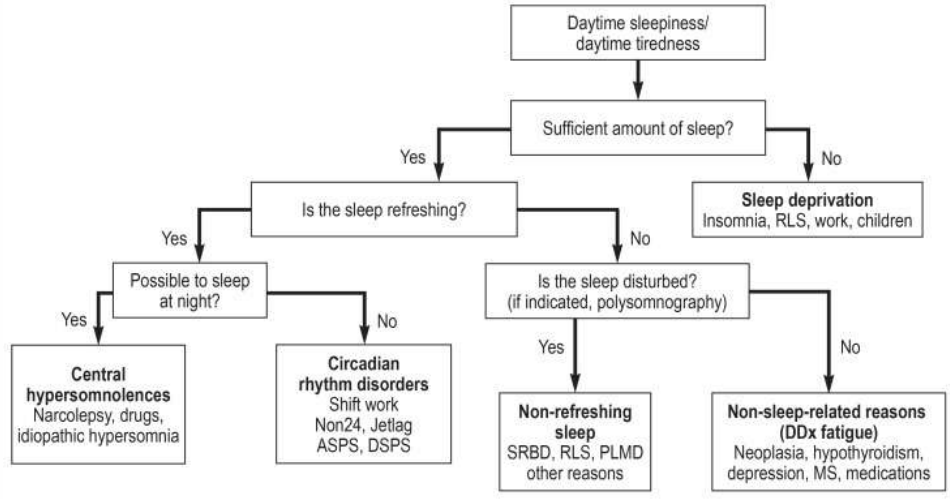

Figure 1. Diagnostic flowchart for hypersomnia. Cited from Dtsch Arztebl Int. 2019 Oct 11;116(41):681-688.

Classification Central Disorders of Hypersomnolence :[3]
- Narcolepsy type 1
- Narcolepsy type 2
- Idiopathic Hypersomnia
- Kleine-Levin Syndrome
- Hypersomnia due to a medical disorder
- Hypersomnia due to a medication or substance
- Hypersomnia associated with a psychiatric disorder
- Insufficient sleep syndrome
- Long sleeper (isolated symptoms and normal variant)

Secondary hypersomnias can be caused by other sleep disorders, central nervous system (CNS) conditions or psychiatric conditions. Other sleep disorders that cause excessive sleepiness are

SRBD (Seleep Related Breathing Disorders), behavioral sleep deprivation, circadian rhythm disorders, sleep related movement disorders, and parasomnia. CNS conditions with hypersomnolence are head trauma, stroke, cancer, encephalitis, neurodegenerative (Parkinson, dementia), myotonic dystrophy, and multiple sclerosis. Psychiatric conditions that may cause hypersomnia are depression, dysthymia, generalized anxiety disorder, and bipolar disorder.

Narcolepsy is a syndrome with a prevalence close to 0.04%. It is a chronic neurologic sleep disorder resulting from the abnormal regulation of the sleep–wake cycle, resulting in abnormal sleep tendencies, including excessive daytime sleepiness, disturbed nocturnal sleep, and manifestations related to rapid eye movement (REM) sleep such as cataplexy (an abrupt drop in muscle tone), sleep paralysis, and hypnopompic or hypnagogic hallucinations.[5] the diagnosis of narcolepsy requires a clinical history of excessive daytime sleepiness and a positive MSLT (Multiple Sleep latency Test), with a mean sleep latency of no more than 8 minutes and two or more SOREMPs (Sleep Onset REM Period) . Narcolepsy with and without cataplexy are now considered two different diagnostic entries. In almost all cases with cataplexy and in a minority of cases without cataplexy, narcolepsy is associated with a deficiency in the hypothalamic neuropeptide system hypocretin (orexin). The hypocretin deficiency can be assessed by the demonstration of very low to undetectable hypocretin-1 in the cerebrospinal fluid (CSF), a test more specific than the multiple sleep latency test but only recommended in selected cases.[6]

SLEEP-RELATED MOVEMENT PHENOMENA

Involuntary individual movements or movement patterns during sleep are only partially perceived by the patient; in the majority of cases with sleep-related movement disorders, the condition is detected by injuries of the patient or the bedpartner, or by reports of the bed partner. Diagnoses typically associated with motor symptoms are parasomnias and restless legs syndrome. Parasomnias are classified into rapid eye movement (REM) sleep and non–rapid eye movement (NREM) sleep parasomnias. Nocturnal seizures—typically requiring examination in a sleep laboratory or seizure monitoring unit—are the main differential diagnosis of parasomnias.[2]

Parasomnias are undesirable physical events that occur: during entry into sleep, within sleep, during arousal from sleep. Characterized by abnormal nocturnal behaviours, experiences, and autonomic responses emanating from sleep. May occur during: NREM, REM, transitions to and from sleep.[3]

Parasomnia classification according to ICSD-3 :

- NREM related: Disorders of arousal, Sleep related eating disorder, Sexsomnia
- REM related: REM Sleep Behavior Disorder (RBD), Reccurent isolated sleep paralysis, Nightmare disorder
- Other parasomnias: Exploding head syndrome, Sleep related hallucinations, Sleep enuresis
- Isolated symptoms & normal variants: Sleep talking

Characteristics of non-REM parasomnias are recurrence of episodes of incomplete awakening from sleep and amnesia. These episodes can have variable clinical presentations of disruptive abnormal behavior, such as ambulation, eating, and talking during sleep. These events can lead to clinical consequences to the patient, such as injuries and distress to the patient's family. Commonly, NREM parasomnias start in childhood or adolescence and become less intense or stop in adulthood.2 Characteristic of NREM parasomnias can be seen in table.[1]

Table 1. Characteristics of NREM parasomnias. Cited from Irfan (2017)7

Parasomnia	Behavior	Autonomic Symptoms	Amnesia	Provoking Factors	Sex	Timing	Duration
Confusional arousal	Disoriented, simple to complex movements in the bed	Absent	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes, rarely prolonged
Sleepwalking	Ambulation, leaving the bed, wandering	Absent	Present	Sleep deprivation with forced awakening, restless legs syndrome	No predominance, but injurious in males	First part of night	Several minutes to prolonged
Sleep terrors	Distraught, agitated, screaming, inconsolable	Present	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes
Sleep-related eating disorder	High-calorie, bizarre eating after arousal from sleep	Absent	Present/ variable recall	Sleep deprivation, restless legs syndrome, hypnotic use	Females more than males	Usually first part of night	Several minutes
Sexsomnia	Abnormal sexual behavior during sleep/partial arousal	Absent	Present	Sleep deprivation	Males more than females	Anytime	Minutes

REM Sleep Parasomnias consisted of REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder.3 REM Sleep Behavior Disorder (RBD) onset is at least 30 minutes after sleep onset. Dreams “acted out”, e.g: fishing, shoveling, delivering a speech, being chased, fighting. There is a predominance of violent behavior that include: talking, laughing, singing, yelling, swearing, gesturing, reaching, grabbing, arm flailing, punching, kicking, sitting up, jumping out of bed, crawling, running. These activities can result in repeated injury, including ecchymoses, lacerations, and fractures . The potential for injury to the patient or the bed partner raises interesting and difficult forensic medicine issues.

The minimal diagnostic criteria for RBD proposed by the International Classification of Sleep Disorders (ICSD)-3 are the following :

A. Repeated episodes of sleep related vocalizations and/or complex motor behaviors
B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep.

C. Polysomnographic recording demonstrates REM sleep without atonia (RWA)
D. The disturbance is not better explained by another sleep disorder, medication, or substance use.

The two most common movement disorder of sleep are Restless Legs Syndrome and Periodic Limb Movement Disorder. Characteristics of Restless Legs Syndrome (RLS) are almost irresistible urge to move the legs, it is caused by disagreeable sensations in the legs, these feelings are worse during inactivity. There are idiopathic as well as symptomatic forms of RLS, the latter being associated with e.g. pregnancy, iron deficiency and chronic renal failure.[9] Periodic Limb Movement Disorder (PLMD) is characterized by repetitive stereotyped movements of the limbs during sleep that involve flexion of the limbs, legs are involved more frequently than arms, duration of these movements are 0.5-5 seconds.[3]

Essential diagnostic criteria for RLS are :[9]

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

SLEEP DISTURBANCE IN NEUROLOGICAL DISORDERS

Parkinsonism is characterized by slow movements (bradykinesia), muscle rigidity (hypertonia), resting tremor, and postural instability. Sleep disturbances that can be found in parkinsonism are insomnia, abnormal movement during sleep, and excessive daytime sleepiness. Insomnia in these patients may be associated with RLS, dystonia, bradykinesia, frequent nocturia, or medication. Abnormal movements in sleep are often caused by Periodic Limb Movement Disorder (PLMD), REM Behavior Disorder (RBD), or Dystonic myoclonia. Some patients with Parkinson's Disease experienced sleep attacks (or sudden onsets of sleep) when treated with dopamine agonists .[10]

The relationship between sleep disorders and vascular risk factors and stroke has been well-documented but not fully understood. Stroke may cause sleep-wake disturbances, sleep architecture changes, circadian disturbances, and sleep disordered breathing (SDB). Sleep-wake disturbances in stroke patients may include hypersomnia, Excessive Daytime Sleepiness (EDS), insomnia, fatigue, parasomnia, and dream-reality confusion. Sleep architecture changes in supratentorial strokes are reduced NREM sleep, total sleep time, and sleep efficiency. In infratentorial strokes the changes are loss of sleep spindle, K complex, vertex wave, reduced REM sleep, insomnia. Circadian aspects and disturbances may include loss of blood pressure and other circadian rhythms after acute stroke , disturbance of normal circadian variation in autonomic

functions, secretion of growth hormone and melatonin, sleep-wake cycle, and body temperature. 60-70% stroke patients have SDB, some develop SDB as a consequence of stroke, there are deleterious effects of OSA on stroke, and OSA can be a risk factor for stroke. Figure 2 showed the association between sleep disorders, vascular disease and stroke. Sleep disorders potentiate vascular mechanisms, and vascular disease, in turn, contributes to sleep disorders (or exacerbate sleep disorders).[11]

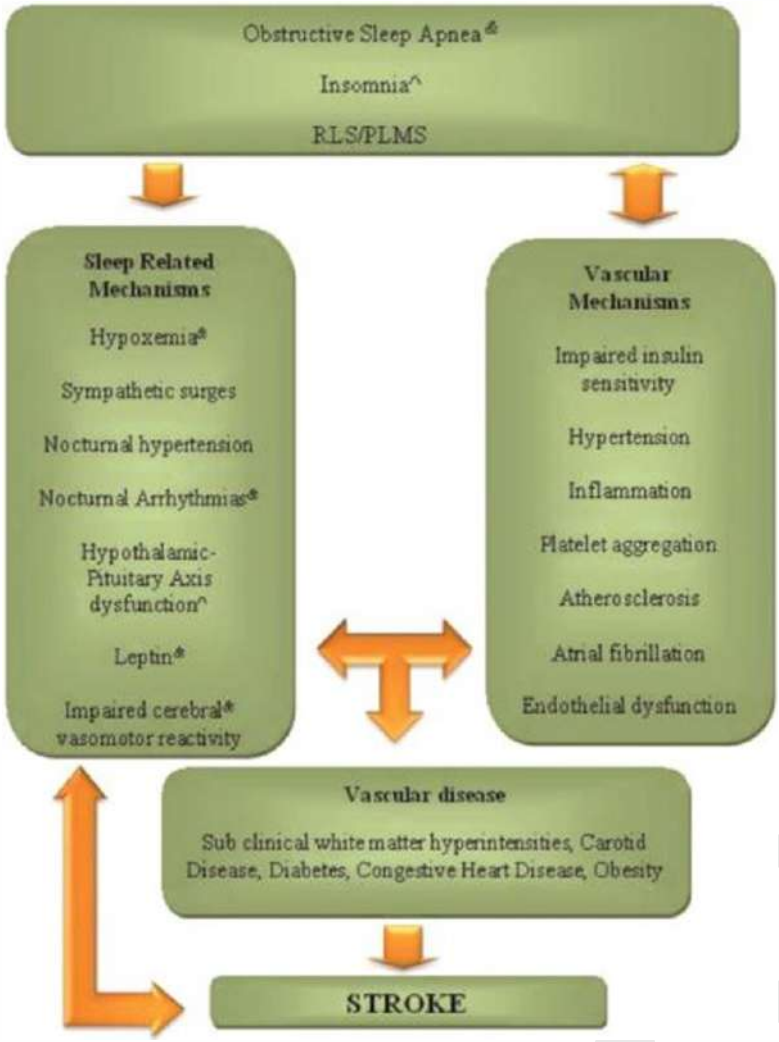

Figure 2. The association between sleep disorders, vascular disease and stroke. Cited from Wallace et al (2012).

Neuromuscular disorders consist of central and peripheral neurologic disorders with impairment of the motor system. Nocturnal sleep disruptions in neuromuscular disorders include pain and discomfort related to weakness, rigidity, or spasticity that limit movement and posture; autonomic dysfunction, and sleep-related hypoventilation. Autonomic dysfunction may cause poor sphincter control and problems with clearance of secretions.[12]

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by progressive decline in memory and other cognitive domains. Sleep disturbances in AD occur 25% in mild to moderate cases and around 50% in moderate to severe cases. Patients napping excessively during the daytime and having difficulty falling asleep at night, frequent nocturnal awakenings, and waking up to start the day too early, also sundowning (a delirium-like state characterized by nocturnal agitation or wandering). Sleep disturbances are associated with greater functional impairments in AD.[13]

Epilepsy refers to a host of seizure disorders characterized by uncontrolled abnormal brain electrical discharges associated with undesirable motor, verbal, or experiential phenomena. There is an overlap between sleep and epileptic phenomena i.e seizures often occur during sleep (NREM), arousal from sleep can provoke or mimic seizures or parasomnias. The converse is also true; epilepsy may disrupt sleep, either directly through seizures and epileptiform activity, or indirectly through medication-related effects. Other primary sleep disorders can trigger seizures, and conversely, seizures can trigger abnormal sleep phenomena.[14]

CONCLUSION

Sleep medicine is relevant in neurology. A disordered sleep–wake cycle can have major effects on many common neurological complaints such as headache and epilepsy, and it may also directly affect important general health issues, such as blood pressure. Sleep related disorders such as parasomnias, particularly with agitation, can be hazardous to patients and bed partners while also being diagnostic clues in some neurodegenerative diseases. Sleep disorders are common in people with diseases of the central nervous system (CNS).

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PULMONARY OR NON PULMONARY DYSPNEA

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Introduction

Dyspnea is defined as a subjective experience of breathing discomfort. Because dyspnea can only be perceived by the patient's experience, adequate assessment by the clinician relies on the patient's self-report (Mendez MP, 2018). Dyspnea is a common and life-threatening symptom among patients admitted to Emergency Departments (EDs). Therefore, the rapid and accurate diagnosis of the pathology causing dyspnea is essential (Bekgoz B, 2019). Acute dyspnea—breathing discomfort occurring within hours to days—is a common cause of emergency department visits and hospital admissions and may be a sign of cardiorespiratory decompensation among hospitalized patients (Mendez MP, 2018). The many potential causes of dyspnea makes it difficult to form a simple algorithm for dyspnea diagnosis. Although traditional methods, such as physical examination and chest X-rays, are the most frequently used methods in the differential diagnosis of dyspnea, they remain insufficient for final diagnosis (Bekgoz B, 2019).

A CXR is frequently helpful in evaluating patients with dyspnea. Characteristic roentgenographic findings occur in patients with congestive heart failure and pneumonia, and pulmonary fibrosis. The chest radiograph may also be abnormal in patients with obstructive pulmonary disease, but the chest film (particularly the bedside chest film) have low sensitivity above all for the detection of airflow obstruction or pulmonary embolism (Cardinale L, 2012) Chest computerized tomography (CT) is currently the most sensitive and feasible modality for diagnosing most lung pathologies, such as pneumonia, pneumothorax, pulmonary thromboembolism, and interstitial lung diseases (Bekgoz B, 2019).

The definition of dyspnea

In a consensus paper, the American Thoracic Society defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses.”
A more precise classification of the patient's symptoms is helpful in the differential diagnosis. There are multiple criteria to be considered:

- Temporal

– acute onset, vs. chronic (present for more than four weeks), vs. acute worsening of pre existing symptoms
– intermittent vs. permanent

– episodic (attacks)
● Situational
– at rest
– on exertion
– accompanying emotional stress
– depending on body position
– depending on special exposure(s)
● Pathogenetic
– problems relating to the respiratory system (central control of breathing, airways, gas exchange)
– problems relating to the cardiovascular system
– mixed cardiac and pulmonary causes
– other causes, e.g., anemia, thyroid disease, poor physical condition (i.e., muscle deconditioning)
– mental causes

The diagnosis and treatment of dyspnea are sometimes made more difficult by the simultaneous presence of more than one underlying disease, particularly in elderly, multimorbid patients. In addition to the history and physical examination, the initial diagnostic evaluation in ambulatory general medical practice includes laboratory tests (including a complete blood count, thyroid function tests, D-dimers), an ECG to detect possible arrhythmias, right-heart strain, and other abnormalities, and ultrasonography if indicated. If a lung disease is suspected, pulmonary function tests should be performed.

Diagnosis

The American Thoracic Society suggests that "dyspnea results from a mismatch between central respiratory motor activity and incoming afferent information from receptors in the airways, lungs and chest wall structures." This dissociation can result from increased metabolic demand, decreased compliance, increased dead-space volume, or many other disorders that are discussed later. Each patient presenting short of breath uses a different set of phrases to describe the symptoms and examination reveals a different combination of disorders. The clinician's ability to interpret these varying constellations is necessary to provide appropriate treatment to these patients, who are often in serious distress. A careful history can begin to narrow this wide differential. In addition to common symptoms, consider risk factors such as past medical and family history, trauma, travel, medications, and exposures. Schwartzstein and Lewis use the analogy of a machine to identify different causes of dyspnea based on pathophysiologic data. Dysfunctions of the respiratory system may be caused by faulty controllers, ventilatory pumps, or gas exchangers. (DeVos E, et al, 2016)

Physical Examination

A detailed physical examination also provides important guidance (Table 1). Respiratory rate and oxygen saturation are obtained with vital signs. The clinician should assess the patient's work of breathing, looking for any tripoding or retractions. Crepitance in the chest may indicate subcutaneous air and pneumothorax. Lung sounds such as wheezing, rales, and rhonchi further

guide the differential. Decreased sounds, hyperresonance, or egophony may also provide additional clues. Jugular venous distension, S3 gallop, and peripheral edema indicate that a patient has fluid overload. Conjunctival pallor, capillary refill, and temperature of extremities can provide clues about blood volume and general circulation (DeVos E, et al, 2016).

Table 1 Physical examination findings and correlating diagnoses

Symptom	Differential Diagnosis
Wheeze	COPD/emphysema, asthma, allergic reaction, CHF (cardiac wheeze)
Cough	Pneumonia, asthma, COPD/emphysema
Pleuritic chest pain	Pneumonia, pulmonary embolism, pneumothorax, COPD, asthma
Orthopnea	Acute heart failure
Fever	Pneumonia, bronchitis, TB, malignancy
Hemoptysis	Pneumonia, TB, pulmonary embolism, malignancy
Edema	Acute heart failure, pulmonary embolism (unilateral)
pulmonary edema	Acute and chronic heart failure, end stage renal and liver diseases, ARDS (sepsis)
Tachypnea alone	pulmonary embolism, acidosis (including aspirin toxicity), anxiety

Testing

Multiple tests are available to narrow the differential diagnosis of acute dyspnea. When using tests to augment clinical decision making, be sure to weigh the information they may provide with any risks involved in performing the tests (Table 2). Ultrasonography provides valuable information about the origin of symptoms, and, often, diagnosis in the initial assessment of an acutely dyspneic patient. These images may be obtained during or shortly after initial assessment, potentially guiding therapy faster than laboratory tests or other imaging studies would be available.

The Bedside Lung Ultrasonography in Emergency (BLUE) protocol offers one approach to differentiate several causes of respiratory failure. Computed tomography (CT) use to evaluate acute dyspnea has increased in the last decade (Feng LB, 2013). Risks include contrast reactions and nephropathy as well as radiationinduced cancers (Huckins DS, 2012). Recent American College of Physicians recommendations advocate avoidance of CT as an initial test to evaluate patients at low risk for pulmonary embolism (PE) (Qaseem A, 2012). Further, nearly one-fourth of patients undergoing CT for PE evaluation have clinically significant incidental findings. Although CT may provide vital diagnostic information, clinicians must not only consider the scan's necessity but also plan appropriate follow-up for any clinically important incidental findings. Always consider whether CT is necessary or whether less risky modalities, such as chest radiograph or ultrasonography, will answer pertinent questions (DeVos E,et al, 2016)

a. Pulmonary

i. **Pneumothorax** is a sudden event caused by accumulation of air in the pleural space. It is often accompanied by very acute dyspnea and pleuritic chest pain. The diagnosis should be considered carefully in patients with significant bullous lung disease or recent chest wall trauma, patients presenting with pain or hypoxemia after forceful coughing, and those on a mechanical ventilator.

ii. **Pulmonary embolism** is a difficult clinical diagnosis because of the poor sensitivity and specificity of the history and physical examination. Consider the diagnosis early because specialized testing is required.

iii. **Airflow limitation** should be suspected in patients with known obstructive lung disease, such as chronic obstructive pulmonary disease (COPD) or asthma. Airflow limitation leads to hyperinflation and air trapping in the lungs. Increased activation of pulmonary stretch receptors is perceived as dyspnea. **Wheezing** is the hallmark physical finding of airflow limitation.

iv. **Aspiration** should be suspected in patients with swallowing dysfunction, alcohol abuse, seizure disorder, or diminished level of consciousness for any reason. Always ask family members or nurses about witnessed aspiration. Remember, aspiration events are often not witnessed.

v. **Pneumonia.** Patients will usually have other symptoms of infection, including fever or hypothermia, rigors, or a productive cough. A localized infiltrate on the chest radiograph is diagnostic.

vi. **Upper airway obstruction.** Acute onset of inspiratory **stridor** with a report of dyspnea should prompt consideration of this diagnosis. Consider foreign body and/ or upper airway edema as contributory causes.

vii. **Acute respiratory distress syndrome (ARDS).** ARDS is associated with bilateral infiltrates on the chest radiograph caused by noncardiogenic pulmonary edema. It commonly occurs in patients with sepsis, trauma, massive blood transfusion, or

b. Non Pulmonary Cardiac

i. **Myocardial ischemia or infarction.** Dyspnea may occur in the absence of chest pain and may represent angina, also known as an “anginal equivalent.”

ii. **Heart failure.** In hospitalized patients with heart failure, acute dyspnea is often precipitated by fluid administration or myocardial ischemia leading to cardiogenic pulmonary edema. A significant elevation in brain natriuretic peptide (BNP), which is primarily released by atrial myocytes, may occur and suggests increased atrial wall stretch and a cardiogenic cause of dyspnea.

iii. **Arrhythmias.** Patients may have a history of palpitations. Specific etiologies cannot be reliably diagnosed on physical examination; a 12-lead electrocardiogram (EKG) or a rhythm strip is required.

iv. **Cardiac tamponade** is rare but should always be considered in patients with breast and lung cancer, renal failure, recent myocardial infarction, or blunt trauma to the chest.

c. Non Pulmonary Metabolic

i. **Sepsis.** Tachypnea and acute respiratory alkalosis may be the earliest findings in sepsis.

ii. **Metabolic acidosis**. Dyspnea is common because patients hyperventilate to compensate for their acidosis. Respiration with large tidal volumes, known as Kussmaul breathing, is a common breathing pattern associated with metabolic acidosis.

d. **Non Pulmonary Hematologic.** Acute anemia (from hemorrhage or hemolysis) can cause acute dyspnea due to the decreased oxygen carrying capacity of blood. Anemia can easily be missed on history and physical examination.

e. **Non Pulmonary Psychiatric.** Anxiety can be a primary cause of acute dyspnea; however, a diagnosis of primary anxiety should be considered only after ruling out the conditions listed above (Mendez MP, 2018)

2. Diagnostic testing for dyspneic patients

Test	General Information	Pros	Cons
Chest radiograph	Often primary imaging	Low radiation, can assess consolidation, pleural fluid, hyperinflation, pneumothorax, and subcutaneous air. Heart size is apparent	Low sensitivity in acute dyspnea. In one series only 8 of 26 pneumonias diagnosed on CT met CXR criteria[37]
Ultrasonography	Multiple protocols to assess acute dyspnea	No radiation, fast, reproducible bedside test, can be done on unstable patients in department and in semirecumbent position	Requires some skill to acquire and interpret bedside images. Patient factors such as subcutaneous air, body habitus, and so forth may limit images
D-dimer	Marker of fibrinolytic activity. When measured by ELISA or second-generation latex agglutination can be used to rule out PE in selected patients	Serum test readily available	Requires risk assessment and clear clinical question. Also increased in consumptive coagulopathy, infection, malignancy, trauma, dissection, preeclampsia, and other cardiovascular disorders

Arterial blood gas	Provides additional information about ventilation ($Paco_2$) to patients with reliable pulse oximetry and bicarbonate level available on BMP	May be faster than general laboratory tests. Useful in assessing anxiety-induced hyperventilation[36]	Limited evidence for routine use in undifferentiated dyspnea
Electrocardiogram	Initial cardiac assessment for assessing dyspnea	Fast and inexpensive. Easy to compare with prior examinations. Specific for dysrhythmias or ACS limiting perfusion	May be nonspecific in findings such as right heart strain and P pulmonale
Troponin	Serum indicator of myocardial damage	Serum test readily available	Can narrow differential to cardiac causes. PE with right heart strain may have increased troponin levels; this finding predicts worse outcomes
BNP and proBNP	Useful in assessing for acute heart failure	Serum test readily available	Limited in obesity, mitral regurgitation, flash pulmonary edema, and renal insufficiency. Context is essential
Complete blood count	Provides information about oxygen carrying capacity based on hemoglobin and hematocrit. White blood cell count may indicate infection	Serum test readily available	Nonspecific
CT scan	Provides detailed imaging of cardiorespiratory system. Use is increasing, but practitioners should maintain clinical context and consider whether other modalities can answer the clinical question	Offers sensitive and specific results	Significant radiation exposure, contrast nephropathy, intravenous contrast dye reactions

Ventilation/ perfusion scan	Radiolabeled aerosol and albumin aggregates are used to study ventilation and perfusion. Read as negative or low, medium or high probability for pulmonary embolism	Low in radiation	Limited by underlying pulmonary disease and availability of isotopes

(DeVos E, et al, 2016)

Therapy

The physiologic bases for the treatment of dyspnea is rooted in the discussion of the mechanisms underlying shortness of breath. In disease states associated with dyspnea, the amplitude of motor command output from the central controller is often increased and, depending on the degree of intrinsic mechanical loading (or impedance) that prevails, the relationship of motor output to the mechanical response of the ventilator system (i.e., degree of neuromechanical dissociation, is variably altered. It follows that any therapeutic intervention that reduces ventilator demand (relative to capacity), reduces mechanical loading (which improves ventilatory capacity), or strengthens weakened inspiratory muscles should relieve dyspnea by reducing motor command output and/or by reducing neuromechanical dissociation. Further, approaches that target the central perception of dyspnea may also ease the breathing discomfort associated with these pathophysiologic alterations.

In this discussion, treatments for dyspnea are categorized and related to pathophysiologic mechanisms rather than to specific diseases. It is recognized that many of the therapeutic interventions currently available relieve dyspnea by addressing different mechani). For a given intervention, some mechanisms may be more relevant than others. In addition, modest alterations in a number of physiologic and psychologic variables, as a result of a particular treatment, can culminate in clinically meaningful reduction in symptoms. Unfortunately, at this point in our understanding of mechanisms and treatment many unanswered questions remain. For example, how important are psychologic compared with physiologic treatments in alleviating or reducing dyspnea in any particular situation? Is there a drug that can reduce dyspnea without reducing ventilation? While there is much work to be done in this area, an approach to treatment that links mechanisms and treatments will assist in resolution of these questions as well as minimize the impact of this intractable symptom on the patient. (ATS BOARD, 1999).

Table 4. Therapeutic Interventions And Their Tie to Pathophysiologic Mechanism

Pathophysiologic Mechanism	Therapeutic Intervention
Reduce ventilatory demand	
Reduce metabolic load	Exercise training: improve efficiency of CO_2 elimination
	Supplemental O_2 therapy
Decrease central drive	Supplemental O_2 therapy
	Pharmacologic therapy:
	Opiate therapy
	Anxiolytic therapy
	Alter pulmonary afferent information:
	Vibration
	Ventilator settings
	Inhaled pharmacologic therapy
	Fans
	Improve efficiency of CO_2 elimination:
	Altered breathing pattern
Reduce ventilatory impedance	
Reduce/counterbalance lung hyperinflation	Surgical volume reduction:
	Continuous positive airway pressure
Reduce resistive load	Pharmacologic therapy
Improve inspiratory muscle function	Nutrition
	Inspiratory muscle training
	Positioning
	Partial ventilatory support
	Minimizing use of steroids
Alter central perception	Education
	Cognitive–behavioral approaches
	Desensitization
	Pharmacologic therapy

Summary

Acute dyspnea presents commonly to the Emergency Departement and it is imperative that emergency physicians be prepared to stabilize patients' oxygenation and ventilation, which requires careful and efficient consideration of the differential diagnosis. Using cues from the history and physical examination, practitioners may guide the work-up and treatment to identify a parenchymal, obstructive, circulatory, or compensatory cause of dyspnea. Early use of bedside testing, including ultrasonography, may limit unnecessary tests and save time in determining the best treatment course. Thus ensuring both the best care for the patient and also the physician's ability to readily respond to the next case.

A complete therapeutic plan must also consider behavioural and emotional response of the patient and his or her family to the symptom and any attendant disability. As therapeutic interventions are implemented, one must assess the impact of treatment on the characteristics of the sensations and any resulting change in the individual's functional status.

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RIGHT VENTRICULAR FAILURE IN PULMONARY DISEASE

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Abstract
As the primary presentation of acute decompensated heart failure and cause of hospitalization, right heart failure accounted for 2.2% of heart failure admissions. Right heart failure tends to develop in patients with left ventricular failure. Right ventricular failure is generally caused by cardiac or pulmonary disease. Cor pulmonale and failing right ventricular syndrome in lung disease is part of a disease spectrum. Furthermore, right ventricular failure in pulmonary disease is divided into those caused by acute or chronic lung disorders. Management should be addressed to treat underlying lung conditions to improve oxygenation and right ventricle function. Oxygen therapy works by relieving hypoxemic vasoconstriction. Decreasing afterload is usually the most effective way to improve RV function. Unfortunately, RV failure associated with chronic lung diseases usually cannot easily be reversed. Efforts should be focused on removing any factors that can contribute to an increased pulmonary vascular tone, followed by the judicious use of selective pulmonary vasodilators.

Introduction
Heart failure (HF) is a condition in which the heart's ability to pump blood to the rest of the body efficiently is compromised. It is a complicated syndrome characterized by anatomical or functional cardiac problems that impede the ability of one or both ventricles to fill or discharge blood. However, as with pulmonary edema or cardiogenic shock, it might manifest as an acute syndrome within 24 hours. Due to a rise in the prevalence of predisposing factors in the community, including LV failure and myocardial infarction, right HF is now more frequently detected in current clinical practice.[1]
The right ventricle (RV) has long been overlooked as a non-essential component of the cardiac pump and only a conduit for pulmonary circulation. The right ventricle (RV) was once considered merely a conduit for returning systemic venous blood to the lungs for reoxygenation. However, it is now clear that the RV plays a critical role in maintaining systemic circulatory homeostasis, as evidenced by the numerous excellent reviews on RV function in health and disease.[2,3]
RV failure is important because of the massive prevalence of left ventricular failure (LVF), which develops into pulmonary hypertension and RV failure. Furthermore, RV failure is an important prognostic indicator of heart failure, and its presence is a strong predictor of mortality in CHF patients. As a result, there has been relatively little focus on how right ventricular dysfunction can be detected and measured, what specific molecular and cellular mechanisms contribute to the maintenance or failure of normal right ventricular function, how right ventricular dysfunction evolves structurally and functionally, or what interventions can best preserve right ventricular function.[4,5]

The right ventricle is affected by and contributes to several disease processes, including perhaps most notably pulmonary hypertension caused by various lung or pulmonary vascular diseases (cor pulmonale). This review summarizes the clinical features of right heart failure, precisely due to pulmonary disease, its epidemiology, diagnostic work-up, and the principles behind treatment and management options that focus on preload optimization, afterload reduction, and improvement of contractility.

Causes and pathophysiology of right ventricular failure

Right ventricular failure (RVF) is usually caused by pressure and volume overload in the left ventricle. RVF can be caused by various pressure overload conditions, including LVF. Pneumonia, pulmonary embolism (PE), mechanical ventilation, and acute respiratory distress syndrome (ARDS). Furthermore, RVF can be caused by prolonged pressure overload. Primary pulmonary arterial hypertension (PAH) and secondary pulmonary arterial hypertension (PH) (as found in chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis), and congenital heart disease are examples of these.[6,7]

Preload, contractility, afterload, ventricular interdependence, and cardiac rhythm all play optimal RV function. The majority of cases of RV failure are caused by pre-existing or newly diagnosed cardiac or pulmonary illnesses or a combination of the two, which can raise RV afterload, diminish RV contractility, modify RV preload or ventricular dependency, or produce arrhythmias. It is critical to evaluate these five components to comprehend RV failure.[1,8] The mechanisms and causes of RV failure are summarized below.

1) Increased afterload
   · LV backward failure
   · Acute pulmonary embolism
   · Pulmonary artery hypertension
   · Exacerbated chronic pulmonary disease
   · Acute lung injury / acute respiratory distress syndrome
   · Sleep-related breathing disorders
   · Mechanical ventilation
   · Post-CABG
2) Reduced contractility
   · RV ischaemia / RV infarction
   · RV injury, systemic inflammatory response (SIRS)
   · Myocarditis
   · Cardiomyopathies
   · Arrhythmogenic RV cardiomyopathy
3) Abnormal preload
   · Hypo- or hypervolemia
   · V forward failure
   · Capillary leak

- Sepsis
- Superior vena cava (SVC) syndrome
- Pericardial tamponade
- Mechanical ventilation
- Chronic left-to-right shunt

4) Altered interdependence
- Pericardial tamponade
- Pericardial disease
- Septal shift

5) Altered rhythm
- Bradyarrhythmia
- Tachyarrhythmia

Right ventricular failure in pulmonary disease[8]

As a consequence of lung disease, RV failure is commonly described as cor pulmonale. These changes might occur as an acute condition, such as in fulminant pulmonary embolism, or might be due to chronic disorders resulting in chronic alterations of RV structure and function.

1. RV failure due to acute pulmonary disease

The RV compensates via the Frank-Starling mechanism by increasing its contractile state as a response to increased pressure. An increase in ventricular inotropy due to a sudden increase in afterload, known as the Anrep effect, is mediated through changes in calcium dynamics and occurs by maintaining the adrenergic state. Catecholamines also contribute to the increase in RV pressure by increasing inotropy. The subsequent dilated RV relies on the Frank-Starling mechanism to function with a further increase in the afterload. However, when all of the adaptive mechanisms in response to pressure overload are exhausted, the systemic pressure begins to fall, with a sudden, dramatic, and irreversible decrease in the contractile function of the RV. A steady rise in the pressure of the RV secondary to the progressive constriction of the main pulmonary artery to the point where the RV can no longer compensate would lead to a sudden decrease in systemic pressure and cardiac output. If there is an acute pulmonary embolism and the RV is exposed to greater pressure values and can tolerate them, a pre-existing increase in pulmonary pressure with antecedent RV adaptation must be presumed.[8]

The RV responds to increased pressure by increasing its contractile state via the Frank-Starling mechanism. The Anrep effect, which causes a rise in ventricular inotropy as a response to a sudden increase in afterload, is mediated by changes in calcium dynamics and happens via sustaining the adrenergic state. Catecholamines promote inotropy, which contributes to an increase in RV pressure. The Frank-Starling mechanism is used by the subsequent dilated RV when the afterload is increased further. When all of the adaptive mechanisms in response to pressure overload have been exhausted, the systemic pressure declines, resulting in an abrupt, drastic, and permanent reduction in the RV's contractile activity. A steady rise in the pressure of the RV secondary to the progressive constriction of the main pulmonary artery to the point where the RV can no longer compensate would lead to a sudden decrease in systemic pressure and cardiac output.[1]

Abrupt pulmonary embolism is the model for RV failure caused by acute pressure overload. The cascade events seen in pulmonary thromboembolism are influenced by pre-existing cardiac or pulmonary illness and the anatomic severity of the obstruction. The pulmonary vascular resistance increases as vasoconstrictive substances are released from the thrombus and, in reaction to hypoxia, increases pulmonary artery pressure. The RV becomes dilated and hypokinetic as a result. The increase in myocardial oxygen demand eventually leads to ischemia or infarction. Ischemia or infarction produces a reduction in RV ejection and a septal shift, lowering LV preload. Cardiogenic shock occurs when the heart cannot sustain cardiac index and arterial pressure.

2. RV failure due to chronic lung disorder

Although several chronic lung disorders impact the pulmonary circulation and the right heart, the most common cause of respiratory insufficiency and cor pulmonale is chronic obstructive pulmonary disease (COPD). COPD causes lung hyperinflation, airway resistance, endothelial dysfunction, and hypoxia, raising RV afterload. Hypoxia is perhaps the most important cause of pulmonary hypertension and consequent RV failure among these variables. When hypoxic pulmonary vasoconstriction occurs (the Euler-Liljestrand effect), pulmonary pressure rises, vascular remodeling occurs, and fixed pulmonary hypertension develops. The pulmonary vascular resistance increases in reaction to hypoxia, and the pulmonary artery pressure rises. A dilated and hypokinetic RV is the end outcome.[8]

As shown in PAH, chronic pressure overload causes multiple episodes of decompensation. Myocardial enlargement and a shift in shape from the usual conformation to a spherical geometry are the RV's adaptive responses to pressure overload. Increased protein synthesis and cell size are the causes of this. Protein synthesis is induced by paracrine, autocrine, and neurohormonal signals such as the renin-angiotensin-aldosterone system (RAAS), increased sympathetic activity, and strain. Pressure overload is a long-term effect that causes the heart contractile force to decrease. The extracellular matrix production that follows impacts RV function and shape, resulting in electrical instability.[1]

The presence of pulmonary hypertension has long been considered mandatory for developing a cor pulmonale. Recent data have challenged this assumption and suggested that structural alterations in cardiac myocytes predate the development of clinically manifested pulmonary hypertension in patients with lung disease. Moreover, Hilde et al. found that Impaired RV systolic function, hypertrophy, and dilation were present even at a slight increase of mPAP, which indicates an early impact on RV function and structure in patients with COPD. The dissociation between PH and RV remodeling and impaired function in the early stages of COPD suggests additive mechanisms to increased afterload, such as lung hyperinflation, systemic inflammation, and endothelial dysfunction.[9]

As such, cor pulmonale and failing RV syndrome in lung disease may be part of a disease spectrum rather than being distinct entities. With its impact on RV function, pulmonary hypertension – more than airflow limitation – is the strongest predictor of an adverse outcome and mortality in patients with lung disease.[8]

Clinical manifestation and evaluation

Backward failure generating systemic congestion is the leading cause of RV failure clinical symptoms. In extreme cases, the right heart dilates, compromising LV filling, lowering LV function, and inducing forward failure due to interventricular dependency (i.e., hypotension and hypoperfusion). Backward failure is characterized by increased central venous pressure and jugular vein distension, leading to organ dysfunction and peripheral edema.[8]

Dyspnea is the most common symptom in individuals with acute right HF who arrive in the emergency room. On the other hand, dyspnea is a non-specific symptom that can be caused by a variety of respiratory and cardiac conditions, including asthma and COPD exacerbation. The sensitivity of dyspnea is high, but the specificity is low. Orthopnea, weariness, weakness, lethargy, peripheral edema, and abdominal distention are other clinical manifestations. 10 Because most symptoms of acute right HF have little sensitivity or specificity, a thorough medical history, and physical examination are required. Recommended investigations for each patient include: (1) 12-lead electrocardiogram, (2) laboratory evaluation, (3) chest radiograph, and (4) echocardiogram.

EKGs are commonly used to check heart rhythm, QRS duration, and the existence of atrioventricular conduction block. EKG is sensitive but not very specific. The use of echocardiography in the diagnosis of right heart failure is crucial. Patients with RHF have RV hypertrophy, RV systolic dysfunction, tricuspid regurgitation, pulmonary hypertension, congenital heart abnormalities, valvular heart disease, or left heart disease. Without making geometrical assumptions, three-dimensional echocardiography can be utilized to determine volumes and ejection fractions. Compared to cardiac MRI, this is accurate and repeatable. The main prognosticators in PAH are right atrial pressure and cardiac index, which are more precise reflections of RV function than PAP.[1]

Magnetic resonance imaging (MRI) is the gold standard for measuring the RV chamber, right heart anatomy, and function in magnetic resonance imaging (MRI). This is notably important in patients with complex congenital heart anomalies such as Ebstein's abnormality and hypoplastic RV and precise valvular regurgitation assessment and surgery planning. Recent research has also demonstrated that RV end-diastolic volumes and pulmonary compliance measured by MRI in PAH have predictive relevance. Furthermore, cardiac catheterization remains the gold standard for evaluating pulmonary circulation hemodynamics. It directly measures pressures and estimates flow indirectly. Right heart catheterization effectively verifies the presence of pulmonary hypertension (mean pulmonary arterial pressure at rest of less than 25 mmHg), clarifies the underlying causes, and provides prognostic information. Assessment of pulmonary vascular resistance or impedance, pulmonary pressures, cardiac output shunt fraction, and pulmonary vasoreactivity are all indications for a right heart catheterization.[1]

Management of right ventricular failure

A detailed statement on the management of acute RV failure was recently published by the Heart Failure Association and the European Society of Cardiology's Working Group on Pulmonary

Circulation and Right Ventricular Function. The goal of triage and first examination of patients with acute RV failure is to determine clinical severity and the cause of RV failure, focusing on those who require particular therapy. Preload optimization, afterload reduction, and contractility improvement are the three main goals of acute right heart failure treatment. In the case of acute RHF, the main goal is to avoid systemic hypotension to minimize complications, including myocardial ischemia and other hypotension.[8]

Acute RV failure management necessitates knowledge of the RV's anatomical and physiological features and prompt diagnosis and treatment of the underlying causes and associated pathophysiological problems. Early revascularization for RV infarction, thrombolysis for pulmonary embolism, antibiotics for endocarditis, and surgical repair are all alternatives for etiology-specific therapy.

Acute RV failure is generally a mix of established pulmonary vascular disease complicated by acute derangements in one or all of the following in critically sick patients hospitalized in the intensive care unit (ICU): (1) RV contractility, (2) RV afterload, and (3) RV preload. Two examples are a patient with cor pulmonale due to emphysema who gets severe pneumonia or a patient with persistent right heart failure due to pulmonary arterial hypertension who becomes septic. The circumstances that produce chronic RV failure cannot be reversed in these situations, so management should focus on improving RV function while minimizing the cause of RV failure. A sudden rise in RV afterload, such as that seen with a significant pulmonary embolism, can cause acute RV failure. In this situation, the priority should be relieving the increase in afterload.[8,10]

1) Optimizing preload

Fluid management is crucial for successful RV failure management. Intravascular volume can rapidly decrease in the early stages of critical illnesses due to hemorrhage, increased vascular permeability, and insensible losses. Sedatives and analgesics diminish venous tone and right-sided return by blunting sympathetic vasoconstriction of the systemic venous circulation. Positive pressure ventilation can also reduce RV transmural filling pressure and increase intrathoracic pressure, reducing RV preload. In patients with acute RV failure, maintaining cardiac output requires adequate right-sided filling pressure.

