Management of Bacterial Secondary Infections in Viral Pneumonia, focus on:

Bacterial Secondary Infection in COVID-19

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RESPINA-PAMKI

Introduction

- limited reference to non-viral co-infections and superinfections in COVID-19
- Studies in animal models: demonstrating that respiratory viral infections predispose patients to bacterial **co-infections** and **super-infections**
- most fatalities in the 1918 influenza pandemic → due to subsequent bacterial infection and similar observations during the later 20th century influenza pandemics:
  - H2N2: 1957
  - H3N2: 1968–1969
  - H1N1: 2009– 2010

J.A Bengoechea & CGG Bamford. EMBO Mol Med (2020) 12: e12560.
Published online 15 June 2020

Co-infection

- Possible scenarios:
  - secondary SARS-CoV-2 following bacterial infection/colonisation;
  - combined viral/bacterial pneumonia;
  - secondary bacterial “super-infection” after SARS-CoV-2
- Any scenario will worsen the clinical outcome and the severity of COVID-19
- Longer stay; mechanical ventilator → increasing risk of HAP
- Gut-lung axis: SARS-CoV2 infection may disturb gut homeostasis → bacterial pneumonia

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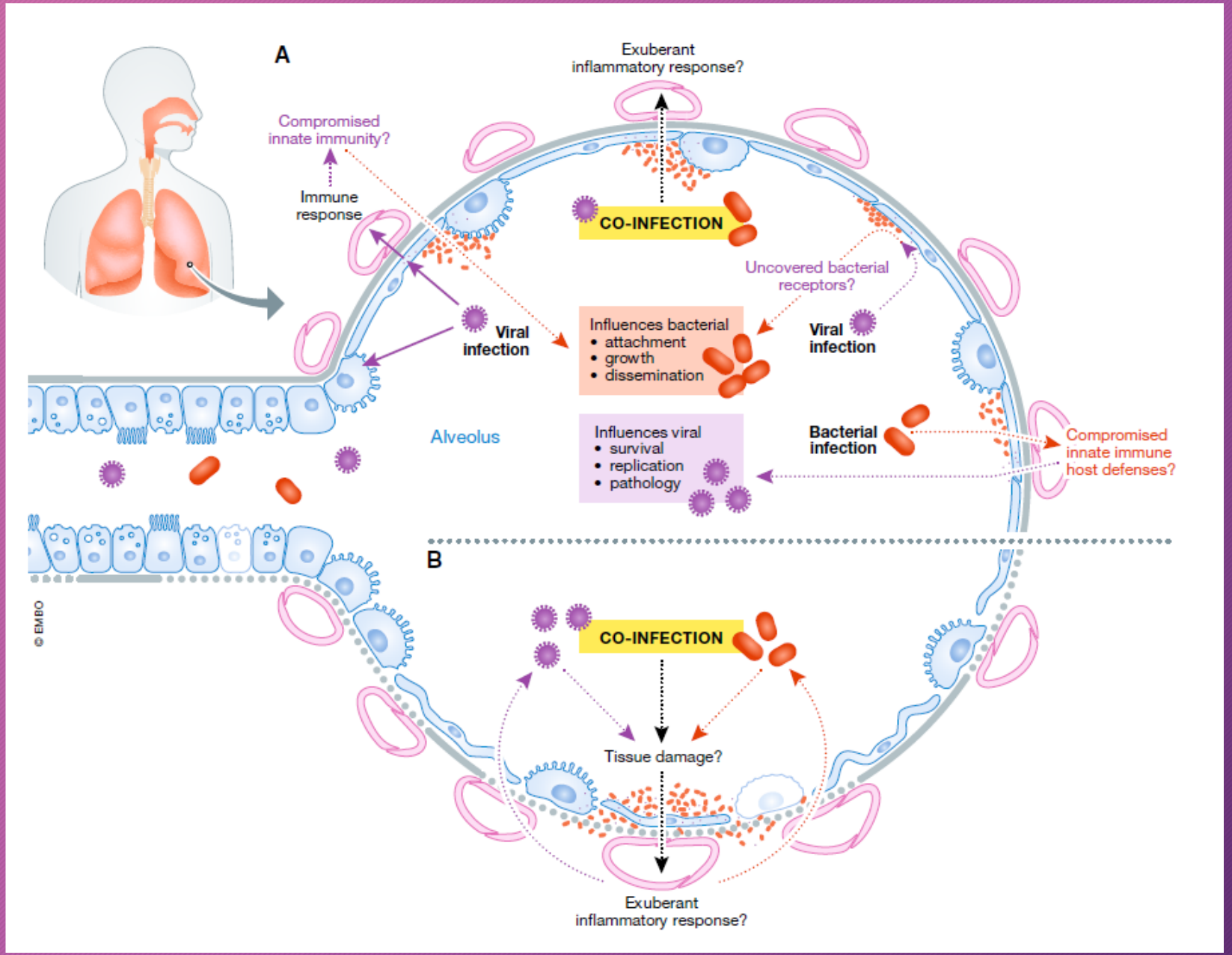

