Secondary bacterial infections in COVID-19 patients

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Patients admitted to hospital are exposed to a greater risk of secondary infectious complications that more frequently affect the respiratory, urinary and circulatory systems, constituting one of the main causes of healthcare-associated infections (HAIs).

These infections are often due to multi-drug-resistant microorganisms that require the use of next-generation antimicrobials with a serious impact on antimicrobial stewardship programs, on the appropriateness of the use of antibiotics and on a pharmaco-economic level.
The presence of other pathogens in patients with SARS-CoV-2 infection has been reported, either at the time of a SARS-CoV-2 infection diagnosis (co-infection) or subsequently (superinfection).

However, data on the prevalence, microbiology, and outcomes of co-infection and superinfection are limited.

Co-infections and secondary infections existed in hospitalized COVID-19 patients and were relevant to the disease severity.

Screening of common respiratory pathogens and hospital infection control should be strengthened.
Superinfection with bacteria, other respiratory viruses, and fungi in COVID-19 patients has been reported to occur, with bacteria being a major causative agent of superinfection.

- Bacterial coinfection in particular is a worrying problem as it complicates treatment in COVID-19 patients and may worsen the prognosis and increase the likelihood of fatality.

- However, inappropriate prescribing of antibiotics when not needed can amplify the increasing antibiotic resistance problem, especially as the prescribed antibiotics tend to be broad-spectrum.
The reason that it is important to identify superinfections in patients with COVID-19 and the need for initial empiric antibiotic treatment, is due to concerns of adverse event of the routine use (and overuse) of antibiotics, with subsequent development of resistant hospital acquired, bacterial and fungal pathogens, which are contrary to antimicrobial stewardship program.
Antimicrobial stewardship programs and the use of antimicrobials were severely challenged during the early stages of the pandemic due to a scarcity of data on bacterial superinfections and a lack of therapeutic options.
One large study from the US documented that early empiric antibiotic therapy was used in 56.6% (965/1705) of patients hospitalised with COVID-19, whereas only 3.5% (59/1705) of patients had a confirmed community-onset bacterial coinfection.
In a meta-analysis of bacterial co-infection and secondary infection, using the CDC definition:

- Bacterial co-infections were reported in 3.5% of patients on admission with COVID and
- secondary infections were reported in 15.5%;
- while the overall rate of bacterial infections was 7.1% and more common in critically ill patients.

In 289 adults hospitalised in the US for SARS-CoV-2 infection, 48 (16.6%) had co-infections (defined as co-pathogens detected within 72 h of confirmed SARS-CoV-2 infection) and 25 (8.7%) of these were **bacterial respiratory co-infections**.

The patients with bacterial co-infections had higher WCC, LDH, CRP, PCT and IL-6 levels.

In addition, ICU admission, mechanical ventilation, and in hospital mortality were higher in those with bacterial co-infection than those without.

The possible reasons for differences in the reported bacterial co-infections as being due to regional variations in patient populations, their access to care, and infection prevention control measures implemented.

Most of the studies reported high rates of antibiotic use (71.3% to 85.5%), mostly broad spectrum, and suggested that most patients may not require them.
Classes of antibiotic prescribing in patients with COVID-19

Systematic review
Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis

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<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>North America</th>
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• a **prospective study** of patients admitted to a **Spanish ICU**, reported both early infections (within 48 h of admission to the ICU) and later infections in 92 patients. Overall, 32 microbial isolates were found within 48 h in 24 patients (26%, 24/92), most commonly S. aureus, S. pneumoniae, and H. influenzae.

• In some of these patients **P. aeruginosa** was isolated, but these patients had a **longer hospital stay before ICU admission** (median 9 days), than that of the general group (median 3 days).

• In the study in China, there was a higher rate of superinfections with hospital-acquired bacteria (like Acinetobacter, Pseudomonas and Enterococcus) in patients with severe COVID-19 infections, who were also more likely to suffer complications and death.

Supportive evidence for secondary bacterial pneumonia includes one or more of the following:

- new or recrudescent fever;
- new onset or change in the character of sputum;
- new leukocytosis or new neutrophilia (or both);
- new relevant imaging findings;
- and new or increasing oxygen requirements.
However, if a patient develops **new worsening respiratory failure** or **sepsis**, after an initial phase of consistent improvement (considered to be days), then nosocomial acquisition of secondary bacterial **infection** is likely unless proven otherwise.

It is also important to consider all other sources of hospital-acquired infections in these patients, such as indwelling central venous catheters or UTI.
• Secondary bacterial pneumonia in a patient on invasive mechanical ventilation has a presentation similar to HAP but warrants aggressive use of empiric broad-spectrum antibiotics with coverage for MRSA, Pseudomonas aeruginosa, and possibly other MDR organisms in accordance with the guidelines.

• It is also important to consider the side effects of antibiotics and institutional antibiograms.
To date, no new drugs against Gram-negative resistant bacteria have been produced, and so we observe a prevalence of them.

Several genes resistant to antimicrobial agents have been markedly discovered in a number of patients, and mostly Gram-negative resistant bacteria were ESBL and/or carbapenemase producers.

The presence of both ESBL and MBL enzymes is the basis of antibiotic resistance, and carbapenemases are also part of these.

This is one of the main reasons for the failure of an antibiotic therapy.
During the pandemic, **proper hygiene procedures** and **protective measures** may decrease the spread of the infection.

Furthermore, patients with SARS-CoV-2 infection have a higher incidence of MDR bacterial infections matched with non-COVID-19 patients of the same year.

**Staphylococcus Aureus**, extended-spectrum beta-lactamase **Klebsiella pneumoniae**, **Clostridium difficile** and **Acinetobacter baumanii** were the MDR pathogens that were isolated.
Many authors believe that, in patients with SARS-CoV-2 infection, especially in the first months of pandemic, the treatment with azithromycin, which acts primarily against Gram-positive bacteria, may be the cause of the predominance of Gram-negative coinfections.

Moreover, a compromised immune system in patients with severe forms of SARS-CoV-2 infection represents a significant risk factor for MDR bacterial infections.
WHO is worried about the abuse of antibiotics during the SARS-CoV-2 pandemic.

- A wide quantity of reviews report that only a limited number of these patients need antibiotics to heal bacterial infections;
- therefore, WHO published guidelines **not to treat patients with mild infection with antimicrobial** compounds and similarly, **patients with moderate illness, except on clinical indication**.
- Antimicrobial agents have to be wisely used, while empirical therapy should be rarely reserved to those cases which have a high chance of bacterial infection.
- Hence, **it is mandatory to re-evaluate empirical antibiotics management according to microbiological results.**
Conclusions

- Maintaining a high level of healthcare workers’ hand hygiene and preventive hygiene procedures may reduce the spread of hospital-associated infections.

- However, to allow a statistical decrease in MDR pathogens, it is necessary to increase antimicrobial stewardship programs, designed to promote the right use of antimicrobial compounds and a better strategy to face antibiotic resistance in hospitalized COVID-19 patients.

- The rising number of MDR pathogens and our decreasing capacity to eradicate them have notable influence on outcome of patients suffering from SARS-CoV 2 disease that are more exposed bacterial infections.
Thanks for your attention!