Volume resuscitation should be started as soon as possible if a low intravascular volume is indicated. However, the RV preload needs vary significantly depending on whether the afterload is normal or increased. When RV failure develops in normal pulmonary vascular resistance, as in right-sided myocardial infarction, RV end-diastolic pressure must frequently be raised to above-average values to sustain cardiac output. When RV failure occurs due to increasing RV afterload, however, volume loading might cause the interventricular septum to migrate toward the LV and impair LV diastolic filling. RV dilatation raises free wall tension simultaneously, resulting in higher oxygen demand and lower RV perfusion. Intravascular volume may need to be reduced in this situation.

Reduced central venous pressure via diuresis or dialysis should be accompanied by increased cardiac output, as measured by SvO2 or systemic organ perfusion if RV preload is too high. An

echocardiogram may also be beneficial. RV dilatation and impingement on LV filling suggest that preload should be reduced further. If these evaluations of RV function are insufficient, a pulmonary artery catheter may be required.

2) Reducing afterload

Excessive afterload is a factor in nearly every case of acute RV failure, and lowering it is usually the most effective strategy to improve RV function. Many occurrences of acute RV failure are unfortunately accompanied by chronic heart or lung problems that are difficult to correct. In these cases, efforts should be concentrated on reducing any factors that may contribute to elevated pulmonary vascular tone, followed by using selective pulmonary vasodilators with caution.

Increased pulmonary vascular resistance and, as a result, an increase in RV afterload are caused by many unfavorable circumstances associated with a critical illness. Hypoxic pulmonary vasoconstriction occurs when oxygen tension in the alveoli, pulmonary arterial blood, or bronchial arterial blood falls below a certain level and is exacerbated by hypercapnia or acidemia. Although decreases in oxygen tension in alveolar air cause the highest vasoconstrictive response, hypoxic pulmonary vasoconstriction is more significant in the context of decreased pulmonary arterial O2. In the intensive care unit, adequate systemic SaO2 assessed by pulse oximetry effectively excludes alveolar hypoxia, but it is not a reliable predictor of pulmonary arterial oxygenation. Because pulmonary vascular resistance is lowest when the lung is near functional residual capacity, high or low lung volume might worsen RV afterload.

Correction of hypercapnia, acidemia, and alveolar hypoxia should be the first step in lowering RV afterload. SaO2 should ideally be maintained above 92 percent, and ventilator settings should be modified to obtain a lung volume near functional residual capacity and a Pco2 and pH as close to normal as possible. These objectives are incompatible with current critical-care ventilation techniques, particularly the low lung volumes and permissive hypercapnia utilized in patients with acute respiratory distress syndrome. Given the benefits of low-volume ventilation on survival, utilizing it in patients with acute respiratory distress syndrome seems reasonable. At the same time, it is worth noting that increased pulmonary artery pressure has been linked to poorer results in this scenario. Pulmonary vasodilators may be used when preload and afterload adjustments do not result in a satisfactory improvement in RV function. For pulmonary arterial hypertension, several classes of pulmonary vasodilators have been developed in the last 20 years, including prostacyclin nitric oxide, prostacyclin derivatives, and endothelin receptor antagonists (ambrisentan, bosentan), and phosphodiesterase type-5 inhibitors (sildenafil, tadalafil).

3) Improving RV contractility

In acute RV failure, three interrelated factors cause loss of RV contractile force: (1) overstretching of the RV free wall, putting myocytes at a mechanical disadvantage; (2) cellular metabolism disturbances, resulting in decreased myocardial contractile forces; and (3) insufficient oxygen delivery due to decreased coronary arterial perfusion. RV systolic pressures may approach or exceed systemic pressure in patients with acute RV failure and chronic pulmonary vascular disease. The first goal of vasopressor therapy in this condition is to raise systemic blood pressure

above RV systolic pressure (70, 71). Drugs that promote myocardial contractility should be avoided until this primary goal is met.

Several vasoactive medications have been utilized in the intensive care unit to treat RV failure. A vasopressor that improves systemic arterial pressure and RV contractility without increasing pulmonary vascular resistance would be suitable for use in acute RV failure. In hypotensive patients with acute RV failure, norepinephrine is a reasonable drug, and it is frequently the first pressor given in our institution for this purpose. Epinephrine, like norepinephrine, is a mixed/receptor agonist that causes vasoconstriction and increases inotropy. In an animal investigation, epinephrine increased cardiac output without affecting pulmonary vascular resistance, and it improved RV contractility in a limited trial of septic shock patients.

4) Mechanical support

Mechanical assistance may be explored when medicinal therapy for acute RV failure in the intensive care unit is inadequate. Extracorporeal life support, particularly venovenous and venoarterial extracorporeal membrane oxygenation, has been successfully used in patients with RV failure due to massive pulmonary embolus, chronic thromboembolic pulmonary hypertension, and pulmonary arterial hypertension, usually as a bridge to endarterectomy or lung transplantation. Unlike venovenous extracorporeal membrane oxygenation, which oxygenates venous blood but needs the RV to pump the entire cardiac output through the pulmonary circulation, venoarterial extracorporeal membrane oxygenation unloads the RV while maintaining systemic oxygenation. RV performance and oxygen delivery are improved by venoarterial extracorporeal membrane oxygenation, which has been utilized successfully in conscious, spontaneously breathing patients. Recent studies have described the use of venoarterial extracorporeal membrane oxygenation to support RV function during pulmonary vasodilator therapy initiation in a treatment-naive patient with pulmonary arterial hypertension presenting in severe RV failure, as well as as a bridge to recovery in pulmonary arterial hypertension patients presenting with worsening pulmonary hypertension.

Conclusions

RV failure is a crucial condition that strongly predicts mortality in CHF patients. Lung disease could progress to RV failure due to increased afterload and pulmonary arterial hypertension. The most common lung disease that causes RV failure includes COPD, pulmonary hypertension, and pulmonary embolism. Treatment of acute right heart failure focuses on preload optimization, afterload reduction, and improvement of contractility. The primary goal of RV failure in pulmonary disease is to treat the underlying disease and relieve hypoxemic pulmonary vasoconstriction (oxygen therapy). RV afterload should be reduced by correcting the factors that increase PVR (hypoxia, hypercapnia, abnormal lung volume). Finally, mechanical support should be considered if medical therapy is ineffective.

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THE ART OF BREATHING TECHNIQUES IN CHRONIC DYSPNEA

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Introduction
Breathing is a complex process that relies on the coordination of the respiratory muscles and the control of the brain. The main function of the lungs is to facilitate gas exchange between inspired air and the circulatory system. This will help to exchange oxygen and CO2 from the body. Each respiratory cycle begins with inspiration and ends with expiration.

The structure of the respiratory system
After passing through the nose or mouth, pharynx, larynx, air enters the tracheobronchial tree. Starting from the trachea, air will pass through several branches before reaching the alveoli. The first generation is the conduction zone, where there are no alveoli which anatomically do not allow gas exchange with venous blood. Alveoli begin to exist in generations 17-19 which is a transitional zone. Generations 20-22 are branches lined by alveoli. Alveolar ducts and alveolar sacs, which are the terminals of the tracheobronchial tree, are called the respiratory zone.

Respiratory muscles and the chest wall are important components of the respiratory system. The lungs are not able to profitably expand by themselves. The pressure to inflate must be assisted by the respiratory muscles. The chest wall should be intact and able to expand if air enters the alveoli normally. The primary components of the chest wall consist of the rib cage, internal and external intercostal muscles and the diaphragm which is the main muscle in breathing. Other respiratory muscles, namely the abdominal muscles, include the rectus abdominis, parasternal intercartilagenous, SCM and scalene muscles.

Basic elements of respiratory system control. Information from various sensors goes to the central control and then the output from the central control goes to the respiratory muscles.

The 3 basic elements of respiratory control are:
· Sensors: which will collect information
· Central control in the brain that will coordinate information and send impulses
· Effectors (respiratory muscles) that will cause ventilation

Oxygen that comes from the free air is converted into carbon dioxide which is produced by the alveoli from the lungs. Free air containing oxygen is inspired into the lungs through conducting

airways. Respiratory muscles that work from commands initiated by the central nervous system (CNS) produce pressure that will allow air to flow into the respiratory tract. At the same time, blood in the veins returns from various body tissues to the lungs via the right ventricle of the heart. This venous blood has high CO2 and low O2. In the pulmonary capillaries, carbon dioxide is exchanged for oxygen from the alveoli. Blood leaves the lungs in a state of high oxygen and low carbon dioxide to be distributed to body tissues through the left side of the heart. During expiration, gases with a high concentration of carbon dioxide are expelled from the body.

The respiratory system participates in acid-base balance by removing CO2 from the body. The CNS has a sensor for CO2, and hydrogen ion levels in the arteries and in the cerebrospinal fluid transmit information to control breathing.

a. Phonation
Phonation is the production of sound due to the movement of air through the vocal cords. Speaking, singing, and other sounds are produced due to central nervous system control of the respiratory muscles, causing air to flow through the vocal cords and mouth.

b. Defensive mechanisms
Every time we breathe microorganisms such as bacteria, dust, silica or asbestos particles, toxic gases, smoke, and other pollutants into the lungs. Air conditioning to protect the alveoli from temperature and humidity variations from the outside air. Adjustment of air temperature and humidification occurs in the nasal mucosa, oropharynx and nasopharynx which are rich in blood vessels.
Olfaction (receptors are in the posterior nasal cavity) to detect noxious gases during inspiration. With rapid and shallow inspiration, the gas is carried to the olfactory sensor without being carried into the lungs

c. Filtration
Filtration and removing inspired particles. Particles deposited in the respiratory tract are the result of impaction, sedimentation, and other mechanisms. Air passing through the nose will undergo the first filtration (10-15 m diameter particles). Tonsils and adenoids located near the impaction site provide immunological protection. Particles with a diameter of 2 – 10 m are captured by mucus in the upper respiratory tract. Particles < 0.1 m are usually in aerosol form and about 80% will be exhaled.

d. Removal
Mechanical or chemical stimulation of the receptors of the nose, trachea, larynx will produce bronchoconstriction to prevent deeper penetration by coughing or sneezing.

Physiology of breathing
The most important inspiratory muscle is the diaphragm. When the diaphragm contracts, the contents of the abdomen are pushed downwards and forwards so that the chest cavity increases

(vertical dimension). In addition, the ribs are raised and pushed forward, causing an increase in the transverse diameter of the thorax. The external intercostal muscles contract so that the ribs are pulled up and forward, and rotate between the tubercle and the head of the ribs. Thus, the lateral and anteroposterior diameters of the thorax are increased.

Before inspiration, all respiratory muscles are relaxed. During inspiration, the diaphragm contracts thereby increasing the vertical dimension of the thoracic cavity. External intercostal contractions elevate the ribs, increasing the thoracic cavity. During passive expiration, the diaphragm relaxes, reducing the volume of the thoracic cavity. The external intercostal muscles relax and the ribs descend due to gravity. During active expiration, contraction of the abdominal muscles increases, increasing intra-abdominal pressure, and putting upward pressure on the diaphragm. Contraction of the internal intercostal muscles will reduce the dimensions of the front and back and the right and left sides so that the ribs and sternum flatten.

This is in accordance with Boyle's law. When breathing, contraction and relaxation of muscles aims to change the volume of the thoracic cavity. Changes in lung volume will change the pressure in the lungs. Boyle's law states that the volume of a gas is inversely proportional to the pressure when the temperature is constant. As the volume of the thoracic cavity increases, the lung volume increases and the pressure in the lungs decreases.

Normal value of lung volume

The maximum mean air in the lungs is about 5.7 L (men) and 4.2 L (women). During normal breathing, the lungs do not expand maximally, and deflation is toward minimal volume. At the end of a normal expiration, the lungs still contain about 2200 mL of air. Each time you breathe at rest, about 500 mL of air is inspired and the same amount is exhaled. During maximal expiration, the lung volume will decrease to 1200 mL (men) and 1000 mL (women), but the lungs will never completely deflate.

Breathing pattern assessment

Breathing can be assessed by relaxing the patient, in a supine, sitting, standing or position that causes pain or discomfort. During the assessment the patient should be breathing normally, no instructions to take deep breaths were given during the assessment. Manual Assessment of Respiratory Motion (MARM) is a palpable method that assesses breathing patterns. MARM has been used to assess diaphragmatic function and differentiate thoracic, abdominal and lateral respiration. The MARM value is calculated by measuring the difference in the angle between the upper and lower ribcage when inhalation is normally 0 – 180°. Positive values indicate chest breathing/vertical movements and negative values indicate abdominal breathing/lateral movements.

Pursed lip breathing

Pursed lip breathing is a technique to control oxygenation and ventilation. This technique requires inspiration through the nose and expiration through the mouth in a slow, controlled flow. The

expiratory phase of respiration is longer than inspiration. This technique will put pressure on the posterior side to produce PEEP. Pursed lip breathing helps breathing by opening the airways during expiration and increasing the excretion of acid in the form of CO2 to prevent or reduce hypercapnia due to trapped CO2 in the lungs. By using purse lip breathing, it will reduce shortness of breath, decrease work of breathing, and increase gas exchange.

Diaphragmatic Breathing (DB)

Diaphragm breathing is breathing slowly and deeply through the nose using the diaphragm with minimal movement of the chest in a supine position with one hand placed on the chest and the other hand on the stomach. DB can increase antioxidant activity and reduce post-exercise oxidative stress in athletes. DB has potential as a non-pharmacological treatment for patients with stress disorders such as chronic respiratory disease. In addition, DB is effective for the management of patients with COPD, post-surgery, asthma, cardiorespiratory performance, cancer, heart failure, and anxiety disorders.

Active Cycle Breathing Technique (ABCT)

ACBT is one way to help remove sputum from the lungs. This technique consists of breath control, deep breathing and huffing. The function of ACBT is to mobilize and clean pulmonary secretions/sputum so as to help reduce the risk of lung infection, improve lung function, and increase the effectiveness of coughing.

Segmental breathing

Segmental breathing is defined as breathing that is localized and directed at one segment of the lung while the other segment remains relaxed. The segmental breathing technique plays an important role in the development of the damaged lung. The advantages are increasing aeration and expansion thereby reducing the risk of atelectasis, stimulating coughing, stimulating normal movements in the operating area thereby reducing the incidence of paradoxical breathing, and preventing panic responses in patients.

Chronic lung disease is a chronic disease of the structure of the airways and lung structures. Chronic lung diseases that can be prevented are asthma and allergies, COPD, occupational lung disease, sleep apnea and pulmonary hypertension. Chronic lung disease will interfere with the quality of life and can cause disability. Risk factors for chronic lung disease: hypertension, cigarette, hypercholesterolemia, low consumption of vegetables and fruit, overweight / obese, physical inactivity and exposure to solid fuel

Respiratory Rehabilitation

Pulmonary rehabilitation is an important treatment for someone who has chronic lung disease. According to ATS/ERS, pulmonary rehabilitation is a comprehensive intervention based on patient assessment followed by tailor-made treatment, not only limited to exercise education and behaviour change but includes designing to improve physical and psychological conditions as well as promoting long-term healthy behaviour. Based on the ATS, it is stated that there are important

components of pulmonary rehabilitation: training capacity, QoL, dyspnea, nutrition, endurance and resistance training, educational method and quality safety

Chronic Obstructive Pulmonary Disease

Respiratory techniques for patients with COPD: pursed lip breathing, deep breathing, diaphragmatic breathing, singing practice that give positive effect on SF-36 components and Yoga that can improve lung function in subjects with COPD by increasing the predicted percent FEV1. The increase in FVC in subjects with COPD after 5 minutes of PLB eating improved pulmonary function by decreasing hyperventilation.

Asthma

Breathing exercises in asthma are aimed at controlling the symptoms of hyperventilation in asthma and can be performed using the Papworth method, the Buteyko breathing technique, yoga or similar interventions that manipulate breathing patterns.

The Papworth method focuses on the use of appropriate breathing patterns to reduce hyperventilation and hyperinflation leading to an increase in CO2 levels and a decrease in the effects of hypocapnia and some of the symptoms of a potential asthma crisis. This method aims how to breathe regularly and slowly through the nose and comes from the diaphragm, besides that it aims at stress management. Several studies have shown that certain techniques can improve quality of life and reduce symptoms of shortness of breath in asthmatic patients. Steps to perform Papworth's method: slow inspiration through the nose

Then expiration using a pursed lip is like blowing out a candle. Expiration must be 2x longer than inhalation and repeated this technique 3-5 cycles.

Buteyko was developed for a more efficient respiratory pattern by using breathing control and holding the breath so that it will increase the tension of the alveolar and arterial which will improve bronchospasm, normalize breathing patterns and reduce shortness of breath.
The Buteyko steps: First Sit up straight, then relax your abdominal muscles and chest muscles as if you were taking a deep breath. Next do the Inspiration through the nose and mouth remain closed, take a deep breath Then exhale slowly until the lungs feel not filled with air. Hold the breath for as long as the patient can before return to normal breathing.

Yoga aims to reduce psychological overactivity and emotional instability, decrease vagal efferent work, increase autonomic control, decrease vagal outflow to the lungs causing bronchodilation and decrease bronchial reactivity. Yoga includes deep breathing exercises, breathing control, postures, cleansing techniques, meditation, prayer and often a change in diet can reduce asthma symptoms.

The long-term benefits of respiratory rehabilitation

The benefits of respiratory rehabilitation will diminish after 6-12 months, with QoL being maintained more than exercise capacity. The reasons for the decline that occurred were multifactorial. Decreased adherence to therapy, especially long-term regular exercise, progression of the underlying disease and comorbidities and exacerbations. Regardless of the cause, enhancing the effects of pulmonary rehabilitation is the main goal. The increase in functional exercise capacity will plateau at 12 weeks from the start of the respiratory rehabilitation program. The frequency of exercise is 2-3 days/week in outpatients and inpatients 5 days/week.

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ARE WE MANAGING COPD BETTER?

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.[1]

Globally, chronic obstructive pulmonary disease is the fourth major cause of mortality and morbidity and projected to rise to third within a decade as our efforts to prevent, identify, diagnose and treat patients at a global population level have been insufficient. Prevalence of COPD obtained mainly from epidemiological studies varies greatly depending on the clinical and spirometry criteria used to diagnose COPD, and this subsequently affects the rates of under- and over-diagnosis. Under-diagnosis was defined as those individuals with or without symptoms and chronic airflow obstruction (AFO) who were not yet diagnosed with COPD or those with presence of other comorbidities but symptoms common to COPD wrongly labelled for another disease. Overdiagnosis was defined as those who were labelled as COPD but without the associated symptoms of COPD or evidence of AFO or symptoms of other diseases labelled as COPD. Large variation COPD prevalence with 10–95% under-diagnosis and 5–60% over-diagnosis, due to:

- lack of disease awareness
- misdiagnosis
- access to healthcare
- unavailability of spirometry

Especially in rural areas of low- and middle-income countries where the prevalence of COPD is likely to be high[2].

Chronic obstructive pulmonary disease prevalence in Indonesia was 5.6% and become the 7th leading causes of death. Interestingly the prevalence of COPD in non-smoking individuals from rural and urban Indonesia was 6.9%, of which a significant proportion (94%) were previously undiagnosed[3].

THE PHYSICIAN'S VIEW

A range of relevant outcomes need to be considered in COPD.

Exacerbations of COPD are important events in the management of COPD because its negatively impact health status, rates of hospitalization, readmission, disease progression, increase costs and ultimately increase the risk of death. There is no cure for COPD, but early diagnosis and treatment are important to slow the progression of symptoms and reduce the risk of exacerbations. Up to 20% of patients with COPD require re-admission within 30 days of discharge after hospitalization for acute exacerbations of the disease significantly associated with all-cause readmission. Previous exacerbations and hospitalizations are increase costs and ultimately increase the risk of death[4.5.]

THE PATIENT'S VIEW

Treatment goals to delay the clinical course of COPD.

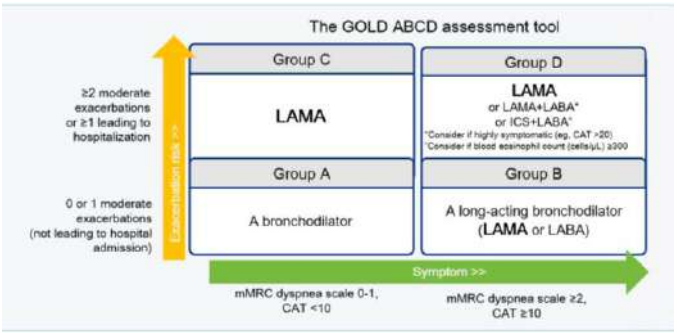
Pharmacological treatments on patient-centred outcomes such as dyspnea, exercise tolerance, exacerbations and health-related quality of life (HRQoL) patients with COPD. Effective bronchodilation reduces airflow limitation, with consequent reductions in air trapping and hyperinflation, which relieves dyspnoea and improves exercise tolerance, thereby interrupting the cycle of chronic inactivity and physical deconditioning. This ultimately leads to improvements in patients' HRQoL[6].

GOLD TREATMENT GUIDELINE[1]

Goal for treatment of stable COPD:
Relieve symptom:
- relieve Symptoms
- improve Exercise Tolerance
- improve Health Status

Reduce risk:
- prevent Disease Progression
- prevent and Treat Exacerbation
- reduce Mortality

Long acting muscarinic antagonist (LAMA) monotherapy is recommended for all COPD groups.
The initial pharmacology treatment should be based on patient's exacerbation history and reported symptoms. Long acting muscarinic antagonist (Tiotropium) is recommended in all groups of COPD.



Combination Treatment

Long acting muscarinic antagonist (LAMA) monotherapy is recommended for all COPD groups. The initial pharmacology treatment should be based on patient's exacerbation history and reported symptoms. Long acting muscarinic antagonist (Tiotropium) is recommended in all groups of COPD.

GOLD limits a combination treatment in GOLD D.
Criteria of Group D:

1. Moderate to severe exacerbations history
2. High symptoms

Long acting muscarinic antagonist monotherapy is recommended in Group D
While, combination treatment, can be given if

- **highly symptomatic (eg CAT >20) LAMA+LABA****
- **blood eosinophil count (cells/µL) ≥300 LABA+ICS**

In COPD, eosinophil counts identify patients well suited for ICS therapy.

Tiotropium has a greater effect on exacerbation reduction vs LABA

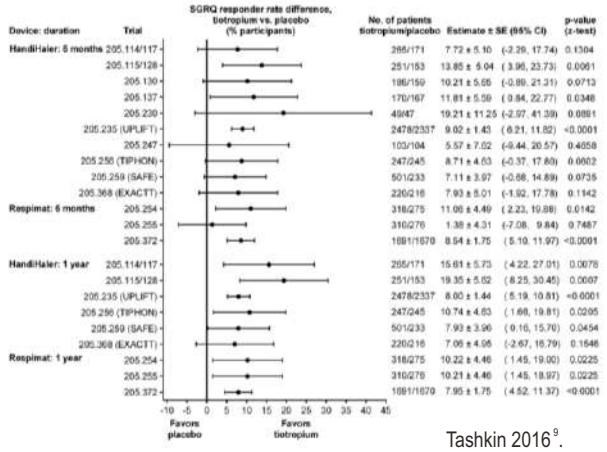
Among patients with moderate to very-severe COPD and a history of exacerbation, tiotropium was more effective than salmeterol in all the exacerbation end points that were assessed and across all major subgroups. The results of this large trial provide data on which to base the choice of long-acting bronchodilator therapy for maintenance treatment of COPD7.

Not all LAMA/LABA are better than LAMA monotherapy (Tiotropium)

Indacaterol and glycopyrronium was superior in preventing moderate to severe COPD exacerbation compared with glycopyrronium, with concomitant improvement in lung function and health status. The rate of moderate or severe exacerbations in the Indacaterol and glycopyrronium treatment group was significantly reduced by 12% compared with glycopyrronium. The 10% reduction in the rate of moderate or severe exacerbations with Indacaterol and glycopyrronium treatment compared with tiotropium was not significantly different[8].

Tiotropium consistently improve HRQoL

Tashkin 2016 have analyzed the consistency of changes in SGRQ total score observed in patients with COPD receiving tiotropium in 13 previously reported clinical trials. Tiotropium maintenance therapy significantly and consistently improved HRQoL in moderate-to-very severe COPD patients in a durable manner. These results may provide a benchmark for assessing benefits on HRQoL of other COPD treatments[9].



Tashkin 2016[9].

Tiotropium long term efficacy & safety

Long acting muscarinic antagonist monotherapy is recommended as initial treatment for GOLD groups B, C, and D. In most comparative studies of tiotropium and placebo, ipratropium, or salmeterol, tiotropium provided significantly improved lung function, exacerbation related outcomes such as reduction in the number of exacerbations/PY and exacerbation related hospitalizations, increase in the time to first exacerbation, and reduction in HCRU compared with placebo and salmeterol. In addition, tiotropium treatment improved HRQoL and significantly reduced dyspnea, need for "as-needed" SABA use, and lung hyperinflation, resulting in improvement in exertional dyspnea and exercise endurance

The long term efficacy of tiotropium was demonstrated in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial. Finally, tiotropium was comparable to ICS/LABA (fluticasone/salmeterol) in improving lung function and reducing exacerbations and had a greater effect on exacerbation rates than LABAs. Because long-term use of ICS is associated with systemic and local side effects, tiotropium is a suitable alternative to ICS/LABA combinations[10].

The soft mist inhaler (SMI) generates a low-velocity, long-duration aerosol spray with a high fine-particle fraction, which results in marked lung drug deposition. In addition, high inspiratory flow

rates are not required. Overall, tiotropium is safe and efficacious as a long term, QD LAMA for the maintenance treatment of COPD and for reducing COPD exacerbations or for the maintenance treatment of COPD as part of long term, QD, fixed-dose LAMA/LABA (tiotropium/olodaterol)[10].

In COPD, ICS is less effective and high side effect

Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) is the first large-scale trial to evaluate the impact of two different treatment approaches bronchodilatation with a long-acting inhaled anticholinergic agent or the combination of bronchodilatation using an LABA and anti-inflammatory therapy with an ICS on COPD exacerbations over a 2-year period. Of 1,499 patients screened, 1,323 were randomized and comprised the intent-to-treat population[11].

Both treatments had a similar impact on COPD exacerbation rate, but the ICS/LABA combination reduced the perceived need for systemic corticosteroids and improved health status compared with anticholinergic therapy. Antibiotics were prescribed more frequently and clinician-diagnosed pneumonia was more common in the ICS/ LABA group compared with anticholinergic therapy. Treatment with SFC and tiotropium achieved similar exacerbation rates with different mechanisms (as evidenced by the difference in use of oral corticosteroids and antibiotics to treat HCU exacerbations), and this resulted in different outcomes[11].

Delays COPD progression

TIO/OLO delays CID vs Tiotropium monotherapy in early COPD.

Post hoc analysis of data from the TONADO studies, tiotropium/olodaterol delayed the time to, and reduced the risk of, clinically important deterioration (CID) compared with tiotropium alone in the overall trial population, in patients with low exacerbation history, patients with GOLD 2 COPD and in maintenance-naıve patients. Taken together with previous studies on tiotropium/
olodaterol, LAMA/LABA combination therapy versus monotherapy, these results suggest that early treatment with tiotropium/olodaterol may be more effective than tiotropium in reducing the risk of CID in these important patient populations[12].

Real World Evidence

Tiotropium/Olodaterol was significantly more effective vs LABA/ICS.

Non-interventional, real-world study (n=61,985) showed that, in patients who initiated maintenance therapy with tiotropium/olodaterol versus LABA/ICS, irrespective of baseline eosinophil count and exacerbation history, there was a reduction in the risk of COPD exacerbations, community-acquired pneumonia and escalation to triple therapy, as well as a 54% reduction in the combined risk of any one of these events. The combined measure provides a useful and clinically relevant comparison of the two treatment options, given that the prescription of a treatment may be based on avoiding a number of possible events.[13]

Real World Evidence with in LAMA/LABAs

Not all LAMA/LABAs are the same, TIO/OLO is better than others.

Cheng 2021 reported three fixed dual long-acting bronchodilators (UME/VIL, IND/GLY, and TIO/OLO) used on patients with COPD in a Taiwanese medical centre (FEMH), significant improvement in pulmonary function parameters and symptom relief in all three medications after 12 months of treatment. Most importantly, TIO/OLO demonstrated higher therapeutic effects compared with the two other drugs, especially in the reduction of acute exacerbation. Whether this effectiveness is clinically relevant will require further well-designed randomized studies to confirm the treatment benefits[14].

Real World Evidence vs other LAMA/LABAs

TIO/OLO having lower costs & all cause healthcare's utilization

In order to guide treatment decisions, understanding the impact of different treatment choices on health outcomes and associated costs in a real-world setting is important. In a real-world setting, differences in HCRU and costs were observed between FDC LAMA + LABAs, with patients initiating TIO + OLO having lower ED visits/costs, COPD-related pharmacy fills/ costs, and all-cause pharmacy use and outpatient visits/costs than those initiating other FDC LAMA + LABAs or UMEC + VI specifically. The remaining HCRU and cost measures were not significantly different[15].

Switched LAMA or LABA or LABA/ICS to TIO/OLO

More than 80% patients achieved treatment goals with TIO/OLO.

The non-interventional study evaluated clinical control, assessed using the Clinical COPD Questionnaire (CCQ), following approximately 6 weeks of treatment with tiotropium/olodaterol in 4700 patients with COPD, mostly classified as GOLD B (51.6%) or D (42.7%) in routine clinical practice. In this study, over 80% of patients achieved therapeutic success, with an improved CCQ score seen in more than 90% of patients taking tiotropium/olodaterol. Indeed, the 0.4-point threshold in CCQ score that was used to define therapeutic success was far exceeded, with a mean change of 1.02 points overall.

Tiotropium/olodaterol also improved the general condition of the patient and reduced the use of rescue medication, with 75% of patients either satisfied or very satisfied with their treatment. Tiotropium/olodaterol was well tolerated, with a low incidence of drug-related adverse events in these typical COPD patients. Key data from this study, which evaluated treatment success with tiotropium/olodaterol in patients with COPD in a real-world setting, confirm findings from the tiotropium/olodaterol clinical trial program[16].

SUMMARY

1. There is no cure for COPD, but **early diagnosis and treatment are important** to slow the progression of symptoms and reduce the risk of exacerbations **to delay the clinical course of COPD**
2. Inhaled bronchodilators are central for COPD treatment and **LAMA (Tiotropium) is the essential for initial treatment in all COPD groups. Tiotropium has long term efficacy & safety**

   Tiotropium improves:
   - ✓ Lung function
   - ✓ Health-related quality of life
   - ✓ Exercise endurance

   Tiotropium reduced:
   - ✓ **Dyspnea**
   - ✓ **Lung hyperinflation**
   - ✓ **Exacerbations**
   - ✓ Use of rescue medication
3. **Tiotropium has a greater effect on exacerbation reduction vs LABA**
4. **Not all combinations are better than Tiotropium (LABA/ICS or LAMA/LABA)** in reducing exacerbation (Tiotropium vs Glycopyrronium /Indacaterol)
5. **Tiotropium/Olodaterol better than Tiotropium monotherapy and other LAMA/LABAs**

   Tiotropium improves:
   - ✓ delays CID vs Tiotropium monotherapy in early COPD
   - ✓ having lower costs & all cause healthcare's utilization
   - ✓ Patients are (very) satisfied with Tiotropium/Olodaterol Respimat in terms of inhaling and handling

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HOW THE PANDEMIC AND DISASTERS CHANGED US

Alexander K Ginting
Indonesia National Task Force Handling COVID-19

THE NEW EMERGING DISEASE

Covid-19 or Coronavirus Disease-2019 is an infectious disease caused by a new virus called SARS- Cov-2. This disease first identified in Wuhan, China, in the end of 2019. The virus widely spread over many countries and then in March 2020, WHO declared Covid-19 a pandemic. This disease attacks respiratory system. Covid-19 also makes people who get infected experience several symptoms. The common symptoms are fever, dry cough, and tiredness. Some also experience aches, sore throat, diarrhoea, conjunctivitis, headache, and loss of taste or smell. Meanwhile the serious symptoms are shortness of breath, chest pain, and loss of speech. However, there are many who do not experience symptoms.

It takes about 5-6 days to the symptoms to show. However, the incubation period takes 14 days. People who has mild to moderate illness usually can recover without hospitalization. Meanwhile those who experience serious symptoms have to seek medical attention. The virus spreads through the droplets when infected people sneeze or cough. Therefore, WHO gives the way to prevent infection such as washing hands regularly with soap and water, avoiding touching face, covering mouth and nose while sneezing or coughing, staying at home, refraining from smoking, and practicing physical distancing.

PRESIDENTIAL DECREE ON PANDEMIC

In Indonesia, the first case of Covid-19 reported on March 2, 2020. After WHO declaring Covid- 19 a pandemic, all the activities such as working and studying are done in homes. However, the case of novel coronavirus keeps growing. In the end of March 2020, the total case of this disease reaches 1528 cases. The President also issued regulations regarding the pandemic.

After President Joko Widodo announced that Indonesian citizens were positive for Covid 19 on March 2, 2020, the government took steps to form a Task Force for the Acceleration of Handling Covid 19 on March 13, 2020 based on Presidential Decree No. 7/2020. The Task Force for the Acceleration of Handling Covid-19 led by the Head of BNPB (Indonesian Agency for Disaster Countermeasure) namely Satgas Covid-19 Nasional. This task force involving other ministries, institutions, and government units such as the Ministry of Health, Ministry of Home Affair, the State Police, the Indonesian National Armed Force, and local governments. The Government formed this task force at the national, provincial and district/city levels.

The President Decree Perpres No. 21/2020 is issued to regulate the large-scale social restrictions or PSBB and is implemented in coordination and collaboration with various parties, in accordance with statutory provisions. The Government of Indonesia has officially extended the emergency status due to the COVID-19 pandemic through **Presidential Decree Number 24 of 2021**, which was enacted on 31 December 2021. The Presidential Decree stipulates that the COVID-19pandemic, which the WHO has declared a global pandemic, is still ongoing and has not ended in Indonesia. During the pandemic, the **Government implements economic and financial policies**, as well as special health and social measures and regulations. In order to manage, control, and/or prevent the COVID-19 pandemic and its impacts, particularly in the health, economic, and social sectors, the decree establishes that the Government may set up a policy through the establishment of a funding scheme between the Government and business entities that are engaged in financing health services and other schemes, in order to support citizens' access to health services.

THE GOVERNMENT RESPONSE

The government is evaluating the Implementation of Restrictions on Community Activities (PPKM) in all regions. PPKM in the Java-Bali and outside Java-Bali regions previously took effect on **May 23 and ended on 6 June 2022**.During this period of PPKM, many regions changed their status to level one. Eventually that level one areas in Java and Bali have increased from 11 regions to 41 regions. Along with the increase in level one, the level two regions in Java-Bali decreased from 116 regions to 86 regions. Only Pamekasan Regency has level three status.Provinces outside Java-Bali, there were also additional level one regions from 88 regions to 170 regions. The second-level regions are 196 regions, while the third-level regions are 22 regions.The government claims the data on changes in the number of regions at each PPKM level, both in Java-Bali and outside Java-Bali, shows that conditions are getting better.

In order to suppress the rate of transmission of Covid 19, the government has made policies, one of which is to limit people's mobility. Since the beginning of the covid 19 pandemic in 2020 until mid-2021, the policy of limiting community mobility began with the several terms. Large-Scale Social Restrictions (PSBB), Transitional PSBB, Enforcement of Community Activity Restrictions (PPKM), Micro-Scale PPKM, Emergency PPKM to PPKM Level 1-4 in early July 2021. According to Inmendagri No. 43/2021, the latest PPKM-level regional policies and lists in Java-Bali are valid for the next two weeks, from September 21 to October 4, 2021, which is the 10th extension of levelization 1-4 and so on will be the government's instrument in controlling Covid 19.

As of September 18, 2021, foreigners or non-Indonesian citizens are allowed to enter Indonesia as long as they have been completely vaccinated for COVID-19. This is stipulated under Minister of Law and Human Rights Regulation No. 34/2021 (or Permenkumham No. 34/2021) on the Granting of Visa and Immigration Permit During the COVID-19 Pandemic Handling Period and Towards National Economic Recovery.

THE PENTA HELIX MULTISECTORAL

The penta helix method is a form of problem solving or program development by involving parties from various sectors (Cross-sector). This method focuses on cooperation between the government and stakeholders to the community. In other words, the Penta helix method can be called a way of mutual cooperation from all parties to solve problems. The Penta helix Model as the Civil-Military Collaboration and Engagement in Indonesia Five primary objectives for establishing this task force, namely :

1. Improving national resilience in the health sector
2. Accelerating the handling of Covid-19 through synergies between ministries/agencies and local governments.
3. Increase the anticipation of developments in the escalation of the spread of Covid-19.
4. Increase the synergy of operational policymaking
5. Increase readiness and ability to prevent, detect, respond to Covid-19

Indonesia Campaigns to fight against Covid 19 , **3 M by the** community : Wearing mask, Washing hands , Physical distancing , **3 T by the government** : Tracing ,Testing, Treatment. The implementation of PSBB is regulated based on Government Regulation (PP) Number 21/2020 concerning PSBB.

The replacement of the Minister of Health at the end of 2020 also brought changes to the policy of dealing with Covid-19, as well as the functioning of the Committee for Handling Covid-19 and National Economic Recovery (KPCPEN) chaired by the Coordinating Minister for the Economy which was formed in June 2020. One of the new policies is the end of the PSBB and changes to the **Enforcement of Restrictions on Community Activities (PPKM)** which was proclaimed by the Chairman of KPCPEN on January 7, 2021 with the first phase implementation locus in Java and Bali19. The government has begun to restrict community activities due to the high number of corona cases from January 11 to 25, 2021 in Java and Bali.

Like PSBB, PPKM is also evaluated every 2 weeks and is extended by 2 weeks. The government continues to extend the PPKM validity period until April 202120. The government stated that PPKM was quite successful in halting the rate of adding Covid-19 cases. The PSBB and PPKM policies have been running for about a year and various obstacles have appeared here and there. Considering that Indonesia has never imposed a lockdown policy, automatically the success of dealing with Covid-19 is very dependent on the PPKM policy.

Quarantine is the process of reducing the risk of transmission and early identification of COVID-19 through efforts to separate individuals who are healthy or do not have COVID-19 symptoms but have a history of contact with confirmed COVID-19 patients or have a history of traveling to areas where local transmission has occurred. All close contacts / close contacts and history of traveling to infected areas.

Isolation is the process of reducing the risk of transmission through efforts to separate sick individuals who have either been confirmed by the laboratory or have symptoms of COVID-19 from

the wider community. All confirmed and suspected symptoms.

The PSBB stipulation imposes requirements such as the number of cases and/or the number of deaths due to the disease, which has increased significantly and spread rapidly to several regions and has epidemiological linkages with similar incidents in other regions or countries. Minister of Health Regulation (Permenkes) Number 9/2020 concerning PSBB Guidelines as of April 3, 2020 further regulates the elaboration of the PP , which includes:
1) School and workplace holidays;
2) Restrictions on religious activities;
3) Restrictions on activities in public places or facilities;
4) Restrictions on socio-cultural activities;
5) Restrictions on the mode of transportation; and
6) Restrictions on other activities related to defence and security aspects.

The Permenkes cites WHO standards and criteria in outlining guidelines for the prevention and control of Covid-19. In terms of implementing the PSBB policy, local governments must submit a PSBB application for their area to the Minister of Health. The first PSBB approved by the Minister of Health was in DKI Jakarta which began on April 10, 2020. The implementation of the PSBB was initially only for 14 days, but was then extended several times until the Governor of DKI Jakarta announced a transitional or easing PSBB on June 5, 2020.

PSBB Policy in DKI Jakarta then followed by West Java since April 15, 2020, Banten on April 18, 2020, and other provinces. Of the 18 regions that initially implemented PSBB (two provinces: DKI Jakarta and West Sumatra, and 16 districts/cities), as of September 10, 2020, only 7 regions were still implementing PSBB.

PSBB is an effective intervention to slow down people's mobility, directly affecting the Covid-19 reproductive rate (R). The PSBB is also considered to be able to limit the movement of the community better than the policy on the prohibition of going back and forth to the national government on April 21, 2020 or the policy for determining the status of a public health emergency which was stipulated on March 31, 2020.

However, the implementation of the PSBB is considered ineffective. One of the causes is the still mobility of a number of workers, or mobility between locations, and provinces in Java or outside Java. Until early October 2020, entering the 41st week of the pandemic, Indonesia's region's positivity rate is still relatively high, namely 13.6% or 2.7 times higher than the WHO target.

In addition, although the cumulative mortality rate seems to have decreased, until week 41 it is still relatively high (3.5%). Of all regions, apart from DKI Jakarta, which have implemented the PSBB, no one has succeeded in reducing the rate of the spread or transmission of Covid-19. In the period from June to September 2020, positive cases ofCovid-19 in Indonesia accelerated rapidly, with an additional 50,000 new cases in less than a month.

THE EMERGENCE OF NEW VARIANTS

The virus that causes COVID-19, change over time. Most changes have little to no impact on the virus' properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

WHO in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. During late 2020, the emergence of variants that posed an increased risk to global public health prompted the characterisation of specific Variants of Interest (VOIs) and Variantsof Concern (VOCs), in order to prioritise global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic.

WHO and its networks of experts are monitoring changes to the virus so that if significant amino acid substitutions are identified and inform countries and the public about any changes that may be needed to respond to the variant and prevent its spread. The established nomenclature systems for naming tracking SARS-CoV-2 genetic lineages by GISAID, Nextstrain and Pango are currently and will remain in use by scientists and in scientific research.

At the present time, this expert group convened by WHO has recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta which will be easier and more practical to be discussed by non-scientific audiences. When using this naming scheme and referring to the genomic sequence of SARS-CoV-2 identified from the first cases (December 2019), the term 'index virus' should be used.

COVID-19 VACCINATIONS

The government began its COVID-19 Vaccination Program on January 13, 2021. It is split into four phases with healthcare workers receiving the first batch of vaccines, followed by public servants and then other members of the public. The government aims to inoculate a total of 208,265,720 people by the end of the year 2021.

As of May 30, 2022, as many as 200 202 182 Indonesians have received their first vaccinations. Meanwhile, 167 330 132 people have received their second vaccination, or 5002 more than the previous day. A further 45 412 157 people have received their third or booster vaccine. For Indonesia's capital city of Jakarta, as of May 23, 2022, as many as 12,526,283 people have received their first vaccination, while 10,695,488 people have received their second vaccination. A further 3,841,538 people have gotten their third vaccine.

Indonesia is the fourth nation with the largest number of COVID-19 jabs in the world as of January 4, 2022, Indonesia has injected as many as 284,554,361 dosages of COVID-19 vaccines, just below China, India, and the United States. Indonesia will provide COVID-19 booster vaccination for free. The decision was made following a previous announcement from the President that the injection of booster vaccines to the masses would start as early as January 12, 2022.

Those eligible for the booster vaccines are citizens who have received their complete vaccination at the earliest six months before receiving the booster vaccine. The Indonesian Food and Drug Supervisory Agency (BPOM) has issued Emergency Use Authorizations (EUA) for five COVID-19 booster vaccines. The five booster vaccines are the Sinovac, Pfizer-BioNTech, AstraZeneca, Moderna and Zifivax vaccines.

INMENDAGRI AND THE LEVELIZATION PPKM

The COVID-19 Task Force has issued Circular No. 17/2022 on international travel during the COVID-19 pandemic. The Circular effectively eliminates the requirement of taking an on arrival PCR-Test when entering Indonesia for those who have received the second dose of COVID-19vaccine at least 14 (fourteen) days before departure and passing symptom and body temperature check (below 37.5° C). It should be noted that people entering Indonesia from abroad are still required to show a negative RT-PCR Test result from the country of origin that is valid for up to 2x24 hour at the time of departure

The Government have launched a mobile application that could precisely monitor those under quarantine. The application was launched to prevent a possible outbreak of the latest COVID-19 variant known as Omicron. The use of the mobile application would be strengthened in Indonesia's entry point for international travel, such as Soekarno-Hatta Airport in Banten and Batam Seaport in Riau islands

The Ministry of Home Affairs has issued Minister of Home Affairs Instruction **(Inmendagri) No. 26/2022** on the implementation of PPKM Level 3 to Level 1 in the islands of Java and Bali and **Inmendagri No. 27/2022** on the implementation of PPKM Level 3 to Level 1 in areas outside of Java and Bali. The Inmendagris stipulates the extension of the prevailing lockdown policy in Indonesia, known as PPKM, until June 6, 2022. To note, the latest regulations further relaxed a number of social restrictions, including by allowing restaurants to open until 2am. The COVID-19 Task Force has issued amendments to Circular No 16 and 17 year 2022 on domestic and international travel during the COVID-19 pandemic, respectively. Circular no. 16/2022 effectively allows children between the ages of 6 and 17 to no longer require negative Antigen test results to travel domestically. Circular No. 17/2022 added Tarempa Seaport in Riau islands to the country's list of international entry ports.