Interplay between SARS-CoV2-Bacteria-Host

J.A Bengoechea & CGG Bamford. EMBO Mol Med (2020) 12: e12560. Published online 15 June 2020

Co-Infection with multiple pathogens

received
17 Feb.2020

- Shenzhen-China, 186 patients, 18-65 years old
- Clinical manifestation: fever (76.3%), abnormal chest CT (66,67%)

- 49.46% (92) SARS-CoV2 positive
  - 6 patients positive for other respiratory viruses
  - RSV, rhinovirus (hRV), human metapneumovirus (hMPV), PIV2, Coronavirus HKU1

- 50.54% (94) SARS-CoV2 negative:
  - 18 patients (9.7%) positive 1-2 other respiratory viruses
  - 5 patients positive 3 other respiratory viruses
  - hRV, RSV, adenovirus, FluA, FluB, PIV2, PIV3, HKU1, hMPV

Lin, D. et al. Science China. Life science. March 2020

Review

Co-Infection in COVID-19

received
15 May 2020

- Co-infection in SARS:
  - *Chlamydophila pneumoniae* (30%) and *Mycoplasma pneumoniae* (9%)
  - Human metapneumovirus
- Co-infection in MERS-CoV:
  - Influenza Virus, M.tuberculosis
  - Critical ill: bacterial (18%) and virual (5%)

Lai, CC., et al. J. of Microbiology, Immunology and Infection (2020). 53, 505-512

Table 1 Summary of studies that reported the incidence of co- and secondary infection among COVID-19 patients.

Study	City, country	No. of patients with COVID-19 reported	No (%) of co—or secondary infection			
			Virus	Bacteria	Fungus	Total
Huang et al.[11]	Wuhan, China	41	Not mentioned			4 (9.8)
Chen et al.[12]	Wuhan, China	99	0	1 (1.0%)	4 (4.0): *Candida albicans* (n = 3) and *C. glabrata* (n = 1)	5 (5.1)
Arentz et al.[13]	United States	21 (critically ill)	3 (14.3)	1 (4.8)	0	4 (19.0)
Chen et al.[14]	Wuhan, China	29	0	1 (3.4)	0	1 (3.4)
Wang et al.[15]	Wuhan, China	104	6 (5.8): coronavirus (n = 3), influenza A virus (n = 2), rhinovirus (n = 2), and influenza A virus subtype H3N2 (n = 1)	0	0	6 (5.8)
Wu et al.[16]	Wuhan, China	201 (acute respiratory distress syndrome)	1 (0.6): influenza A virus	0	0	1 (0.6)
Young et al.[17]	Singapore	18	0	0	0	0
Zhou et al.[18]	Wuhan, China	191	27 (50) of 54 non-survivors with secondary infections			
Ding et al.[19]	Wuhan, China	115	5 (4.3): influenza A virus (n = 3) and influenza B virus (n = 2)	0	0	5 (4.3)

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Kim et al.[20]	Northern California, United States	116	24 (20.7): rhinovirus/enterovirus (n = 8), RSV (n = 6), other coronaviridae (n = 5), parainfluenza (n = 3), metapneumovirus (n = 2), and influenza A (n = 1)	0	0	24 (20.7)
Xing et al.[21]	Qingdao and Wuhan, China	68	Influenza A (n = 18), influenza B (n = 16), and RSV (n = 1)	*Mycoplasma pneumoniae* (n = 8) and *Legionella pneumophila* (n = 6)	0	25 (36.8)
Li et al.[22]	Wuhan, China	40 (children)	4 (10.0): influenza A or B virus (n = 3) and adenovirus (n = 1)	14 (35.0): *M. pneumoniae* (n = 13) and *Streptococcus pneumoniae* (n = 1)	0	18 (45)
Richardson et al.[23]	New York, United States	5700	39 (1.95): Rhinovirus/enterovirus (n = 22), other coronaviridae (n = 7), RSV (n = 4), parainfluenza 3 (n = 3), metapneumovirus (n = 2), and influenza A (n = 1)	3 (0.15): *Chlamydophila pneumoniae* (n = 2) and *M. pneumoniae* (n = 1)	0	42 (2.1)
Zangrillo et al.[24]	Milan, Italy	73 (acute respiratory distress syndrome)		Bacterial pneumonia (n = 9, 17.2%) and secondary bacteremia (n = 27, 37.0%)		