COVID-19 UPDATE JUNE 2022

The Covid-19 Handling Task Force stated that there were 342 additional positive confirmed cases of Covid-19 on Monday (6/6) and the total number is 6,057,142.There were an additional 270 cases of recovered Covid-19, bringing the total recovered cases to 5,897,022. The number of deaths increased by 7 and the total mortality number 156,622.There were 3,498 active cases of Covid-19 and in addition, there are 2,052 suspected Covid-19 cases.

The Government reported examining 68,055 specimens in the past 24 hours.The number of people who have received the first dose of Covid-19 vaccination is 200,490,260 people (96.27 %), the second dose is 167,730,074 people (80.54 %), and the third dose or booster is 46,619,169 people (22.38 %).

PANDEMIC TO ENDEMIC

Transition from pandemic to endemic cannot be decided only by a country and must be coordinated with the World Health Organization . This is a global pandemic, Indonesia cannot make decisions on its own to declare it as endemic. That there are a number of considerations in deciding the transition from a pandemic to endemic, one of which is public awareness in implementing health protocols.

The Government would gradually transfer the responsibility for maintaining health protocols to each individual. If the public already understand and well educated to follow the health protocolsas it should be, as well as already know what to do to handle the virus, these are the characteristics of a disease that has become endemic

In addition mentioned three community transmission factors that must be fulfilled for three consecutive months before deciding the transition from pandemic to endemic.
The WHO rule for community transmission consists of three factors:
1. The number of cases per 100,000
2. The number of hospitalizations per 100,000
3. The number of deaths per 100,000 which is categorized at Level 1 for three consecutive months

Furthermore, suggested that the decision to transition from pandemic to endemic could be made if the second dose of vaccination has reached 70 percent and the rate of transmission or effective reproduction is below 1. Other than being at Level 1 for three months in a row, other factors are the reproduction rate is below 1 for three months in a row, and the vaccination rate is above 70 percent for the second dose. That's what we consider from the health sector to make a transition from pandemic to endemic

Moreover that the transition is not only based on considerations of the health sector, but also economic, social and political sectors. It's not only 100 percent health considerations. There are also economic considerations, social considerations, and political considerations, namely the Head of State at the state level, or group of Heads of State at the global level

CONCLUSION

1. Penta helix is very useful to see and carry out the handling of covid-19 from all sides but this method needs to be carried out in mutual cooperation by all parties.
2. The success of the Penta helix strategy can also be applied to the prevention of COVID-19 in other countries. Learning from the experience of handling disasters, both natural and non-natural, the TNI has and will continue to play an important role in efforts to achieve global health resilience.
3. Multi-sectoral and multi-lateral cooperation is needed in the framework of global health resilience.
4. In the future there will still be storms and challenges that will be faced by Indonesia, we must always be ready .

LONG TERM EFFECT OF COVID-19: WHAT WE KNOW SO FAR RELATED TO VARIANT

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Most patients with COVID-19 infection experience mild symptoms or moderate illness. Around 10-15% patients will progress to severe disease and about 5% become critical illness. While most patients with COVID-19 recover after 2-6 weeks and return to normal health, some patients can have symptoms that last for weeks or even months after recovery from acute illness. These patients are not infectious to others during this time.[1]

There is no consensus on the definition and terminology for Long Covid. Long covid can be called long haulers, post COVID-19 syndrome, post-acute COVID-19, sequalae post-acute COVID-19, and chronic COVID syndrome. Long COVID is defined as post COVID-19 respiratory syndrome, according to Indonesian treatment guidelines for COVID-19.[2] Post COVID-19 respiratory syndrome is a symptom/lung and respiratory disorder that persist ≥ 4 weeks since onset of COVID-19 symptoms. Based on how long the symptoms occurred, there are two categories, which are acute post COVID-19 (Persistent symptom 4-12 weeks since first COVID-19) and chronic post COVID-19 (Persistent symptom 12 weeks or more since first COVID-19).[2]

Over 20,000 subjects participated in UK COVID-19 Infection Survey who tested positive for COVID-19 between 26 April 2020 and 6 March 2021. Approximately 13.7% continued to experience symptoms for at least 12 weeks.[4] The number is eight times higher than in a control group. In Indonesia, survey conducted by The Indonesian Society of Respirology (PDPI) found that in 463 patients with post-acute COVID infection, around 63,5% patients experienced Long COVID.[2]

There are some risk factors that contributes to Long COVID. For example, female have higher risk than men. The study also showed that Caucasian have more risk than other ethnicity. Patients with two or more comorbidities before acute COVID-19 infection have higher risk to experience Long COVID. Patients with high BMI also have higher risk to develop Long COVID. More severe symptoms in acute infection will also have higher risk of Long COVID.[3,4] Ages over 50 years also pose higher risk but the study is still inconclusive. In PHOSP-COVID, age have non-linear risk.[5] However, study conducted by Sudre et al[6] showed linear risk with age, and concluded that higher age has higher risk.

International Cohort Study with 3.762 respondent form 56 countries by Davis et al[7] found that most common symptoms in Long COVID are fatigue, malaise, and cognitive impairment. Survey

conducted by PDPI also found that most common symptom are fatigue, cough, myalgia, headache, insomnia, and joint pain.[2-3] Cohort Study in 1733 patient in Jin Yin-tan Hospital, Wuhan, China found in 6 months post COVID-19 experienced at least one symptom. Most common symptoms are fatigue or muscle weakness (63%, 1038/1655) and difficulty sleeping (26%, 437/1655). Anxiety or depression is found in 23% (367 /1617) patient.[8] Study by Carfi et al9 also stated that A total of 44.1% of subjects have decreased quality of life.[9] Study by Dennis et al10 found in low risk patient in COVID-19, 66% of subjects have at least one or more organ disorders due to Long COVID with the percentages for organ impairment are lung (33%), heart (32%), kidney (12%), liver (10%), and pancreas (17%).[10]

Mutations in viruses are a normal occurrence. Viruses that had genetic mutation or viral recombinant are called variants. Variants of concern in COVID-19 are when recently detected variant is known to pose higher risk to humans, both regarding transmission, virulence, and effectiveness of treatment and vaccines. The higher infection occurs in a population, the greater the chance of viral mutations.[11]

Study by Dr Michele Spinicci et al presented in European Congress of Clinical Microbiology & Infectious Diseases (ECCMID 2022, Lisbon, 23-26 April) show different long COVID symptoms related to variant. Retrospective observational study of 428 patients comparing the symptoms reported by patients infected between March and December 2020 (when the original SARS-COV-2 was dominant) with those reported by patients infected between January and April 2021 (when Alpha was the dominant variant). Results showed that when the Alpha variant was the dominant variant, the prevalence of myalgia (10%), dyspnea (42%), brain fog/mental confusion (17%), and anxiety/depression (13%) significantly increased relative to the wild-type (original, Wuhan) variant, while anosmia (2%), dysgeusia (4%), and impaired hearing (1%) were less common. When the wild-type (original, Wuhan) variant was dominant, fatigue (37%), insomnia (16%), dysgeusia (11%), and impaired hearing (5%) were all more common than with the Alpha variant. Dyspnea (33%), brain fog (10%), myalgia (4%), and anxiety/depression (6%) were less common.[12]

Another study using data from Coronavirus (COVID-19) Infection Survey (CIS) in UK show Self-reported long COVID was less common after infections compatible with the Omicron BA.1 variant than the Delta variant in double-vaccinated study participants, but more common after Omicron BA.2 than Omicron BA.1 infections in triple-vaccinated participants.[13]

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DIAGNOSIS OF LUNG MYCOSIS IN PANDEMIC ERA AND BEYOND

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Lung mycosis is fungal the infection of the lungus, usually in an immuno-compromised patients.The most frequent causative organisms are Aspergillus and Candida species and less frequently, Cryptococcus sp. Among Aspergillus sp, A. fumigatus is the most frequent, while among Candidas, the most common agent is C. albicans. According to new data from literature, however, nonfumigatus Aspergillus and nonalbicans Candida are beginning to emerge.[1]

As seen in figure 1, the underlying conditions for invasive pulmonary asper-gillosis are: hematological malignancies (57%), pulmonary diseases (19%), solid organ transplantation (11%), systemic diseases (7%), AIDS (1%) and unknown (2%).[2] Rozaliyani, in a study in Jakarta, found that pulmonary tuberculosis is the most important underlying pulmonary disease for invasive asper-gillosis, the frequency among which being 14%.[3]

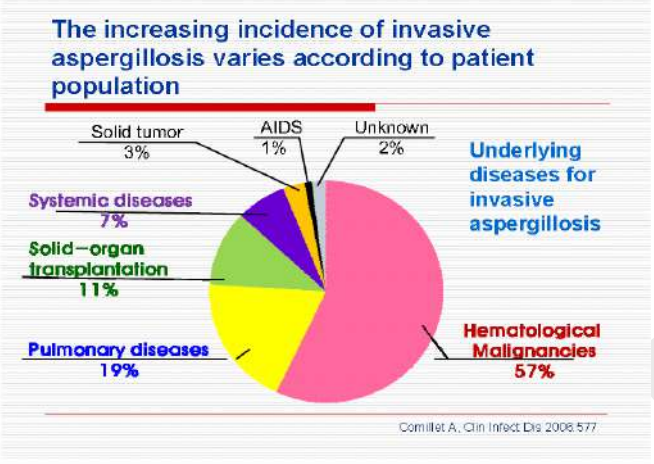

Fig 1. Underlying diseases for invasive aspergillosis (3)

Figure 2 shows the major risk factors for candidemia according to the datas from 12 hospitals in Korea. Broadspectrum antibiotic therapy, central venous catheter, total parenteral nutrition, transfusion, ICU stay, malignancy, nutropenia and surgery and neutropenia are the major risk factors for candidemia. Pulmonay candidiosis are less present, except in the very grave condition such as acute leucaemia treated with chemotherapy.

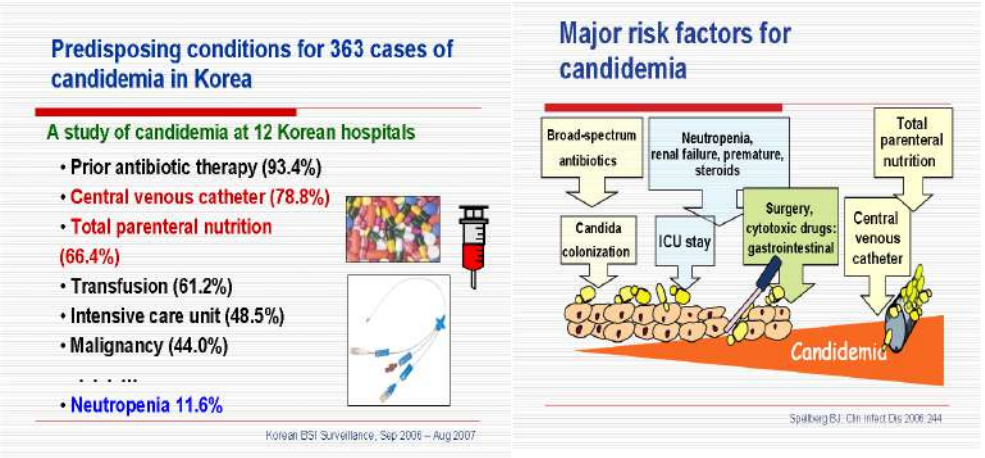

Figure 2. Predisposing major risk factors for candidemia (Sepsis due to Candida) (3)

Some fungus may occur as in a normal person, namely in the mouth, in certain places of the the skin and in genital organs. It remains as a commensal as long as the integuments are intact and healthy, but when some damage occurs, the fungus can be invasive and cause the disease. Candida is available as normal flora in the intestine. When the person has broadspectrum antibiotic or anticancer treatment, for instance, given through a central venous catheter, normal bacteria may disappear from the intestine, thus Candida may be dominant. If some injury happens to the intestinal wall, Candida may go into the blood vessel, causing candidemia and the person may show the clinical signs of sepsis.[1,4]

The diagnosis of systemic/lung mycosis may be posible, probable or proven. A proven diagnosis needs a positive culture fungus in the material derived from the affected organ, or a tissue biopsy that contains the fungus. Besides, a clinical feature of symptoms, physical findings and Xray film that shows the abnormality of the lung, plus the host factors must also be seen in the patient When histological prove is absent, the findings of clinical features plus other mycological examinations and the existance host factors, makes a probable diagnosis. The diagnosis is possible when the patient has host factor(s), clinical featues, but no mycological findings, or, the patient has host factors and positive mycological findings in the absence of clinical features (figure 3).[3,5]

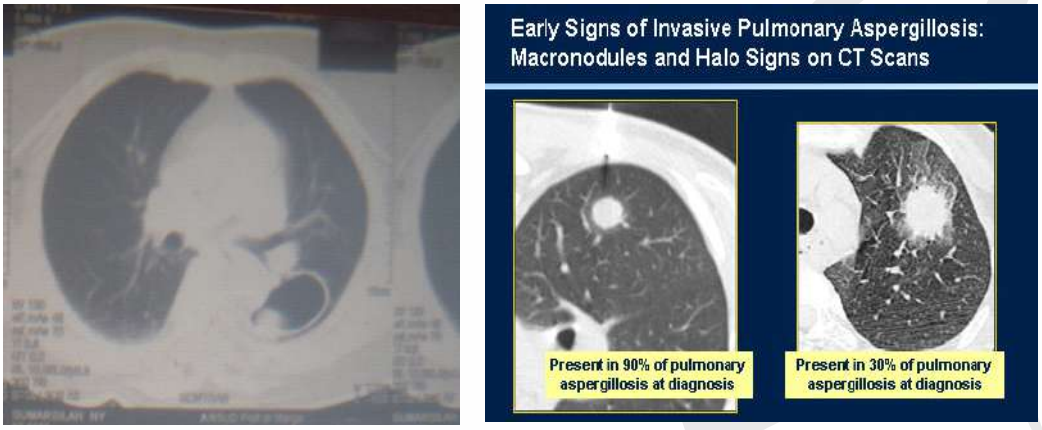

Figure 4. Pulmonary aspergillosis: fungus ball in a cavity (left) and halo signs around a macronodule in the lung (4)

Problems may occur in establishing the diagnosis of invasive pulmonary mycosis, due to several reasons:

- Symptoms and signs such as chronic cough, fever, malaise, dyspnea, wheezing, hemoptysis, resemble those of other pulmonary disorders .
- Physical findings are usually nonspecific.
  Chest X-ray features of the majority of respiratory fungal infections mimic other lung diseases,
- so it has limited value in predicting the causative organism, while still an important examination

Procedures to obtain specimens from respiratory organs for mycologic investigations are: sputum smear, blood culture and fungus marker (galactomannan etc, also from sputum), tissue biopsy or (fine) needle aspiration, bronchoscopy with brushing and/or washing, bronchial needle aspiration, transbronchial lung biopsy.[1,3] Galactomannan is a substance produced by fungus as it infiltrate the lung tissue, thus can be detected from sputum as well as from the serum. Typical spore and/or hyphae may be seen in sputum or bronchial secretions, or histologic materials. Figure 5 shows the culture and microscopic appearance of Aspegillus flavus, Candida albicans and Cryptococcus neoformans, figure 6 shows hyphae seen in a TTNA smear.[5,7]

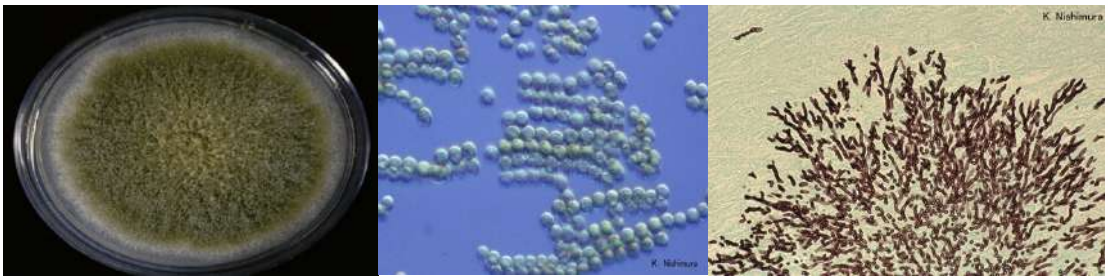

Figure 5. Culture and microscopic appearance og A, flavus (top), Candida albicans (mid) and Cryptococococcus neoformans (bottom) (5)

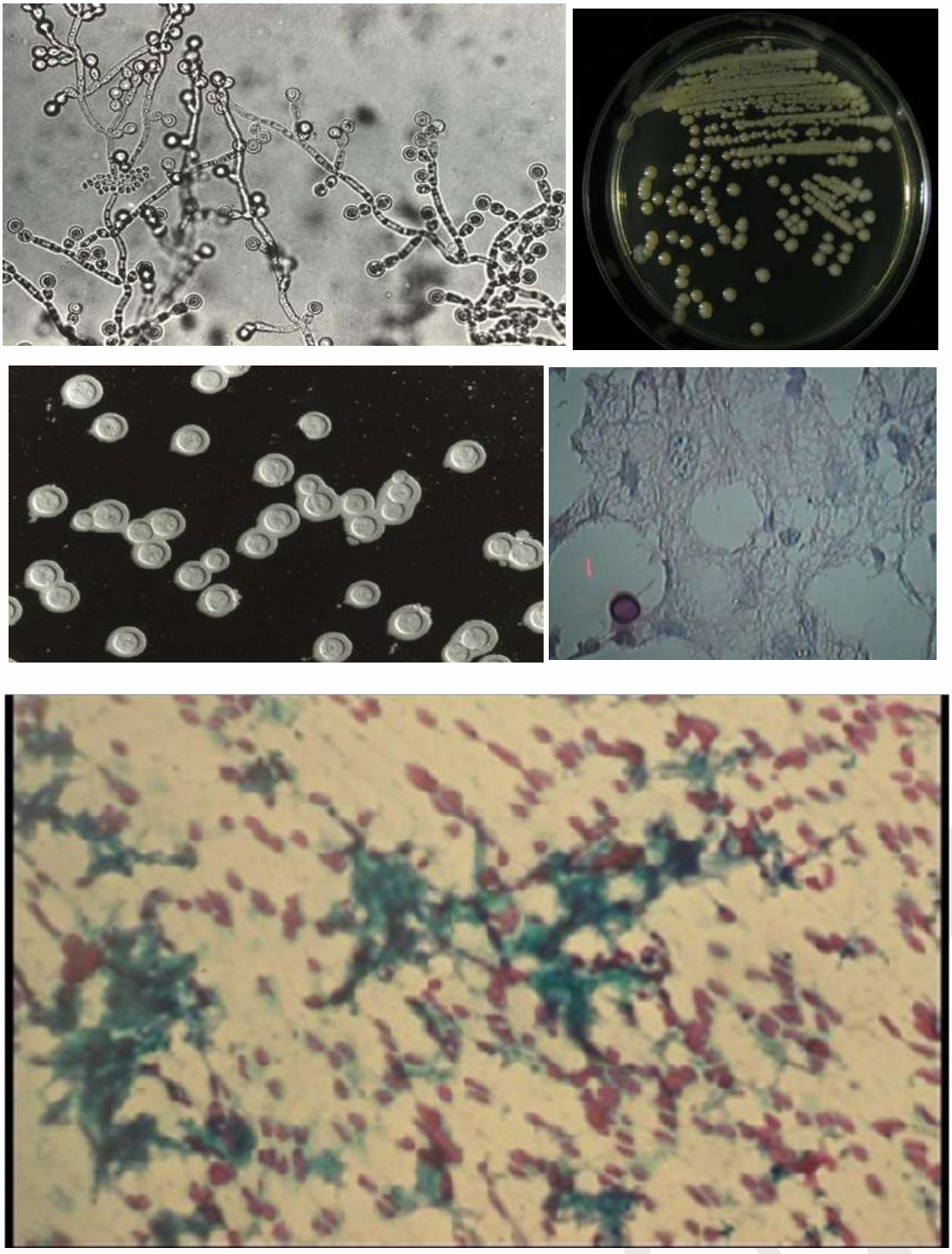

Figure 6. Hyphae of fungus (Cryptococcus) are seen in the TTNA material from a patient with cancer like appearance in thoracic CT scan,

Fortarezza el al report the incidence of histologically diagnosed CAPA in a series of 45 consecutive COVID-19 laboratory-confirmed autopsies, performed at Padova University Hospital during the first and second wave of the pandemic. Clinical data, laboratory data and radiological features were also collected for each case. Proven CAPA was detected in 9 (20%) cases, mainly in the second wave of the pandemic (7/17 vs. 2/28 of the first wave). The population of CAPA patients consisted of seven males and two females, with a median age of 74 years. Seven patients were admitted to the intensive care unit. All patients had at least two comorbidities, and concomitant lung diseases were detected in three cases.[5,6,7]

Fekkar et al found out that in patients with no underlying immune-suppression, severe SARS-CoV-2–related pneumonia seems at low risk of invasive fungal secondary infection, especially aspergillosis. Their study population included a total of 145 patients; the median age was 55 years old, most of them were male, were overweight, and had hypertension and diabetes. Few patients presented preexisting host risk factors for invasive fungal infection. Their global severity was high; all patients were on invasive mechanical ventilation, and half were on extracorporeal membrane oxygenation support. Mycological analysis included 2,815 mycological tests (culture, galactomannan, β-glucan, and PCR) performed on 475 respiratory samples and 532 sera. A probable/putative invasive pulmonary mold infection was diagnosed in 7 (4.8%) patients and linked to high mortality. Multivariate analysis indicates a significantly higher risk for solid organ transplant recipients. False-positive fungal test and clinically irrelevant colonization, which did not require the initiation of antifungal treatment, was observed in 25 patients (17.2%).[6,7,8]

The optimal diagnostic algorithm for diagnosing Covid 19 associated pulmonary aspergillosis (CAPA) is currently unknown, and this question is actively being investigated in an ongoing multinational explorative trial in conjunction with the European Confederation of Medical Mycology (ECMM). The most common methods to date include attempting to recover Aspergillus spp. on culture media of bronchoalveolar fluid (BALF) and tracheal aspirate, as well as utilizing serologic biomarker testing such as the conventional Galactomannan (GM) from BALF, tracheal aspirate, and serum specimens. Other diagnostic tests that may prove useful also include Aspergillus PCR, serum (1→3)-β-d-glucan (BDG), the Aspergillus galactomannan lateral flow assay.[5,8]

BALF and tracheal aspirate culture and conventional GM testing from BALF appear to be the most promising diagnostic modalities. Bronchoscopy can potentially aerosolize virus in patients with COVID-19 infection, thus posing a risk to patients and personnel from SARS-CoV-2 virus. In many centers, the role of bronchoscopy is limited and testing from blood samples may be safer and more optimal and allow also for twice weekly screening which has been implemented in many centers, although the low levels of GM positivity from serum in these reports is discouraging, and the sensitivity of serum BDG, which is less specific for IA, was only 44% (4/9).[7,8]

The followings are 2 case reports on systemic mycosis from The National Respiratory Center Persabatan Hospital.

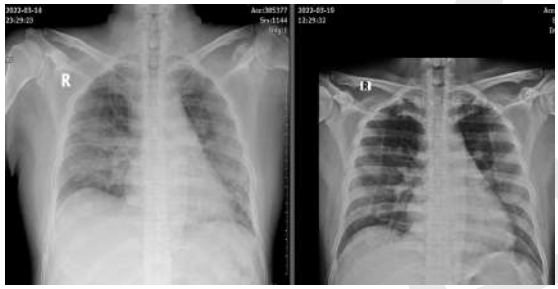

Figure 7. Xray photos of Mr.BP(Case#1), with Covid-19 pneumonia. Ground glass appearance on both lungs.

Case report #1. Mr.BP, 42 yrs, admitted to PINERE Ward Persahabatan Hospital with the diagnosis Covi19 pneumonia (severe respiratory dysfunction). His Xray picture shows infiltrate on both lungs (figure 7), his PCR swab was positive for Covid 19, probable Omicron. He also has positive HIV infection under HRV treatment and inactive lung tb. He was diagnosed as probable lung mycosis, based on clinical symptoms (which are also the symptoms of Covid 19), radiologic picture and positive spores and hyphae in sputum.

Case report #2. Mr AA, 76 yrs, with the diagnosis of Covid 19, HAP and lung cancer (histology not confirmed yet). He also has CVD ischemia, Type 2 diabetes (uncontrolled). He also developed hematuria. Chest Xray films show a big mass in the right lower lobe and ground glass appearance on both lungs. His laboratory result showed positive urine culture of Candida glabrata which was resistant to Caspofungin. So this case is a case of Covid 19 plus systemic (urinary tact) candidiasis and possible pulmonary mycosis.

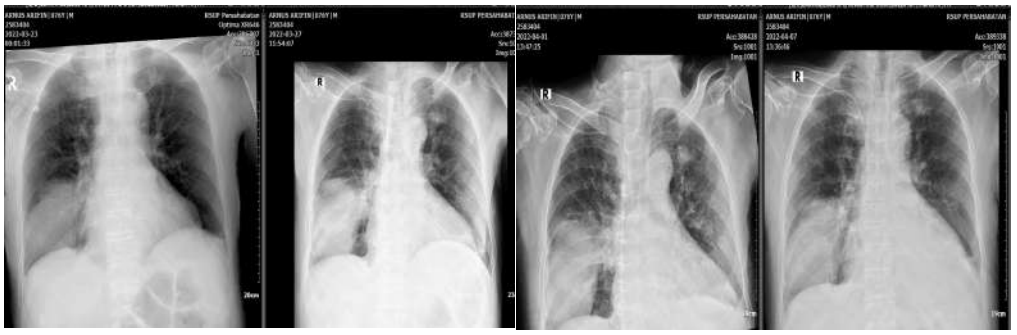

Figure 8. Chest Xray films of Mr.AA with possible lung cancer and possible pulmonary mycosis.

SUMMARY :

1. The key to early diagnosis of pulmonary mycosis is the suspicion to the possibility.
2. Must remember various predisposing factors, including Covid-19
3. Diagnosis of pulmonary mycosis can be possible, probable or proven
4. BALF and tracheal aspirate culture and conventional GM testing from BALF appear to be the most promising diagnostic modalities
5. Covid 19 is a risk faktor for lung mycosis, due to:
   a. colonisation of fungus before Covid 19
   b. as viral infection: leukopenia may occur
   c. ICU stay, total parenteral nutrition, central intravenous catheter, treatment with broadspectrum antibiotic & antiviral
   d. Severe disease and Long covid

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AWARENESS FOR COMMUNITY USE OF ANTIBOTIC

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A. EPIDEMIOLOGY OF ANTIBIOTIC

Infections caused by bacteria are a leading source of illness and death across the world. Antibiotic usage is influenced by a variety of factors. Infections caused by bacteria are a leading cause of illness and mortality. Antibiotics are one type of medicine that is effective in keeping germs from growing in the respiratory system.

1. Use of antibiotics in the worldwide

Antibiotics, along with improvements in nutrition, clean water, sanitation, and vaccination provision, have aided in the global reduction of under-5 mortality from 216 deaths per 1000 livebirths in 1950 to 39 deaths per 1000 livebirths in 2017, as well as an increase in male life expectancy from 48 to 71 years during the same time. The goals of SDG 3.8 are focused on "access to safe, effective, quality and affordable essential medicines and vaccines for all". The lack of access in some countries to the availability of antibiotics is also an indicator of increasing morbidity and mortality rates. Medicines' beneficial effects on health have been found to raise rates of antimicrobial resistance (AMR) over the world, but this becomes a concern when access to important antibiotics is limited in many low- and middle-income nations (LMICs) (Browne et al., 2021).

Antibiotic use was highest in the superregion of Central Europe, Eastern Europe, and Central Asia in 2018. The research conducted by (Browne et al., 2021) declare that the highest antibiotic median nation usage was in Ukraine that reach out 80-95%, Antibiotic usage was found to be lowest in Sub-Saharan Africa, with a median national usage of 42%. Antibiotic usage, on the other hand, was significantly greater in North Africa and the Middle East which reach to 61%. Antibiotic use in Southeast Asia was extremely varied, with a median of 51%.

Antibiotic usage was 23 defined daily doses (DDD) per 1000 people per day in Ireland during the fourth quarter of 2016, up from 20 DDD per 1000 inhabitants per day in 2009. Antibiotic usage in Ireland is in the mid range when compared to other EU nations. In response to the rising problem of antibiotic resistance, the Scientific Advisory Committee of the Irish National Disease Surveillance Centre (NDSC) was assigned in 2001 to prepare a strategy plan. It called as the Strategy for the Control of Antibiotic Resistance in Ireland (SARI), and it generated various national recommendations and advised the Irish Health Services Executive (HSE) on antimicrobial

resistance and healthcare-associated infection prevention and control, this statement is contained in the research made by (O'Connor et al., 2018).

Antibiotic use has been increased significantly in recent decades, particularly in low- and middle-income nations (LMIC). In the research made by (Al-Amin et al., 2021) , Greater morbidity and mortality due to disease, large patient volumes, a lack of diagnostic facilities, and attitudes of both patients and health care professionals are all factors that contribute to increased antibiotic usage in LMICs. The widespread usage of antibiotics in South Asia is also owing to a lack of effective medication regulation. In underdeveloped nations, acute respiratory infections (ARIs) are a leading cause of illness and mortality. In 2010, World Health Organization (WHO) estimated that 1.9 to 2.2 million children died from ARI over the world. Around 70% of these people died in Africa and Southeast Asia. Future study might be guided by the findings of the proportion of patients getting antibiotic therapy for ARI, the proportion of different kinds of antibiotics administered, and resistance to respiratory pathogens. This highlights the importance of developing regional and national AMR mitigation strategies, as well as modifying clinical practice guidelines for clinicians to guarantee the sensible use of antibiotics for ARI.

Antibiotic resistance (ABR) has been rising to seriously high levels around the world, fueled by antibiotic misuse and overuse, particularly in Vietnam. Antibiotics are widely available at pharmacies in Vietnam, and patients can easily obtain them. Around 88–97% of pharmacies offer antibiotics without a prescription, and 87 % of the public buys antibiotics without a doctor's prescription in private pharmacies. As a result, Vietnam has a high prevalence of bacterial infections as well as high levels of ABR. For example, Vietnam exhibited a high prevalence (80.7%) of erythromycin-resistant Streptococcus pneumoniae, a concerning carbapenem resistance rate (22 % and 9 %) in Klebsiella pneumoniae and Escherichia coli isolates and a high prevalence (29.5%) of hospital-acquired infections (Survey et al., 2022).

According to Malaysia's national antibiotic surveillance report, increasing resistance to Streptococcus pneumoniae, Klebsiella pneumoniae, and Salmonella typhi was discovered. Antibiotic campaigns at the national level in Malaysia should be held on a regular basis to raise awareness about antibiotics and antibiotic resistance. This form of public awareness activity is less common in private hospitals than in public hospitals, and this needs to change, thus more public awareness efforts are needed. It must be communicated (Hanish Singh et al., 2021).

2. Use of antibiotics by sociodemographic groups in the world (age, gender, level of knowledge, type of occupation, prescribing (doctor or medical officer))

According to the research conducted by (Survey et al., 2022), there are socio-demographic and knowledge aspects related with inappropriate antibiotic practices in the Vietnamese public, which can help us better understand the country's antibiotic usage and ABR. Most participants were male (56.4 %), 18–25 years old (40.4 %), from Southern Vietnam (67.1 %), well educated (93.7 %), and had health insurance (95.3 %). Higher education levels (college and above) were associated with 2.663 times higher knowledge scores than lower education levels (p 0.001). The knowledge of high-income respondents was higher than that of low-income respondents (OR = 1.555, CI 95

percent 0.835–2.910, p = 0.024). Students, non-skilled employees, skilled workers, professionals and managers, and professionals and managers all scored 0.052, 0.150, 0.732, and 0.393 times worse in practice than the jobless group (p 0.001). The findings showed that participants' occupation and level of knowledge were each significantly correlated with their practice of using antibiotics. Due to socio-demographic differences in knowledge and practice of antibiotic use.

The current study made by (Hanish Singh et al., 2021), found that literacy has a considerable impact on patients' knowledge and attitudes concerning antibiotics, and our findings are comparable to those of a prior study. The respondents average age was 36.11 years, and 50.37 % of them had a moderate understanding of antibiotics. In relation to literacy, there was a significant difference (p=0.001) in knowledge and attitude towards antibiotic use among these patients. The findings revealed that literate responders have significant knowledge of antibiotic identification (p=0.021), roles, and side effects (p=0.004). The respondents' willingness to follow the medication was substantially related to their literacy (p=0.004). Respondents have the least awareness about antibiotic course compliance and therapy cessation, which could contribute to antimicrobial resistance, according to this study.

Antibiotic misuse and overuse are reduced, which limits the spread of antibiotic resistance. According to the research conducted by (Henaine et al., 2021), age was inversely connected to higher knowledge scores (r = 0.118; P = 0.003), but no gender differences were seen (females: 12.6 versus males: 12.3; P = 0.191). However, differences in housing type (P = 0.002), educational level (P 0.001), and total household income (P 0.001) were determined to be statistically significant. A strong relationship between dwelling type and knowledge was discovered using a linear regression model. In addition, a greater knowledge index was linked to a higher income when combined with higher education. In this study, there were no significant relationships between income and age, gender, or type of housing.

Acute respiratory infections (ARIs) being the single largest reason for antibiotic use in under-5 children in Bangladesh. In the research made by (Hassan et al., 2021), Under-5 children from rural households were 60% (adjusted OR (aOR): 1.6; 95% CI 1.2 to 2.1) more likely to receive antibiotics compared with those from urban households, largely driven by prescriptions from unqualified or traditional practitioners. Private health facilities were 50% (aOR: 0.5; 95% CI 0.3 to 0.7) less likely to be sources of antibiotics compared with public health facilities and non-governmental organisations. Age of children, sex of children or household wealth had no impact on use of antibiotics.

In (Al-Shawi et al., 2018)'s study, the relationship between demographic data and knowledge of antibiotic use was investigated further using bivariant analysis. Parents having a lower educational level, children in government schools, and parents with a lower income were all linked to poorer knowledge. 52.7 % had an intermediate degree of understanding, while 13 % showed outstanding knowledge. Even among those with superior knowledge, 58.6% expected an antibiotic prescription from a doctor for acute URTI.

3. Use of antibiotics in Indonesia

Infectious illnesses are still among the top 10 diseases in Indonesia. Antibiotic prescribing, which is common in Indonesia and is not done wisely, will increase the prevalence of resistance. Antimicrobial resistance research in Indonesia (AMRIN Study) shows that 43 % of 2,494 patients had E. coli resistant to medications such ampicillin (24%), cotrimoxazole (29%), and chloramphenicol (25%). According to the findings of a study including 781 hospitalized patients, 81% of Escherichia coli strains are resistant to medicines such ampicillin (73%), cotrimoxazole (56%), chloramphenicol (4 %), ciprofloxacin (22%), and gentamicin (18%). Excessive usage of antibiotic medications, along with a long period of doctor's advice and prescriptions, is the most common cause of antibiotic drug misuse in Indonesia. According to statistics from the Ministry of Health of the Republic of Indonesia's Health Research and Development Agency, 103,860 out of 294,959 households (35.2%) in Indonesia keep pharmaceuticals for self-medication, with the proportion greatest in DKI Jakarta (56.4%) (Dirga et al., 2021).

LOS (Length of Stay) divisor formula may be used to determine the amount of antibiotics used in hospital using DDD units/100 patient-days. Antibiotics that were eventually classified based on system anatomical therapeutic chemical categorization (ATC). Quantity information on usage Antibiotics can predict drug usage rationality and irrationality. According to researcher (Dirga et al., 2021) findings, there are 19 different types of antibiotics utilized in the Internal Medicine Ward. Dr. H. Abdul Moeloek Hospital had a total value of DDD 100 patient days of 118.57 from July to December 2017. The greater the degree of usage or amount of antibiotic use, the greater the value of DDD is 100 patient days. When compared to a study conducted in one of Germany's hospitals, the total use of antibiotics in hospitals is 67.1–51.0 DDD/100 patient days. Even when compared to various studies done in several households in Indonesia, Dr.H. Abdul Moeloek of Lampung Province Hospital may state it's still high. The high DDD values of several kinds of antibiotics, which exceeded WHO DDD standards, were an early indicator of the risk of antibiotics being given or used inappropriately. The amount of antibiotics used in prescription antibiotics is to approach the concept of irrationality in antibiotic usage, on the one hand, and on the other hand.

Antibiotic resistance is on the rise across the world, owing to the overuse of antibiotics for upper respiratory tract infections. In the research made by (Ovikariani et al., 2019) , Antibiotic usage was recorded at Karangayu Health Center with a proportion of 42.3% from January to March 2019. This indicates that antibiotic use in ARI patients remains high, above the error indicator standard limit of less than 20%, as determined by puskesmas indicator instruments supplied by the Ministry of Health. In ARI, 92% were given amoxicillin antibiotics with an evaluation of the accuracy of the drug at 23%, the right patient, the right drug, and the right dose with a duration of use of antibiotics of 5 days. The use of antibiotics in ARI patients for the period January 2019-March 2019 was 42.3%.

According to research conducted by (Dewi et al., 2020) , the most widely used antibiotics from the penicillin group were amoxicillin (88.5%), with parameters for indication accuracy (100%), patient accuracy (98.5%), drug accuracy (54.2%), dose accuracy based on the frequency of administration (48.5%), and duration of administration (1.4%). This research was conducted at the Olak Kemang Health Center with a case of ARI in 2018. According to a study conducted by A, the

most widely used antibiotics from the penicillin group were amoxicillin (88.5%), with parameters for indication accuracy (100%), patient accuracy (98.5%), drug accuracy (54.2%), dose accuracy based on the frequency of administration (48.5%), and duration of administration (1.4%). This research was conducted at the Olak Kemang Health Center with a case of ARI in 2018. Amoxicillin is widely used in the treatment of respiratory tract infections because it is included in a broad-spectrum antibiotic, so for empirical therapy this antibiotic is considered effective. Amoxicillin is contraindicated if the patient is hypersensitive to penicillin. For antibiotics from different groups, but the antibacterial spectrum is almost the same as penicillin, namely erythromycin, where erythromycin cannot be given to patients who have liver disease (estolate salts) or impaired liver function and kidney failure, the same as erythromycin, the antibiotic cefadroxil should not be given to patients who are hypersensitive to cephalosporins and patients with impaired renal function.

According to a study conducted by (Rachmawati et al., 2020), the use of antibiotics in Indonesia frequently results in resistance. It has been proven that Staphylococcus aureus bacteria have developed resistance to gentamicin, tetracycline, chloramphenicol, erythromycin, oxacillin, and trimethoprim-sulfamethoxazole in Indonesia, particularly in hospitals in Surabaya and Semarang. Gentamicin, chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin, cefotaxime, and ciprofloxacin were all resistant to Escherichia coli. Antibiotic resistance because of improper usage leads to a slew of issues, including increased morbidity, mortality, and healthcare expenses. As a result, it is vital to assess the usage of antibiotics to overcome this. The ATC/DDD approach was used to assess the usage of antibiotics. It was shown that the most utilized antibiotics were cephalosporins (46.22 %) and cefotaxime (31.15%), with intravenous administration being the most common mode of administration (90.82%). While the ATC/DDD technique was used to assess the quantity of antibiotic usage, it revealed that ceftriaxone had the highest DDD/100 patient days value of 11.30 and amikacin had the lowest DDD/100 patient days value of 0.03. It is necessary to conduct qualitative research using the Gyssens method to determine the rationality of the use of antibiotics and conduct interviews with related parties to strengthen the results of the evaluation of the use of antibiotics in hospitalized pediatric patients at RSD dr. Soebandi Jember 2017.

Misuse of antibiotics has the potential to lead to treatment misdiagnosis. Many factors influence this, one of which being the Indonesians' propensity for stockpiling antibiotics. According to the findings of Basic Health Research (2013), 35.2 % of Indonesian families keep drugs for self-medication, whereas 27.8% of homes keep antibiotics. In a study conducted by (Fitriah & Mardiati, 2019) which was conducted in the Landasan Ulin Subdistrict, Banjarbaru, South Kalimantan, it was stated that according to the results of the Basic Health Research, which also showed that South Kalimantan was the second highest province in storing drugs for self-medication with a proportion of 55.5%, while for households that store antibiotics without a prescription in Kalimantan alone, it was in the third highest rank with a proportion of 90.6%. From this statement, it can be inferred that the use of antibiotics also affects sociodemographic conditions.

The use of antibiotics in Indonesia often causes resistance. This has become a problem in Indonesia, so the Ministry of Health has established a policy for the Antimicrobial Resistance

Control Program (PPRA) in Hospitals (RS). In the research conducted by (Rukmini et al., 2019), the researcher analyzed the extent to which the implementation of the PPRA policy at Dr. RSUP. Wahidin Sudirohisudo, Makassar. In this study, it was found that the PPRA Policy at the RSUP, Dr. Wahidin Sudirohusodo, has implemented it in the form of providing policy documents on the use of antibiotics and information on surveillance results, but it has not been socialized and implemented properly. The implementation of PPRA activities has not been optimal due to various program challenges, including lack of funding, commitment, and coordination with internal hospitals between the PPRA team, management, and clinicians/departments/SMF/clinical pharmacy/clinical microbiology not yet well established, program socialization and PPRA activities are still low, the high workload of the PPRA team, inadequate infrastructure, and problems with referral patients who have experienced resistance.

4. Use of antibiotics by sociodemographic groups in Indonesia (age, gender, level of knowledge, type of occupation, prescribing (doctor or medical officer))

Antibiotic usage in Indonesia is projected to have a favorable impact, such as lowering morbidity, mortality, and economic losses, as well as lowering the incidence of antibiotic resistance. (Ovikariani et al., 2019) performed a study at the Karangayu Health Center in Semarang to assess the appropriateness of antibiotic treatment in patients diagnosed with ARI. In this study, the existence or lack of contraindications in the patient was used to assess the accuracy of antibiotic usage. Amoxicillin was used in this research. Because of the advantages of amoxicillin antibiotics, such as low cost, the taste of medicines that children can take, being safe, effective, and limited spectrum antibiotics, amoxicillin antibiotics are increasingly commonly used to treat upper respiratory tract infections. In research done at the Karangayu Public Health Center in Semarang, the percentage of males (50.0%) was not significantly different from the percentage of girls (49.4%). The age of children who are vulnerable to ARI is determined by patient demographic data, which includes children aged 0 to 5. In Karangayu Health Center's ARI, 92.2% were given amoxicillin antibiotics with medication accuracy evaluation, specifically 23.6% correct indication, right patient, right drug, and right dose with antibiotic usage for 5 days (70.9%).

Antibiotics are used to treat ARI caused by bacteria. Many cases of resistance, including ARI, are caused by the misuse of antibiotics. In a study conducted by researcher (Naibobe et al., 2020) conducted at the Sikumana Health Center, it was found that the age and sex group were mostly 20-29 years old (46%) and the sex most affected by ARI was female (56%). This is related to several factors, namely the presence of dust in the room, the frequency of sweeping the house, and the use of masks when leaving the house. According to the Pill Count data from 15 randomly selected patients in the test group, two patients did not take antibiotics owing to busy work, and on the second day, the patient entered the hospital and ceased taking the drug retrieved from the puskesmas, resulting in leftover antibiotics. According to the Pill Count data in the control group, 11 of the 15 patients who were randomly selected did not take antibiotics (non-adherent) or had leftovers, while four others took antibiotics at the scheduled time (compliance). Some people discontinue taking antibiotics because their condition improves, they no longer have symptoms, and they move to conventional treatment / traditional treatment.

Antibiotic usage that is rational is predicted to improve medication efficacy while also limiting the rate of resistance. Bronchopneumonia is one of the respiratory disorders that may be treated with antibiotics. Antibiotics for bronchopneumonia should only be used when there are good and adequate reasons. If the indications aren't correct, resistance might develop, impairing the disease's healing process. It was discovered in research done by (Alaydrus, 2018) at the Central Sulawesi Provincial Hospital from January to June 2017 that pediatric patients with pneumonia at the hospital. In the Central Sulawesi Province of Palu, more cases of pneumonia in children of male sex occurred between January and June 2017. The age range of pediatric patients suffering from pneumonia was 0-11 years, and 42 patients (100%) had corrected indications, 42 patients (100%) were on the right drug, 42 patients (100%) were on the right patient, and 42 patients (100%) were on the right dose (100%). The administration of antibiotics prioritizes the third generation of cephalosporin antibiotics, namely Cefadroxil (14.29%), cefotaxime (45.24%), cefixime (21.43%) and ceftriaxone (19.04%). So that 100% rational antibiotics were obtained from a total of 42 pediatric bronchopneumonia patients aged 0-11 years at the Central Sulawesi Provincial Hospital for the period January - June 2017.

Antibiotics are the most widely used drugs in the treatment of infections caused by bacteria. Antibiotic treatment in infectious diseases aims to inhibit the growth or kill the bacteria that cause it. But in fact, antibiotics have been used widely by the Indonesian people without knowing the impact of using antibiotics that are not appropriate. According to research conducted by researcher (Nurani et al., 2019) at Syarifah Ambami Rato Ebu Bangkalan Hospital, it showed that most of the patients were female (68.9%). In terms of age, most of them are in the age range of 18-31 years (36.9%) with the last education being high school (55.3%). From the type of work dominated by private employees (39.8%), most patients earn less than Rp. 1,000,000 (54.4%) and most are married (79.6%). The researcher concluded that the patient's knowledge and beliefs had a substantial impact on antibiotic adherence. This is in line with the health belief model notion (HBM). From a demographic standpoint, there is a strong link between educational attainment and patient understanding of antibiotics. Perceived advantages (benefits of taking antibiotics) and antibiotic use adherence from the standpoint of belief.

One of the factors that influence the use of antibiotics without a prescription among the community is sociodemographic factors. In study A, which was conducted in the Landasan Ulin sub-district, Banjarbaru, South Kalimantan, Indonesia, it was stated that the age group over 30 years old began to feel that their health was not optimal so that it could lead to increased drug use. This can support the decision to do self-medication. One of the drugs that is often inappropriately used by the community through self-medication is antibiotics. Based on the data found, it shows that in the Landasan Ulin District, Banjarbaru, there are more women than men, with a total of 204 people and a percentage of 53.4%. The most respondents are those who work with a total of 195 people and a percentage of 51.0% with a job category, namely private employees, amounting to 94 people with a percentage of 24.6%. In this study, most respondents were those with the last education of high school, with a total of 204 people, and the percentage was 53.4%. The most respondents are those with an income UMP (Rp 2,651,781), with a total of 243 respondents and a percentage of 63.6%. It can be concluded that in this study, the effect on the use of antibiotics is education. This is reinforced by the large number of respondents with high school education, who indicated that the

higher a person's education level, the more rational and careful they are in choosing drugs for self-medication.

B. EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE

1. Antibiotic/antimicrobial resistance rates worldwide

Based on what was written by the Antimicrobial Resistance Collaborators, there were an estimated 495 million deaths associated with bacterial antimicrobial resistance (AMR) in 2019, including 127 million deaths attributable to bacterial AMR. At the regional level, they have estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 273 deaths per 100 000, and lowest in Australasia, at 65 deaths per 100 000. Lower respiratory infections accounted for more than 1·5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. AMR Collaborators also mentioned that the six most common pathogens for deaths associated with resistance are Escherichia coli, followed by Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. They were responsible for 929 000 deaths attributable to AMR and 357 million deaths associated with AMR in 2019.

2. Antibiotic/antimicrobial resistance rates classified by sociodemographic groups

According to a study by Narmeen Mallah in early 2022, people with low education are more susceptible to comorbidities, so they are more exposed to medicines than individuals with higher education. Education is strongly associated with socioeconomic status, especially with income. On the one hand, financially disadvantaged people regularly report forgone care, and shorten their treatment or buy fewer doses than prescribed, due to the medical cost. In addition, self-medication is most often the only available choice for people with limited financial resources, especially in countries with constrained access to health facilities. On the other hand, individuals with higher socioeconomic status, i.e., higher education, have more social networking which favors their access to unprescribed antibiotics. Moreover, they are more likely to have better economic afordability to buy and store non-reimbursed antibiotics. Tis could, at least partially, explain our findings concerning a higher misuse likelihood in European countries. Regulations to control the dispensing of antibiotics should be further enforced as more than half of the antibiotics worldwide are still dispensed without prescription. Health literacy significantly contributes to health status and medicines use. Individuals with low education level are characterized by poorer health literacy skills than those with high education. The lack of access to healthcare of less educated people also reduces their health literacy.

Cultural differences and divergence in opinions and beliefs may also influence population´s behaviours towards a specific health issue, including towards the medicines used in it. In the context of antibiotics, it was reported that in certain settings health literacy concerning antibiotic use was insuficient among highly educated people. Insuficient knowledge and misconceptions about antibiotics were also reported both in developed and developing countries. The majority of respondents who bought antibiotics without prescription ranged from age 21-30 years old (36.33%),frequency buying antibiotics 1/month (45.70%), intended for themselves (56.55%),

buying antibiotics soon after the symptoms appeared (33.70%), and intended for runny nose/flu indication (21.30%). (Dewi,2018)

C. SELF MEDICATION WITH ANTIBIOTIC

1. Reason for Self-medication with Antibiotics

Self-medication is a form of self-case which individual consumes un-prescribed medicines based of their self-recognized illness or symptoms (Sunny, et al., 2019). Self-medication may lead to serious problem especially when it comes to antibiotics. If individual consume irrational antibiotics, the main consequence of this action is antibiotics resistance. This phenomena brings out a lot of problems in the future: a burden on cost, morbidity, and mortality (Sunny, et al., 2019). This irrational antibiotics medication is influenced by human instinct to be responsible for taking care of their self, including health. People tend to manage their own health by their own way. Their habit on health is based on several factors. Shibly et al mentioned that "common reasons for self-medication practice included the symptoms of disease were too minor to be checked by a doctor, long waiting period for doctor consultation, and avoiding cost of doctor consultation". This statement is in line with studies by Muhammed et al, that most of respondents agree that self-medication with antibiotics is more convenient, cheaper, more time efficient, and based on previous successful treatment experience. On the other hand, studies of Haque et al focused on lack of a country's drug control regulation and agencies or individuals' practice of selling antibiotics without prescription. This means that people can freely buy prescription-only drugs without prescription in the counters or pharmacists. Among all of those reasons, the main root of this problem is poor knowledge of individual. Studies by Issaka concludes that knowledge plays an important role on the action of antibiotics self-medication, the less educated individual about antibiotic resistance, the more likely an individual do the self-medication for antibiotics. Therefore, this irrational usage of antibiotics problem needs to be handled by every elements of the community.

2. Socio-demography Factors of Self-medication with Antibiotics

Self-medication with antibiotics is influenced by multifactorial factors and every individual might not have the same reason on doing so. But as the times goes, antibiotics resistance case become a major problem in the global health system. There are some characteristics of individuals that can be found as the more people have this antibiotics resistance condition. First characteristic is based on gender, females are likely self-medicate with antibiotics (p-value = 0.0004) (Aslam, et al., 2020). And it is in line with previous studies by Aditya, et al that showed 76% of the respondents are female and self-medicate with antibiotics as well as studies of Elmahi, et al, 444 out of 675 respondents are females. But, these finding was different with previous studies, there is no significant relationship between gender and self-medication with antibiotics (Issaka, 2021). Other studies shows that male gender predominates female gender in the use of self-medication (Sunny, et al., 2019; Ateshim, et al., 2019).

The second characteristic is based on age. The range of individuals' age that self-medicate with antibiotics is between 18-30 years old (p= 0,001) (Shibly, et al., 2022). This finding is similar with Issaka's studies in Northern Ghana, which in the range of 25-34 years old. Other studies found the

range is between 31-60 years old (p= 0.001). But this is completely contrast with studies of Aditya, et al. and Aslam, et al, their studies reported that there is no significant relationship between age and self-medicate with antibiotics action.
The third characteristic is individual's monthly income. Since most of research states that self-medicate is cost effective or cheaper. The monthly income is less than Rp. 2.500.000 (Kurniawan, et al., 2017). Or even less Rp. 1.381.700 (Aditya, et al., 2017). Those numbers are categorized as low income in Indonesia. Other studies shows the same conclusion, but only with different currency.

The forth characteristic is level of education. Individual who self-medicates with antibiotics is associated with senior high school graduated (Kurniawan, et al., 2017).But Ateshim, et al found self-medicated with antibiotics individuals more into collage graduated individuals or even studies by Aslma, et al., shows that mostly are post graduated individuals. Those statements are totally contrast with the findings of there is no significant relationship between level of education and this irrational use of antibiotics (Shibly, et al., 2022; Aditya, et al., 2021).

3. Prevention of Self-medication with Antibiotics

Most published journals have the same statement that antibiotics can be dispensed by pharmacists or pharmacy auxiliaries (Kurniawan, et al., 2017; Ekambi, et al., 2019). When one's dispensing medicines, pharmacists have responsible to explain the drugs as it's the best way prevent any self-medicating with antibiotic. But reality it's not always as it's supposed to be. “78% of dispensers were the pharmacy assistants, This can be explained by the fact that pharmacists have other activities outside the pharmacy and that the profession no longer requires their permanent presence for the extemporaneous preparation of medicines” (Ekambi, et al., 2019).Furthermore, some drug stores or pharmacy auxiliaries don't obey the rule of selling prescript-only medicines for the one who has prescription from the physicians. Indonesia has the law governing the sale of medicines and categories of medicine which one can be bought without prescription. But, the implementation in community is as expected. The legal enforcement should be more maximized because legal enforcement alone cannot reduce self-medication.

Every healthcare provider is responsible for public health. The main focus of public health is primary prevention which is health promotion and specific treatment which leads to mass education or private counselling. Studies proved that insufficient knowledge about antibiotics and antibiotic resistance among individuals caused by poor education and counselling that is provided by the healthcare providers (Alhomoud, et al., 2018). Doctors, where by patient can get prescription, must explain every detail about the medication of the patient, especially the adverse effects and consequences of self-medication practice (Sunny, et al., 2019). The urge of antibiotic resistance high prevalence can be a reason for planning further multifaced educational program such as bringing up 'bad impact of self-medication with antibiotics' topic as mass campaign or even further publication to improve public knowledge about antibiotics and to raise public awareness of antibiotic resistance so that the increase of antibiotic resistance can be prevented (Kurniawan, et al., 2017).

Lastly, one of individual's characteristics of self-medication with antibiotics is low income family. This problem only can be solved by improving each country's health regulation or universal health coverage policy. Every country must ensure the citizen especially the one who couldn't afford and cover health care cost to get free and optimal medical services (Shibly, et al., 2022).

D. WIDELY USED ANTIBIOTIK

1. Types of antibiotics that are widely used

The most common lung diseases in the world and in Indonesia are Chronic Respiratory Diseases (CRDs) known as main public health problems that causes morbidity and mortality, which includes Chronic Obstructive Pulmonary Disease (COPD), asthma, pulmonary sarcoidosis, interstitial lung disease, and pneumoconiosis. The highest risk factors were recognized and consist of tobacco use, exposure to pollution, allergens, unhealthy diet, weight problems, and the other factors. Globally, the entire variety of CRD cases were elevated by 39.5% since 1970 until 2017. Big percentage was attributed to COPD and asthma. From 1990 to 2017 COPD became the most frequent CRD, predicted for 54.9% of all CRDs cases (Xie et al, 2020).

There are several groups of antibiotics used by patients. The most common used antibiotics is the cephalosporin groups around 51.41%. Cephalosporin antibiotics given to patients includes ceftriaxone, cefadroxil, cefazolin, cefuroxime, cefixime, cefotaxime, and ceftazidime. This groups of antibiotics is the most widely used compared to other antibiotics. Cefriaxon commonly used for infectious diseases such as diabetic foot wound infections, sepsis, etc. This condition caused by Streptococcus sp. And Staphylococcus aureus. Ceftriaxone considered as a broad spectrum antibiotics that commonly used in the hospital (Rahmawati et al, 2020).

In the other side, there are 10 groups of antibiotics used for treatment of pediatric patients. The most broadly prescribed antibiotics have been cephalosphorins (46.23%). In comparison to 2016 study, the most often used antibiotics no longer change, it is the cephalosporin groups. Similar study at Panembahan Senopati Hospital Bantul Yogyakarta confirmed that the maximum antibiotics used for treatment have been cephalosporins (59.8%). In additional, cephalosporins are category of antibiotics for empiric treatment (treatment for sickness of unknown causes, without laboratory evidence, and usually given for primary treatment. The broadly prescribed antibiotics turned into cefotaxime (31.15%). Cefotaxime is the most common used for pneumonia. Cefotaxime is a 3rd generation of cephalosporin (Rachmawati et al, 2020).

The most commonly used antibiotics group in research is the 3rd generation of cephalosporin for 90.48%. The 3rd generation cephalosporin is a broad spectrum antibiotics and usually used as a empiric treatment. In research, the most popular cephalosporin antibiotics is ceftriaxone for 63 from 114 antibiotics (55.26%). The use of ceftriaxone in children should be avoid because this antibiotics is highly bound to protein (85-90%). It can replace the bilirubin binding with the proteins. Monitoring and maintaining the bilirubin levels in children should be done regularly to prevent a significant increase in bilirubin levels (Monica et al, 2018).

Based on a study by Suharjono et al. (2009) the most widely used antibiotics are the third generation of cephalosporin and penicillin. These two groups of antibiotics is a wide spectrum that has a good effect against gram-negative bacteria, gram-positive bacteria and S. Pneumonia actively. In the other hand, research by Fendinu Grojo et al. (2011) has proven that the most common used antibiotics in district hospital in Purbalingga in 2009 is ampicillin. Ampicillin is an antibiotics in penicillin groups. it has a bactericidal by inhibiting the cell wall synthesis. This antibiotics is suitable for therapeutic use Pneumonia. In other research, Pingkan et al. (2014) shown that common used antibiotics in pediatric pneumonia patient in Manado Hospital is a combination between ceftriaxone and gentamicin. Most widely used antibiotics in various hospitals shown that beta lactams such as antibiotics from penicillin groups (ampicillin and amoxicillin) and the 3rd generation cephalosporin (Pratiwi et al, 2020).

In Saint. Carolus Bengkulu shown that the common used antibiotics treatment for patients diagnosed with ARI is Cefadroxil (60%), Amoxicillin (36%), Erythromycin (3%), and combination of TMP (Trimethoprim) and SMZ (Sulfamethoxazole) (1%). Most treatment used cefadroxil because this antibiotics is a secondary line id there is an allergies with penicillin groups. erythromycin shown as a second line drug if resistant to penicillin and it is the first choice for pneumonia treatment. Cotrimoxazole is used for infectious airways diseases (bronchitis) and a high dosage for prevention of pneumonia in AIDS patients (Rikomah et al, 2018).

2. Antibiotics used in lung diseases

Antibiotics therapy is purposed to eradicated the pathogens that cause infectious diseases. Empirical antibiotics therapy is very important to reduce morbidity and mortality as soon as possible after the disease confirmed (Farida et al, 2020). Antibiotics are used for exacerbations COPD that caused by a viral or bacterial infection. The treatment of antibiotics should be started when at least two of the following symptoms: increase dyspnea, sputum volume, and suppurayion of sputum. Macrolide antibiotics as a first line has been shown to have anti-inflammatory effects of COPD patients. More specifically, azithromycin has been shown to improve phagocytic function of lung macrophages, and it has a strong anti-inflammatory effect. Meanwhile, using 4th generation cephalosporin included in drug selection inappropriate for COPD (cefepime and cefpirome). It is the last line selection to use 4th group cephalosporin in complex exacerbations with high risks by the pseudomonas aeruginosa (Zulkarni et al, 2019).

Combination of levofloxacin antibiotics and dexamethasone or with the use of methylprednisolone has a high risk that the tendons will become inflamed or ruptured. This worst case can occur in patients who use it continuously. Erythromycin increases dexamethasone circulation levels. With the side effect of wight gain, swelling, increased blood pressure, increased blood sugar, weakness, decreased bone density, and menstrual disorders. The use of dexamethasone also can affect childrens, they will ecounter impaired physical growth. Pharmacokinetic show that dexamethasone induces enzymes CYP3A4 that plays an important role in erythromycin metabolism. It can causes a decrease in the level of erythromycin in the blood. The combination of this two can induce bacterial resistance to erythromycin. Administration of erythromycin to COPD patients actually increases the sensitivity of corticosteroids (Alaydrus, 2020).

There were 5 cases of karya Medika I that use antibiotics for in patient with COPD. The most common used antibiotics are azithromycin and cefixime. Lefofloxacin was found in only 1 case (Muriyanto et al, 2022). Drug most used in the prescribed are cefotaxime in 16 patients (53.33%) and gentamicin in 14 patients (46.66%). The 3rd generation cephalosporin is widely used because it has a broad spectrum which can be used for treatment for pneumonia that has unknown cause. Cefotaxime has an active effect against gram negative bacteria and active on causative Streptococcus pneumoniae compared to other cephalosporin (Musdalipah et al 2018).

In Madiun Hospital, East Java, ceftriaxone is the leading antibiotic used in patients with pneumonia. Pneumonia that caused by Pseudomonas aeruginosa resistant to ceftriaxone, but other bacteria such as Klebsiellapneumoniae are still showed a sensitivity of 33.33%. In regional Referral Hospital in Surakarta shown that ceftriaxone is also an antibiotic that most empirically prescribed for adult pneumonia pastients. Highly resistant antibiotics are macrolides, eruthromycin and azithromycin. Overall, most pastient received monotherapy with levofloxacin (38.2%). It such an empirical treatment for pneumonia in hospitalized patients. Levofloxacin is a high fluoroquinolone respiratory antibiotics that recommended with a high level of evidence. The most common combination of antibiotics are ceftriaxone and azithromycin (8.2%). Beta antibiotics can be used to treat adult such as ceftriaxone combined with macrolides such as azithromycin. This two is effective as levofloxacine as a singular therapy. Ceftriaxone has a bactericidal effect by inhibiting mucopeptide synthesis bacterial cell wall. Azithromycin is effective against a large number of microorganism includes gram positive cocci, anaerobic bacteria, and atypical pathogens. Levofloxacin is available in the following dosage: tablets: 250mg, 500mg, and 750mg, syrup solution: 25mg/mL, intravenous: 250mg/50mL, 500 mg/100mL, 750mg/150mL (Farida et al, 2020)

E. STRATEGIC AND MONITORING OF ANTIBIOTIC USE

The strategic and monitoring of antibiotic use are adequate awareness, regulatory environment, enabling social structure, and incentives material or emotional. The urge of antibiotic resistance high prevalence can be a reason for planning further multifaced educational program such as bringing up 'bad impact of self-medication with antibiotics' topic as mass campaign or even further publication to improve public knowledge about antibiotics and to raise public awareness of antibiotic resistance. Every country must ensure the citizen especially the one who couldn't afford and cover health care cost to get free and optimal medical services.

According to Abdel-Qader, there's a UK study that showed how the people in poor areas are less knowledgeable on antibiotic usage compared to those in affluent areas. Another UK study showed that 38% of the public thought antibiotics are effective against most types of cough or colds and 43% did not know that antibiotics have an effect on normal flora. Participants from a study conducted in Sweden were confused about the difference between viruses and bacteria and around 20% of them thought that antibiotics cure common colds. In Italy, only 9.8% of the public defined AR accurately and based on the study, predictors for taking antibiotics without a prescription were found to be age, and the belief that antibiotics are indicated for treating common

cold. In a study conducted in Malaysia, the majority confused viral and bacterial infections and they did not know that antibiotics are not effective against common cold. However, in a study conducted in Hongkong showed another result, it showed adequate knowledge and appropriate behaviour regarding antibiotics use. In the Arab world, around two thirds of the Jordanian community thought that antibiotics treat common cold and cough, and around half of participants in Kuwait had low knowledge on use of antibiotics and AR.

According to Thuy Van Ha, antibiotic resistance (AR) is driven by many factors including low quality of antibiotics and improper use of antibiotics (including self medication). They also said an inappropriate antibiotic use is the primary cause of antibiotic resistance (AR). Self-medication, which refers to the use of any medical products without a prescription or following unprofessional recommendations in treating any illnesses, is particularly leading to the AR. Self-medication practice possibly raises incorrect drug selection, drug resistance, uncontrolled adverse effects or drug reactions, misdiagnosis, and delay in medical care. Self-medication is a common phenomenon, and the prevalence varies from 12.7% to 18% in Spain, 32% to 45.4% in China, 53% in Mexico, and 75% in the United Kingdom and Chile. Also, the excessive antibiotic utilization in the agriculture sector causes the pool of AR bacteria in the animals, which are then transferred to the human through consuming food from these animals. It is estimated that, in 2050, there will be more than 10 million deaths and 100 trillion USD lost due to AR if no substantial actions have been made to eliminate this emerging threat.

It is evidenced that public awareness about AR is insufficient even in wealthy countries, and it is more severe in low- and middle-income countries, where antibiotic use without a prescription is prevalent. A recent survey conducted by the World Health Organization indicated that most of the respondents in developing countries believed that antibiotics could be used to treat viral infections. This problem is driven by many factors such as low quality of antibiotics and improper use of antibiotics (including self-medication).

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ROLE OF PHYSICAL ACTIVITY AND EXERCISE IN ASTHMA ATHLETE: OPTIMIZING THE CARDIORESPIRATORY FUNCTION

L. Grace Tumbelaka

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Asthma symptoms can be provoked or worsened by exercise that is known as exercise-induced bronchoconstriction (EIB). This situation reduces physical activity and participation in sports and leads to cardiorespiratory dysfunction. The persistence of the poor condition leads to less intense physical activity and worsening exercise tolerance and asthma symptoms. However apart from concerns for the occurrence of EIB, studies on exercise training for asthmatic athlete, reveal that increases in cardiorespiratory endurance and work capacity and decreased exercise dyspnoea, but little or no effect on resting pulmonary functions.

Many recent randomized controlled studies have demonstrated that exercise training can reduce airway inflammation, asthma severity, the number of symptom days, the number of visits to the emergency room, anxiety and depression symptoms, and also improves health-related quality of life. A systematic review conclude that physical training improved cardiopulmonary fitness as measured by a statistically and clinically significant increase in maximum oxygen uptake (MD 5.57 mL/kg/min; 95% confidence interval (CI) 4.36 to 6.78; six studies on 149 participants) and maximum expiratory ventilation (6.0 L/min, 95% CI 1.57 to 10.43; four studies on 111 participants) with no significant effect on resting lung function.

According to the researches, approximately 10-20% of professional athletes are asthmatic. It can be claimed that most asthmatic athletes won medals in the summer olympics of 1984-1996 and in the winter of 1998, as evidence that asthma does not prevent sports activities. It should be noted that despite asthma, athletes such as David Beckham (football), Dennis Rodman (basketball), Justine Henin (tennis), Paula Radcliffe (marathon), have gained international fame in their sports branches. It is undeniable that the elite athletes have good cardiorespiratory fitness.

To achieve optimal benefits from exercise and prevent the occurrence of EIB it is necessary to notice special considerations for asthmatic individuals as follows: (a) individuals who experience exacerbations in their asthma should not exercise until their symptoms and respiratory functions improve, (b) use of short-acting bronchodilators may be necessary before or after exercise to

prevent or treat EIB, (c) warm-ups before exercise increases bronchial blood flow and helps to keep the airways moist, (d) exercise should be limited in cold environments or in the environment with airborne allergens or pollutants to avoid triggering bronchoconstriction in susceptible individuals and (f) exercise-induced bronchoconstriction can be triggered by long exercise times or high-intensity exercise session. It should be noted that in the use of bronchodilators have to consider the latest world anti-doping code prohibited list.

Exercise training is generally well tolerated in asthmatic individuals successfully managed with pharmacotherapy when trigger to bronchoconstriction (cold or dry air, are pollutants, allergen) are removed to bring about symptom relief. Exercise recommendation by American College of Sports Medicine (ACSM) for asthmatic individuals is as follows: aerobic exercise frequency minimally 3 days a week up to 5 days a week. Intensity begin with moderate (40%-59% HRR or VO2R) if well tolerated, progress to 60-70% HRR or VO2R after 1 month. Time progressively increase to at least 30-40 minute a day and type of exercise aerobic activities using large muscle groups.

The conclusions are (a) exercise training can improve cardiopulmonary fitness (VO2max and VEmax) and was well tolerated among individuals with asthma, (b) people with stable asthma should be encouraged to partake in regular exercise training without fear symptom exacerbation and (c) to achieve optimal benefits from exercise and prevent the occurrence of EIB it is necessary to note the special considerations exercises for asthmatics individuals.

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THE ROLE OF COMBINATION VITAMIN AND IMMUNOMODULATOR IN RESPIRATORY INFECTION

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ABSTRACT
The main functions of body's immune system are to protect the host against infection from pathological microorganisms, to clear damaged tissues, and to provide constant surveillance of malignant cells that grow within the body. Nutrition as a modifiable factor in impacting immune function has been studied for several decades. Combinations of drugs, micronutrients, or herbs are common. Combination supplementation of Echinacea purpurea, black elderberry, zinc, pureway C, and vitamin D3 can be given for prevention and adjuvant therapy in respiratory tract infections due to bacteria/viruses such as the common cold, influenza, COVID-19 without symptoms or mild symptoms and long-term COVID-19. Administration as adjuvant therapy when infection occurs can be done according to the doctor's recommendation. This review may present a detailed perspective related the combination and its advantage to human immune system and prevent COVID-19 morbidity and mortality.

Keywords : immune system, vitamin, immunomodulator

1. Introduction

The immune system fights germs and foreign substances on the skin, in the tissues of the body and in bodily fluids such as blood. The immune system is made up of two parts: the innate, (general) immune system and the adaptive (specialized) immune system. These two systems work closely together and take on different tasks. The innate immune system is the body's first line of defense against germs entering the body. It responds in the same way to all germs and foreign substances, which is why it is sometimes referred to as the "nonspecific" immune system. It acts very quickly: For instance, it makes sure that bacteria that have entered the skin through a small wound are detected and destroyed on the spot within a few hours. The innate immune system has only limited power to stop germs from spreading, though. The innate immune system consists of protection offered by the skin and mucous membranes and protection offered by the immune system cells (defense cells) and proteins. When a part of the skin is infected, immune system cells move to the area or immune system cells that are already there are activated. Specific immune system cells release substances into the immediate area that make the blood vessels wider and more permeable. This causes the area around the infection to swell, heat up and redden, and inflammation results. A fever may develop as well. Then the blood vessels expand further and even more immune system cells arrive .

Bacteria or viruses that enter the body can be stopped right away by scavenger cells (phagocytes). Scavenger cells are special kinds of white blood cells (leukocytes). These cells enclose germs and "digest" them. The remains of these germs move to the surface of the scavenger cells to be detected by the adaptive immune system. Several proteins (enzymes) help the cells of the innate immune system. The natural killer cells are the third major part of the innate immune system. They specialize in identifying cells that are infected by a virus or that have become tumorous. To do this, they search for cells that have changes in their surface, and then destroy the cell surface using cell toxins[1].

The adaptive immune system takes over if the innate immune system is not able to destroy the germs. It specifically targets the type of germ that is causing the infection. But to do that it first needs to identify the germ. This means that it is slower to respond than the innate immune system, but when it does it is more accurate. It also has the advantage of being able to "remember" germs, so the next time a known germ is encountered, the adaptive immune system can respond faster. The adaptive immune system is made up of T lymphocytes in the tissue between the body's cells and B lymphocytes, that also found in the tissue between the body's cells. T cells have three main jobs, first they use chemical messengers to activate other immune system cells in order to start the adaptive immune system (T helper cells), they detect cells infected by viruses or tumorous cells and destroy them (cytotoxic T cells), and some T helper cells become memory T cells after the infection has been defeated. They can "remember" which germs were defeated and are then ready to activate the adapted immune system quickly if there is another infection. The B cells are activated by the T helper cells: T helper cells contact B cells that match the same germs that they do. This activates the B cells to multiply and to transform themselves into plasma cells. These plasma cells quickly produce very large amounts of antibodies and release them into the blood. Because only the B cells that match the attacking germs are activated, only the exact antibodies that are needed will be produced[1].

2. Immunomodulators in Respiratory Tract Infection

The concept of immunomodulation was first discovered in 1976 in the business of making small pox vaccines with the mechanism of certain infectious agents being weakened so that they can increase the human immune system to fight subsequent infections with the same infectious agent. The immune system will continue to try to maintain its homeostasis, but in everyday life, the body continues to be exposed to pathogens so that it often causes chronic stress, disease, which adversely affects the immune system. With the invention of antibiotics and conventional chemotherapy, homeostasis can be restored, but the use of chemicals as medicine has further detrimental effects on the immune system. Considering the increasing awareness about the side effects of chemotherapy, the use of phytomedicines has increased rapidly in recent decades. Prophylactic and treatment modalities with "Phytomedicin" and natural immunomodulators offer a safer alternative[2].

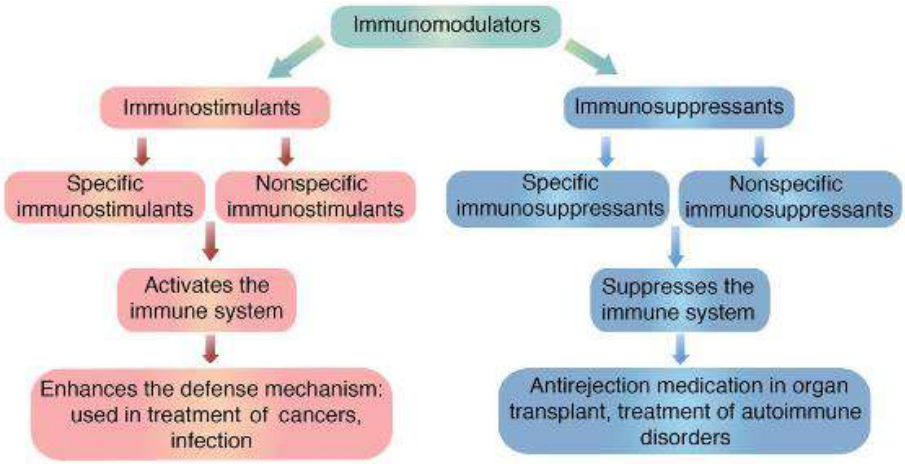

Figure 1. An overview of the action of immunomodulators[3]

Immunomodulators are drugs that can restore and repair the immune system whose function is impaired or suppress the immune system that is excessive. The function of immunomodulatory is to improve the immune system by stimulating (immunostimulants) or suppressing/normalizing excess immune reactions (immunosuppressants). Based on their effect on immune system, these agents are categorized as a "suppressor," or a "stimulant," or an "adjuvant." In autoimmune disorders, a hyperactive immune system fails to recognize self from non-self and leads to the destruction of self-entities. Here, immunosuppressors play a pivotal role in suppressing the immune system to restore normalcy. Immunostimulators are used to replenish the deficiency in the immune system and Immunoadjuvants on the other hand can enhance the efficacy of vaccines, for example, Freud's adjuvant. Immunomodulators can modulate various celular events such as apoptosis, protein synthesis, antigen presentation, etc. and target various transcription factors and immune mediators Attempts are being made to generate adjuvants that would enable eliciting selective immune responses such as cellular or humoral, as well as IgE or IgG response[4].

3. Natural Immunomodulator Agent

Plants have been used for the prevention and cure of various diseases. According to the World Health Organization (WHO), about three quarters of the world's population relies on herbal medicines.[5] Plant immunomodulators play an important role in the treatment of infection, inflammation, and immunodeficiency.[6] with their effects on various cells through cytokines and interleukins. The mode of action can be as an immunostimulator, immunosuppressant, or immunoadjuvant.[7] To enhance the antigen-specific immune response. Phytoimmunomodulatory agents can increase the body's immune-responsiveness against pathogens by activating the immune system in a specific or a non-specific manner that includes both the innate and adaptive immune systems.

1. Echinacea Sp

Echinacea purpurea (L.) Moench is one of the most important and well-known medicinal plants in the world, belonging to the Asteraceae (Compositae) family.[8] Echinacea plants have traditionally been used in North America for the prevention and treatment of cold and flu symptoms and are now one of the most widely used medical plants in both North America and Europe.[9] Some species of the Echinacea genus including E. angustifolia, E. pallida, and E. purpurea were reviewed in previous papers.[10]

The plant is the most widely cultivated medicinal plant in this species, which has been mainly used in chemo-preventive and chemotherapy for infectious diseases in both upper and lower respiratory systems.[11] Alkamides, caffeic acid derivatives, and polysaccharides have been considered important constituents of the plant. A number of studies revealed that alkamides are involved in the immunomodulatory properties of Echinacea extracts in vitro and in vivo.

In 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in human populations. The virus proved to be transmissible between humans and led to a global pandemic of coronavirus disease 2019 (COVID-19). In COVID-19, cytokine storm can lead to ARDS which carries a 40 % mortality rate. Cytokines associated with cytokine storm include pro-inflammatory inter- leukin (IL)-6, IL-8, IL-1B, IL-12 and tumor necrosis factor (TNF)α, while other cytokines, such as IL-10, have established anti- inflammatory effects and a role in downregulating excessive immune activity. In COVID-19 specifically, cytokine storm is a significant factor in driving a more severe clinical course with patients requiring Intensive Care Unit admission showing higher levels of cytokines TNFα and IL-6. The public has sought various alternative and complementary therapies to support prevention and treatment of COVID-19. Therefore, a number of studies have tried to find the effect of echinacea on respiratory infections. Aucoin et al, find that with respect to the impact of Echinacea on cytokine levels, the majority of evidence suggests a decrease in levels of pro-inflammatory cytokines associated with cytokine storm.

While the potential for Echinacea to provide a clinical therapeutic benefit is speculative, animal studies using pharmaceuticals that decrease production of IL-1α, IL-6 and TNFα cytokines have increased survival of mice infected with severe influenza. And five study reported statistically significant reductions in symptom severity. This is probably caused by the immunostimulant activity of the plant or its preparations is caused by three mechanisms: Phagocytosis activation, fibroblast stimulation, and the enhancement of respiratory activity that results in augmentation of leukocyte mobility.[12] There are numerous in vivo studies on the immunomodulatory and anti-inflammatory effects of E. purpurea that suggest that innate immunity is enhanced by administration of the plant and that the immune system is strengthened against pathogenic infections through activation of the neutrophils, macrophages, polymorphonuclear leukocytes (PMN), and natural killer (NK) cells.[10] For this reason, it can be suitable for prevention against and treatment of various infectious diseases such as infections of the upper and lower respiratory systems, wound infections.[10] Study showed that N-alkamides from a root and herb tincture induce synergistic activity on CB2 and ultimately lead to immunomodulatory effects along with the superstimulation of interleukin-10 (IL-10) and the inhibition of tumor necrosis factor (TNF-α) in vitro.[13] They are also able to inhibit both

cyclooxygenase enzymes (COX-1 and COX-2) and 5-lipoxygenase (F-LO), causing the inhibition of NK cells and anti-inflammatory activity.[14] Another important type of bioactive compound of this plant is polysaccharides, which have been reported to increase production of interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α by macrophage, along with the enhancement of their phagocytosis, microbicidal activity (both in vitro and in vivo).[15] No adverse events were reported suggesting that this herbal therapy is reasonably safe. No human trials could be located reporting evidence of cytokine storm when Echinacea was used for up to 4 months.[16] Support the results of this study, Jawad et al stated in their study using a dose of 2400 mg/day that prophylactic treatment with Echinaforce over 4 months appeared to be beneficial for many reasons.[17] The Echinacea dosage and duration of treatment employed also varied widely, ranging from a one-time injection containing 5 mg of Echinacea polysaccharides to a daily dose of 8000 mg of Echinacea capsules for 28 consecutive days.[18] As finalization, A systematic review, based on clinical studies, case reports and surveillance programmes of national medicines regulatory authorities and WHO, concluded that Echinacea products have a good safety profile.[19]

2. Black Elderberry (Sambucus nigra)

Various parts of the elderberry plant (Sambucus spp.) have historically been used both as foods and as remedies for health problems.[20] A recent systematic review looked at elderberry for the treatment of upper respiratory symptoms and suggested that elderberry could be helpful in shortening the duration of colds or influenza.[21] Based on three studies testing elderberry versus placebo for its effect on symptoms of influenza, it is possible that illness may be shorter and less severe with elderberry than with placebo. This probably due to anthocyanins that contains in elderberry, such a subset of flavonoids which may have immunomodulating and possibly anti-inflammatory effects. nthocyanins can attach to (and render ineffective) viral glycoproteins that enable viruses to enter host cells, thereby potentially having an inhibitory effect on viral infection. Extracts of elderberry have demonstrated in-vitro to have inhibitory effects on influenza A and influenza B viruses. There is some evidence that elderberry decrease the production of inflammatory cytokines (i.e., TNF-alpha, interleukins).[22]" There is study suggests that elderberry is as effective or less effective than diclofenac in IL-1 reduction over time.[23] Clinical studies involving 936 adults indicate that mono-herbal preparations of Sambucus nigra L. berry (S.nigra), when taken within 48 hours of the onset of acute respiratory viral infection, may reduce the duration and severity of common cold and influenza symptoms in adults. And there is no evidence suggest that elderberry overstimulates the immune system and this does not show any significant side effects.[24]– The internal daily dose of elder flowers is about 10–15 g in three divided doses. 1.5–3 mL fluid elder extract (1:1 g/mL), 2–3.75 g soft elder extract (5:1) in three divided doses are recommended to use internally.[25]

Neuraminidase inhibitors are recommended for the early treatment of influenza but associated with adverse effects, including nausea, vomiting, psychiatric effects, and renal event so, raud et all tested the efficacy and safety of a newly developed preparation of Echinacea purpurea called Echinaforce Hotdrink (A. Vogel Bioforce AG, Roggwil Switzerland) for the treatment of acute influenza symptoms compared with the neuraminidase inhibitor oseltamivir. The study found, that

combination of Echinacea purpurea and black elderberry has the same effectiveness as Oseltamivir at the start of influenza virus treatment with a lower risk of complications and side effects. Proportion of patients with improvement in influenza symptoms per day. A total of 90.1% responded to EP + BE vs. 84.8% responded to oseltamivir on day 10. Echinaforce Hotdrink has been demonstrated to be an attractive therapy for acute influenza treatment with a better safety and a comparable efficacy profile to the neuraminidase inhibitor oseltamivir but still further studies are warranted.[26]

2. Multimodalities Supplement to Support Immune Function

The main functions of body's immune system are to protect the host against infection from pathological microorganisms, to clear damaged tissues, and to provide constant surveillance of malignant cells that grow within the body.[27] Nutrition as a modifiable factor in impacting immune function has been studied for several decades. The nutrients such vitamin C, vitamin D, and zinc, have specific EFSA (European Food Safety Authority) scientific opinion on the substantiation of health claims related to vitamin D , vitamin C zinc, and normal function of the immune system.[29]

1. Vitamin C and Immunity

Vitamin C, also known as ascorbic acid, is a water-soluble micronutrient that plays a central role in the regulation of normal immune function.[30]– This micronutrients supporting various aspects of both the innate and adaptive immune system including promotes neutrophil migration to the infection site that improves phagocytosis, oxidant generation, and microbial killing. Simultaneously, it keeps the host tissue safe from excessive damage through the enhancement of neutrophil apoptosis, clearance using macrophages, and decreasing the neutrophil necrosis. Vitamin C treatment can cause an increase in the levels of three main classes of antibody immunoglobulins: IgA which protects the body against infections mostly on mucosal surfaces, including the respiratory and digestive tracts, IgG which provides long-term protection in the bloodstream, and finally IgM which is the earliest immunoglobulin that appears in blood in response to invading threats. The other study shows the effect of vitamin C on the proliferation and survival on T cells, increase the level of lmphocytes in the peripheral blood and particularly, the numbers of naive T cells, memory T cells in the spleen, and mature T cells in the thymus were increased.[31] A 4-week vitamin C-free diet showed a continuous increase in the percentage of B lymphocytes. Huijskens et al. pointed out that ascorbic acid (95 μM) can raise the proliferation of NK cells. They showed that ascorbic acid increases the production and expansion of NK-cell progenitors from hematopoietic stem cells and from T-/ NK-cell progenitors in vitro in a cytokine-stimulated culture. The current recommendation for average daily level of intake of vitamin C (according to the RDA) is about 90 mg/day for men and 75 mg/day for women 26, Supplementation with vitamin C, especially in groups such as the elderly, has been shown to reduce the duration and severity of cold symptoms.[32]

2. Immune Modulatory Effects of Vitamin D

Vitamin D (Calciferol) plays a multitude of biological roles in the human body. Vitamin D Receptors (VDRs) can be found in nearly all cells of the body and many sites of the genome (2) Vitamin D has immunomodulating properties that affect both innate and adaptive immunity by enhance chemotaxis, antimicrobial peptides, and macrophage differentiation to stimulates the innate

immune responses. In addition, Vitamin D also stimulates the adaptive immune responses. For example, at the level of the antigen-presenting cells, like dendritic cells, Vitamin D inhibits the surface expression of the MHC-II-complexed antigen, co-stimulatory molecules, and the production of IL-12 and IL-23 cytokines leading to indirectly shifting the polarization of T cells from a Th1 and Th17 phenotype towards a Th2 phenotype.23' Clinical trials demonstrate that 400 IU/d vitamin D supplementation is needed for the prevention of respiratory infections.– It is reasonable and safe to take approximately 1000 IU of vitamin D daily, as suggested by Zittermann et al., in order to optimize nonspecific immunity and prevent infection. – – – —

3. Zinc and Covid 19

Zinc is an essential metal being involved in a variety of biological processes due to its function as a cofactor, signaling molecule, and structural element. At the same time, the most critical role of zinc is demonstrated for the immune system. Briefly, zinc regulates proliferation, differentiation, maturation, and functioning of leukocytes and lymphocytes[36] Zinc significantly improves cilia morphology.[37] and increases ciliary beat frequency thus improving mucociliary clearance and removal of bacteria and virus-containing particles. By up-regulating tight junction proteins ZO-1 and claudin-1.[38] and increasing antioxidant activity of respiratory epithelia zinc also increases barrier function of the latter. In turn, coronavirus infection was shown to impair mucociliary clearance. Zinc may also possess antiviral activity through inhibition of RdRp and blocking further replication of viral RNA as demonstrated for SARS-CoV. Indirect evidence also indicates that Zn2+ may decrease activity of ACE2, known to be the receptor for SARS-CoV-2.[39] Maggini et al., 2012, used a dosage of 1000 mg plus 10 mg zinc and showed that supplementation with vitamin C and zinc may represent an efficacious measure, with a good safety profile, to help ameliorate the symptoms of this infectious viral disease.[40]

Zinc and vitamins C and D are integral parts of the immune system and show synergistic functions at various stages of the host defenses, such as the maintenance of the integrity of biological barriers and the functionality of cells that make up the innate and adaptive systems. Overall, the medical literature demonstrates that the supplementation with zinc, vitamin C and vitamin D can mitigate viral respiratory infections. Thus, in the context of the COVID-19 pandemic, the supplementation with such nutrients may be characterized as a widely available, safe and low cost measure that can be useful to cope with the increased demand for these nutrients in case of contact with the virus and onset of the immune responses, as well as to lower the risk of severe progression and prognosis of this viral infection.[41]

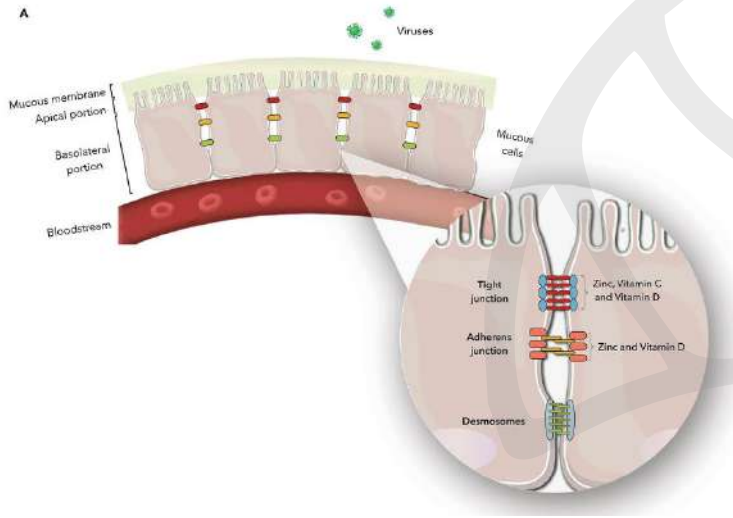

Figure 2. Junctional complex in epithelial cells. The magnification shows the arrangement of these structures in the paracellular space and the action of zinc and vitamins C and D on tight and adherens junction proteins.[41]

5. Summary of The Role of Echinacea, Minerals and Vitamins in the 3 Line of body defense

Items	1st Physical Barrier	2nd Innate Immunity	3rd Adaptive Immunity
Echinacea purpurea(1)	Promotes dendritic cell maturation by modulating activation of JNK, p38-MAPK and NF-κB pathways.	Reduced expression of ICAM-1, fibronectin, PAFr (platelet activating factor receptor) Regulation of IL-6, IL-10, IL-17 . cytokine balance	Increases the number of CD4+ and CD8+ . T lymphocytes
Black Elderberry(2,3)	Antiviral by blocking viral glycoproteins (HA/hemagglutinin) Increases the secretion of IgA in the mucosa thereby inhibiting viral replication	Cytokine regulation IL-6, IL-8, IL-12, TNF-α	Increases influenza A specific neutralizing antibody titers

Zinc[1]	Maintain the integrity of the physical barrier and mucous membranes	Increases the production and function of macrophages, neutrophs, and NK . cells Antiviral by blocking ICAM-1 . receptors	Enhances T cell function by modulating the secretion of IL-2 and its receptors and increasing the sensitivity of its receptors
Vitamin C[1]	ROS Scavenger	Reduces superoxide formation Inhibits lipid peroxidation	Improve the function of T lymphocytes
Vitamin D[1]	Increases the production of catelicidin and defensins as antimicrobial peptides	Stimulation of maturation of monocytes into macrophages thereby increasing phagocytic activity	Decreases cytokines and CD4+ Th1/Th17 . T cells Regulation (suppresses/increases) Treg . cells

6. Conclusion

1.) Combinations of drugs, micronutrients, or herbs are common. This combination prioritizes maintaining the bioavailability of each component. Micronutrients such as vitamin C, vitamin D, and zinc are needed by the body in modulating the immune system so that it can reduce the risk of infection.