Co-pathogens

Bacterial co-infection

- *Mycoplasma pneumoniae*
- *Legionella pneumoniae*
- *Streptococcus pneumoniae*
- *Chlamydia pneumoniae*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*

Viral co-infection

- Rhinovirus, Enterovirus, Influenza A
- Coronavirus
- RSV
- PIV
- MPV
- Influenza B

Fungal co-infection

- *Candida albicans*
- *Candida glabrata*
- *Aspergillus flavus*

Systematic Review

Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis

received
18 June 2020

- 1308 publications → 24 (3506 patients, lab-confirmed COVID-19), mostly (n=21) in Asia
- 25 Dec 2019-31 March 2020
- Inclusion: laboratory-confirmed SARS-CoV-2 infection; all healthcare settings and age groups; bacterial inf (co- and secondary); isolates only from respiratory tract and blood
- Main reason of exclusion: lack reporting bacterial co-infection or bacterial secondary infection data

Langford BJ et al. Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.07.016

Results:

- **Co-infection: 3.5%** and **secondary infection: 14.3%** of COVID-19 patients
- Overall bacterial infection 6.9%: 5.9% in hospitalized and 8.1% in critically ill patients.
- Bacterial co-pathogens reported in 11/24 studies (45.8%) → <14% of patients with reported infections.
- Organisms reported: *Mycoplasma sp.* (11); *M. pneumoniae* (3), *Haemophilus influenzae* (5) and *Pseudomonas aeruginosa* (5)
- >70% of patients received antibiotics: broad-spectrum agents (FQs) and 3rd gen. cephalosporins.

Langford BJ et al. Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.07.016

Results and Conclusion

- H1N1 influenza pandemic, 2009: bacterial co-infection was reported in up to 30% of critically ill patients and 12% of hospitalized patients
- most commonly pathogens: *S. aureus* and *S. pneumoniae*
- Influenza virus damage epithelial cells in the lower airway with mucociliary dysfunction → facilitate binding of pathogenic bacteria to cell surfaces → bacterial infection is established
- SARS-CoV-2?
- **Conclusion:** insufficient evidence to support widespread use of empirical antibiotics in patients hospitalized for COVID-19, particularly those without critical illness.

Langford BJ et al. Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.07.016

Research Article:

Bacterial infections and patterns of antibiotic use in patients with COVID-19

received
19 July 2020

- Aim: incidence of bacterial coinfection in hospitalized patients with COVID-19 and evaluate the association of bacterial coinfection and empiric antibiotic therapy with the clinical outcomes

- single-center retrospective analysis; >18 years old; admitted 1 March – 24 April 2020; confirmed COVID-19

- Bacterial coinfection: presence of characteristic clinical features and positive blood, sputum, urine, or tissue culture results

Neto, AGM et.al. J Med Virol. 2020;1–7.

Results

- 242 patients; concomitant bacterial infection: 19% (n = 46)
- Infections: Genitourinary (57%), skin infections (10%), respiratory infections (8%) → *E.coli* (26%) and *Enterobacter cloacae*
- Antibiotic therapy: 67% (n = 162) and 72% of these patients without source of infection
- Antibiotics use: cefepime (45%), ceftriaxone (54%), vancomycin (48%), and azithromycin (47%)

Neto, AGM et.al. J Med Virol. 2020;1–7. (Accepted: 14 August 2020)

Results

- Mortality: 21.5% (n = 52) and 50% of them with concomitant bacterial infection → a predictor of increased mortality in older patients?
- Patients with antibiotic had poorer outcome
- Bias?? Sicker patients get antibiotic therapy
- *Antibiotic stewardship remains a challenge*

TABLE 3 Differences in inflammatory markers in patients treated with antibiotics vs without

	With antibiotics median (IQR)	Without antibiotics median (IQR)	*P* value
Ferritin	925 (380-2181)	687 (215-1542)	.108
D-dimer	2110 (1095-3405)	1195 (705-2802)	.006
Procalcitonin	0.25 (0.1-1.12)	0.11 (0.06-0.33)	.003
CRP	144 (65-236)	47 (24-131)	.002
LDH	466 (317-609)	333 (241-435)	.001

Neto, AGM et.al. J Med Virol. 2020;1–7. (Accepted: 14 August 2020)