2.) The combination of various herbal & vitamin supplements with small doses can synergize to increase efficacy, reduce side effects, and provide practicality to their use so as to improve patient compliance.

3.) The combination of Echinacea purpurea 500 mg, Black Elderberry 400 mg, Zinc Picolinate 10 mg, Pureway C 300 mg, Vitamin D 400 IU, and Citrus Bioflavonoid Extract 25% 100 mg is included in an effective and safe therapeutic range.

4.) Micronutrient and herbal combination supplements have a role as complementary therapy, especially for populations who are more susceptible to infection. The main micronutrient needs still come from food intake.

5.) Combination supplementation of Echinacea purpurea, black elderberry, zinc, pureway C, and vitamin D3 can be given for prevention and adjuvant therapy in respiratory tract infections due to bacteria/viruses such as the common cold, influenza, COVID-19 without symptoms or mild symptoms and long-term COVID-19 . Administration as adjuvant therapy when infection occurs can be done according to the doctor's recommendation.

6.) The maximum duration of use of supplements containing Echinacea purpurea is 8 weeks, then a 2-week break can be given before continuing its use according to doctor's recommendations.

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SURGICAL MANAGEMENT OF BRONCHOPLEURAL FISTULA

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Introduction

Bronchopleural fistula (BPF) is defined as a direct communication between the bronchus and the pleural space.(1,2,3) BPF can be classified as central, which are fistulous connections between the trachea or a lobar bronchus and the pleural space, or peripheral, which are fistulous connections between the distal airway (segmental bronchi or lung parenchyma) and the pleural space.(3,9) Nonsurgical conditions like trauma, chronic necrotizing pneumonia, empyema, radiotherapy, bulla, or cyst rupture can cause BPF, but the most common cause is lung resection.(3,4,9) Frequency ranges from 4.5 to 20% after pneumonectomy and from 0.5 to 1% after lobectomy. BPF-related mortality ranges from 18 to 71% in the literature.(2,3)

Clinical Presentation

Varoli et al 2 classified fistulas according to the time of onset after the operation: early [1 to 7 days], intermediate [8 to 30 days], and late fistulas [more than 30 days]. These almost always occur within three months after surgery.(3,9,12) Bronchopleural fistulas developing as a complication of pleuropulmonary infections may develop at any point of time during the course of illness. The symptoms and signs of cough and changes in the air-fluid pattern on chest radiograph are critical as warning signs of BPF.(9) Other manifestations include fever with serosanguinous or purulent sputum. Acute respiratory distress may occur if a large fistula results in aspiration to the contralateral lung or if a tension pneumothorax develops. Many cases are associated with empyema.(9,12)

Etiologi

Bronchopleural fistula (BPF) is most commonly encountered after lung resection surgery (pneumonectomy, lobectomy, segmentectomy), with a frequency ranging from 4.5% to 20% after pneumonectomy and 0.5% to 1% after lobectomy.(9,12,15) The most common risk factors associated with bronchopleural fistula (BPF) in the postoperative setting include right-sided pneumonectomy and right lower lobectomy. The fistula is commonly found on the stump beside the residual lobe due to the increased risk of ischemic necrosis or the pooling of secretions leading to bacterial overgrowth and colonization. The increased risk of BPF associated with right pneumonectomy is due to the more extensive resection required. (3)

Other causes include : (3,9)

- Chemotherapy and radiation therapy
- Lobectomy-right, bi-lobectomy, and lower lobectomy
- Diabetes mellitus
- Heavy smoking and chronic obstructive pulmonary disease
- Bullous lung disease
- Spontaneous pneumothorax or other parenchymal abnormalities
- Low nutritional status or poor wound healing
- Previous ipsilateral thoracotomy
- A large diameter bronchial stump (greater than 25 mm)
- Extensive lymph node dissection
- Age older than 60 years
- Fever
- Corticosteroid use
- Leukocytosis
- Tracheostomy
- Bronchoscopy for sputum suctioning/mucous
- Residual tumor in the resection margins
- Tightness of the individual sutures
- Excessive peribronchial and paratracheal dissection
- Prolonged postoperative mechanical ventilation
- Tuberculosis
- Hemophilus influenza
- Streptococcus viridans
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Pneumococcus
- Non-hemolytic streptococcus
- Aspergillus
- Histoplasma capsulatum
- Gastroesophageal reflux disease with Barrett esophagus
- Boerhaave syndrome
- Broncholithiasis
- Lung cancer
- Thyroid cancer
- Esophageal cancer
- Lymphomas
- Thoracic trauma with tracheobronchial tree disruption
- Bougie intubation
- Necrotizing lung disease associated with radiation or chemotherapy
- Acute respiratory distress syndrome (ARDS): Especially in patients requiring ventilation with high airway pressures

- Ventilator-induced barotrauma
- Overzealous manual ventilation
- Central line placement

Pathophysiology

Postoperative bronchopleural fistula (BPF) may be classified as acute, subacute, and chronic.(9,10) The acute form is caused by surgical dehiscence and requires prompt surgical intervention.(10) When acute, BPF can be life-threatening due to tension pneumothorax or asphyxiation from pulmonary flooding. Patients present with sudden appearance of dyspnea, hypotension, subcutaneous emphysema, cough with expectoration of purulent fluid, tracheal or mediastinal shift, persistent air leak, and a reduction or disappearance of pleural effusion on the chest radiograph. The subacute and chronic forms are primarily related to infection and are often seen in immunocompromised or debilitated patients with multiple comorbidities. The subacute presentation is more insidious and is characterized by wasting, malaise, and fever. The chronic form is associated with an infectious process and fibrosis of the pleural space.[9,10]

Management

The management of the BPF is management of the life-threatening conditions like sepsis, tension pneumothorax, and respiratory failure.(3,9,12) Protection of the contralateral lung from aspiration of the pleural fluid is important to reduce the risk of pneumonia and respiratory failure. Chest tube must be applied to ensure the drainage of the pleural cavity. Broad spectrum antibiotictherapy against Gram-Positive, Gram-Negative, and anaerobic microorganisms must be initiated, and it should be tailored based on the results of culture.(9,12) Early BPFs are mostly associated with failure in the surgical technique.(2,6) Repairment of the bronchial stump with re-operation is the best treatment modality in these patients. (2,6) Patients with late BPF mostly have poor medical condition and major surgical approaches cannot be applied. Conservative treatment modalities like drainage and reduction of the pleural space, pleural irrigation, antibiotics, and nutritional supplementation.(3,9,12) Besides conservative treatments, several surgical procedures to treat BPFs have been defined in the literature. Main objectives in these surgical interventions are debridement of the pleural space, minimizing the residual pleural cavity, closure of the fistula, and reinforcement of the bronchial stump with autologous tissue. VATS is a useful method to obtain drainage and debridement of the infected pleural cavity. Single port is usually sufficient in most cases; material and debris can be safely removed with surgical instruments and in the presence of small BPF. In the presence of empyema drainage of the pleural cavity is essential to control the septic status of the patient. Open-window thoracostomy was first described by Robinson in 1916 in patients with nontuberculous empyema and Eloesser has revised this procedure for patients with tuberculous empyema. This procedure contains : 1.Segmental resection of 2–3 ribs 2.Creation of a skin flap (Muscle should be preserved if possible) 3.Marsupialization of the cavity.[3,4,6,7,9,10,12]

Surgically closure of a bronchopleural fistula can be considered if large BPF can cause loss in the tidal volume, aspiration of infected pleural fluid, and respiratory distress. Transpleural approach is the most common method to closure of the BPF and bronchus must be mobilized as close to the

Surgically closure of a bronchopleural fistula can be considered if large BPF can cause loss in the tidal volume, aspiration of infected pleural fluid, and respiratory distress. Transpleural approach is the most common method to closure of the BPF and bronchus must be mobilized as close to the carina as possible to provide adequate length. dissection and devascularization of the proximal bronchus should be avoided because of the risk of failure of the repair and recurrence of BPF. Stapler devices can be used if there is a sufficient length in the bronchial stump. Manual suturation also can be applied above the BPF. After repairment, bronchial stump must be buttressed with well-vascularized tissue such as extrathoracic muscle, omentum, or diaphragm flap. In some cases, surgical management of BPF may be challenging through a lateral transpleural approach. Presence of short bronchial stumps, left-sided BPF, necrotic bronchial stumps and/or history of prior BPF closures via thoracotomy are the main reasons that make transpleural approach difficult. In these cases, transsternal transpericardial approach would be a good alternative to transpleural approach. Thoracoplasty is originally considered as a treatment foractive tuberculosis but this procedure is also functional for obliterate pleural space with the viable tissue of the chest wall in the cases of BPF. This is achieved by resection of multiple ribs.[4,6,7,9,11,13,14]

Various endoscopic techniques like bronchoscopic application of sealants, fibrin glue, silver nitrate cautery, coils, and endobronchial stents for the control of small BPFs have been reported. This techniques only for the patients with poor clinical condition and not for proper major surgical intervention. Proper technique must be selected depending on the length of the bronchial stump, the location, and size of the fistula.[8,9,10,12]

Conclusion

Bronchopleural fistula is still associated with significant morbidity and mortality. There are many options to use in patients with BPF, therefore surgeon must evaluate clinical status of the patient, the size, and location of the BPF and the status of the pleural cavity to select the treatment method that will show the most benefit.

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ANTI-INFLAMMATORY RELIEVER CONCEPT TO PREVENT EXACERBATION

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Abstract
Asthma is a chronic inflammatory disease, with sudden flare-ups, regardless of severity and adherence, so Anti-Inflammatory plays a substantial role in asthma treatment. Global Initiative in Asthma (GINA) has made a fundamental change in asthma management guidance since 2019 by eliminating SABA only as part of asthma treatment, in order to prevent SABA over-reliance from the very beginning. Starting therapy with SABA will train patients to assume that SABA is the primary treatment for their asthma. GINA recommends that all adolescent and adult asthmatic patients should receive ICS-containing treatment which can be given as daily therapy or in mild asthma, given as needed low dose ICS-formoterol[1].
Starting in 2021, GINA slightly modifies stepwise by dividing asthma management into 2 tracks. Track 1 is the preferred option, which is low dose of ICS-formoterol as a reliever (step 1-5) and as reliever and controller (step 3-5). Track 2 is an alternative option due to less effective in reducing severe exacerbation[1].

The rationale behind ICS-formoterol as preferred reliever is due to Formoterol that have fast onset of action (1-3 min)[2]. Moreover, based on robust clinical evidence that shows ICS/formoterol combination as anti-inflammatory reliever, harnessing window of opportunity by adding ICS whenever patients need (when symptom occur), leads to minimize likelihood of exacerbation risk[3]. Some big-sample study such as SYGMA-1, NOVEL START, COMPASS, as well as meta-analysis by Edwards in 2010, shows that Budesonide/Formoterol as Anti-Inflammatory reliever significantly lower the exacerbation risk VS SABA (+/- ICS/LABA) in mild, moderate, and severe asthma:

- In mild asthma, Budesonide-Formoterol as Anti-Inflammatory reliever reduce severe exacerbation rate 60-64% VS SABA[4,5]
- In moderate-severe asthma, Budesonide-Formoterol as Anti-Inflammatory reliever (+ controller) reduce severe exacerbation rate 21 to 48% vs other ICS-LABA[6-9]; with 25% lower ICS load[8]

In asthma management, challenge that occur continuously is patient adherence. They usually need 2 type of medicines which are Controller for baseline disease activity and Reliever for fast-relief medication when symptom occur. Unfortunately, based on study, when symptoms worsen, most patients simply increase their use of a short-acting β2-agonist (SABA) and are less likely to increase use of their controller medication. This behaviour leads to SABA over-use[10]. SABINA (SABA use in Asthma) study in Indonesia, also shows 37% of asthma patients has been prescribed ≥3 canister/year[11].

SABA has been important part of asthma management for more than five decades, but regular use and over-use SABA related with several side effect such as downregulation β-receptor, decrease bronchoprotection, rebound hyperresponsiveness, decrease bronchodilator response[12]; increase allergic response and increase eosinophilic airway inflammation[13]. SABA treatment, even though can rapidly relieve symptom, do not protect patient from exacerbation risk. Moreover, SABA over-use, consider as ≥3 canister/year, can lead to increase exacerbation risk[14]. These all leads to fundamental change of GINA guidance for better asthma care.

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THE ROLE OF VITAMIN AND MINERAL IN LUNG DISEASE

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The lungs are fundamental organs of the respiratory system, whose main function involves extracting oxygen from the environment and making it available for aerobic respiration at the cellular level. Oxygen is used for the synthesis of ATP (adenosine triphosphate) and carbon dioxide is eliminated with other metabolic by-products.[1,2] However, in addition to their primarily respiratory functions, they are also important in other non-respiratory processes.[3] The lungs are chronically exposed to various pathogenic or non-pathogenic environmental antigens. Therefore, maintaining a network of resident cells that continuously monitor the external environment and promote tolerance to innocuous particles is essential for pulmonary homeostasis. On the other hand, the deficiency in the immune response counts pathogens or intense inflammatory responses as a result of failures of mechanisms of tolerance, can generate damage to the tissue and lung function, contributing to the development of chronic inflammatory diseases for exemple chronic obstructive pulmonary disease (COPD) and asthma, and infections.[4]

Vitamins are micronutrients available in several kinds of foods and can be of animal or vegetable origin. Minerals are inorganic substances present in food, such as magnesium, selenium, iron, and zinc.5 In addition to their nutritional role, they also participate in immunity and homeostasis of the mucosa, such as the pulmonary mucosa. They also play an important role in cellular metabolism. Regarding lung health and homeostasis, vitamins A, C, D, E, and other minerals can be considered the most important, not only for their anti-inflammatory action but also for participating in the immune response against pathogens.[6,7]

Nutrition is an important tool that can be used to modulate the immune response during infectious diseases. In addition, through diet, important substrates are acquired for the biosynthesis of regulatory molecules in the immune response, influencing the progression and treatment of chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD).8 In this way, nutrition can promote lung health status. A range of nutrients, such as vitamins (A, C, D, and E) and minerals (zinc, selenium, iron, and magnesium), play important roles in reducing the risk of pulmonary chronic diseases and viral infections. Through their antioxidant and anti-inflammatory effects, nutrients are associated with better lung function and a lower risk of complications since they can decrease the harmful effects from the immune system during the inflammatory response. In addition, bioactive compounds can even contribute to epigenetic changes, which can contribute to the maintenance of homeostasis in the context of infections and chronic inflammatory diseases.[9]

These nutrients also play an important role in activating immune responses against pathogens, which can help the immune system during infections. Here, we updated the roles played by dietary factors and how they can affect respiratory health. Therefore, we will show the anti-inflammatory role vitamins and minerals, important for the control of chronic inflammatory diseases and allergies, in addition to the antiviral role of vitamins and minerals during pulmonary viral infections, addressing the mechanisms involved in each function. These mechanisms are interesting in the discussion of perspectives associated with severe acute respiratory infection and its pulmonary complications since patients with severe disease have vitamins deficiency.[10-12]

Nutrients are able to ameliorate the development and severity of pulmonary diseases, since they can act on several immune cells and modulate immune response in inflammatory processes. In this context, vitamins and minerals reduce the expression of inflammatory mediators (such as cytokines and chemokines), as well as, have antioxidant effect, decreasing the deleterious effects of asthma and chronic obstructive pulmonary disease (COPD) in the lungs.8 Regarding pulmonary viral infections, vitamins, and minerals are the main dietary components with antiviral action.[13]

Taking into account the anti-inflammatory and immunoprotective role that nutrients play in the pulmonary mucosa, it is not absurd to think that nutrients can be used as an important strategy against SARS-CoV-2 infection. Indeed, some studies, mostly using vitamins and antioxidant nutrients or demonstrating their deficiencies, have already shown some effect during COVID-[19.14-16]

Vitamins and minerals can inhibit viral replication in many pulmonary infections, and they already demonstrated ability to decrease viral replication of SARS-CoV-2. These nutrients also have antioxidant role (inhibition of reactive oxygen species—ROS) and anti-inflammatory activity (inhibition of transcription proinflammatory factors transcription) and may inhibit the deleterious effects of the cytokine storm and tissue damage present in COVID-19.[17] Nutrients, in general, play an important role in the control of SARS-CoV-2 infection, which can be used as treatment strategies that may reduce the length of hospital stays and the need for respiratory support in these patients.[18]

In conclusion, the nutrients have a relevant role in maintaining lung health; therefore, adequate consumption of these nutrients is essential to promote an efficient immune response in the control of inflammatory diseases and infections. Moreover, the in vitro use of some nutrients with antiviral activity has been shown to be efficient against SARS-CoV-2 infections, which highlights the importance of these components in the current moment of the pandemic that we are facing.

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HOW IMMUNOMUDULATOR CAN IMPROVE THE PNEUMONIA TREATMENT

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Pneumonia is very common and continues to exact a high burden on health. The Global Burden of Disease Study 2015 found lower respiratory infections (LRIs) were the leading infectious cause of death and the fifth leading cause of death overall. Pneumococcal pneumonia caused 55% of LRI deaths in all ages (1.5 million deaths). Pneumonia may be defined as an infection of the lung characteristically involving the alveolar space. The presence of microorganisms in the alveolar space without an accompanying inflammatory response represents colonization and does not constitute pneumonia. A range of other types of infection may also affect the lung and can be classified according to their principle site of infection.

Novel pathogens, **particularly viruses**, continue to emerge as causes of pneumonia. The rise of drug-resistance among common respiratory pathogens is a further challenge. Pneumonia is commonly classified according to patient location at the time of infection, leading to the categories of community-acquired, hospital-acquired and ventilator-acquired pneumonia.[1]

The most frequent viral infection around the globe is an acute respiratoy infection, which its severe from is responsible for approximately 3,9 million deaths per year and it is one of the leading cause of morbidity and mortality worldwide. These numbers can increase significantly after the current uncontrolled spread of Covid- 19. Acute respiratory infections are categorized as either upper or lower respiratory infections and are caused by well- recognized viral pathogens, including but not limited to influenza virus (types A and B), parainfluenza virus, respiratorysyncytial virus (RSV), metapneumovirus (types A and B), coronavirus, rhinovirus, enterovirus, reovirus, bocavirus, and adenovirus. There is a substance with immunomodulatory effect and antiviral properties can be use to improve the pneumonia treatment.

Inosine pranobex (IP) commonly known as inosine acedoben dimepranol (IAD), isoprinosine or methisoprinol is a synthetic compound with immunomodulatory and antiviral properties. The drug was initially authorized in 1971 and currently marketed in more than 70 countries worldwide for treatment of viral diseases including acute viral respiratory infection, subacute sclerosing panencephalitis (SSPE), herpes virus simplex (HSV), varicella infection, human papilloma virus (HPV) cytomegalovirus, Epstein -Barr virus infection, measles and immunosupressed states.[2,3]

IP demonstrate that the Immunomodulatory activity is charactirized by enhanced T-cell lymphocyte proliferation, increase level cytokines production and Natural Killers (NK) cell

lymphocyte proliferation, increase level cytokines production and Natural Killers (NK) cell cytotoxicity, and threreby restoring deficint responses in immunosuppressed patient. At the same time it has been shown that it can affect viral RNA levels and hence inhibits growth of several viruses. IP affect via NK cell almost all the viruses that replicate in the human body.[2,3] Isoprinosine a combination of the p-acetamidobenzoate salt of N,N-dimethylamino-2- propanol:inosine in a 3:1 molar ratio.

It is a synthetic purin derivatie with immunomodulatory antiviral properties which result from an apparent in vivo enhanchement of host immune responses due to the drug. Immunomodulatory activity, : a substance that stimulate or affect the function of immune system.[4]

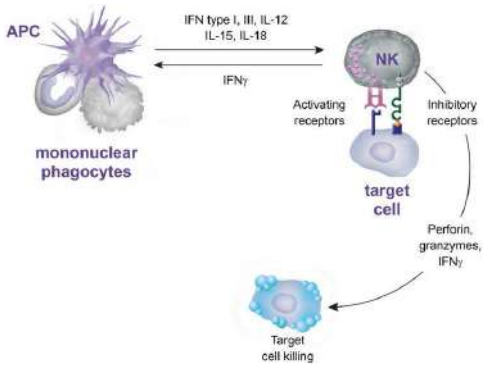
IP or Isoprinosine Stimulate the immune system by :[2,3]
· Enhanced Lymphocyte proliferation
· Cytokine production, Th1 cell-type response (IL-1, IL-2, IFN-y)
· Cytotoxicity, NK cell+ CTL

For decades now, IP has been a widely used drug due to its immunomodulatory and antiviral properties, and several mechanisms of action have been postulated in an effort to explain these properties. Studies have shown that IP can impact both the humoral as well as the cell-mediated aspects of the immune system, in such a way that it enhances the host immune responses and can also exhibit antiviral effects considered secondary to this immunopotentiation. *Its efficacy, either as monotherapy or as part of a combination therapy, has been re-visited for various diseases.* Moreover, new, potentially therapeutic indications for IP or new agents for concomitant administration have been investigated.[3]

THE MAIN EFFECTOR FUNCTIONS OF NK CELLS INCLUDE:

· **CYTOTOXIC ACTIVITY** - NK cells kill the virally-infected cell by
1. Cytotoxic factors (mediators) - are stored inside compartments called granules:
2. Perforin - a protein makes pores in cell membranes
3. Granzymes - through the holes made by perforin - programmed cell death or apoptosis

***CYTOKINE SECRETION** – NK cells – interferon-γ (INF-γ) – Tumour necrosis factor -a TNF-a, activates macrophages and T-cells*[4]



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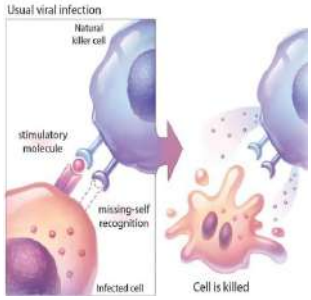
Natural Killer (NK) Cells

Natural killer (NK) cells are a type of white blood cell that fights infection and cancer. Their job is to patrol the body and help protect it from disease. To prevent an attack on healthy cells, however, NK cells are normally restrained. When needed, they spring into action by two mechanisms. One occurs when stimulatory receptors on NK cells bind to stimulatory molecules on cells infected with a virus or tumour cells. This interaction, called "induced-self" recognition, tells the NK cell to release a lethal protein that tells diseased cells to die.

The other, which leads to the same outcome, is called "missing-self" recognition: NK cells sense a loss of self-recognition proteins on their surface that is caused by pathogens. The loss of these proteins acts as a signal that something foreign has invaded and unleashes the NK cells' offensive, which is how the body fights infection.[6]

NK CELL IDENTIFIES A VIRALLY INFECTED CELL AS "FOREIGN AND KILLS IT



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Clinical Study in the Czech Republic and Slovakia

Clinical and immunological research which was performed during past 5 years can explain the very effective role of Inosine Pranobex (IP) and Natural Killers (NK) in treatment of the majority of viral infections hopefully also against Covid-19 as one of the currently spread acute viral respiratory infection.

In order to evaluate the clinical use of IP for the treatment of acute respiratory viral infections. The primary efficacy endpoint was a comparison between IP and placebo groups in terms of the time to resolution of all influenza- like symptoms present at baseline to none. IP 500- mg tablets or placebo were self-administered by the subjects for 7 days (2 tablets orally 3 times daily). The first dose was taken immediately after randomization at the study site, and the remaining doses were to be self-administered at home. Doses were taken approximately 8 h apart but consistent with the subject's lifestyle, ie, scheduling of dosing did not disturb the subject's usual sleep patterns. The subjects were provided with kits containing (randomized medication sufficient for 1 subject for 7 days of treatment.[7]

Compare : Efficacy and safety 463 subjects by Isoprinosine (N=231) X placebo (N=232) in patients with clinically diagnosed **Acute Respiratory Viral Infection (ARVI) or ILI**. The study was randomized, double-blind and multicentric. Two 500mg tablets orally 3 times daily, is most suitable for subject less than 50 years of age without related ongoing disease.

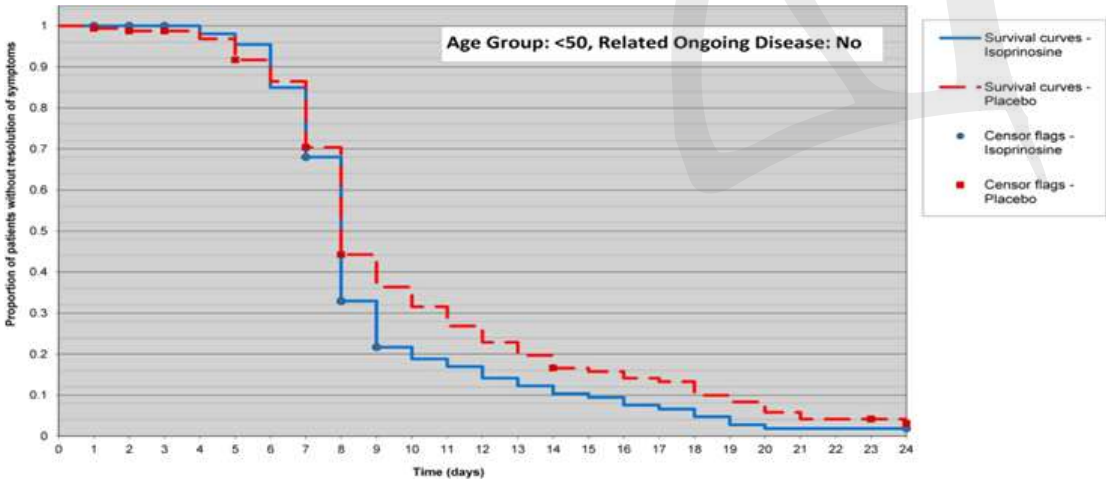
Faster time to resolution off all influenza-like symtoms. Statistically significant :
- Subjects less than 50 years of age
- Non obese persons (BMI < 30 kg/m2)
- Risk ratio:1,307 (1,010-1,691) -> P-Value 0,018

Results

In the subgroup analysis, for subjects, less than 50 years of age without related ongoing disease, the difference in time to resolution of all influenza-like symptoms between treatment groups was statistically significant (p = 0.050) and showed faster improvement in subjects in the IP group compared with subjects in the placebo group (Figure 1). The novel clinical and laboratory findings of IP activity can be in this context used as a treatment option (off-label in some countries) for at least some cases of infection during the current pandemic of Covid-19 with standard treatment schedule for young and otherwise healthy people 1g (2 tablets)/3 times per day up to 50 tablets. In the elderly, who are immunosenescenced and for people with a significant chronic disease the standard dose can be increased to 1g (2 tablets)/4 times per day for 7-14 days or 2 days after symptoms resolution. Inosine pranobex was generally well tolerated, and no deaths were reported.[2,7]

Conclusions

The study results indicate the safety of inosine pranobex for the treatment of subjects with confirmed acute respiratory viral infections and confirm the efficacy of inosine pranobex versus placebo in healthy non-obese subjects less than 50 years of age with clinically diagnosed influenza-like illnesses. Results proved great safety profile of Isoprinosine in ARVI or ILI treatment.[7]



Time to Resolution of Influenza-Like Symptoms in Subjects <50 Years Without Related Ongoing Disease. Analysis carried out in the intent-to treat analysis set. Note: Time to resolution was the total number of days from randomisation to the first instance at which all influenza-like symptoms had a score of 0 (date of resolution of all influenza-like symptoms minus the date of randomisation.[7]

Beran et al. BMC Infectious Diseases (2016) 16:648

Ahmed et al. report the results from a clinical trial Isoprinosine / Inosine Acedoben Dimepranol (IAD) where multiple lymphocyte subsets - CD19+ B cells, CD3+ T cells, CD4+ T- helper cells, FoxP3hi/CD25hi/CD127lo regulatory T cells (Tregs), CD3-/CD56+ NK cells, and CD3+/CD56+ NKT cells - were, together with serum immunoglobulins and IgG subclasses, followed during 14 days of IAD administration to ten healthy volunteers; these selected from 27 individuals pre-screened in vitro for their capacity to respond to IAD as gauged by increases in the percentage of Treg and/or NKT cells arising in PHA-stimulated cultures. While a transient spike and dip in Treg and T-helper fractions, respectively, was noted, the outstanding consequence of IAD administration (1g po, qds) was an early and durable rise in NK cells. For half the cohort, NKcells increased as a percentage of total peripheral blood lymphocytes within 1.5h of receiving drug. By Day 5, all but one of the volunteers displayed higher NK cell percentages, such elevation - effectively a doubling or greater - being maintained at termination of study. The IAD-induced populations were as replete in Granzyme A and Perforin as basal NK cells. The novel finding of IAD boosting phenotypically competent NK numbers in healthy individuals supports the drug's

indicated benefit in conditions associated with viral performance may be compromised.[8]

Isoprinosine is a synthetic purine derivative with immunomodulatory and antiviral properties, which result from an apparent in vivo enhancement of host immune responses. We assigned 10 healthy volunteers to receive isoprinosine 1 g, 3 times daily, 5 consecutive days weekly. Both treatment and follow-up phase last 3 weeks. We have demonstrated the immunomodulating properties of isoprinosine in healthy adults. It suggests resumption of the research with up-to-date methods to elucidate the mechanisms of action of inosine pranobex and maybe the other inosine compounds in different clinical settings.[8]

Isoprinosine normalizes the cell-mediated immunity stimulitating of t-Lymphocytes differentiation into T-cytotoxic cells and t-helper cells and increasing lymphokine production. It increases the production of interleukin-1 (IL-1) and IL-2 and significantly those of interferon-Y (IFN-Y) and IL-12 and decreases IL-3 and IL-4 production in vivo. Inosine pranobex also augments NK cell function. Furthermore Isoprinosine increase the humoral of B lymphocytes into plasma cells and by enhancing antibody production. It increases number of IgG and complements surface markers and potentiates neutrophil, monocyte and macrophage chemotaxis and phagocytosis.[4]

Our results support the nonspecific modulation of immune responses as all treated subjects were in good clinical state. We could the speculate that Isoprinosne leads to nonspesicific stimulation of early or nondifferntiated cells which can produce different cytokines (NK-, T-B cells). Our work holds promise for an important aspect of clinical immunopharmacology . we have demonstrated the immunomodulating properties of Isoprinosine in healthy adults.[4]

Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy of InosinePranobex.[9]

Pharmacodynamic:
The in vivo antiviral and antitumour effects of inosine pranobex are secondary to the immunomodulating activity of the drug. Although reports of poor in vitro antiviral activity of inosine pranobex are often in conflict with the reported in vivo antiviral activity of the drug, synergistic antitumour activity has been reported both in vitro and in vivo when the drug was used in combination with fluorouracil.
In vitro exposure of cells to inosine pranobex induces T-lymphocyte differentiation and potentiation of induced lymphoproliferative responses. The drug has been shown to modulate T-lymphocyte and natural killer cell cytotoxicity, suppressor and helper cell functions, as well as to increase the number of IgG and complement surface markers. Interleukin-1 and - 2 production, and neutrophil, monocyte and macrophage chemotaxis and phagocytosis are also potentiated by inosine pranobex.[10]

Pharmacokinetics:
Following a single oral dose of inosine pranobex, peak plasma concentrations of inosine occur after 1 hour. However, 2 hours after administration, plasma concentrations decrease to

undetectable amounts. **Inosine pranobex has a very short plasma half-life of 50 minutes following an oral dose.** The major excretion product of the inosine moiety is uric acid, while the p-acetamido-benzoic acid and N-N dimethylamino-2-propranol components are excreted in the urine as glucuronidated and oxidised products, respectively, as well as being excreted unchanged.

Side Effects:
Inosine pranobex has not produced serious side effects. The only side effects associated with inosine pranobex therapy to date have been transient increases in serum and urinary uric acid concentrations and occasional transient nausea associated with the large number of tablets ingested.

Dosage and Administration:
The recommended adult oral dosage of inosine pranobex is 1g 4 times daily. In children the usual dosage is 50 mg/kg per day given in divided doses throughout the waking hours.[10]

Research by Jiri Beran et al during the COVID-19 pandemic, in the elderly population, especially those in nursing homes (NH). Inosine pranobex (IP) has been previously demonstrated to be effective in treating acute viral respiratory infections. This study was performed in three nursing homes in three towns (Litovel, Sanatorium Topas Holice, and Beránek Úpice) in the Czech Republic. The study ran from June 2020 until September 2020, The dosage regimen was based onpractical limitations, i.e., elderly patients 65 years and older: received two tablets 3 times a day. The average duration of treatment was seven days.

The primary efficacy endpoint was considered the "time to resolution of all influenza-like disease-associated symptoms." IP 500 mg tablets or placebo were self-administered orally for 7 days (i.e., two tablets, three times per day). The first dose was taken immediately after case randomization at the clinic, and the remaining doses were self-administered at the nursing home. In our study with 301 residents, the case-fatality rate (CFR) was significantly reduced (OR: 2.8) to 11.9% (17/142) in comparison to a study in Ireland with 27.6% (211/764). We think the effect of IP was significant in this reduction; nevertheless, these are preliminary results that need larger- scale trials on COVID-19 patients.[11]

Summary
Isoprinosine/IAD/Methisoprinol/Inosine Pranobex is a very good choice for no-specific treatment of any viral infection. It influences viral infection indirectly by stimulation of immune system mostly via increasing of NK cells population and cytotoxic activity. It can be used as adjuvant therapy for pneumonia treatment, reduce symptoms faster and improve immunity.

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STANDARDIZED RISK ASSESSMENT AND OPTIMAL STRATEGY FOR VENOUS THROMBOEMBOLISM (VTE) PREVENTION

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Introduction

Venous thromboembolism (VTE) is a cardiovascular disorder that is in the third rank regarding prevalence[1]. Defined as deep venous thrombosis (DVT) and/ or pulmonary embolism (PE), VTE is associated with a significant disease burden in medical patients.[2] The proportion of venous thromboembolism in medical patients ranges between 10% and 40%.[3] The estimated annual incidence rates of VTE among people of European ancestry range from 104 to 183 per 100,000 person-years. Overall VTE incidence might be higher in African American populations and lower in Asian, Asian American, and Native American populations, and might vary in the African American population according to US geographical location. Reported incidence rates for PE (with or without DVT), and for DVT alone (without PE), range from 29 to 78, and 45 to 117, per 100,000 person-years, respectively.[4] Thromboprophylaxis for the prevention of VTE has been shown to be the most effective method to reduce the health and economic burden of this disease, however, several studies have consistently shown underuse of thromboprophylaxis in hospitalized patients.[5] Hospital-acquired VTE is preventable, with interventions including anticoagulants and mechanical measures, including compression stockings and intermittent pneumatic compression.[6]

How do clinicians stratify patients in the medical ward who are at increased risk of VTE?

Risk factors for VTE can be subdivided into factors that promote venous stasis, factors that promote blood hypercoagulability, and factors causing endothelial injury or inflammation. These three broad categories, frequently taught as “Virchow's triad”, and the vast majority of medical ward patients have risk factors for VTE.[7] Risk assessment models (RAMs) have been developed to help stratify the risk of VTE among hospitalised patients. These models use clinical information from the patient's history and examination to identify those with an increased risk of developing VTE who are most likely to benefit from pharmacological prophylaxis. As clinicians, we can use 3 assessment tools to stratify patients in the medical ward who are at increased risk of VTE: Padua score, Geneve score, and IMPROVE score. The 2012 ACCP guidelines for VTE prevention in nonsurgical patients advocated for pharmacological prophylaxis for 6 to 21 days, until full restoration of mobility, or until discharge from the hospital in patients characterized as high risk with the Padua score.[8]

Table 1. Geneva, Padua, and IMPROVE risk score for VTE in medical ward patients.

Geneva risk score Low risk 0–2 High risk ≥3		Padua risk score Low risk 0–3 High risk ≥4		Improve risk score Low risk 0–2 High-risk ≥3	
Malignancy	2	Active cancer (metastasis or treatment <6 mo)	3	Previous VTE	3
Myeloproliferative syndrome	2	Previous VTE	3	Known thrombophilia	2
Previous VTE	2	Reduced mobility (3 d)	3	Cancer	2
Hypercoagulable state	2	Thrombophilia	3	Lower limb paralysis[a]	2
Cardiac failure	2	Recent trauma/surgery (<1 mo)	2	Immobilization > 7 d[a]	1
Respiratory failure	2	Age > 70 y	1	Age > 60 y	1
Recent stroke (<3 mo)	2	Heart/respiratory failure	1	Stay in ICU or CCU[a]	1
Recent myocardial infarction (<1 mo)	2	Acute myocardial infarction/ischaemic stroke	1		
Acute infection	2	Acute infection or rheumatologic disorder	1		
Acute rheumatic disease	2	BMI > 30 kg/m^2	1		
Nephrotic syndrome	2	Hormonal treatment	1		
Immobilization (<30 min/d)	1				
Age > 60 y	1				
BMI > 30 kg/m^2	1				
Hormonal treatment	1				
Recent travel (>6 h)	1				
Chronic venous insufficiency	1				
Pregnancy	1				
Dehydration	1				

Abbreviations: BMI, body mass index; CCU, coronary care unit; ICU, intensive care unit; MI, myocardial infarction; VTE, venous thromboembolism.
[a]Proxy variables and a slightly different definition of immobilization was used in the ESTIMATE study (see section Methods).

How do clinicians assess the risk of bleeding in patients with indication of VTE prophylaxis?

If the patients in the medical ward have indication of venous thromboembolism prophylaxis, we as clinician should consider contraindication risk of bleeding, such as: Active bleeding, lumbar puncture/epidural/spinal anesthesia within the previous 4 hours or expected within the next 12 hours, concurrent use of anticoagulants known to increase the risk of bleeding (eg, warfarin with INR > 2) acquired bleeding disorders (eg, acute liver failure), mucosal lesions (eg, active peptic ulceration, bronchiectasis), acute stroke (within 24 hours), thrombocytopenia (platelets less than 75.000/L) , uncontrolled systolic hypertension (>= 230/120 mmHg), or untreated inherited bleeding disorders (eg, hemophilia or von Willebrand disease).[9] Other method we can use IMPROVE bleed score below:[10]

Bleeding risk factors	Points
Renal failure GFR 30–59 vs ≥60 ml/min/m^2	1
Male vs female	1
Age 40–80 vs <40 years	1.5
Current cancer	2
Rheumatic disease	2
CV catheter	2
ICU/CCU	2.5
Renal failure GFR <30 vs ≥60 ml/min/m^2	2.5
Hepatic failure (INR >1.5)	2.5
Age ≥85 vs <40 years	3.5
Platelets <50 × 10^9 cells/l	4
Bleeding in 3 months before admission	4
Active gastroduodenal ulcer	4.5

ICU, intensive care unit; CCU, critical care unit; CV, central venous; GFR, glomerular filtration rate; INR, international normalised ratio. * A score of 7 or more constitutes high bleed risk.

How do clinicians administer VTE prophylaxis?

As clinician, we consider to administer venous thromboprophylaxis with low molecular weight heparin, fondaparinux, or low dose heparin to patient in the medical ward with high risk of VTE and low risk of bleeding, but we consider to administer mechanical prophylaxis if the risk of bleeding is high instead, including compression stockings and intermittent pneumatic compression.[11] ACP recommended assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate quality evidence). ACP also recommended pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).[12]

Conclusion

Clinicians should consider venous thromboprophylaxis to all patients in the medical ward. Standardized assessment with Padua, Geneva, and/or IMPROVE risk score and IMPROVE bleed score to stratify patient with high risk of bleeding.

Clinicians may consider administering low molecular weight heparin, fondaparinux, or low dose heparin to patient in the medical ward with high risk of VTE and low risk of bleeding.

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CASE SHARING:
VENOUS THROMBOEMBOLISM IN CORONAVIRUS DISEASE 2019

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Introduction

Venous thromboembolism (VTE) is a spectrum of continuum vascular problems comprising deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is characterized by thrombus formation within the venous lumen which predominantly occur in the lower extremity but can also develop in the lung, resulting in pulmonary embolus.[1] VTE is a common vascular problems found in clinical setting and could potentially be fatal and associated with significant morbidity and mortality.[2] The survival rate of VTE is worse than expected, particularly for PE. The risk of early mortality in patients with symptomatic PE is 18 times higher than DVT and as much as 30% of patients with PE die within the first year after diagnosis.[3-5]—— VTE has also been considered a major health burden in the western countries. In the United States, the annual costs for VTE ranged from $13.5 to $27.5 billion.[1]

The incidence of first acute VTE is estimated to be between 0.7 to 1.4 per 1000 person-years and was observed predominantly in population older than 55 years.[2,5] Previously, VTE was found to be more prevalent among western populations compared with Asian populations, however, there has been an increased report of VTE cases among Asian populations in the past 15 years.[6,7] Lee et al., summarized the results from 73 studies performed in Asian population between 1995 and 2016 and found the incidence of VTE in Korea, Taiwan, and Hongkong was reported to be 13.8, 15.9, and 19.9 cases per 100,000 population, respectively. And from hospital admission perspective, the incidence was 11 to 88 cases per 10,000 admissions and age was found to be a significant risk factor.[6] In the United States, the incidence of DVT remained constant overtime, while the has been a two-fold increase in the incidence of PE over the last decades that might have been partly associated with massive use of more sensitive imaging modalities.[8,9]

In the past two years, there has been an increased incidence of VTE and many have linked it with COVID-19 infection. The incidence of VTE among Coronavirus Disease 2019 (COVID-19) patients ranged from 4.6% to 48%.[10-14]—— Majority of these studies shared similarities in their results where the incidence of VTE was higher in ICU patients.[10,13,14] The development of VTE in COVID-19 patients is associated with poor outcomes as it doubles the risk of mortality.[14] Hence, it is very important to be aware and to understand the course, diagnosis, and management of VTE, particularly in attribution to COVID-19.