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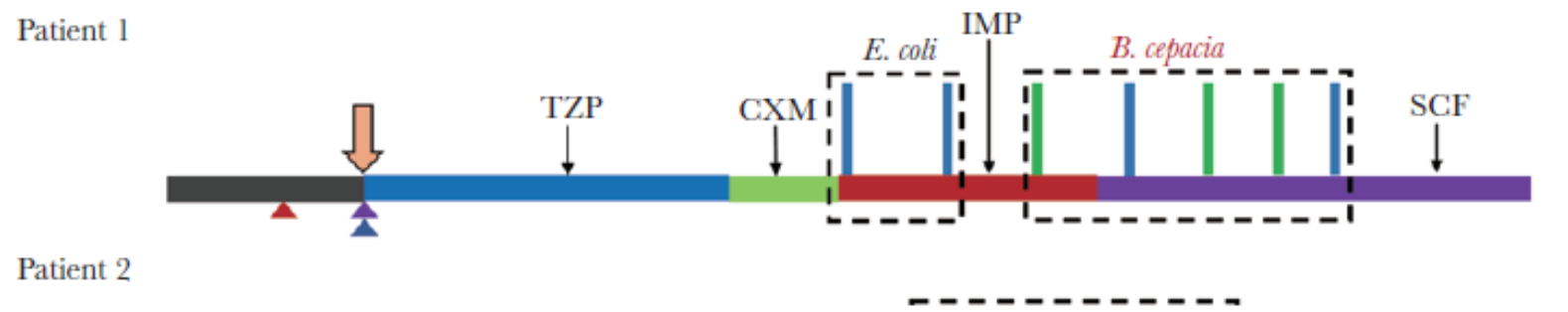


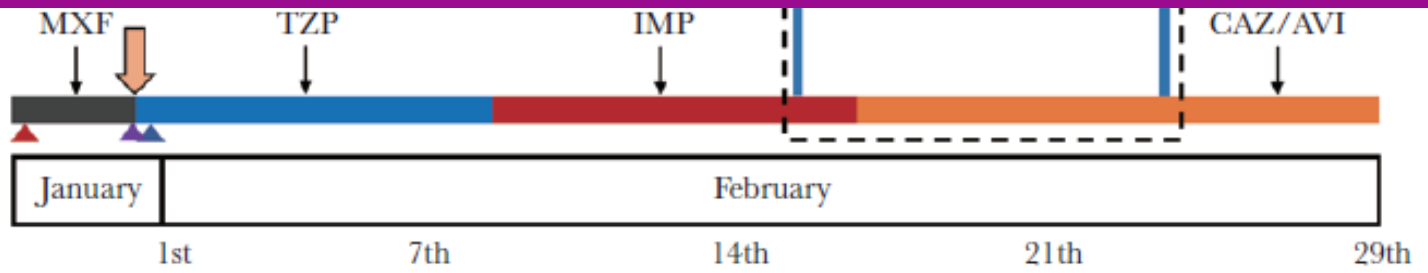
Conclusion

Incidence of secondary bacterial infections in COVID-16 is low

Secondary bacterial infection in influenza: early stage

It does not support common antibiotic prophylaxis

Prevention is essential



Safety Considerations in the Laboratory Testing Specimens Suspected or Known to Contain SARS-CoV-2

- Risk analysis: Ebola Virus vs. SARS-CoV2?
- Coronavirus: lower concentration of virus in **non**-respiratory specimens (stool, urine, blood) → use BSL-2 precautions
- BSL-2 laboratory: pathologic exam and processing of formalin-fixed/inactivated tissues, molecular analysis of extracted NA preparations, electron microscopic with glutaraldehyde-fixed grids, bacterial and mycotic cultures, staining and microscopic analysis of fixed smears, packaging of specimens for transport, inactivation of specimens (drop specimens in NA extraction buffer)

Iwen, PC. Am J Clin Pathol 2020;XX:1-4

Basic Core Processes when handling specimens from suspected COVID-19

- Training:
  - proper collection of specimens
  - Donning and doffing of PPE
  - Packaging and shipping of category B specimens
- Equipment
  - Use of a point-of-care device outside the BSC
- Inventory control
  - Adequate supply of specimen collection devices
  - Appropriate disinfection materials
  - Adequate transport materials for on-site and off-site transport
- Communication
  - Open lines with the medical care team
  - Collaboration in place with the local public health laboratory

Iwen, PC. Am J Clin Pathol 2020;XX:1-4

Take home messages

- Bacterial co-infection in COVID-19 patients :
  - Following bacterial colonization
  - Longer stay and ventilator → HAP
  - Pathogen = etiologies of CAP or HAP
- The use of empirical antibiotics in patients hospitalized for COVID-19, particularly those without critical illness → stewardship should be applied
- Multidrug resistant bacteria: leading to an increase in the mortality due to the limited arsenal of antibiotics to treat HAIs.
- Specimen handling in COVID-19 patient: BSL2 precaution