Risk Factors

To better predict the possibility of recurrence and direct long-term management of VTE, it is important to categorize VTE patients into provoked and unprovoked group based on the presence of precipitating risk factors.[15] It is considered unprovoked if there is no clear risk factor that precipitates the development of thrombosis and is considered provoked if at least one predisposing risk factor is identified.[15] The risk factors include cancer, acute medical illness, surgery, trauma, immobility (including prolonged computer-related seated immobility), obesity, inflammation, infection, hormone therapy, pregnancy, puerperium period, recent hospitalization, antiphospholipid syndrome, and hereditary risk factors such as familial thrombophilia.[15] The risk factors are further categorized into major transient, minor transient, and persistent risk factors. Patients who experience VTE related to major transient risk factors, including trauma or surgery, estrogen therapy, pregnancy, and puerperium, possess the lowest risk of recurrence following termination of anticoagulant therapy if the risk factor is no longer present.[15-16] When compared to patients with unprovoked VTE, patients with transient risk factors carry lower risk of VTE recurrence after cessation of anticoagulant therapy.[17.18] There recurrence risk is significantly higher in patients with persistent and progressive risk factors, such as cancer.[15]

Pathophysiology

It has been well-understood that the pathophysiology of VTE involves three events that promote the activation of coagulation known as the Virchow's triad.[19] These include impaired blood flow (venous stasis), venous endothelial damage, an increased activity of procoagulants.[15,19] Venous stasis may result from a wide variety of causes, including prolonged immobilization, venous obstruction caused by residual proximal vein thrombosis or external compression by adjacent structures, such as aneurysm, enlarged lymph nodes, pregnancy and tumor; as well as increased blood viscosity and venous dilation.[15,19,20] Injuries to venous endothelium could trigger coagulation. Blood exposure to subendothelial environment triggers platelet adhesion, activation, and aggregation. Hypercoagulable state may develop through contact of blood with collagen on the vessel wall, prosthetic surfaces, polyphosphates released by activated platelets, or genetic material of damaged cells. Coagulation is initiated by blood exposure to tissue factor, by activation of endothelial cells, or by activated monocytes on the site of vascular damage. Among patients with malignancies, factor X can be activated spontaneously by extracts of malignant cells containing cysteine protease.[20] In PE, thrombus formation could result in interference of both circulation and gas exchange. PE induces thromboxane A2 and serotonin expression that subsequently results in vasoconstriction, increased pulmonary vascular resistance, right ventricular (RV) dilation, impaired RV contractility, ventricular desynchronization, and eventually reduced cardiac output and hemodynamic instability.[21]

The increased incidence of VTE among COVID-19 patients has triggered rigorous investigation to elucidate its pathomechanism. Studies have proposed inflammation and hypercoagulation as the primary mechanisms of VTE development in COVID-19 patients.[22] SARS CoV-2 causes endothelial disruption via angiotensin converting enzyme 2 (ACE2) receptor, particularly in microvasculature, leading to formation of microthrombi.[22,23] It is reported that the risk of capillary microthrombus in COVID-19 is up to 9 folds higher.[24] This microthrombus leads to exaggeration of

tissue factor expression. The abundant tissue factor, local hypoxia, and liver dysfunction induce cytokine storm that results in further endothelial dysfunction, increased tissue factor, reduced tissue factor pathway inhibitor, increased activation of coagulation cascade, and impaired anti-thrombin formation.[22] Moreover, COVID-19 has also been associated with fibrinolytic shutdown that is associated with increased morbidity and mortality.[24,25]

Clinical Presentation

Patients with DVT usually present with swelling, pain or cramping, erythema and tenderness of the affected extremity.[1,19,20,26] Majority of patients present with unilateral disease. On the physical examination, a palpable cord, warmth, ipsilateral edema, and visible superficial vein dilation may be found.[1] On measurement, the affected limb has larger calf circumference compared to the contralateral limb.[19] An accelerated discomfort in the calf muscles during passive dorsiflexion of the foot with straight knee can also be found and is referred as Homans sign.[27] To help aiding in making decision for further diagnostic testing, a pre-test probability assessment should be performed. It can be done using a standardized scoring system. Currently, the Wells DVT score has been recommended to evaluate the probability of DVT in patients presenting with suspected DVT symptoms. The results can be interpreted in a three-level (low, moderate, high) or two-level (DVT likely and unlikely) way.[15] However, the prevalence of DVT is around 5% in patients with the lowest Wells score, and hence, this cannot be used as a sole tool for directing clinical judgment.[28]

The clinical presentation of PE is often non-specific.[21] Some patients may be asymptomatic, but for those who develop symptoms, they usually present with either sudden onset breathing difficulties, pleuritic chest pain, pre-syncope or syncope, or hemoptysis in the absence of other causes.[1,19,21] Patients may also present with signs of circulatory collapse which usually correlate with central or extensive PE.[1] On the physical examination, some features may be found, including tachypnea, tachycardia, cyanosis, hypotension, RV heave, a loud pulmonary second sound, and a gallop rhythm.[20] Several features may be found on chest X-ray, including prominent central artery (Fleischner sign), enlarged hilum and mediastinum, oligemia (Westermark sign), and pleural-based areas of increased opacity (Hampton hump).[29] Several non-specific electrocardiographic (ECG) features may also be found, including signs of RV strain (T wave inversion in leads V1-V4, QR in lead V1, S1Q3T3 pattern, and signs of right bundle branch block), particularly in more severe cases.[30] Similar with DVT, in order to direct work-ups for establishing PE diagnosis, it is important to assess clinical probability. This can be done by either relying on clinical judgment based on the patient's clinical presentation and the results from readily available modalities, such as ECG and chest X-ray, or by using standardized prediction rules. Two most frequently used prediction rules include Geneva and Wells score. The result can be translated into three-level (low, intermediate, and high) or two-level (PE unlikely and PE likely) score.[21]

Diagnosis

A series of supporting examinations are needed to aid physician in confirming VTE diagnosis. D-dimer, a fibrin degradation product, would provide significant value to further increase the suspicion towards VTE. In patients with suspected DVT, d-dimer test should be performed in patients with unlikely pre-test probability (Wells score <2).[15]– In patients with suspected PE, d-dimer testing should be performed in patients with stable hemodynamic and unlikely pretest-

probability.[21] A cut-off value of 500 ug/L has previously been recommended as the standard cut-off value owing to its very high sensitivity[15,19] (≥95%)– and negative predictive value (92%-100%)[15,16] particularly when being combined with pre-test probability. However, it is known that d-dimer levels increase with age which leads to a challenge in diagnosing VTE in older patients.[26] Therefore, an age-adjusted cut-off (age x 10 ug/L) has been proposed for use in population >50 years to increase its specificity.[15,21,26]

Diagnosis of VTE relies on the use of imaging modalities as it has a pivotal role in confirming the presence of thrombus in the venous lumen. Venography is considered a gold standard diagnostic modality of VTE; however, it has rarely been performed owing to its invasive nature, use of contrast agent, and radiation exposure as well as the emergence of less invasive yet accurate imaging modalities.[15,21] For DVT, duplex ultrasound (DUS) is the first line imaging study in patients with likely pre-test probability or unlikely pre-test probability with positive d-dimer testing.[15,26] In patients with either likely pre-test probability or positive d-dimer testing, a 2- or 3-point compression ultrasound (CUS) is recommended. Whilst, in patients with both likely pre-test probability and d-dimer testing, a whole leg ultrasound (WLUS) is encouraged.[15] Findings may include non-compressible vein, thrombus visualization within venous lumen, venous dilation, and abnormal spectral and color doppler. The thrombus can be further categorized into acute, acute on chronic, chronic post-thrombotic, or indeterminate. In acute DVT, the thrombus appears in a deformable shape with anechoic or hypoechoic characteristics, centrally localized, and can be accompanied with venous dilation. In a more chronic DVT, the thrombus may be seen as an echogenic non-deformable intraluminal mass with irregular surface. There could also be recanalization of the occluded vein and formation of collateral vessels.[26,31,32] If the results are inconclusive or the examination is not feasible, another imaging study is needed, such as computed tomography venography (CTV), magnetic resonance venography (MRV), or venography.

There is currently no recommendation on which modality serves as the preferred alternative to DUS in diagnosing DVT. CT has a very high sensitivity (89%-100%) and specificity (94%-100%) that is comparable to that of DUS.[15,33] Compared to DUS, it provides better visualization of the pelvic veins and inferior vena cava, helps to evaluate for other concurrent medical conditions producing similar manifestations, and helps to facilitate vessel measurement and intervention planning.[33] However, it is relatively expensive and subjects the patients to the use of iodinated contrast and radiation that limit its use, particularly in selected patients.15 MRV has comparable sensitivity (93%) and specificity (96%) to both DUS and CTV.[34] It's advantages over CTV is debatable, but it can help in distinguishing acute recurrent from chronic persistent thrombus.[15] Nevertheless, it is costly and the use of contrast agent and magnetic wave has limited its use in selected patients, particularly those with ferromagnetic implants.[15,34,35] On the other hand, venography has long been replaced by other previously mentioned modalities and is currently used as the last resort or concurrently with catheter-based intervention.[15] In patients with unprovoked DVT, a series of investigation should be perform to identify other possible causes which include sex-specific cancer screening as well as testing for antiphospholipid antibodies and hereditary thrombophilia.[15]

In suspected PE patients with hemodynamic instability, bedside transthoracic echocardiography (TTE) has been recommended as the first line imaging study to evaluate for any signs of RV dysfunction (including RV dilation, McConnell sign, flattened intraventricular septum, distended and non-collapsible inferior vena cava, decreased tricuspid annular plane systolic excursion (TAPSE), and decreased peak systolic velocity of tricuspid annulus) as a consequence of PE. Patients with evidence of RV dysfunction should be transferred for immediate CT pulmonary angiography (CTPA) if feasible. If not, patients should be treated promptly as high-risk PE. However, in hemodynamically stable patients, those with likely pre-test probability or with positive d-dimer testing should be transferred for CTPA for confirmation of PE diagnosis.[21] Other alternative modalities include planar V/Q scan, V/Q SPECT, and pulmonary angiography.[21]

Treatment

Anticoagulation has been the mainstay treatment for VTE cases. Generally, anticoagulant therapy for DVT patients is divided into three phases. The first is initial phase that lasts for up to 10 days and aims to rapidly instigate anticoagulant therapy and prevent thrombus propagation. The second is the principal phase that lasts for three months and aims to maintain therapeutic levels of anticoagulant, to prevent thrombus propagation, and to reduce the risk of early recurrent VTE. The last is the extended phase with indefinite duration of anticoagulation that specifically aims to reduce long-term risk of VTE recurrence, particularly in patients with persistent risk factors. [36]

Parenteral anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) overlapping with vitamin K antagonist (VKA) in the initial phase followed by VKA monotherapy in the principal patients was traditionally recommended. The introduction of direct oral anticoagulants (DOAC), such as dabigatran, edoxaban, apixaban, and rivaroxaban; has shifted the paradigm in the management of VTE.

Currently, the 2021 Guidelines form the European Society of Vascular Surgery (ESVS) has recommended the use of DOACs over LMWH/VKA for the treatment of both provoked and unprovoked DVT. The treatment strategy is based on bleeding risk stratification. In patients with non-cancer or pregnancy-related provoked proximal DVT who are considered having low bleeding risk, early thrombus removal by means of surgical thrombectomy, catheter-directed thrombolysis (CDT), or pharmaco-mechanical CDT, is recommended in selected patients with symptomatic iliofemoral DVT while maintaining anticoagulant therapy. In patients with low to high bleeding risk, therapeutic anticoagulation should be given for at least three months and DOACs are preferred over LMWH/VKA. For patients with extremely high bleeding risk or with active bleeding, temporary inferior vena cava filter is recommended until bleeding risk subsides to start anticoagulation. Throughout the course of anticoagulation, it is recommended to give compression therapy at 30-40 mmHg to help reduce DVT symptoms and to prevent the development of post-thrombotic syndrome. Discontinuation of compression therapy is based on the assessment of Villalta score.

If the treatment is uneventful, the decision to stop anticoagulation should be based on the underlying risk factors. Patients with DVT related to major transient risk factor, anticoagulation can be stopped at three months and another WLUS evaluation can be considered. In patients with

minor transient or persistent risk factors, extended treatment is recommended with periodic re-assessment. If there is recurrent event, several strategies can be considered, including switching the type of anticoagulation, increasing the dose of current anticoagulant, or switching to VKAs with a higher INR target. For these patients, an extended approach is recommended. Treatment strategy for unprovoked DVT is quite similar. However, bleeding risk stratification should be reassessed at three months. In patients with low to moderate bleeding risk, follow-up DUS and/or d-dimer can be considered and extended anticoagulation is recommended. In patients with high bleeding risk, anticoagulation should be discontinued and follow-up DUS examination and antiphospholipid antibodies can be considered. If there is an episode of recurrent DVT, an extended approach is recommended.[15]

In patients diagnosed with acute PE, anticoagulation should be administered immediately. If there is hemodynamic instability, the patient is considered high risk and should be transferred for early reperfusion treatment along with hemodynamic support. For hemodynamically stable patients, clinical severity assessment with pulmonary embolism severity index (PESI) or its simplified version (sPESI) and assessment of RV dysfunction through TTE or CTPA is recommended to distinguish low from intermediate risk patients. Patients with PESI class III-IV or sPESI ≥ or postive RV dysfunction should undergo troponin testing. Those with troponin positive are considered intermediate-high risk and should be monitored and considered for rescue reperfusion strategy if there is clinical deterioration. Those with troponin negative are considered intermediate-low risk and should be hospitalized and continue anticoagulation treatment. If neither high PESI nor RV dysfunction is found, patients can be discharged for home treatment if there is no other reasons for hospitalization, the patients have adequate family or social support, and have an easy access to medical care. If not, hospital care is recommended.[21]

As the incidence of VTE increases with COVID-19, attention has been focused on constructing preventive and therapeutic strategy of COVID-19-related VTE. For ambulatory patients, there is no evidence in prescribing prophylactic anticoagulation, hence this strategy is currently not recommended. Patients with mild condition who are subjected to home isolation should maintain adequate hydration and mobilization throughout the course of COVID-19 infection. Some also recommend to perform risk stratification using PADUA score for non-surgical patients and CAPRINI score for surgical patients. For stable hospitalized patients, thromboprophylaxis should be given throughout the course of hospital care. Guidelines recommend the use of LMWH or fondaparinux over UFH, however, UFH is more recommended than DOAC. For critically-ill patients, thromboprophylaxis with LMWH is preferred over UFH and fondaparinux. In patients who are contraindicated to anticoagulant prophylaxis, mechanical thromboprophylaxis is recommended. Routine DUS screening is currently not recommended in all patients.[37–39]

Ambulatory COVID-19 patients with confirmed VTE should be given oral anticoagulation with DOACs if there is no drug-to-drug interactions. It is recommended that parenteral anticoagulation should precede the administration of dabigatran and edoxaban. VKA can be another alternative and should initially overlap with parenteral anticoagulant. The treatment should be maintained for at least three months. For stable hospitalized patients, parenteral anticoagulation with LMWH or

UFH should be given throughout the course of hospitalization. If no drug-to-drug interaction is present, DOAC/VKA can be given accordingly. The treatment should also be maintained for at least three months. In patients with critical illness, anticoagulation should be given with LMWH or fondaparinux. UFH can be given in patients with high bleeding risk, renal failure, hemodynamic instability, and those planned for reperfusion therapy. Thrombolysis is only recommended for patients with hemodynamic instability.[37–39]

Case Report and Discussion

A male patient, 63 years, presented to our emergency department complaining an abrupt onset of severe pain accompanied by calf swelling and red-blue discoloration on his left lower extremity for two days. Two weeks before his complaints emerged, the patient experienced upper respiratory symptoms which included non-productive cough, rhinorrhea, sore throat, and anosmia, and underwent polymerase chain reaction (PCR) testing for SARS CoV-2 of which he was declared positive for COVID-19. He was in self-quarantine for two weeks before presenting with the lower limb symptoms. Significant clinical findings included unilateral left-sided lower limb edema with red-purple discoloration, small ulcers on the dorsal of third, fourth, and fifth toes, reduced local sensory and motor functions, poikilothermy, as well as pulseless left popliteal, posterior tibial, and dorsal pedis arteries.

The only remarkable laboratory findings were reduced renal function and highly increased c-reactive protein (CRP) (248.3 mg/L) elevated d-dimer (35,200 mg/dL), while the Chest X-Ray image showed signs of pneumonia. The clinical presentation also indicated a high suspicion for acute deep venous thrombosis (Wells score 3). Since the patient is considered likely for acute DVT, a DUS examination was performed which revealed thrombosis of the left distal superficial femoral, popliteal, and posterior tibial veins as well as occlusion of the left common femoral artery all the way to the anterior tibial artery.

The patient was diagnosed with moderate COVID-19 with pneumonia, concomitant grade IIB acute limb ischemia (ALI) and DVT, acute kidney injury, and suspected sepsis. As an initial treatment, anticoagulation therapy was immediately given with continuous UFH infusion of 15,000 U/24 hours that was later increased to 20,000 U/24 hours. Since the patient was diagnosed with grade IIB ALI, a more aggressive strategy was directed towards limb salvage. Therefore, the patient was planned for urgent arterial revascularization through percutaneous aspirational thrombectomy. Whilst, the treatment for DVT relied on the use of optimal anticoagulation. The procedure was eventful and immediately terminated. The patient was then transferred to intensive care unit. After a long course of hospitalization and a series of fluctuating clinical conditions, the patient passed away at day 22 of hospitalization due to septic and cardiogenic shock and suspected pulmonary embolism.

Summary

We presented an acute VTE patient who came with no prior history of VTE risk factor other than COVID-19. It also is interesting that the incidence of VTE occurred concomitantly with acute limb ischemia. This coincidence has made the treatment strategy more complicated. Comprehensive

understanding of VTE is important since early recognition and prompt treatment are fundamental. It is very important to be aware of VTE risk in the era of COVID-19 infection as the incidence has been proven to be increasing and the overall effect is detrimental. Studies have shown that early prophylactic anticoagulation has been associated with better survival. Clinical decision in such patients should be individualized as the course of illness might be different from one to another.

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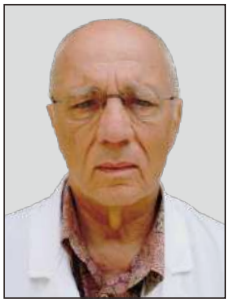
HOW TO SPEAK TO PATIENTS



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Abstract
Bad news: any news that negatively changes the patient's view of future. Comunication with patients/relative is of utmost importance. It is difficult as it is not teached at Universities. During comunication: be honest, be careful with the prognosis, do not vanish patient's hope, do not give unrealistic hope, use evidence based medicine. Use words carefully. Check patient's understanding. Use available protocols.

Comunication with patients/relatives is crucial. It is difficult as there is no teaching at most Universities. This is especially true for bad news: *"any news that negatively changes the patient's view of future"* [1,2]. One more challenge is due to the powerful influence of media on knowledge about health [3]: indeed newspapers reported more frequently less quality studies [4]. This has been clear in the current anti-vaccination campaign by No-Vax people during the COVID-19 pandemic [5].
Bad communication can be a reason for legal action actions against doctors. Relations and communication with physicians—and eventually dissatisfaction—also have a major role [6,7]. Dissatisfaction may result from poor patient-physician relationships and/or inadequate communication.
Another important issue to consider when discussing with patients/relatives is prognosis. A study reported that when evaluating the prognosis of terminal patients, only 20% of doctor's predictions were accurate, whereas 63% were overoptimistic and 17% overpessimistic [9].
A survey of patients with chronic obstructive pulmonary disease (COPD) reported that patients' knowledge of their cholesterol levels and blood pressure was greater than of their FEV1 [10].

How to improve our communication skills.
Usually neither medical students nor residents are taught communication, and to be optimistic skills are learned from watching seniors and teachers, to be realistic, each doctor will learn by her/his professional life, at his/her and patients' expenses.
Some protocols can be used:

The SPIKES protocol [11] involves 6 steps:
- **S**-SETTING up interview
- **P**-Assessing the Patient's PERCEPTION
- **I**-Obtaining patient's INVITATION
- **K**- Giving KNOWLEDGE and information to the patient

- **E**-Adressing the Patient's EMOTIONS with Emphatic Responses
- **S**-STRATEGY AND SUMMARY

Other protocols like the ABCDE [2] have been proposed:
Advance preparation.
Building a therapeutic relationship.
Communicating well.
Dealing with patient and family reactions.
Encouraging/validating emotions.

Conclusion

Breaking bad news is one of a physician's most difficult duties, yet medical education typically offers little formal preparation for this task. Without proper training, the discomfort and uncertainty associated with breaking bad news may lead physicians to emotionally disconnection from patients. Focused training in communication skills and techniques to facilitate breaking bad news has been demonstrated to improve patient satisfaction and physician comfort.

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OVERCOMING LANGUAGE AND CULTURE BARRIERS IN TRAINING

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It may seem odd to use references mostly to Western medicine and the Greek philosophers to discuss overcoming language and cultural barriers. One reason for this is, in fact, to help raise awareness about Western thinking so physicians from non-western cultures might better understand intrinsic biases based on societal constructs and history of philosophical thought. The topic itself is actually quite complex and broad in scope. It helps to have some understanding in areas of educational methodologies, philosophy of teaching, human psychology, and cognitive behavior. My purpose is simply to present a few of my thoughts on the subject and to indicate why it warrants consideration for further reflection and presentations at our own respiratory conferences and even more so, in writings submitted for publication in our specialty journals.

The fresco by the sixteenth-century Italian Renaissance artist, Raphael, is *The School of* Athens1 was painted sometime between 1509 and 1511. It depicts some of the greatest philosophers and mathematicians of classical antiquity. In the center is an older man who strangely resembles Leonardo da Vinci. There is also the Greek philosopher Plato. He has long grey hair and is walking in his bare feet.

Plato was born in 428 BCE and died about eighty years later, in 348 BCE. His life covered the tumultuous period between the Peloponnesian War and the capture of Olynthus by Philip II of Macedonia, father of Alexander the Great. When Plato was forty, he founded The Academy, which he directed until his death. In Raphael's painting, Plato points upwards towards the *cosmos,* wherein truth, beauty, justice, and wisdom lie. Among his teachings is the *Dialogues,* and in these are perhaps Western Civilization's first thought experiments regarding systems of knowledge[2].

One of the Dialogues is called *The Meno*. In this story, Plato describes how Socrates can lead one an uneducated young slave boy who has never had geometry lessons-through a series of questions until the boy finds for himself several facts about squares and triangles. This raises the question of how the boy is able to discover geometric truths without prior instruction. Plato's answer is that Socrates reawakened in the boy's mind knowledge remembered from an earlier existence. In other words, that some aspects of knowledge and understanding are innate—they are part of our human nature, as biologically endowed as the color of our skin.

To Plato's left in the painting is a younger man with brown hair, sandals, and a golden robe. This is Aristotle, Plato's student, the founder of a school in Athens called the Lyceum. He carries one of his books, *Nichomachean Ethics*, in his left hand. His right hand is held downward because, in his

philosophy, the only reality is what we can observe and experience through our physicality. In other words, only what we can see and touch is real. Aristotle, therefore, has been called the father of empirical biology, ethics, political sciences, and logic.

Aristotle and Plato represent two clearly opposing philosophical cultures. By culture, we usually mean "the collective programming of the mind that distinguishes the members of one group or category of people from others".[3] The linguistic anthropologist, Alessandro Duranti, taught that, "A common view of culture is that of something learned, transmitted, passed down from one generation to the next, through human actions, often in the form of face-to-face interaction, and through linguistic communication."[4]

Cultures are identified according to national or professional groups but might also be defined by ethnicity, gender, disability, sexual orientation, educational background, socioeconomic factors, religion, language, and communication styles. These include eye contact, time orientation, touch, verbal and nonverbal messaging, personal space, or conversation style. People across different cultures may appear to be similar, or look and act differently. They may differ in how they perceive the world, in how they communicate with those outside of their group or with each other, and they may have different values and opinions for what they consider important in their lives.

Culture also comes from a place of shared experiences, behaviors, history, traditions, or when people are bound together by a common purpose. It gives rise, however, to many prejudices, manners, and opinions. Cultural barriers exist when disagreements or misunderstandings are caused by differences in expectations and behaviors, most often related to differences in language, semantics, values, beliefs, or the presence of ethnocentrism and stereotyping. This means that for educators to be most effective, they should take into account their own cultural biases as well as become aware of which attitudes, beliefs, values, and behaviors are shared or might differ among their students.

Providing another definition, the anthropologist, Clifford Geertz, wrote that "Humans are almost infinitely variable by nature…each of us is made what we are, in other words, our beliefs, values, tastes, intellectual predispositions, and practices, by the culture into which we are born."[5]
These definitions illustrate how culture is identified at both the physical and social levels. While culture refers to a unity of arts, literature, music, and humanities, it is also expressed by a series of commonalities between groups of people.[6] Culture also reflects interpersonal differences and human psychology.

Experts in cross-cultural research, however, are uncertain about how much group-level culture impacts a given individual. In other words, one size does not always fit all. According to Kim and Markus,[7] cultures should also be conceptualized as constantly changing, so we need to be cognizant of the overlap that might exist among elements that constitute individual- and group-level cultures. Generalities should not be taken for granted, particularly as new generations are influenced by cross-cultural practices, travel, and communication technology such as social media. Research in cross-cultural psychology shows that as we engage with sociocultural

contexts, we reinforce and sometimes change the ideas, practices, and institutions of our environments.[8]

It is easy to imagine how culture is coupled to cognition and communication. In Japan, for example, social harmony is a priority. The Japanese language is consequently an indirect language, which is important for people to maintain harmony or to save face. Despite having strong opinions, there is usually no desire to offend, and in an effort to avoid conflict, the Japanese may try to avoid using the word “no” as much as possible. In fact, at least sixteen ways to signal “no” have been described, many of which are impossible to decipher for non-native speakers unless they are perfectly bicultural and linguistically fluent.[9]

A well-known example of how culture and language can be harmful was a study of airline pilot behavior in the cockpit. In the 1990s, a culture of deferring to one's superior impaired honest communication that might have prevented the crash of two airliners. These were Avianca flight 52 from Bogota and Korean Air flight 801 to Guam.[10]

Another example, though risking stereotyping, is related to differences in verbal and non-verbal communication. Scandinavians are known for being quiet people who, in conversation, will each talk in turn as a demonstration of attention or respect. To speak simultaneously with another is considered impolite. Many Southern Europeans, on the other hand, including Spaniards, Greeks, and Italians, might engage in passionate discussions where listeners show interest and passion through lively hand gestures and talking loudly simultaneously.[11]

Several different models have been proposed to study the effects of culture. One of the more commonly used is Hofstede's cultural six-dimension model. Based on data collected from International Business Machine corporation (IBM) sites in 70 countries, Dutch social scientist and engineer Geert Hofstede conducted comprehensive studies of how values in the workplace are influenced by culture. He originally proposed four, now expanded to six different bipolar dimensions validated by numerous researchers. These are (1) Power Distance; (2) Uncertainty Avoidance; (3) Individualism/Collectivism; and (4) Masculinity/Femininity, and two additional dimensions introduced to reduce potential ethnocentric biases; (5) Long and Short-term orientation; and (6) Restraint/Indulgence.[12-15]

An example of how these cultural dimensions might change over time is a comparison study of Japan, traditionally a country with high Collectivism scores, and the United States, traditionally a country with high Individualism. The collective tendencies of Japan's culture suggested Japan was less likely to tolerate individual behaviors that jeopardized societal norms and group interests.[16] Recent findings show reductions in such collectivism, suggesting a changing workplace environment where employees might be more inclined to speak their minds and where success is increasingly measured by individual achievement.[17]

An example of how cultural dimensions might be used to design educational programs is found in a recent study by Ibanez and Sisodia.[18] The investigators examined the role of culture on SARS-

CoV-2 pandemic management in Scandinavian and European Mediterranean countries, using prevention of COVID-related death as a major outcome variable. One conclusion was that Scandinavian public policies might be designed according to the region's lower Masculinity and Power Distance indices, suggesting a consensus-based strategy might have broad acceptance and compliance for norms, regulations, and recommendations to reduce the number of COVID-related deaths. A more top-down approach might be needed to implement public policies in European Mediterranean countries that have significantly higher Power Distance and Masculinity indices.

Educators are often more effective when they are familiar with various concepts of culture. They can thus learn how to address potential cultural barriers. Based on my own experience conducting dozens of Faculty Development Courses around the world,[19,20] I would like to suggest that educators use a 4-point strategy. This strategy includes one precautionary measure and three different approaches.

The precautionary measure is to be aware of the dangers of ethnocentrism.[21] Ethnocentrism denotes a positive orientation toward those sharing the same ethnicity and a negative one toward others. It is also a term anthropologists use to describe the opinion that one's own way of life is natural or correct. This problem affects all cross-cultural interactions. We are all naturally ethnocentric, and it isn't easy to imagine that people elsewhere might think and want things differently from what we believe and want ourselves. Practically speaking, ethnocentrism, which is also a form of colonialism, is seen when Western Europeans and North Americans assume that theories tested on subjects from their own cultures are universally applicable. Educators, and especially those from developed countries, should be vigilant of the potential dangers and ill effects of projecting their beliefs, values, and biases on others.

With this constantly in mind, educators can implement their favorite combination of different approaches. The first of three is to adopt what is referred to as an ASK™ perspective when working with groups and individuals. By using this technique, teachers can become more aware of cultural similarities and differences with and among their students.[22] ASK™ is a time-proven, realistic approach to providing cross-cultural health care. The A.S.K stands for *Awareness, Sensitivity, and* Knowledge. Using this approach, educators should assume that treating everyone equally and with respect is not enough, and that applying cultural “facts” to a particular group might actually lead to stereotyping and insensitive, though usually unintentional ethnocentric signals and behaviors. Philosophically, A.S.K means taking the 'me' out of life's equation and replacing it with a learner-centric perspective where the teacher's interests are secondary to those of the student. The approach begins with generalizations about culture but proceeds with an inquiry into whether individual learners consider themselves typical or different from others in their cultural group. Educators can then adapt their verbal and non-verbal communication styles and teaching methods accordingly.

A second approach prompts educators ponder the fundamental question; *“how should I teach?”* It does not matter whether teaching is in the context of online or distant learning, a flipped classroom,

a group workshop, individualized instruction, or an auditorium. Fenstermacher and Soltis, for example, describe an Executive, Liberationist, and Facilitator method of teaching.[23]

Using the *Executive* method, knowledge might be seen as an end in itself, as something to be acquired. On the other hand, *Liberationists* view knowledge as a set of insights, ideas, theories, and understandings that must ultimately be used practically and effectively. *Facilitators* focus on building relationships and methods of inquiry as a means to acquiring knowledge. They refuse to see learners as passive recipients of information and prefer to serve as guides or coaches in order to help learners in their journey of self-discovery and improvement.

It is clear that cultural differences can present challenges to any teaching method, partly because cognitive change is an individual process and because learning usually occurs collaboratively within a social or professional context.[24] For this reason, educators should ideally be able to identify their teaching methodologies and learn to adapt or combine their methods to achieve training goals within a particular context and teaching environment. Flexible programmatic structures and the judicious use of *multicultural teams* with diverse skill sets strengthen educational endeavors.

A third approach to overcome cultural barriers pertains to one's *personal philosophy of teaching*. A good practice is for educators to write their philosophy down on paper, and to revise it overtime as needed. This cognitive exercise brings methodology to the forefront of one's consciousness, and provides opportunity for critical analysis and revision. Writing down one's personal philosophy does not require in depth knowledge of academic studies or an understanding of educational philosophies such as Perennialism or Essentialism. Instead, it relies simply on educators taking ownership and being accountable their personal vision. Such a narrative can be as simple as making a one paragraph declarative statement or jotting down a few sentences that describe the educator's goals, motivations, favorite role models, and preferred teaching methods. The exercise can be made even more personal, and relevant to each particular setting, if the educator adds a few examples from their personal experience.

Articulating a personal philosophy provides educators with a roadmap for daily practice and helps foster changes in teaching behaviors. In addition to enhancing professional growth, and providing greater awareness of potential and real obstacles, this approach provides strategies to overcome those obstacles and provides an opportunity for the educator become a better person.

In light of what has been said in this essay, and returning to Raphael's painting, *The School of Athens,* the portrayal of cultural opposition between Plato and Aristotle takes on a new significance. Complicating matters somewhat is the presence of a third person. One whose historical significance cannot be doubted in the history of Western philosophy. Dominating the foreground on the steps to the right of Plato sits a man wearing a tunic and brown leather boots. He is scribbling. His head is rested on his hand in the classic *Thinker's* position, and strangely the man resembles Michelangelo. Experts presume he actually represents the pre-Socratic philosopher Heraclitus, who lived around 500 BCE in Ephesus, then part of Ionia, a Greek-inhabited region under Persian control. Today, the region is known as Izmir in modern-day Turkey.

Heraclitus was probably self-taught. He distanced himself from other thinkers of his age, and preferred coming up with original aphorisms and short sentence to describe philosophical truths, if one believes in that sort of thing. Today, Heraclitus is perhaps most known for his doctrine of constant change…that we cannot step in the same river twice because the river is ever-changing. On a similar note, he also taught that opposites such as night and day, sleep and wakefulness, and life and death actually coincide, each becoming one. This is often referred to as the interconnectedness of contrary states.[25]

Teachers and learners have deep-seated cultural assumptions that easily complicate cross-cultural interactions in a training environment. Sometimes these assumptions create what appear to be contradictory or contrary states that make learning and the transmission or exchange of knowledge difficult. Heraclitus taught that "learning many things does not teach understanding." We can all learn to apply techniques, theories, and different methodologies, but understanding, in its many forms, seeing the other through a different lens than our own, is an important step toward unlocking most if not all cultural barriers.

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PREVENTION OF PNEUMOCOCCAL INFECTION

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PREVENTION OF PNEUMOCOCCAL INFECTION

Lower respiratory tract infections, including pneumonia, represented the fourth leading cause of death worldwide in 2019. Community-acquired pneumonia (CAP) is additionally associated with high hospitalization rates (50%–77% for patients aged ≥60 years), high intensive care unit (ICU) admission rates (18%), and high mortality rates (11.4% within 30 days). Importantly, cardiovascular complications are observed in many CAP patients — between 14% and 18% in two meta-analyses — and are associated with increased short-term and long-term mortality. Streptococcus pneumoniae is the most frequently isolated bacterial pathogen in CAP and is a leading cause of CAP, meningitis, and bacteremia. Invasive pneumococcal disease (IPD) includes pneumococcal pneumonia, bacterial meningitis, bacteremia, and septicemia.

Pneumococcal infection begins by contact with saliva or nasopharyngeal secretions and proceeds to nasopharyngeal carriage. Local spread culminates in mucosal disease (non-bacteremic pneumonia, otitis media, or sinusitis), whereas aspiration can potentially lead to IPD. A preceding viral upper respiratory tract infection often triggers the onset of more severe pneumococcal disease. There are a number of established risk factors for CAP. Patients aged ≥ 60 years account for a majority of cases and hospitalizations, with incidence rates much higher in this age group than in the rest of the population. Symptoms in older adults are often more subtle, potentially delaying diagnosis and treatment, and patients aged ≥ 65 years have a higher mortality rate within 1 year after hospitalization than that of the general population or people hospitalized for other reasons.

Frailty is a related risk factor for CAP, associated with higher 1-year mortality resulting from CAP and inversely related to serotype-specific immune responses to pneumococcal conjugate vaccine administration. Behavioral factors, including cigarette smoking, passive smoking in non-smokers aged >65 years, and high alcohol consumption also are risk factors for CAP. Similarly, environmental factors such as long-term care and homelessness present increased CAP risk. Comorbidities (e.g., heart disease, diabetes, and chronic respiratory diseases) are known to increase the risk of pneumococcal pneumonia in adults. Risk is further increased by the presence of multiple underlying conditions or immunocompromising conditions. Compared with healthy individuals in the same age group, risk of CAP is magnified approximately 3-fold in the at-risk population and 4-to 6-fold in the immunosuppressed population.

Vaccination is the only public health strategy proven to reduce IPD and non-bacteremic pneumococcal pneumonia incidence, by activating an immune memory against the vaccine-specific serotypes.

Two types of pneumococcal vaccines are recommended for adults - 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck and Co., Inc., Whitehouse Station, NJ), with antigens of serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F; and 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar/Prevenar 13, Pfizer Inc, New York, NY), containing antigens of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to non-toxic diphtheria CRM197 protein. Conjugation involves covalently linking polysaccharide antigens to a carrier protein, stimulating T cells to help B cells produce antibodies and generate immune memory (ie, T-cell−dependent immune response), as opposed to the less efficacious T-cell−independent immune response induced by PPSV23. Evidence for PPSV23 vaccine efficacy against non-invasive (non-bacteremic) pneumococcal pneumonia is inconclusive.

A meta-analysis of nearly 30,000 older adults showed that with the exception of 1 study in Japanese nursing home residents, PPSV23 has not been proven to be effective against pneumococcal pneumonia in older and at-risk adults but seems to reduce the risk of bacteremia. Findings from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), which randomized 84,496 vaccine-naive subjects aged ≥65 years in the Netherlands to receive PCV13 or placebo, demonstrated PCV13 efficacy in preventing first episodes of vaccine-type (VT) pneumococcal CAP (primary endpoint; 46% vaccine efficacy, $p<0.001$), VT non-bacteremic/non-invasive pneumococcal CAP (secondary endpoint; 45% vaccine efficacy, $p=0.007$) and VT invasive pneumococcal disease (IPD) (secondary endpoint; 75% vaccine efficacy, $p<0.001$).

Despite the overall decrease in IPD after widespread use of PCV, there is substantial remaining invasive and non-IPD in the post-PCV era attributed to non-PCV13 serotypes, highlighting the need for further expanded valent PCVs to broaden protection against PD. The global PD burden remains considerable, with an estimated 44.7 million cases of pneumococcal lower respiratory tract infections and 341,029 associated deaths occurring in children <5 years of age in 2016. An increase in non-vaccine type IPD has been observed, especially in adults over the age of 65, a process known as replacement disease. Non-vaccine serotypes are now the major source of pneumococcal antimicrobial resistance.

To expand serotype coverage, a 15-valent (Vaxneuvance, PCV15) and a 20-valent PCV (Prevnar 20, Apexxnar,PCV20) containing PCV13 components and either 2 or 7 additional serotypes have been developed (22F, 33F in PCV15 and 8, 10A, 11A, 12F, 15B, 22F, 33F in PCV20). Registration trials have demonstrated a robust immune response to these additional serotypes and, accordingly, the FDA in the US and EMEA in Europe, have approved their usage.

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ESSENTIAL LABORATORY TESTS IN RESPIRATORY FAILURE

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INTRODUCTION

Respiratory failure is defined as a failure of gas exchange due to inadequate function of one or more essential components of the respiratory system. Clinically, respiratory failure can be manifest either as hypoxemia (Po2< 60 mmHg at sea level), i.e. inadequate blood oxygenation; hypercarbia (Pco2 > 45 mmHg) i.e. excess of circulating carbon dioxide; or frequently, a combination of both types of gas exchange abnormalities. Respiratory failure is classified as hypoxemic, hypercarbic; or combined.[1]

Respiratory failure may develop either acutely or chronically. In acute respiratory failure, a sudden, catastrophic event leads to life-threatening respiratory insufficiency. In chronic respiratory failure, gradual worsening of respiratory function leads to progressive impairment of gas exchange, the metabolic effects of which are partially compensated by adaptations in other systems. In patients with long-standing respiratory disease, compensated chronic respiratory insufficiency may exist for many years, resulting in a state in which patients do not have true respiratory failure but have little or no functional respiratory reserve. In such cases, even a mild disturbance respiratory system can precipitate acute on chronic respiratory failure.[1]

Etiology

Etiology of respiratory failure can be classified according to the type of dysfunction which can be classified as:[1]

1. Controller
2. Pump
3. Airway
4. Alveolar
5. Pulmonary vascular.

Controller dysfunction

The most frequent cause of controller dysfunction is the presence of medications that impair respiratory drive, many of which also impair the level of consciousness. A history of the use or respiratory depressants or an impaired level of consciousness prior to the administration of medications to facilitate intubation suggests the possibility of controller dysfunction.[1]

Causes of controller dysfunction are sedative medications, chronic obstructive or interstitial lung disease, toxic overdoses, hypothermia post operatively and brainstem stroke.[1]

Laboratory tests for dysfunction of controller is blood gas analysis (BGA) and the other laboratory tests depend on the etiology which are listed in table [1.1,2]

In sedative medications, blood gas analysis (BGA) reveals hypercarbia. In chronic obstructive or interstitial lung diseases, BGA reveal hypoxemia and hypercarbia.[1,2]

In toxic overdoses, BGA reveals hypoxia and hypercarbia. Besides BGA, toxicology screening is important to find the causative agent.[1-3] In hypothermia post operatively, BGA reveals hypercarbia.[1,2]

In brain stem stroke, BGA reveals hypercarbia. It is important to look for the risk factors of stroke such as dislipidemia (high total and LDL cholesterol, low HDL cholesterol), diabetes mellitus (blood glucose, HbA1c) and hypercoagulable state (thrombocyte hyper-aggregation, shortened Prothrombin time/PT and shortened activated partial thromboplastin time/APTT).[1,2]

Pump dysfunction

Pump dysfunction is a common cause of respiratory failure in intensive care unit (ICU) patients with respiratory failure and it is usually multifactorial. Various medications, prolonged period of mechanical ventilator support, and polyradiculopathy associated with critical illness can all affect the respiratory muscles. Laboratory tests for pump dysfunction are listed in table.[1.1,2]
In medications overdoses such as paralytics, aminoglycosides and steroids, BGA reveals hypercarbia. In botulism, BGA reveals hypercarbia.[1,2]

In myopathy and myositis, BGA reveals hypercarbia. Besides hypercarbia there are increase of creatin kinase (CK) and aspartate transaminase (AST) released by myocardium cells.[1,2]
In hypothyroidism, BGA reveals hypercarbia. There are increase level of thyroid stimulating hormone (TSH), decrease level of free triiodothyronine (FT3), and/or decrease level of free thyroxine (FT4).[1,2,4]

In hyperphosphatemia, BGA reveals hypercarbia. There is increase level of serum phosphate > 5.5 mg/dL.1,2 It can happen in renal failure, hypoparathyroidism and neoplasms.[2]

In myasthenia gravis, BGA reveals hypercarbia.[1,2] Anti-acetylcholine receptor antibodies is the standard test. Myasthenia gravis with inflammatory myopathy can reveal elevated level of creatine kinase and deficiency of vitamin D3 may play a role in myasthenia gravis.[1,2,5]

In Guillain-Barre syndrome, BGA reveals hypercarbia. Cerebro-spinal fluid (CSF) analysis shows albumin-cytologic dissociation with normal cell count and increased protein (average 50 – 100 mg/dL). Protein increase parallels increasing clinical severity; increase may be prolonged. CSF may be normal at first.[1,2]

In paraneoplastic syndromes, BGA reveals hypercarbia. Tumor marker tests are important to evaluate the associated cancers i.e. lung, breast, ovary, thymoma and Hodgkin lymphoma.[1,2]
In polyradiculopathy of critical illness, BGA reveals hypercarbia. In postoperative or post-radiation therapy phrenic nerve dysfunction, BGA reveals hypercarbia.[1,2]

In post operative pain/splitting which cause wound dehiscence, BGA reveals hypoxemia and hypercarbia.[1,2]

Airway dysfunction

Airway dysfunction can be assessed at the bedside. Stridor suggests the presence of large airway or laryngeal obstruction. Bronchospasm can be diagnosed by auscultation and detection of wheezing and/or rhonchi. Coarse breath sounds or rhonchi present during the inspiratory phase of respiration usually indicate obstruction of the large airways, frequently from retained secretions. Laboratory tests for airway dysfunction are listed in table[1.1]

In mild asthma, BGA reveals hypoxemia and hypocarbia but in severe asthma, BGA reveals hypoxemia and hypercarbia. The stimuli that can incite acute asthma attack can be grouped into seven major categories: allergenic, pharmacologic, environmental, occupational, infectious, exercise related , and emotional. In allergenic asthma, allergens can be identified by serum allergic testing, there is increase of IgE and the infectious agent can be identified by sputum culture of nucleic acid amplification testing.[1,2]

In emphysema and chronic bronchitis, BGA may reveal hypoxemia and hypercarbia. The complete blood count may show elevated leucocyte count and neutrophilia. In emphysema, deficiency of alpha-1 antitrypsin can be found.[1,2,6]

In bronchiolitis, BGA may reveal hypoxemia and hypercarbia. Complete blood count may show elevated leucocyte count and neutrophilia. Sputum Gram stain and culture may reveal the infectious agent if there is any.[1,2]

In endobronchial tumor, mass, or stricture, BGA may reveal variable results.[1,2]

Alveolar dysfunction

In pneumonia, BGA may reveal hypoxemia and hypercarbia. Complete blood count may show elevated leucocyte count, neutrophilia and some times high stab neutrophils (left shift). C reactive protein (CRP) usually increase and procalcitonin may increase if the pneumonia causes intermittent bacteremia. Sputum Gram stain, followed with sputum culture and susceptibility testing are needed to identify the causative agent and its antimicrobial susceptibility testing.[1,2,7]

In pulmonary edema, BGA reveals hypoxemia and hypercarbia. Complete blood count may show elevated leucocyte count and neutrophilia if there is accompanied pneumonia. If the pulmonary edema is caused by heart pumping dysfunction, there is increase of Brain natriuretic peptide (BNP) or N terminal pro brain natriuretic peptide (NT pro BNP). If the pulmonary edema is caused by acute kidney injury there is increase of blood urea and creatinine level.[1,2,8]

Pulmonary hemorrhage can be caused by autoimmune disorders, cardiac disorders (mitral stenosis), coagulation disorders, drug reactions (propylthiouracil, diphenylhydantoin), hematopoietic stem cell transplantation, idiopathic pulmonary hemosiderosis, or pulmonary

infections by Hantavirus. In pulmonary hemorrhage BGA reveals hypoxemia and hypercarbia. Complete blood count may reveal elevated leucocyte count and neutrophilia. In autoimmune disorders, antinuclear antibody (ANA), anti double stranded- DNA, and anti-phospholipid antibody test can give positive result. In coagulation disorders, thrombocyte count may decrease, prothrombin time and APTT may give prolong result.[1,2]

Acute Respiratory Distress Syndrome (ARDS) belong to alveolar dysfunction. ARDS can be classified into direct injury and indirect injury, which can be seen at table[2,9,10]

Pneumonia caused by bacteria or virus, can cause ARDS which lead to respiratory failure. BGA may reveal hypoxemia and hypercarbia. In bacterial pneumonia, CBC may reveal elevated leucocyte count and neutrophilia, elevated CRP, and elevated procalcitonin (PCT). D-dimer may be elevated when disseminated intravascular coagulation (DIC) happened. Sputum Gram stain, microbiological culture and susceptibility testing can help identify the causative bacteria.[1,2,7,10]

In viral pneumonia caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona virus-2), nucleic acid amplification testing to detect the virus from naso and oro-pharyngeal swab are important to do. It will be useful if laboratory can do multiplex polymerase chain reaction (PCR) testing (syndromic testing) from rhino and oro-pharyng to differentiate the etiology whether it is bacteria or virus because viral pneumonia does not need antibiotic therapy. CBC may reveal decrease level of leucocyte count and also lymphocytes percentage. Increase level of Interleukin-6 and Interleukin-1 are signs of cytokine storm.1,2,11 Increase level of D-dimer can help identify the hypercoagulable state induced by the virus.[1,2,12]

In cases of aspiration of gastric contents, blood gas analysis may show hypoxemia and hypercarbia when pneumonia has developed. Complete blood count may show leukocyte increase and neutrophilia caused by the chemical injury by the gastric acid and also by the bacteria in the gastric content. Sputum Gram stain may reveal the bacteria morphology, and sputum culture may identify the etiology bacteria and also its sensitivity to antimicrobial agent.[1,2,13]

In pulmonary contusion, BGA may reveal hypoxemia and hypercarbia. CRP and leucocyte count may increase because of the lung tissue injury. D-dimer may increase if capillary hemorrhage develop.[1,2]

In near drowning cases, aspiration of water may cause pneumonia. BGA may reveal hypoxemia and hypercarbia. CBC may show an increase of leucocyte count with neutrophilia because of the bacteria contained in water, may cause pneumonia. If pneumonia develop, sputum Gram stain and culture may show the causative bacteria and its sensitivity pattern to antimicrobials, to guide definitive antimicrobial treatment.[1,2,13]

In toxic inhalation injury, BGA may show hypoxemia and hypercarbia. CBC may show increase leucocyte count and neutrophilia. If pneumonia develops, sputum Gram stain and culture may help to identify the causative bacteria and also its sensitivity to antimicrobial agents.[1-3]

In sepsis, BGA may show hypoxemia and hypercarbia if there is pneumonia. CBC may show increase leucocyte count, with neutrophilia and left shift (high count of stab neutrophils). If there is severe infection, neutrophil morphology may show toxic granulation, vacuolization and also hypersegmentation. CRP may increase and procalcitonin may increase above 0.5 ng/mL. If PCT increase more than 2.5 ng/mL, it indicates a severe sepsis. If pneumonia is the origin of infection. sputum Gram stain and culture may help identify the causative bacteria and also its sensitivity to antimicrobial agents. Increase level of D-dimer may suggest there is disseminated intravascular coagulation (DIC) induced by the bacteria in blood stream.[1,2,14,15]

In severe trauma, BGA may reveal hypoxia and hypercarbia. CBC may show increase leucocyte count, neutrophilia and CRP increase because of the tissue injury.[1,2]

In burns, BGA may show hypoxia and hypercarbia. CBC may show increase leucocyte count and neutrophilia. Albumin may decrease.[1,2]

In multiple transfusion, transfusion related acute lung injury (TRALI) could happen. TRALI is a clinical syndrome in which there is an acute, non cardiogenic pulmonary edema associated with hypoxia that occurs during or after a transfusion. BGA reveals hypoxemia and hypercarbia in TRALI. CBC may show elevated leucocyte count and neutrophilia.[1,2,16]

In pancreatitis, BGA reveals hypoxemia and hypercarbia. CBC may reveal elevated of leucocyte count and neutrophilia. There are increase level of pancreatic amylase and lipase.1,2,17
In post cardio pulmonary bypass surgery, BGA may reveal hypoxemia and hypercarbia. CBC may show elevated leucocyte count and neutrophilia.[1,2,18]

Pulmonary vascular dysfunction
In new onset acute pulmonary embolus, BGA may reveal hypoxemia with or without hypercarbia.[1,2]

In pulmonary hypertension, BGA may reveal exertional hypoxemia.[1,2]

In AVM or intracardiac shunt, BGA may reveal hypoxemia that is refractory to oxygen therapy.[1,2]

SUMMARY
Etiology of acute respiratory failure are classified into 5 types of dysfunction i.e. controller, pump, airway, alveolar dan pulmonary vascular. Each type has many representative conditions. The essential laboratory tests are blood gas analysis and complete blood count. The additional essential laboratory tests are specific to each etiology.

Table 1. Clinical syndromes associated with dysfunction of the components of the respiratory system

Type of dysfunction	Specific representative conditions	Predominant gas exchange abnormality	Laboratory tests
Controller	Sedative medications	Hypercarbia	BGA
	Chronic obstructive or interstitial lung diseases	Hypoxemia + hypercarbia	BGA
	Toxic overdoses	Hypoxemia + hypercarbia	BGA, toxicology screen
	Hypothermia post operatively	Hypercarbia	BGA
	Brainstem stroke	Hypercarbia	BGA, cholesterol total, HDL, LDL, blood glucose, HbA1c, PT, APTT, thrombocyte aggregation test,
Pump	Medications/toxins Paralytics Aminoglycosides Steroids Botulism	Hypercarbia	BGA
	Myopathy	Hypercarbia	BGA, CK, AST
	Myositis	Hypercarbia	BGA, CK, AST
	Metabolic abnormalities Hypothyroidism Hyperphosphatemia	Hypercarbia	BGA, TSH, FT3, FT4 ALP
	Myasthenia gravis	Hypercarbia	BGA, AChR Ab test, CK, Vit. D3
	Guillain-Barre syndrome	Hypercarbia	BGA, CSF analysis
	Paraneoplastic syndromes	Hypercarbia	BGA, associated cancers (lung, breast, ovary, thymoma, Hodgkin lymphoma)
	Polyradiculopathy of critical illness	Hypercarbia	BGA,
	Postoperative or post-radiation therapy phrenic nerve dysfunction	Hypercarbia	BGA,
	Postoperative pain/splitting	Hypoxemia + hypercarbia	BGA

Airway	Asthma	Mild: hypoxemia + hypocarbia Severe: hypoxemia + hypercarbia	BGA, IgE, allergy tests,
	Emphysema/Chronic bronchitis	Hypoxemia + hypercarbia	BGA, AAT, CBC, sputum Gram stain & culture
	Bronchiolitis	Hypoxemia + hypercarbia	BGA, CBC, sputum Gram stain & culture, BGA
	Endobronchial tumor, mass, or stricture	Variable	
Alveolar	Pneumonia	Hypoxemia + Hypercarbia	BGA, CBC, CRP, PCT, sputum Gram stain & culture
	Pulmonary edema	Hypoxemia + hypercarbia	BGA, CBC, BNP or NT-pro BNP, ureum, creatinine
	Pulmonary hemorrhage	Hypoxemia + hypercarbia	BGA, CBC, ANA, PT, APTT,
	ARDS	Hypoxemia + hypercarbia	BGA, CBC
	Drug reaction	Hypoxemia + hypercarbia	BGA
	Pulmonary contusion	Hypoxemia + hypercarbia	BGA
Pulmonary vascular	Acute pulmonary embolus	New-onset hypoxemia with or without hypercarbia	BGA
	Pulmonary hypertension	Exertional hypoxemia	BGA
	AVM or intracardiac shunt	Hypoxemia that is refractory to oxygen therapy	BGA

Note: ARDS, acute respiratory distress syndrome, AVM, arteriovenous malformation, BGA, blood gas analysis, PT, prothrombin time, APTT, Activated Partial Thromboplastin Time, TSH, Thyroid Stimulating Hormone, FT3, Free Triiodothyronine, FT4, Free Thyroxin, CK, creatine kinase, AST, Aspartate Transaminase, AChR Ab test, anti-acetyl choline receptor antibody test, Vit. D3, vitamin D3, CSF analysis, Cerebro-spinal fluid analysis, AAT, Alpha-1 antitrypsin test, CBC, complete

blood count (hemoglobine, hematocrit, leucocyte count, leucocyte differential count, thrombocyte count), CRP, C reactive protein, PCT, procalcitonin, BNP, Brain natriuretic peptide, NT-pro BNP, N Terminal-pro Brain natriuretic peptide, ANA, anti nuclear antibody

Table 2. Clinical disorders associated with ARDS.9

Direct lung injury		Indirect lung injury	
	Laboratory tests		Laboratory tests
Pneumonia Bacteria	BGA, CBC, PCT, CRP, D-dimer sputum Gram stain & culture,	Sepsis	CBC, PCT, CRP, sputum Gram stain & culture, D-dimer
Virus	BGA, CBC, PCT, CRP, Interleukin-6, D-dimer	Severe trauma Multiple bone Fractures Flail chest Head trauma Burns	BGA, CBC, CRP
Aspiration of gastric contents	BGA, CBC, sputum Gram stain & culture	Multiple transfusions	BGA, CBC,
Pulmonary contusion	BGA, CBC, D-dimer	Drug overdose	BGA,
Near-drowning	BGA, CBC, sputum Gram stain and culture	Pancreatitis	BGA, CBC, amylase, lipase
Toxic inhalation injury	BGA, CBC, sputum Gram stain and culture	Post-cardiopulmonary bypass	BGA, CBC,

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ACUTE RESPIRATORY FAILURE IN COPD

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Acute respiratory failure due to COPD remains a common medical emergency that can be effectively managed. There is an increase in hospitalization and high risk for death especially when there are other comorbid conditions like cardiovascular disease. The physiological basis is due to significant ventilation/perfusion mismatching with relative increase in the physiological dead space which leads to hypercapnia and hence acidosis. The rapid shallow breathing pattern results from adaptive physiological response which lessen the risk of respiratory muscle fatigue and minimize breathlessness.

In COPD, as in other conditions of respiratory illness, respiratory failure can occur as acute, chronic, or acute-on-chronic failure. In addition to ventilation/perfusion inhomogeneities, lung hyperinflation is a major factor in the pathogenesis of hypercapnic respiratory failure, being associated with a flat diaphragm and thereby diminishing muscle efficiency and increasing energy consumption. The prophylactic strategies against respiratory failure in COPD comprise the avoidance or reduction of disease progression and the prevention or amelioration of exacerbations by vaccination, anti-inflammatory therapy, long-acting bronchodilators , or their combination. In the presence of an exacerbation the treatment of airway obstruction with bronchodilators and the administration of systemic steroids and antibiotics are basic in the management of acute respiratory failure.

Treatment is directed at reducing the mechanical load applied to each breath, correcting specific precipitating factor eg. Bacterial infection, and maintaining gas exchange. Supplemental oxygen and mechanical ventilators are major treatment options. Evidence from clinical trials suggest the use of non-invasive positive pressure ventilation (NPPV) in acute hypercapnic respiratory failure. Its application reduces intubation and mortality rates, and the duration of intensive care unit or hospital stays. The long-term prognosis of patients with COPD and ARF particularly worsens if their clinical state calls for a ventilatory support, irrespective of whether this is applied invasively or non-invasively. Among the non-invasive ventilation techniques, non-invasive positive pressure ventilation (NPPV) via nasal or facial mask or a helmet is meanwhile the therapy of choice for the treatment of acute hypercapnic respiratory failure in acute exacerbations of COPD. Randomized clinical trials as summarized in metaanalyses and comprehensive reviews have clearly demonstrated that the supplementation of standard medical care by NPPV results in a lower mortality and risk for intubation. This is accompanied by a reduction in the number of hospital or ICU days compared to standard medical care only, which in particular might include intubation. The

results make sense in view of the fact that non-invasive ventilation offers significant advantages over invasive approaches, circumventing a number of serious complications that can occur after tracheal tube insertion or tracheostomy. Complications include the possibility of ventilator-induced lung injury and the elevated risk for respiratory infections, both of which are known to be associated with invasive mechanical ventilation. Severe acidosis resulting from acute exacerbation is a relevant predictor for treatment failure of NPPV , in addition to being a prognostic factor for mortality per se. In addition to the severity of failure as reflected by pH, the presence of significant comorbidities raises the probability of NPPV failure. There are further predictors for NPPV failure that have been revealed during the last years and might be helpful for the decision on initiation and continuation of NPPV in patients with COPD and ARF. Table 1 illustrates this.

Table 1 Most important predictors for treatment success/failure in acute hypercapnic respiratory failure in COPD derived from the literature (Ambrosino et al 1995; Brochard et al 1995; Carlucci et al 2001; Carlucci et al 2003; Confalonieri et al 2005; Conti et al 2002; Meduri et al 1996; Phua et al 2005; Plant et al 2000a; Scala et al 2007; Soo Hoo et al 1994; Squadrone et al 2004), and Hill et al (2007) and Garpestad et al (2007)

Predictors for treatment success	Predictors for treatment failure
pH 7.25–7.35, $PaCO_2$ > 45 mmHg	pH < 7.25
GCS > 14	GCS ≤ 11
APACHE-II score < 29	APACHE-II score > 29;
Respiratory rate 24–30/min	Significant comorbidities
Response to NPPV within 1–2 h	Respiratory rate > 30/min
Training/experience of the team with NPPV	Additional pneumonia
Standardized NPPV protocol	Severe mask leakage
	Patient-ventilator asynchrony
	Ineffective triggering
	Agitation or intolerance
	Encephalopathy
	Inability to clear secretions

Moreover, a number of contraindications such as persistent unconsciousness, hemodynamic instability, gastrointestinal or orofacial bleeding, a high risk for aspiration, or the inability to protect the airways have to be kept in mind when using this technique (Table 2)

Table 2 Relative and absolute contraindications for non-invasive ventilation in the acute and chronic setting, modified from

Contraindications in acute setting	Contraindications in chronic setting
Hemodynamic instability and cardiac arrest	Non-motivation or Non-adherence to therapy
Impending or manifest respiratory arrest	Mask intolerance (claustrophobia, facial dysmorphia)
Severely impaired consciousness	Excessive secretions and/or risk for aspiration
Uncontrollable agitation	Severe comorbidities or ethical concerns
Mask intolerance	Severe cognitive impairment (dementia)
Significant upper gastrointestinal bleeding	Lack of any subjective or objective treatment effect
Upper airway obstruction	
Facial trauma or surgery	
Massive secretions/aspiration risk	

PRINCIPLES OF MANAGEMENT:

The principles that determine the management of respiratory failure in COPD are very similar to those involved in treating exacerbations of COPD without respiratory failure, although much more attention is paid to the maintenance of appropriate and safe gas exchange.

Clearly, it is important to treat any identified precipitating factors, particularly if they continue to contribute to the abnormal physiological state. Typically, this involves treating lower respiratory tract infections, although, in some patients, management of coexisting pulmonary edema is equally important. Occasionally people who have inadvertently taken an excess of a sedative drug are still seen. Often, they must be allowed to recover spontaneously, but, when an opiate is involved, the excessive hypoventilation can be reversed by naloxone.

Secondly, it is necessary to reverse the impairment in lung mechanics, which is the commonest precipitating factor for respiratory failure in COPD. This normally involves treatment with bronchodilator drugs and corticosteroids.

Finally, gas exchange itself must be supported. This can often be carried out noninvasively but may require a stay in the ICU. It is always important to review what steps could be taken to prevent or reduce the risk of these episodes after recovery has occurred.

SUMMARY:

The following statements can be made based on clinical trials and data presented:
In severe acute exacerbations of COPD with acute respiratory failure, controlled oxygen delivery is a reasonable and effective approach to relieve symptoms, counteract hypoxemia and reduce the work of breathing.

In COPD with acute hypercapnic respiratory failure, noninvasive ventilation is highly recommended, particularly in patients with mild to moderate respiratory acidosis. Non-invasive ventilation has the potential to reduce the risk for invasive ventilation and the associated complications, as well as to improve overall ICU and in-hospital outcome.

In COPD with clinically relevant chronic hypoxemia, LTOT is strongly indicated to improve hemodynamic parameters, long-term prognosis and HRQL.

In COPD with chronic hypercapnic respiratory failure, the role of long-term non-invasive home ventilation for survival has not yet been unambiguously demonstrated. However, a number of investigations point towards significant benefits in subjective and physiological outcomes.

Taken together, respiratory failure in COPD must be considered as a serious or even life-threatening complication. Controlled oxygen supply and non-invasive mechanical ventilation are two effective components of an evidence-based, comprehensive management of respiratory failure. Their rational use has the potential to significantly ameliorate the patients' symptoms and to improve survival.

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CONTROVERSY ANTITUSSIVE: POSITIVE VALUE OF CODEINE FOR COUGH RELIEF

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DEFINITION

Cough is a natural defense mechanism that along with mucociliary clearance, bronchoconstriction and phagocytosis can effectively protect the respiratory tract from inhaling foreign bodies and by clearing excessive bronchial secretions. Cough may be a voluntary act or a spontaneous reflex arc and in this case involves receptors, an afferent pathway, a center processing information, an efferent pathway and effectors. The receptors are placed throughout the bronchial tree and, although in a lesser extent, also in other areas: ear, paranasal sinuses, pleura, diaphragm, pericardium and esophagus. From receptors the afferent impulses are channeled through the vagus nerve in the medulla oblongata, where they are processed. Then, efferent impulses are conveyed by motor nerves and reach the effectors, which are the respiratory and laryngeal muscles.[1,2]

The management of chronic cough presents a challenge for the clinician. Typically defined as a cough that persists for longer than 8 weeks, this is the most common presenting symptom in adults who seek medical treatment in an ambulatory setting. Chronic cough is estimated to occur in up to 40% of the population. Traditionally, a dichotomy has separated the upper and lower airways, with the upper airway being the domain of the otolaryngologist and the lower airway being the domain of the pulmonologist. Recent research that shows a high proportion of patients with asthma and coexisting allergic rhinitis has paved the way for the "one airway" theory, in which a continuum of inflammation that involves the entire airway can be thought of as the underlying mechanism for disorders that start from the nose and mouth and extend to the most distal aspects of the lungs.[3,4]

Inflammatory mediators in the lower airways are elevated in patients with postnasal drip syndrome, cough variant asthma, and gastroesophageal reflux disease (GERD). Since the etiology of chronic cough can arise from anywhere in the tracheobronchial tree, a multidisciplinary approach is often needed, with the primary care provider coordinating care with appropriate referrals to the otolaryngologist, pulmonologist, or both, as appropriate. Additional specialists also important in the workup include the gastroenterologist, allergist and immunologist, neurologist, and speech therapist.[1,2,3]

Cough Mechanism

Schematically, we may distinguish four different phases of cough, as a vital reflex arc, the first of which is a part in the afferent pathway while the last three in the efferent one:[4,5]

Cough reflex arc

The cough reflex arc is made up of three main pathways: Sensory Afferent Pathway. The cough reflex arc is initiated by irritation of cough receptors, for example, mechanoreceptors or chemoreceptors. Irritants are detected by these receptors and they send sensory information to afferent nerves.

There are three main types of sensory nerve fibres involved in the afferent pathway:

- Rapidly adapting stretch receptors (RARs)
  - These are myelinated fibres found mostly in the pharynx and trachea which rapidly respond to mechanical stimuli, e.g. changes in lung volumes
- Slowly adapting stretch receptors (SARs)
  - These are myelinated fibres which respond more slowly to mechanical stimuli and are involved in the Hering-Breuer reflex
- C-fibres
  - These are non-myelinated nerve fibres which respond to mechanical and chemical stimuli

Sensory information travels from these fibres through the afferent pathway via the vagus nerve to the medulla oblongata.[4,5,6]

Central pathway

Sensory information travels to the **nucleus tractus solitarius (NTS)** of the medulla. The vagus nerve then synapses with motor neurons, delivering information to effector muscles and causing the cough reflex to occur.

Motor efferent pathway

Various respiratory muscles contract to allow initiation of the cough reflex.

- The diaphragm contracts to become flattened which increases the thoracic cavity space
- The laryngeal muscles contract to close the vocal cords
- The external intercostal muscles contract to change the space available in the thoracic cavity
- Rectus abdominis contracts to depress the rib cage and decrease space in the thoracic cavity.[4,5]

Cough phase

1. *Receptorial phase:* there is the stimulation of cough receptors that are activated and, accordingly, send an impulse to the center through the vagus nerve;
2. *Inspiratory phase:* that consists in a wide opening of the glottis by contraction of the arytenoid cartilage with rapid inhalation, which involves an average of 50% of vital capacity with wide variations in relation to the stimulus and the type of receptors;

3. *Compressive phase:* that consists in a prompt closure of the glottis following the contraction of the adductor muscles of the arytenoid cartilages with consequent adduction of the vocal cords. At the same time, there is a strong contraction of the abdominal muscles and other expiratory muscles resulting in an increased intrapulmonary pressure and compression of the alveoli and bronchioles.
4. *Expiratory phase:* in this final phase, vocal cords and epiglottis open suddenly for action of the abductor muscle of the arytenoid cartilages, thereby causing the explosive leakage of air from the lungs to the outside. Subsequently, the exhalation continues, favored by the complete relaxation of the diaphragm.[4,5]

abductor muscle of the arytenoid cartilages, thereby causing the explosive leakage of air from the lungs to the outside. Subsequently, the exhalation continues, favored by the complete relaxation of the diaphragm.[4,5]

COUGH ETIOLOGY

Acute
· Acute bronchitis
· Acute exacerbations of chronic obstructive pulmonary disorder
· Acute rhinosinusitis
· Acute viral upper respiratory infection
· Allergic rhinitis
· Asthma
· Aspiration syndromes
· Congestive heart failure
· Pertussis
· Pneumonia
· Pulmonary embolism

Subacute
· Post-infectious secondary to continued irritation of cough receptors via ongoing or resolving bronchial or sinus inflammation from a preceding viral upper respiratory infection

Chronic
· Chronic bronchitis
· Chronic sinusitis
· Gastroesophageal reflux disease
· Interstitial lung diseases
· Intolerance to angiotensin-converting enzyme inhibitor medication
· Malignancy
· Non-asthmatic eosinophilic bronchitis
· Obstructive sleep apnea
· A post-infectious cough
· A psychosomatic cough
· Upper airway cough syndrome

Very Rare

- Cerumen impaction- vagal nerve stimulation of the afferent branch to the ear, known as Arnold nerve
- Esophageal achalasia
- Tracheoesophageal fistula
- Oesophageal tracheobronchial reflex
- Ortner syndrome: Intermittent left vocal fold paralysis as a result of cardiac ptosis straining the ipsilateral recurrent laryngeal nerve
- Pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS): A pediatric cough where prior Streptococcus infections can trigger motor tics including a chronic cough
- Peritoneal dialysis
- Pneumonitis
- Syngamus laryngeus: A small, roundworm indigenous to the Caribbean, Syngamus laryngeus is acquired by ingesting a contaminated fruit or vegetable. A male and female pair of worms take up residence in the subglottic larynx, and there they remain tenaciously adherent to the mucosa, except when mating. The pair may be coughed up in copula; otherwise, they can be endoscopically removed with a resolution of the host's chronic cough.
- Tracheobronchial collapse
- Vitamin B12 deficiency
- Zenker or distal esophageal diverticulum.[3,4]

CAUSES OF CHRONIC COUGH

The etiologies of chronic cough are numerous and may include pathology from the nose and nasopharynx to the distal bronchial tree. Obvious causes such as smoking and angiotensin-converting enzyme (ACE) inhibitor use can be easily ascertained from the history. After this, the challenge for the clinician lies in how to efficiently and systematically evaluate the patient without an overly exhaustive workup. Further compounding this is the fact that oftentimes more than one condition is simultaneously present. Prospective studies have shown that 3 conditions account for the etiologic cause of chronic cough in 92-100% of immunocompetent, nonsmoking patients with normal chest radiograph findings. In order of frequency, they are as follows:

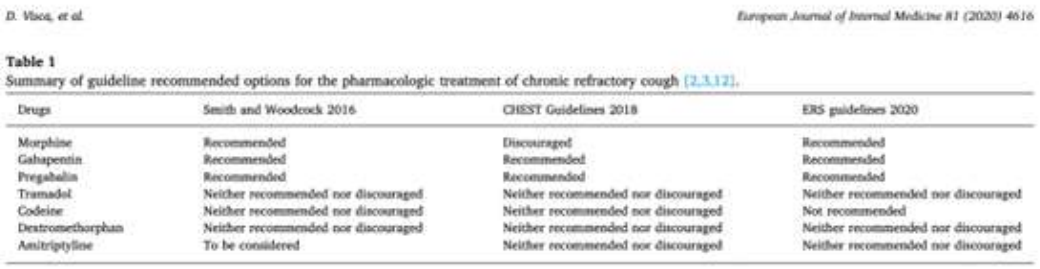
- Upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome (PNDS)
- Asthma
- Gastroesophageal reflux disease (GERD)

These 3 conditions make up what is called the pathogenic triad of chronic cough. A fourth etiology that deserves mention is nonasthmatic eosinophilic bronchitis (NAEB), which is relatively common, easy to diagnose and treat, and should be considered early on in the diagnostic evaluation.[3,4,5]

WORKUP AND MANAGEMENT

Antitussives, such as codeine and dextromethorphan, have been shown to have limited or no efficacy in the treatment of chronic cough and any beneficial effect is largely due to placebo effect. As such, the clinician should try to elucidate and identify the underlying cause of the cough to effectively manage it. Every patient with chronic cough needs a thorough history taken and physical examination performed as part of their evaluation. Each patient should also have a chest radiograph taken. Surprisingly, the medical history (in terms of the patient's description of the character, timing, and presence or absence of sputum production) has been shown to have little or no diagnostic value. What is of value from the medical history is whether or not the patient is or has been a smoker; is taking an ACE inhibitor; is living in a geographic area where tuberculosis or certain fungal diseases are endemic; has any systemic symptoms, a history of cancer, tuberculosis, or AIDS; or has a large pulmonary mass visible on chest radiograph.[3,4,7]

Management should begin with cessation of smoking or ACE inhibitor use in those patients whose history indicates such action. Most patients have a resolution of their cough within 4 weeks of smoking cessation. Cough related to ACE inhibitor use usually subsides within 2 weeks, but the median time has been reported to be 26 days. If the chest radiograph findings are abnormal, further workup depends on the specific finding. Chest CT scan, bronchoscopy, needle biopsy, and sputum studies are all potentially warranted studies if a pulmonary lesion is found. For the immunocompetent nonsmoker who does not use ACE inhibitors and has normal chest radiograph findings, a systematic approach to the most common causes of chronic cough is warranted, keeping in mind that more than one cause may be present. The body of literature regarding specific treatments and the expected time frame of response is extensive, and the accuracy of the diagnosis is confirmed by the patient's response to these treatments. From both theoretical and cost effectiveness standpoints, empiric treatment of the 3 most common causes of cough is favored over extensive testing at the outset. Further, sequential and additive therapy may be needed because more than one cause of cough is often present. [3,4]



D. Vaca, et al. European Journal of Internal Medicine 81 (2020) 4616

Table 1
Summary of guideline recommended options for the pharmacologic treatment of chronic refractory cough [2,3,12].

Drugs	Smith and Woodcock 2016	CHEST Guidelines 2018	ERS guidelines 2020
Morphine	Recommended	Discouraged	Recommended
Gabapentin	Recommended	Recommended	Recommended
Pregabalin	Recommended	Recommended	Recommended
Tramadol	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Codeine	Neither recommended nor discouraged	Neither recommended nor discouraged	Not recommended
Dextromethorphan	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Amitriptyline	To be considered	Neither recommended nor discouraged	Neither recommended nor discouraged

Figure 1. Summary of guideline recommended options for the pharmacologic treatment of chronic refractory cough.8

UPPER AIRWAY COUGH SYNDROME

Because upper airway cough syndrome (UACS) is the most common cause of chronic cough, it should be treated first. In patients in whom the cause of the UACS-induced cough is apparent, specific therapy directed at this condition should be instituted. This includes avoiding environmental irritants and offending antigens, treating sinusitis with antibiotics, and weaning patients off nasal decongestants for rhinitis medicamentosa. Further workup may include allergy testing for allergic rhinitis or sinus CT scan for sinusitis, as indicated. For patients in whom the cause is not apparent, empiric therapy should be instituted with a combination of an antihistamine and decongestant. First-generation antihistamines such as azatadine and dexbrompheniramine plus pseudoephedrine have shown more effectiveness than newer, less-sedating antihistamines. Patients typically respond within 2 weeks of initiating therapy but may sometimes take several months.[3,4]

ASTHMA

Asthma should be considered only after the UACS evaluation and empirical treatment trial are complete. Ideally, patients should undergo spirometry and bronchoprovocation challenge with methacholine, which reveals reversible airflow obstruction. The negative predictive value for a negative challenge approaches 100%. The initial treatment of asthma consists of beta-2 agonists and inhaled corticosteroids (ICS) and response is usually seen within 1 week, with complete resolution taking up to 8 weeks. Some patients may require a trial of oral corticosteroids before a response is seen. However, because leukotriene inhibitors have been shown to be effective in patients with asthma-induced cough, they should be tried prior to oral corticosteroid therapy. [3,4]

NONALLERGIC EOSINOPHILIC BRONCHITIS

Because its diagnosis is made easily, nonallergic eosinophilic bronchitis (NAEB) is the next etiology to consider, even though GERD is more common. An induced sputum test that reveals increased eosinophils is the diagnostic procedure of choice. Treatment includes ICS, with oral corticosteroids reserved for refractory cases. Response is usually seen within 4 weeks.[3,4]

GASTROESOPHAGEAL REFLUX DISEASE

Prospective studies have shown that in a patient who has undergone empiric therapy for UACS, asthma, and NAEB and has had no response or only a partial response, a 92% probability exists that their chronic cough is due to GERD. The criterion standard for diagnosis of GERD is dual-channel 24-hour pH probe monitoring. Alternatively, flexible nasopharyngoscopy can reveal glottic changes associated with reflux. These include laryngeal edema and erythema, laryngeal pseudosulcus, and posterior commissure hypertrophy or pachydermia.[3,4]

Simply because of the percentages, empiric therapy with acid suppression and lifestyle and dietary modification has been advocated as initial management instead of testing, which is reserved for refractory cases. Lifestyle modifications include limiting fat intake; avoiding caffeine, chocolate, mints, citrus products, alcohol, and smoking; and limiting vigorous exercise that increases intra-abdominal pressure. The choice of acid suppressive medication can include histamine 2 (H2) blockers, proton pump inhibitors (PPIs), and prokinetic agents. However, note

that maximal medical therapy refers to twice daily PPI in addition to a prokinetic agent with concurrent lifestyle and dietary modifications. Although response can be seen in as little as 2 weeks, at least a 6-8 week trial is needed to fully evaluate a response to treatment, with some patients requiring as long as 6 months.[3,4]

FURTHER WORKUP AND REFRACTORY CHRONIC COUGH

Only when management of the most common causes has failed to yield a resolution of cough should a more extensive workup begin. This can include induced sputum testing for acid-fast bacillus, high-resolution CT scanning of the chest, and bronchoscopy. Often, these tests should be performed by a cough specialist. If further testing does not reveal the cause, then the patient most likely has chronic cough hypersensitivity syndrome. Owing to inflammation and hyperresponsiveness of the airway from some inciting cause, tissue remodeling has occurred, leading to an enhanced cough reflex that maintains the cough even though the inciting cause has resolved. In these truly idiopathic cases, therapeutics are limited, but ongoing research is focusing on medicines that either directly or indirectly affect the cough reflex.[3,4]

Similarities have been demonstrated between neuropathic pain and chronic cough, and centrally acting neuromodulators such as tricyclic antidepressants (amitriptyline, nortriptyline), gabapentin, and pregabalin have shown benefit in improving cough (albeit with risk of side effects). A randomized, placebo-controlled trial by Vertigan et al indicated that treatment of refractory chronic cough with a combination of speech pathology therapy and pregabalin (300 mg daily) is more effective than treatment with speech pathology therapy plus placebo. The study involved 40 patients, with improvement measured using the visual analogue scale, the Leicester Cough Monitor, and the Leicester Cough Questionnaire. The P2X3 receptor has been shown to mediate pain responses, with promising results obtained from research into chronic cough treatment with P2X3 receptor antagonists. Studies by Smith et al and Morice and colleagues indicated that the P2X3 receptor antagonist MK-7264 is effective against refractory chronic cough.[3,8,10]

ROLE OF CODEINE FOR COUGH RELIEF

Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.[6,7]

April 2017 safety communication from the US Food and Drug Administration announcing a contraindication against the use of codeine in children aged 0 to 11 years. The right vertical line corresponds to the January 2018 Food and Drug Administration safety communication announcing that codeine and hydrocodone cough and cold medications were no longer approved for use in children and adolescents aged 0 to 17 years. B, The vertical line corresponds to the January 2018 Food and Drug Administration safety communication.[8,9,10]

Codeine has been considered to be the most effective antitussive for acute cough and has been regarded as the reference drug with which the effects of other antitussive agents should be compared.4 However, as discussed, codeine apparently does not reduce cough during such an infection. Because codeine is not only ineffective but also frequently associated with gastrointestinal symptoms, the use of codeine as a cough suppressant should be discouraged and acknowledged as a prevalent medical myth.[11,12,13]

CONCLUSION

In the immunocompetent nonsmoking patient who does not take angiotensin-converting enzyme (ACE) inhibitors, the most common causes of chronic cough are upper airway cough syndrome (UACS), asthma, and gastroesophageal reflux disease (GERD). Together, these causes account for more than 90% of all cases of chronic cough. Frequently more than one of these etiologies is present, and cough may be the only presentation. Nonasthmatic eosinophilic bronchitis (NAEB) should also be considered early in the diagnostic evaluation because it is easily diagnosed and treated. Only after these most common causes of chronic cough are ruled out should more extensive testing be performed, usually after referral to a cough specialist. An empiric and integrative approach that uses sequential and additive therapy is needed to systematically evaluate and effectively treat patients with chronic cough.

Until now, the use of antitussives is still controversial. The management of cough refers to the classification and underlying cause of cough. If the cause is difficult to identify, symptomatic therapy including the administration of cough-suppressing medicines is beneficial to improve quality of life. The use of antitussives, one of which is Codeine, is only for symptomatic therapy to relieve cough, definitive therapy that stops coughing is adjusted based on the etiology. In Indonesia, 2 types of Codeine are registered, namely Codeine Anhydrous with a slow release formulation and Codeine Phosphate for a standard formulation.

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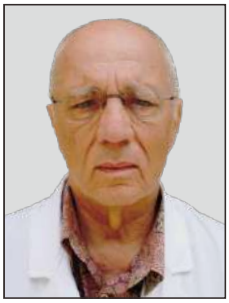
POST COVID-19 PULMONARY FIBROSIS



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ABSTRACT
Post-acute sequelae of COVID-19 may affect 10-30% of survivors. Post-COVID-19 pulmonary fibrosis (PCPF) is associated with great morbidity. Experience from previous coronavirus outbreak forecasts that PCPF will result in long-term respiratory morbidity needing lung function and imaging follow up. Acute COVID-19 pathobiology may account for increased rates of PCPF in addition to duration of illness and mechanical ventilation. Careful follow up of symptoms, lung function (DLCO) and imaging (CT scan, Lung ultrasound) is mandatory. Prospective studies and registries are needed.

Sequelae of acute COVID-19, are defined as "persistent symptoms and/or long-term complications more than 4 weeks after the acute onset", and affect 10–30% of survivors.[1] Post COVID-19 pulmonary fibrosis (PCPF) may be the most severe manifestation of post-infectious lung injury. Age, chronic comorbid conditions, need for invasive or non invasive mechanical ventilation, and female sex are some risk factors of respiratory sequlae.[2]

EPIDEMIOLOGY

Remebering previous pandemics such as SARS and MERS, we can forecast similar if not increased long-term pulmonary complications including PCPF. [1,3] Up to 40% of COVID-19 individuals may develop viral pneumonia and 20% of these may develop severe ARDS [4], an abnormal form of ARDS having been also hypothesized.[5] In addition these patients may require long periods of mechanical ventilation with clinical phenotypes and respiratory mechanics similar to other forms of ARDS. [6] 20-40% survivors of ARDS may suffer from long term dyspnoea, HRCT imaging lung abnormalities and/or poor health related quality of life. [7,8] All these considerations suggest the need of screening and follow up of these patients.

SCREENING

At present there is limited consensus on timing of screening and physiological and imaging follow-up. Screening for PCPF in individuals with persistent dyspnoea after COVID-19 should consists of lung function tests (including mandatory DLCO) and cross-sectional imaging. [1,9,10] Simple chest Xray and delayed follow-up may miss individuals with persistent respiratory morbidity. Various HRCT images in PCPF may be observed: 1) predominantly ground glass; 2) predominantly fibrotic; and 3) mixed ground glass and fibrotic[7]. Lung ultrasound may be useful [11].

PATHOPHYSIOLOGICAL MECHANISMS

The underlying pathology of acute COVID-19 and PCPF has not be elucidated yet. In general pulmonary fibrosis can occur in the setting of maladaptive resolution of lung injury or enhanced reparative process. Despite multiple initial pulmonary or extrapulmonary insults resulting in ARDS, there may be a common pathway leading to fibrosis. [1,12]

PATHOLOGY

Post-mortem studies may be misleading, due to confounding factors in pre-terminal disease, including injury resulting from prolonged mechanical ventilation. At difference, ante-mortem lung biopsies may provide major pathogenetic insights, potentially providing a basis for novel treatment approaches. A case series suggests that intra-alveolar capillary changes as the main anatomic background of ground glass/paving opacification. [13]

Potential therapies.

The roles for antifibrotic drugs in both acute COVID-19 and PCPF are still unclear and are being evaluated in ongoing clinical trials. [1,14]. Currently, the usefullness for PCPF of glucocorticoids and IL-6 antagonists is unknown [1].

CONCLUSION

Post COVID-19 pulmonary fibrosis will potentially affect hundreds of thousands people. Future studies are needed to clarify the natural history, pathophysiology, clinical and psychosocial impact. Additional research includes clinical and serologic phenotyping of patients, epidemiologic identification of risk factors.

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WHAT ARE THE CHALLENGES THAT RESPIRATORY AND CRITICAL CARE PHYSICIANS FACE IN THE POST COVID-19 ERA?

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Abstract
The COVID-19 disease which was first observed in Wuhan city of Hubei province of China at the beginning of Dec 2019, quickly spread to the rest of the world. Currently 526 million people in the world have been infected with Covid-19, with 6.28 million deaths.

A majority of patients experience mild respiratory symptoms and recover without sequelae. However, a significant number of patients develop a severe pneumonia, which can lead to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, multi-organ dysfunction and ultimately death. Many survivors of this serious complication develop chronic respiratory failure and permanent fibrosis.

Observational studies have indicated that 90% of COVID-19 patients experience long-term issues from lung tissue damage, presenting as respiratory problems and decreased exercise tolerance. For about 50% of all these patients, these respiratory complications resolve within 3 months of hospitalization. However, after 3-6 months, and 6-9 months post-hospitalization, the recovery rate drops to 35% and 15% respectively (ie complete recovery rates decline over time). Patients with residual lung damage typically exhibit lung fibrosis. Elderly patients, patients with pre-existing health conditions, and patients with severe COVID-19 symptoms are considered high-risk groups for developing post-COVID-19 fibrosis.

In this paper, we will discuss 2 significant post COVID-19 -19 lung pathologies – post COVID-19 lung fibrosis and post acute COVID-19 syndrome (also termed long COVID).

Keywords: COVID-19, pulmonary fibrosis, post acute covid syndrome

Results Post Covid lung fibrosis
While the majority of COVID-19 patients will have mild or moderate infections, about 10% will develop severe COVID-19 pneumonia and 5% will develop ARDS. The majority of these patients will recover without residual lung damage, however a sizeable number will be left with residual fibrotic sequelae. Given scale of the pandemic COVID-19 sufferers, we will be faced with a large number of patients with long-term, permanent lung damage. Early and adequate therapy does not seem to prevent the development of fibrosis. The use of steroids in the care of the most severely ill

covid-19 patients has been the standard, but the usual doses do not appear to prevent the development of fibrosis. The molecular basis of progression to pulmonary fibrosis is still unclear but appears to be multifactorial. Direct viral effects, the upregulating effect of the virus on cytokines like TGF-β1, and increased oxidative stress has been postulated. For critically ill patients, iatrogenic factors can in addition potentially contribute to the development of fibrosis – oxygen toxicity from use of high concentrations of oxygen in ARDS patients and ventilator-induced lung injury (VILI).

Patients who develop post COVID-19 lung fibrosis typically present with symptoms of dry cough, fatigue and dyspnoea, together with weight loss from physical de-conditioning. These symptoms can be detected as early as 3 weeks after the onset of a COVID-19 infection. In time, these symptoms lead to deconditioning, accelerated functional decline and a reduction in the quality of life.

It is too early to determine the natural history of post- COVID-19 fibrosis. Questions which need to be answered (1) are the CT changes likely to improve, persist or worsen over time, and (2) do current anti-fibrotic therapy used for treatment of IPF and PF-ILD patients alter the course in these patients?

Current treatments such as steroids, anti-fibrotic drugs (Nintadenib and Pirfenidone) are being studied, together with novel agents such as Treamid, Deupirfenidon, Fibroquel MR and Longidase. Traditional treatments such as Tetrandrine and Fuzheng Huayu Tablet (FHZY) are also being studied.

We face a lack of efficacious treatment options, but are hopeful that anti-inflammatory treatment for at least 6 months after COVID-19-associated pneumonia will reduce residual lung inflammation and improve impaired diffusion capacity of the lungs, which in turn will boost lung regeneration and prevent persistent respiratory pathology.

Post acute covid syndrome

A significant number of post COVID-19 patients have been noted to experienced prolonged multiotgan symptoms and complications beyond the initial period of acute infection and illness. The list of symptoms include chronic cough, shortness of breath, cognitive dysfunction and fatigue. Collectively these have been termed long Covid or post-Covid-19 syndrome, and with the increasing number of patients afflicted with COVID-19, this will be growing health concern. It is estimated that 1 in 5 who had tested positive for COVID-19 will have symptoms that lasted for more than 5 weeks, and 1 in 10 people will have symptoms that last beyond 12 weeks.

As such, the Natiopnal Institute for Health and Care Excellence (NICE) published a guideline for clinicians on the management and care of such patients. In the guidelines, 2 definitions of postacute COVID-19 are given: a) ongoing COVID-19 patients who still have symptoms between 4-12 weeks after start of acute symptoms, b) patients who have symptoms 12 weeks or more after

an acute infection.

Clinical investigations of patients with ongoing symptoms 4 weeks after an acute infection include laboratory tests and chest radiography, in addition to exercise tolerance tests. In the absence of a definite pathology, rehabilitation whould be considered, with programmes individualised and adapted to the needs of the patient.

The most common pulmonary symptoms in post-Covid 19 syndrome are shortness of breath and cough. Dyspnoea and reduced exercise tolerance has been demonstarted to developed in 10-40% of patients 2-4 months after discharge, whereas 65% of patients developed shortness of breath after sicharge from the ICU. Rarely, pulmonary embolism, chornic cough, small airway disease, and development of pulmonary hypertension can develop.

CONCLUSION

COVID-19 infection is a complex entity with acute and long-term effects, and especially involves the pulmonary system. Treatment of the disease continues even after the patient is discharged. Studies are needed to identify biomarkers and risk factors for susceptible individuals so that prompt intervention and treatment can be effected to minimize these long-term effects.

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LONG COVID-19-SYNDROME: IMPACT ON PULMONARY SYSTEM

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COVID – 19: WORLDWIDE OCCURRENCE

As of April 15, 2022, there a > 500 millions cases worldwide with more than 6 millions death. There was an evolution of different virus variants: Alpha (B.1.1.7, first in UK), Beta (B.1.351, first in South Africa), Gamma (P.1, first in Brasil), Delta (B.1.167.2, first in India), Omikron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages, worldwide most current variant of concern). Currently there is no variant of high consequences to be monitored.

One of the best guidelines regarding presentation and treatment of Covid-19 comes from the NIH in the US (COVID-19 Treatment Guidelines Panel. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 19.5.22).

Clinical presentation of **Covid -19**: The median incubation time is 4 – 5 days, there is a broad range of clinical severity (initial data from China): 81% mild disease, 14% severe disease, 5% critical disease and a broad range of symptoms:

70% fever, cough, shortness of breath
36% muscle ache
34% headache

In addition, Covid-19 can present with various other ymptoms: diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

CLINICAL FINDINGS

On Chest x – ray, we often see a normal pattern in mild or early disease, in patients with viral pneumonia, we find ground glass opacity in the peripheral lung tissue and sometimes linear opacity in the periphery. In severe ill patients, the pattern can progress to severe ARDS.

Main laboratory findings are leukopenia and lymphopenia, the liver enzymes are elevated, there is an increase in D-Dimer, ferritin, C-reactive protein.

The lung function shows early in disease mostly a restrictive lung function with a reduced diffusion capacity and late in disease a bronchial hyperreactivity with a positive metacholine challenge test. Beside the pulmonary system, there are several other organic complications, especially cardiac,dermatologic, hematologic, hepatic, neurologic, renal involment and often thromboembolic events.

LONG-TERM SEQUELAE OF COVID-19

Currently, there is no clear definition of Long-Covid-Syndrome, the most common names are Post-Covid-19 condition or Long-Covid-19 disease.
The definition of the syndrome is still unclear, but persistent symptoms after acute Covid-19 illness may define this condition.

There are no clear data about incidence, natural history and etiology, the main symptoms are fatigue, myocardial inflammation and neuropsychiatric symptoms like anxiety, depression, headache, myalgia, memory loss and mood changes.

LONG TERM PULMONARY SEQUELAE OF COVID 19

The most common finding is bronchial hyperreactivity with coughing day and night for more than 4 weeks, especially after Omicron variant infection and a positive metacholine challenge test. We also see persistent infiltrates in chest-x-ray after quarantine period with the need of prednisolone treatment. Other symptoms include bronchial hypersecretion with increased sputum production, but not bronchiectasis.

Treatment of short and long-term pulmonary symptoms

Prednison treatment is required if the patient shows impaired lung diffusion capacity and chest x-ray opacities. We use in general 2 x 10 mg prednisolon, at least for 2 weeks, until normalization of lung function and chest radiographs. If SaO2 is reduced, oxygen therapy can be added.

Inhalation therapy: we recommend the inhalation with with NaCl 0,9% - 6% (e. g. with Pari nebulizer system) and, depending on the amount of bronchial hyperreactivity additionally budesonide 0,5 mg – 1 mg twice per day for at least two weeks and ß-agonists. Especially after infection with the omicron variant, ICS + LABA are often required to improve coughing and reduce bronchial hyper reactiviy.

To summarize, after **Covid-19** infection, pulmonary symptoms are frequent and required often treatment corticosteroid, either p. o. or by inhalation. In addition, nebulization of isotonic or hypertonic saline improves pulmonary symptoms.

THE IMPACT OF PANDEMIC ON ANTIMICROBIAL RESISTANCE: LEARN FROM DR. SOETOMO HOSPITAL SURABAYA

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INTRODUCTION

Antimicrobial resistance (AMR) was being a global concern since 2001, as WHO the first time launched the AMR booklet. The Indonesian national structured data of AMR was first conducted the surveillance by AMR Control Committee, MoH Republic of Indonesia in 2016. This national data was awakened for all of Indonesian Clinical Microbiology, due to the high enough of the rate of Extended Spectrum Beta Lactamase (ESBL) producing *Escherichia coli & Klebsiella* pneumoniae as an indicator of Multiple Drug Resistant Organisms (MDROs). It showed that the data from 8 main teaching hospitals in Indonesia, among ESBL producing *E coli* & K pneumoniae was 60% on average. It was quite high compare to the data from The Netherlands, less than 5%. – This data was not re-evaluated again the national data until now.

The data of ESBL-*(E coli & K pneumoniae)* from Dr. Soetomo hospital at this moment was 55%, whereas the highest rate among other hospital was 82%. It means that the situation of AMR in Indonesia was critical. Refers to the Global Action Plan (GAP) on AMR, there were five actions to contain the AMR, 1) awareness; 2) Surveillance & research; 3) effective hygiene & infection prevention control; 4) Optimize use of antimicrobials; 5) sustainable investment through research & development. The hard to comply against this action were point 4 & 5.

During the pandemic season, some world organizations put warning according the abused of antimicrobial for containing COVID-19, even though it is a viral disease. Any antibiotics with no indication were used. Many international organization have also warning for this issue, i.e. WHO, UN and many health practitioners. The antibiotic used were also indicated for any bacterial superinfection that in some cases were also not fully indicated. Clancy & Nguyen in their review showed that all COVID-19 patients get antibiotic, but only 10-31% have an superinfection. Among 5 studies in this report showed that 4 studies used antibiotics among more than 86% of the subjects. It showed that the use of antibiotics was highly frequent among COVID-19 patients.

THE PATTERN OF ANTIMICROBIAL RESISTANCE IN DR. SOETOMO HOSPITAL

It was a limited chance to access the data of the patterns of antimicrobial resistance (AMR) that comparing pre and during the pandemic season of COVID-19 in Indonesia. In this regard, we explore the data of AMR di Dr. Soetomo hospital as the tertiary referral/national hospital that mostly admitted referred patients from secondary hospitals. Comparing the AMR data in Dr. Soetomo

hospital pre and during the pandemic would be problematic due to the Antimicrobial Stewardship Program (ASP) implementation since 2019, whereas Covid-19 was started in March 2020 until the peak season in the 2nd – 3rd trimesters 2021. The full monitor restricted and mostly used as definitive therapy was the reserved antibiotic group, such as the carbapenem group. Otherwise, the antibiotic in a group of 'WATCH', such as third generation cephalosporin (ceftriaxone, cefotaxime, ceftazidime) and in combination with beta lactamase inhibitors (BLIs) was still primarily used as empiric therapy.

Some indicators are analyzed, such as Extended Spectrum beta lactamase (ESBL) producing bacteria and carbapenem resistant Gram-negative bacilli.

The bacterial collection of clinical isolates in Dr Soetomo hospital from January 1st 2018 until February 28th 2021 was analyzed. The bacterial isolates were collected from all samples (sputum, blood, urine, wound, cerebrospinal fluid and others) and from varied wards, namely Internal Medicine, Surgical, Obstetric Gynecology, Pediatric and ICU (regular & emergency). The break point of pre-pandemic and pandemic was agreed on March 15, 2020 that will be included as starting of pandemic season. We provide five indicators for evaluation, namely *Escherichia coli (E coli), Klebsiella pneumoniae (K pneumoniae), and Candida species (Candida spp).*

A total of 26,125 bacterial clinical isolates were collected, the Pre-pandemic season (January 1st, 2018 – March 14th, 2020 = 2 years and 2,5 months) was collected 16,034 isolates, and the Pandemic season (March 15th, 2020 – February 28th, 2021 = 11,5 months) is 8,952 isolates. Table 1. The average number of isolates in Pre-pandemic was 605 per month and during the Pandemic season was 778.4 per month. It was predicted to decrease isolates due to the lower board occupation rate (BOR) for general/non-COVID-19 patients during the pandemic season. As our notes, in the mid of 2020, BOR in Dr. Soetomo hospital reach less than 50%.

Fungi, mainly *Candida spp*, was significantly increase during pandemic, 8.11% versus 12.72% among all microorganisms clinical isolates in this hospital ($p<0.05$). Table 1. As notes in any references that fungi will prevalent in patients with chronical infection of patients with seriously ill.

Table 1. The number of Fungi clinical isolates among total microorganisms in all specimens in Dr Soetomo hospital Surabaya since January 1st 2018 until February 28th 2021

No.	Microorganisms	Pre-pandemic		Pandemic		p
		N	%*	N	%*	
1	*Bacterial isolates*	14,733		8,952		
2	*Fungi (Candida spp)*	1,301	8.11	1,139	12.72	< 0,05
	Total (=5820)	16,034	-	10,091	-	

Note: *=% of total in Pre-pandemic or during pandemic

The pattern of ESBL producing bacteria looks interesting in its prevalence. The ESBL producing *K. pneumoniae* was significantly decreased, but for E. coli. The total picture of ESBL producing *E coli* and *K pneumoniae* was decreasing, but was not significantly different. Carbapenem-resistant microorganisms significantly increased in *K pneumoniae* ($p<0.05$) but for *E coli.* Table 3.

Table 2. The pattern of ESBL producing bacteria *(K pneumoniae & E coli)* during Pre-pandemic and Pandemic season

Bacterial indicators	Pre-Pandemic season			Pandemic season			
	Total	ESBL; n (%)		Total	ESBL; n (%)		p
K pneumoniae	1557	1025 (65.8)		866	451 (52.1)		<0.05
E coli	2777	2016 (72.6)		1036	791 (76.4)		>0.05
Total	4334	3041 (70.2)		1902	1242 (63.3)		>0.05

Table 3. The pattern of Carbapenem resistant (CR) bacteria (K pneumoniae & E coli) in Pre-pandemic and Pandemic season

Bacterial indicators	Pre-Pandemic season		Pandemic season		
	Total	CR; n (%)	Total	CR; n (%)	p
K pneumoniae	1,709	212 (14.4)	979	175 (17.9)	<0.05
E coli	3,153	265 (8.4)	1,225	114 (9.3)	>0.05
Total	4,862	477 (9.8)	2,204	289 (10.8)	<0.05

COVID-19 pandemic was suggested increase the antimicrobial resistance, especially carbapenem resistance. The infection caused by Candida spp was also increased rather than pre-pandemic. The ESBL producing bacterial rate did not change between pre and during the pandemic.

According to the pandemic season, the changes in bacterial resistance in Dr. Soetomo hospital were not a serious problem. It would be due to the intensive implementation of the AMR control program in Dr. Soetomo hospital, which was effectively started in 2019. We note that Dr. Soetomo hospital is a tertiary referral hospital that admits the referral patients from cities in East Java. The admitted patients would also get any medications, including third generation cephalosporins that induce ESBL producer and also carbapenem usage that impacts on carbapenem resistance.

CONCLUSIONS

The pandemic of COVID-19 was predicted as the source of increasing antimicrobial resistance. As we learned from Dr. Soetomo hospital, the impact of COVID-19 was low in the pressure of antimicrobial resistance. It would be the impact of the intensive implementation of the Antimicrobial stewardship program in this hospital that started one year before the pandemic. Fungi from clinical isolates were significantly increased in the pandemic season.

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PROBLEMS OF ANTIMICROBIAL RESISTANCE IN INTENSIVE CARE UNIT

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ABSTRACT
Antibiotics are agents used to treat bacterial infections and intensive care units has largest consumption of antimicrobials is concentrated in hospitals. In 2020, more than half of the *E. coli* isolates reported to EARS-Net and more than a third of the *K. pneumoniae* isolates were resistant to at least one antimicrobial group under surveillance. These created the need of new antibiotics, but a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis. Possible strategies/tools to optimize antibiotic therapies and to reduce the risk of bacterial resistance include: rapid microbiological diagnostics, inflammation markers-guided therapies, the reduction of standard durations of antibiotic courses, to consider dosing according to PK/PD targets and to avoid antibiotic classes carrying a higher risk for induction of bacterial resistance.

Keywords: antibiotic, resistance, ICU

INTRODUCTION
Antibiotics are agents used to treat bacterial infections. it can act as a bacteriostatic (inhibit growth) or bactericidal (destroys).' The largest consumption of antimicrobials is concentrated in hospitals and within them, the intensive care units. The quality of antimicrobial use is not optimal, with up to 50% of prescriptions being unnecessary or inappropriate. Inappropriate antibiotic use leads to severe consequences, such as increased patient mortality and morbidity and bacterial resistance.

In 2020, more than half of the *E. coli* isolates reported to EARS-Net and more than a third of the *K. pneumoniae* isolates were resistant to at least one antimicrobial group under surveillance, and combined resistance to several antimicrobial groups was a frequent occurrence. Among antimicrobial groups monitored for both species, AMR (Antimicrobial resistance) percentages generally were higher in *K. pneumoniae* than in *E. coli*. Carbapenem resistance remained rare in *E. coli*, but almost a quarter of EU/EEA countries reported carbapenem resistance percentages above 10% in K. pneumoniae. Carbapenem resistance was also common in *P. aeruginosa* and *Acinetobacter spp.,* and at a higher percentage than in *K. pneumoniae.* For most gram-negative bacteria under surveillance, changes in the EU/EEA (excluding the United Kingdom) population-weighted mean AMR percentages between 2016 and 2020 were moderate and AMR remained at

high levels, as previously reported.
Meanwhile, 1950-1960s has been the golden age of antibiotics discovery. Since then, a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis. Meanwhile, in projection of AMR situation by 2050, AMR will cause about 10M death during 2050 and this is in England alone." This warrants aggressive attempts to control misuse and combat resistance.

STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE

With the incidence of infections caused by bacteria that are resistant to antibiotics is constantly increasing, focus on possible strategies to optimize antibiotic therapies in everyday clinical practice and reduce the risk of inducing bacterial resistance to antibiotics is imperative.

Antibiotics resistance might be induced by several mechanism. A small portion of bacteria present with innate immunity against certain antibiotics. When a person took antibiotics, antibiotics-sensitive strains died, leaving only resistant strains. This makes resistant strains changes from being minority into majority of bacteria present. While antibiotics-sensitive strains which are not killed due to improper antibiotics dosing, might develop strategies to combat antibiotics. These strategies might include creation of enzymes that break down antibiotics, changes of target site or entry pathways, or attempting to pump out any antibiotics molecules that enters its body. Developed strategies are incorporated in bacteria's DNA sequences. This DNA can then be transferred to other bacteria during reproduction, by bacteriophages, or can be picked up by living bacteria from the remains of dead bacteria.

Possible strategies/tools to optimize antibiotic therapies and to reduce the risk of bacterial resistance include: rapid microbiological diagnostics, inflammation markers-guided therapies, the reduction of standard durations of antibiotic courses, to consider dosing according to PK/PD targets and to avoid antibiotic classes carrying a higher risk for induction of bacterial resistance.

RAPID MICROBIOLOGICAL DIAGNOSTICS

Surviving sepsis campaign release 1-hour bundle, which included administration of antibiotics as soon as possible. Delay in administration of antibiotics might result in increase of mortality. One of the early studies advocating early antibiotic use came from North America, stating that there is 79.9% of survival rate, if antibiotics were given in the first hour of hypotension in patient with sepsis. And for each hour of delay of antibiotics delivery will cause a 7.6% decrease of average survival of sepsis patient, up until the sixth hour. Failure to deliver antibiotics in the first 36 hours of hypotension in sepsis patient is equivalent to death sentence. The problem is conventional identification of bacteria consists of performing Gram stain followed by bacterial identification and antibiotic-susceptibility testing. The process from start to finish can take up to five days. but currently, there are culture methods that provide faster result. These methods might need further evaluation of applicability in Indonesia.

Table 1. antimicrobial susceptibility testing (AST)

Method		YOP	Mean time to results	Main application		EOP	M/A	Results		Determines resistance	Validated with...		
				Clinic	Research			Qualitative	Quantitative		Bacteria	Cells	Antibiotics
Gold-standard	Agar dilution	1929[1]	24 h	X	(X)	Easy	M		X	No	X		X
	Chromogenic agar	2009	18–24 h	X	(X)	Easy	M		X	Yes	X		X
	Broth macrodilution	1971[1]	24 h	X	(X)	Easy	M		X	No	X		X
	Disc diffusion	1959[2]	18–24 h	X	(X)	Easy	M	X		Yes	X		X
	Etest	2010	24 h	X	(X)	Easy	M		X	No	X		X
	Microdilution	1977[3]	24 h	X	(X)	Easy	M		X	No	X		X
	Microcalorimetry	1973[3]	4–5 h	X	(X)	Easy	M		X	Yes	X		X
	PCR-based methods	1992–2016	2 h	X	(X)	Moderate	M/A		X	Yes	X		X
Mechanical	Asynchronous magnetic bead rotation (AMBR) sensor	2014	6–24 h		X	Complex	M		X	UNK	X		X
	Single-cell AMBR sensor	2011	2 h		X	Complex	M	X		UNK	X		X
	Surface acoustic wave sensor	2007	7 h		X	Moderate	M		X	No	X		
	Microbial cell weighting with vibrating cantilevers	2010	20 min to 2 h		X	Complex	M		X	Yes	X		X
Optical	Optical density measurement	1975–2014	2–3 h		X	Easy	M/A		X	Yes	X		X
	Biomimetic polymer sensor	2006	6–18 h		X	Easy	M		X	Yes	X		X
	Flow cytometry	1997–2014	2 h		X	Moderate	M/A		X	Yes	X		X
	Image analysis software	2006–2015	UNK		X	Complex	M/A	X	X	UNK	X		X
	Optical tweezers	2015	100–200 s		X	Complex	M		X	No	X		
	Raman spectroscopy	2004–2010			X	Complex	M		X		X		X
	MALDI-TOF MS	2005–2013	12–24 h	X	X	Complex	M/A		X	Yes	X		X
	Automated systems	1975	UNK	X	X	Moderate	A		X	Yes	X		X
Microfluidics	Microfluidic agarose channels	2013	3–4 h		X	Moderate	M		X	Yes	X		X
	Microfluidic pH sensor	2013	2 h		X	Moderate	M/A		X	UNK	X		X
	Self-loading microfluidic device	2012	18		X	Easy	M	X		Yes	X		X
	Microdroplets	2011–2016	< 4 h		X	Complex	M/A		X	Yes	X		X
Osteoblast infection models	Human osteoblast infection	2013	> 20 h		X	Moderate	M		X	Yes	X	X	X
	Microfluidics Ti alloy model	2010	25 h		X	Complex	M	X	X	UNK	X	X	
	Microfluidics 3D bone tissue	2012	5 weeks		X	Complex	M	X		Yes	X	X	X

INFLAMMATION MARKERS-GUIDED THERAPIES

Personalising antibiotic treatment based on a patient's individual risk for bacterial infection has great potential to improve antibiotic stewardship efforts to encourage judicious and correct usage of these agents and mitigate the emergence of multidrug-resistant pathogens, one of the most urgent threats to global health and directly linked to antibiotic overuse. Integration of host response markers, which correlate with bacterial infection, into the overall assessment and clinical care of patients has high potential to improve individual antibiotic decisions. Among such promising host response markers: procalcitonin (PCT), a marker specific to bacterial infections, and C-reactive protein (CRP), a more general inflammatory marker with high sensitivity, have generated most interest. A meta-analysis based on individual data of 1252 patients with COPD exacerbation found PCT guidance to result in a significant reduction in antibiotic initiation (72% versus 43%) and antibiotic exposure (5.3 versus 3.1 days) with no difference in mortality (4% versus 3%) or risk of treatment failure (17% versus 17%).

REDUCTION OF STANDARD DURATIONS OF ANTIBIOTIC COURSES

At the 45th Annual Meeting of the Infectious Diseases Society of America, Louis Rice delivered the Maxwell Finland Lecture on modalities to reduce antimicrobial resistance; he concluded that reduction in length of antibiotic courses was the antibiotic use strategy most likely to be effective in

reducing antibiotic resistance. The proposed mechanism was that shorter courses of antibiotics reduce selective pressure on bacterial flora and, therefore, prevent emergence of resistance. Without external pressures, prescribers may not willingly curtail antibiotic duration or de-escalate their empirical antibiotic choices. Studies from Europe and the United States have shown that de-escalation was only performed in 11%–55% of patients in whom it would have been appropriate.
Antibiotic therapy initiated for clinically suspected VAP was discontinued if a noninfective etiology for infiltrate was identified or signs and symptoms suggested active infection had resolved. In this study, the duration of antibiotics in the antibiotic discontinuation group was 2 days shorter than that in the conventional treatment group (mean ± standard deviation, 6.0 ± 4.9 days vs 8.0 ± 5.6 days), with no difference in occurrence of a secondary episode of VAP, hospital mortality, and ICU length of stay.

DOSING ACCORDING TO PK/PD TARGETS

Several reports have shown marked heterogeneity of antibiotic pharmacokinetics (PK) in patients admitted to ICUs, which might potentially affect outcomes. Therefore, the pharmacodynamic (PD) parameter of the efficacy of antibiotics, that is, the time that its concentration is above the bacteria minimal inhibitory concentration (T > MIC), cannot be safely extrapolated from data derived from the PK of healthy volunteers. Gonçalves-Pereira et al performed a full review of published studies addressing the PK of intravenous β-lactam antibiotics given to infected ICU patients. The PK of β-lactam antibiotics are heterogeneous and largely unpredictable in ICU patients. Consequently, the dosing of antibiotics should be supported by PK concepts, including data derived from studies of the PK of ICU patients and therapeutic drug monitoring.

Improvements in clinical outcomes have been observed when antimicrobial agents are dosed optimally to achieve their respective PK/PD targets. With the rising rates of antimicrobial resistance and a limited drug development pipeline, PK/PD concepts can foster more rational and individualised dosing regimens, improving outcomes while simultaneously limiting the toxicity of antimicrobials.

AVOID ANTIBIOTIC CLASSES CARRYING A HIGHER RISK FOR INDUCTION OF BACTERIAL RESISTANCE

A too uniform use of antibiotics (few substances / antibiotic classes) might increase selective pressure and promote the spread of antimicrobial resistances. In addition, the use of particular antibiotic classes carries a higher risk for the emergence of resistant bacteria. For example, cephalosporin use has been associated with subsequent infection with vancomycin-resistant *Enterococcus faecium,* extended-spectrum β-lactamase (ESBL)–producing or β-lactam-resistant Gram-negative bacteria, and *Clostridioides difficile.* Quinolone use has been linked to infection with methicillin-resistant *Staphylococcus aureus* and with increasing quinolone resistance in Gram-negative bacilli, such as Pseudomonas aeruginosa. Fluoroquinolones are reported to be associated with induction of resistance in enterobacteriaciae and *P. aeruginosa* during therapy.

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COVID 19 VACCINES: PAST , PRESENT, AND FUTURE

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Vaccines help prevent infection by preparing the body to fight foreign invaders (such as bacteria, viruses, or other pathogens). All vaccines introduce into the body a harmless piece of a particular bacteria or virus, triggering an immune response. Traditional vaccines inject a weakened form or component of a bacterial or viral pathogen, which B Cells then absorb and produce antibodies against. However, scientists have developed a new type of vaccine that uses a molecule called messenger RNA (mRNA) rather than part of an actual bacteria or virus. Messenger RNA is a type of RNA that is necessary for protein production. In cells, mRNA uses the information in genes to create a blueprint for making proteins. Once cells finish making a protein, they quickly break down the mRNA. mRNA from vaccines does not enter the nucleus and does not alter DNA. mRNA provides the genetic code directly to dendritic cells where the ribosomes of the cells read the mRNA to produce COVID-19 proteins. This signals the standard immune pathways to produce protective antibodies. Once produced, antibodies remain in the body, even after the body has rid itself of the pathogen, so that the immune system can quickly respond if exposed again. If a person is exposed to a virus after receiving mRNA vaccination for it, antibodies can quickly recognize it, attach to it, and mark it for destruction before it can cause serious illness.

Vaccination has reduced the burden of infectious disease, second only to clean drinking water in reducing mortality worldwide. However, infectious diseases remain the second leading cause of death worldwide, disproportionately affecting children under the age of 5 and people in low-income countries. In fact, five of the top ten leading causes of death in low income countries are caused by infectious agents: lower respiratory infections (e.g., pneumonia), HIV/AIDS, diarrheal disease, malaria and tuberculosis. While some of these killers lack a current vaccine for disease control, many deaths result from vaccine-preventable disease, indicating substantial room for improvement in vaccine technology and administration.

THE PAST:

A. General overview of vaccines

Historically, live, killed, and subunit vaccines have been critical in controlling the spread of similar diseases such as smallpox and hepatitis, but these diseases have been limited in their international presence, infectivity and case fatalities. COVID-19 presented several novel challenges in this regard; the ease of spread of the disease and the high observed fatality rate made it impossible to ignore or downplay the impact of the virus for the general population.

In the spring and summer of 2020, academic research groups and pharmaceutical companies turned their attention to messenger RNA (mRNA) vaccination, a different vaccination strategy which utilizes the host's cellular machinery to synthesize a viral protein product and establish protective immunity within the host. mRNA therapeutic delivery previously had limited applications in humans due to the instability of mRNA in vivo and was primarily being explored as an experimental strategy for cancer therapy, but the urgency of the pandemic required rapid development of a vaccine with a high safety profile, ease of scale up/production, and strong therapeutic efficacy, which a mRNA vaccination could provide.

Recent advances in nanotechnology, and particularly lipid-based nanoparticles, offered an avenue for researchers to deliver mRNA to the body's tissue and harness the technique to produce a next-generation subunit vaccine, and many leading pharmaceutical companies were eager to try and do so. As of today, companies such as Moderna and Pfizer/BioNTech have been successful in producing COVID-19 mRNA vaccines. Their formulations successfully passed in Phase 3 clinical trials in the fall of 2020 and received a rare emergency use authorization from the United States Food and Drug Administration (FDA).

Both Moderna and Pfizer/BioNTech utilized an mRNA approach requiring 2 shots, while Johnson Johnson a viral vector approach requiring just a single shot. The latter approach utilized a different virus in order to genetically encode instructions intended to fight off COVID-19 infections. Pfizer/BioNTech was the first to get approval on December 11, 2020, with Moderna getting approval a week later. Johnson & Johson's vaccine was approved on February 27, 2021. All of the vaccines are currently approved for use in adults, while the Pfizer vaccine has been approved for adolescents as well.

Additionally, all three of these vaccines were given emergency use authorization in various countries. On August 23, 2021, the US Food and Drug Administration (FDA) officially approved the Pfizer/BioNTech vaccine. Widespread administration of these vaccines began around the same time as their debut and continues today; though there was certainly initial hesitancy in the eyes of the general public (some of which still persists well into 2021), extensive trials and studies have confirmed the safety and efficacy of these vaccines. Over 44% of the global population has now been partially vaccinated against COVID-19 as of September 2021, and world stability is contingent upon the sustained success of vaccination efforts.

The breakneck pace of the development of COVID-19 mRNA vaccines highlights the benefits and utility of mRNA delivery as a vaccination strategy, and it is worth exploring how this technology can be refined and improved upon to provide prophylactic and therapeutic treatment solutions for a wide range of diseases. Looking beyond COVID-19, several infectious and tropical diseases continue to harm populations in developing countries with limited avenues for prevention. The foundational principles behind mRNA vaccines could potentially be applied to create effective solutions for these diseases.

Vaccines are based on the fundamental premise of protective immunity at both the individual and population levels. By exposing a recipient to a noninfectious element of a disease-causing pathogen, the vaccine can stimulate the host's adaptive immune system to generate immunological memory against the pathogen, significantly reducing the chance of infection when exposed to the pathogen in the future. Simultaneously, widespread vaccination can protect the most vulnerable members of a population through a process known as herd immunity -- with enough vaccinated members in a group, the virus will have little opportunity for community spread.

Vaccine types

The innate immune system, consisting of natural barriers such as skin, mucous membranes, nonspecific macrophages, and enzymes serves well as a first line of defense against many disease-causing antigens, but fails to respond robustly and specifically to antigens, possibly resulting in damage to the host through excessive inflammation and delaying the response against pathogens. The human body's adaptive immune system bridges these shortcomings by generating a pathogen-specific immune response and retaining memory of the pathogen's key features. By doing so, the system can direct cellular and humoral elements to rapidly neutralize a pathogen when it re-enters the body, and generating this immunological memory is the key focus of most vaccination strategies .

Vaccine technology has advanced significantly from the initial attempts in the 18th and 19th centuries to induce smallpox immunity through lesion transfusion - modern vaccines are highly precise and carefully engineered formulations that utilize a variety of antigen properties to stimulate adaptive immunity.

THE PRESENT: OTHER VACCINES

DNA/Toxoid

The most common vaccines in use today utilize the techniques described above, but other vaccination strategies have demonstrated potential for human use and are being explored in research settings. For example, toxoid vaccines are centered on the delivery of only the immunostimulatory product of a disease-causing agent to generate protective immunity. Similar to subunit vaccines (but using an antigen product as opposed to the antigen itself), these vaccines have shown high efficiency in protecting against diphtheria, tetanus, pertussis, and C. difficile infections. oved for human use. Of note, the Oxford-AstraZENECA vaccine emerged in late 2020 as an effective vaccine against COVID-19 utilizing the DNA of the SARS-CoV2 spike protein.

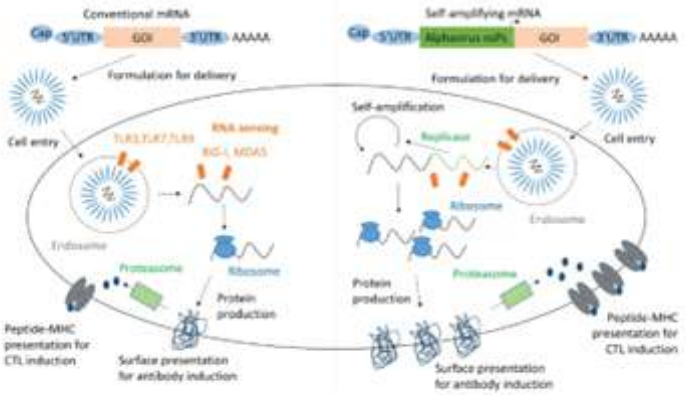
This is not technically considered a DNA vaccine - rather than incorporating into the host genome, the genetic material is delivered to the cell via a chimpanzee adenovirus vector and migrates to the nucleus, where it is transcribed independently of the host genome and then follows a similar path as mRNA vaccines. This vaccine has a much lower efficacy than the mRNA vaccines and is further reduced against novel variants, but it remains a promising option for tropical and lower-income countries due to its low price per dose and less stringent storage requirements. It is yet unclear whether there is a significant advantage of integrating into the host genome in this particular

disease, but the potential drawbacks of off-target effects relegate this as a consideration for the distant future. Another recent vaccine that utilizes an adenovirus vector with non-incorporating DNA strands is the Johnson and Johnson/Janssen COVID-19 vaccine. This vaccine is novel in that it claims to only require one administration, as opposed to the two required by other vaccines. It demonstrated about a 66% efficacy rate against disease prevention, which is lower than other frontrunner vaccines, but it is still being utilized as an important tool in the fight against COVID-19.

mRNA vaccines

Immunotherapy holds the potential to offer an effective and safe form of cancer treatment. One specific approach to re-engineering the body's immune cells is the delivery of messenger RNA encoding tumor antigens to immune cells, allowing the immune system to recognize and create antibodies against tumors. The now-famous 2005 studies by Kariko and Weissman were the first to identify mRNA's immunostimulatory properties via activation of Toll-like receptors (TLRs), as well as demonstration of the fact that slight nucleotide modification could allow mRNA to be engineered as a human therapeutic by avoiding the innate immune system and producing a large amount of protein with a relatively high safety profile.

Despite the promising trials with mRNA based therapeutics in laboratory settings, the facts remained that mRNA is highly unstable inside the body and prone to degradation by immune agents and nucleases, possesses a high potential for adverse immunogenicity, and initially generates weaker protective immunity than conventional vaccines. With the modern advances in lipid nanoparticle technology, researchers saw an avenue to effectively deliver nucleic acid vaccines and transcribe antigenic components in vivo. From 2010 onwards,



pharmaceutical companies such as Moderna, Pfizer, and BioNTech began to explore the development of mRNA therapeutics/vaccines and raised millions of dollars in funding towards this research, though it was only until recently that this work came into the spotlight. With the advent of the COVID-19 pandemic in early 2020 and the unique challenges present in ensuring a fast,

scalable, and effective international vaccination strategy for the novel virus, these companies were well positioned to pivot their experimental explorations with mRNA towards a vaccination solution. Moderna's vaccine was manufactured with smaller independent contracts, and BioNTech partnered with the pharmaceutical giant Pfizer for logistical and manufacturing support . By early summer, mRNA vaccines had exhibited the fastest development timeline along with high generation of immunity, and the first COVID-19 vaccines to receive emergency FDA approval in December were mRNA-based.

In the fall and winter of 2020, mRNA vaccines began concluding their Phase 3 clinical trials; exhibiting very high efficacy against COVID-19, Moderna and Pfizer-BioNTech's formulations received emergency use authorization from regulatory agencies around the world in a historic move and began being distributed for large-scale vaccination. These vaccines built upon the simple principles demonstrated by previous work in the field - an exogenously engineered mRNA strand is introduced to the body and used to produce the antigenic component of the SARS-CoV2 spike glycoprotein.

These peptide fragments are then localized to the cell membrane and presented to immune cells, resulting in immunostimulatory activity and generation of long-term immunity. Clinical trials pointed to over 94% transmission/infection prevention efficacy and 100% severe infection/death efficacy for Pfizer and Moderna's vaccine, and by December 2020, both had received authorization with more traditional formulations by manufacturers such as AstraZeneca and Johnson and Johnson following closely behind.

The development of these vaccines resulted in the largest global vaccination campaign in human history. As of September 2021, an estimated 6.1 billion doses have been administered worldwide with roughly 31 million doses continuing to be given per day. These vaccines have single- handedly altered the trajectory of the COVID-19 pandemic, slowly reducing the need for masks and stringent social distancing measures and allowing society to return to its normal state of functioning.

Unique mechanism of action:

The mRNA vaccines, as the name suggests, are built around the principle of in vitro transcribed (IVT) mRNA. Using the unique developments from the past couple of decades, it has become recently possible to engineer mRNA strands with slightly modified nucleotides that are capable of activating humoral and cellular immune responses through the production and display of protein products but limited immunostimulatory behavior from the mRNA strand itself.

Advantages over current standards of vaccination

Though other vaccination techniques have demonstrated high efficacy against many types of diseases, mRNA vaccination holds promise as a safe, controllable, and efficient alternative to pathogen-based viruses. The key safety advantage offered by mRNA vaccines is the non-integrating mechanism of action - with all activity localized to the cytosol, genomic disruption and offtarget effects are not a concern as they are with DNA-based vaccines. Secondly, mRNA can be

easily modified at the nucleic acid level to further reduce unwanted immunogenicity, increase effective half-life, and improve safety; modifications at the untranslated regions (UTRs) of the molecule can also promote ribosome binding and protein product translation. mRNA molecules are easily produced in bioreactors, safety requirements in the manufacturing process are much less stringent than with live/inactivated vaccines due to the absence of live virulent agents, and nanoparticle technology has improved significantly in the last decade, enabling mRNA based therapeutics to have high in vivo viability, cellular uptake, and gene expression. Clinical and laboratory trials have shown that antigen presenting cells (APCs) are able to exhibit mRNA protein products to a similar degree as vaccination by more conventional methods.

Table 2
A summary of the various mRNA vaccine candidates for the prophylactic treatment of SARS-CoV-2

Manufacturing Company	Vaccine Type	Vaccine Mechanism of Action	Current Regulatory/Approval Status
Moderna	mRNA	LNP-encapsulated modified mRNA encoding for COVID-19 spike protein delivered intramuscularly over two doses with a potential third dose booster	Emergency use authorization in several countries around the world
Pfizer/BioNTech	mRNA	LNP-encapsulated modified mRNA encoding for COVID-19 spike protein delivered intramuscularly over two doses with a potential third dose booster	Emergency use authorization in several countries around the world
Johnson and Johnson/ Janssen	Viral vector	Single dose, antigen-encoding genes delivered in a single dose utilizing a chimpanzee adenovirus vector	Emergency use authorization in several countries around the world
University of Oxford/ AstraZeneca	Viral vector	Antigen-encoding genes delivered in a single dose utilizing a chimpanzee adenovirus vector	Lower-cost alternative to other formulations; worldwide emergency use authorization with focus in developing countries
Gamaleya (Sputnik-V)	Viral vector	Two-dose intramuscular injection of adenovirus-enclosed antigen genes	Limited emergency use authorization around the world, highest use in Eastern Hemisphere
Sinovac (CornoaVac)	Inactivated virus	Two-dose intramuscular injection of chemically inactivated COVID-19 virus	Limited emergency authorization use around the world, highest use in Asia and Africa
Sinopharm	Inactivated vaccine	Two-dose intramuscular injection of chemically inactivated COVID-19 virus	Full authorization in China with emergency use authorization in several developing countries
CanSino (Convidecia)	Viral vector	Single shot adenovirus vector vaccine delivered intramuscularly	Full authorization in China with very limited emergency use authorizations in developing countries
Bharat Biotech (Covaxin)	Inactivated virus	Vero cell-grown COVID-19 virus, chemically inactivated and	Very limited emergency use authorizations in various tropical and developing countries
Valneva	Inactivated virus	Single-dose chemically inactivated virus, promises strong performance against variants	Phase III clinical trials
Novavax	Subunit	Thermostable formulation of COVID-19 spike protein delivered using LNPs	Phase II/III clinical trials
CureVac	mRNA	Unmodified mRNA encoding COVID-19 spike protein encapsulated in LNPs	Preclinical/early clinical trials after poor Phase III results in initial formulation

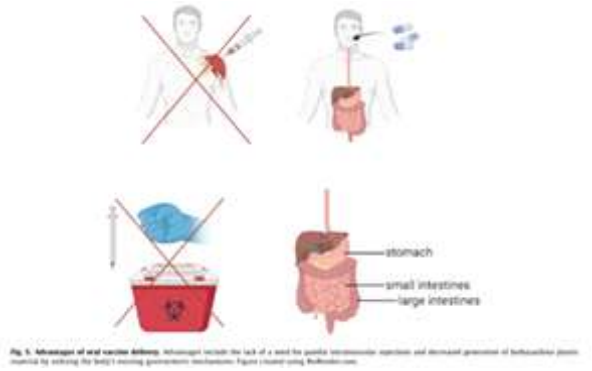
FUTURE DIRECTIONS AND PERSPECTIVES

It was not long ago that mRNA vaccines were on the fringes of the scientific community with a bleak outlook for translation to human therapeutics. The COVID-19 pandemic, as devastating and dangerous as it is, has managed to spur innovation in this novel type of vaccination, and the ongoing and future research in this area potentially holds huge implications for human health. Though mRNA vaccines have come a long way in such a short time, their technology is not perfected yet, as evidenced by their slightly less-than-complete conferment of immunity against COVID-19 and the increasingly alarming number of COVID-19 Delta variant breakthrough infections post vaccination.

The current formulations struggle with thermostability, potential for harsh side effects due to the impurity of the lipid nanoparticles, and may eventually become completely ineffective against new variants as the virus continues to evolve.

One observed issue was a small number of allergic reactions to polyethylene glycol used in stabilizing the lipid nanoparticles of the Pfizer-BioNTech vaccine. Replacing PEG with other biocompatible stabilizing polymers, such as poly(N-vinylpyrrolidone) (PVP) and poly(N-(2-Hydroxypropyl) methacrylamide) (PHPMA) may decrease these adverse reactions, although much more preclinical and clinical testing is required to confirm the immunogenic profiles of these polymers. Another potential strategy for improving the efficacy of mRNA vaccines would be to increase their targeting of dendritic cells via surface conjugation of specific ligands.

Grafting mannose or hydrophobic-interaction-inducing lipids to the surface of lipid nanocarriers would enable them to more effectively target effector cells and generate immunity. Several past and ongoing studies have demonstrated the improved targeting and immunogenic abilities of nanocarriers with targeting moieties attached to the surface. Future strategies for improving the efficacy of intramuscularly administered mRNA vaccines could certainly benefit from incorporating these various aspects of nanotechnology. One promising future direction for mRNA vaccines could be oral delivery applications.



There are several other advantages to oral delivery, including less stringent purification requirements, higher patient compliance due to the elimination of needles, and significantly decreased amount of biohazardous and plastic waste. Additionally, mRNA vaccines could take advantage of developments in nanotechnology, such as the 2014 study by Duran-Lobato et al., which demonstrated the in vitro targeting abilities of surface-modulated nanocarriers. Oral delivery of mRNA vaccines, though promising, does come with several associated challenges. There are significant barriers to oral delivery in general, which are compounded by mRNA's low stability in vivo.

The digestive system is a harsh physical and chemical environment with drastic changes in pH, and even at the mucosal layer, mucosa-associated lymphoid tissue can cause problems of immune avoidance and epithelial layer transport through tight junctions and mucous layers may result in a lower bioavailability. mRNA and/or associated delivery proteins would rapidly become

targets for proteases or exonucleases as well. Despite these challenges, the potential for expansion of mRNA vaccines into the parenteral delivery space remains huge and the renewed interest in mRNA research promises interesting developments in the near future.

Technological devices, such as microneedle arrays [93] and high pressure liquid jets, have successfully demonstrated mucosal penetration capabilities with vaccine formulations, and research in nanofiber-based mucosal patches for sustained vaccine release have also been explored.

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