Antimicrobial stewardship in the ICU in COVID times: the known unknowns

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Since the start of the COVID-19 pandemic, there has been concern about the concomitant rise of another hidden but equally relevant pandemic: antimicrobial resistance (AMR)[1]. Distinction between infectious and non-infectious (inflammatory) causes of respiratory deterioration in COVID-19 patients is difficult and the much-debated relevance of bacterial, fungal and viral co-infections adds to the complexity. In a recent paper, we addressed some of the challenges that are faced in applying stewardship principles in the management of COVID-19 patients admitted to intensive care units (ICU)[2]. Below is a summary of the points raised.

Bacterial infections in COVID-19

Severe COVID-19 infection presents with clinical, radiological and laboratory signs that mimic those of bacterial pneumonia, and initiation of empirical antibiotic treatment has therefore been common practice[3]. However, this widespread empirical antibiotic use upon admission is not supported by contemporary data as bacterial coinfections seem rare in COVID-19 patients admitted to hospital wards and ICUs[4-7].

In addition, it is very challenging to diagnose bacterial superinfection in patients with COVID-19 as there are no specific radiographic features that distinguish between viral and bacterial pneumonia. Moreover, in a recent systematic review and meta-analysis, procalcitonin (PCT) was shown to have a pooled sensitivity and specificity of 0.55 for bacterial infections when using a cut-off value of 0.5 µg/L, making it too low to be of real clinical value[8]. However, the specificity of PCT increases with increasing levels. Thus, the measurement of PCT on diagnosis of COVID-19 may influence the decision to initiate or withhold antibiotics. In addition, serial measurements of PCT offer insight into the "inflammatory dynamics" of patients. PCT-guidance may also be used once antibiotic therapy has been initiated to shorten the duration of treatment[9-11].

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For patients developing septic shock however, empirical antibiotics should be started promptly according to standard antibiotic guidelines and based on local epidemiology with the aim of providing as optimal antibiotic coverage as possible.

On another note, COVID-19 infection often presents with a prolonged state of pro-inflammatory response, and it can therefore be challenging to assess treatment response based on the normalisation of laboratory and clinical markers such as leukocyte count, C-Reactive Protein (CRP), fever, need for vasopressors etc. This may be even more difficult when patients are treated with immunomodulatory agents such as corticosteroids, Tocilizumab or Anakinra. Studies have shown that CRP and PCT levels are markedly influenced by immunomodulatory therapy and do not follow their classic kinetics[12]. Fixed duration of therapy is therefore recommended and available evidence indicates that shorter duration of 5-8 days is without disadvantages compared to older recommendations of 10-14 days [13].

Coronavirus associated pulmonary aspergillosis (CAPA)

Early in the course of the pandemic there was a concern about the emergence of invasive pulmonary aspergillosis[14] complicating severe COVID-19 disease, including reports on azole resistant aspergillus pneumonia[15]. Overuse and abuse of antifungal agents might be partly responsible.

Coronavirus associated pulmonary aspergillosis (CAPA) poses diagnostic challenges as it is difficult to differentiate colonisation from invasive disease in critically ill COVID-19 patients. Previously established diagnostic criteria may not be valid in COVID-19 patients for a number of reasons[16]: first, characteristic radiological features (nodular lesions ± halo signs, cavitation) may not be present in COVID-19 Acute Respiratory Distress Syndrome (ARDS) and findings may overlap with superimposed infiltrates from viral or bacterial infections. Second, the galactomannan (GM) test does not have the same sensitivity as in neutropenic patients[17]. Third, histopathologic diagnosis, which is the gold standard for diagnosis, is difficult to obtain because lung biopsy has been considered unsafe in this pandemic. Similarly, bronchoscopy and bronchoalveolar lavage are not favoured in this population because of the risk of viral transmission to health care workers and the risk of bronchoscopy leading to intubation. On the other hand, relying on deep tracheal or sputum samples may yield false positive cultures (confounded by aspergillus environmental contamination). Therefore, determining clear diagnostic criteria for CAPA helps in guiding the decision to initiate antifungal treatment in order to reduce the risk of emergence of resistance.

Cytomegalovirus (CMV) reactivation during COVID-19

CMV reactivation is important to consider in COVID-19 patients as it may have a role in modulating patient immune response and therefore increasing the risk of other opportunistic pathogens, as well as a potential effect on COVID-19 viral elimination and response to the cytokine storm. CMV reactivation is common in critically ill ICU patients, presenting from viraemia to end-organ damage; and is usually associated with poor outcomes and increased morbidity and mortality[18-20].

Adverse events of CMV treatment include acute kidney injury and bone marrow suppression, among others. Unfortunately, treatment of CMV reactivation in critically ill COVID-19 patients may lead to further complications, especially in the context of existing lymphopaenia and sepsis. Therefore, treatment of CMV reactivation should be considered on a case-by-case basis weighing the risks versus benefits of therapy.

Pharmacokinetics/pharmacodynamics (PK/PD) alterations in COVID-19 patients

COVID-19 patients are at high risk for PK changes, just like any patient in the ICU[21,22]. The most important contributors to PK changes in critically ill patients are changes in the volume of distribution (VD), changes in protein binding and changes in drug clearance[23-31]. Thus, inadequate drug concentrations may be encountered, putting the patients at risk for both under-dosing and over-dosing, with associated toxicity.

In order to increase target attainment, a variety of strategies including extended and continuous infusion of selected antibacterials, with loading dose is mandatory in this setting. Renal function should be closely monitored to identify impairment. Monitoring should not only include creatinine levels / clearance or urine volume, but also other factors, such as the presence of haematuria and proteinuria[32,33]. As reduced kidney function and acute kidney injury may be more prevalent in patients with COVID-19 compared to sepsis from other causes, therapeutic drug monitoring is of particular relevance for antibiotics with potential toxicity such as vancomycin or aminoglycosides[34].

Also, considering that nosocomial pathogens with higher MICs may be more often encountered, the importance of antimicrobial dosing cannot be overestimated and leniency towards higher concentrations for many antimicrobials is justified.

Conclusions

General stewardship principles regarding starting, adapting and stopping antimicrobial treatment remain relevant in COVID-19 patients. However, some of the established principles of ICU antimicrobial stewardship may need adaptation in this population. Therefore, we point to the need for more studies and suggest the direction of such research.

Antimicrobial Stewardship domain	COVID-19 patients
Empirical therapy on ICU admission (community acquired)	Refrain from empirical antibacterial therapy unless in septic patients
Empirical therapy during ICU admission (nosocomial)	Consider using PCT to decide upon starting anti-bacterial therapy in patients who did not receive immunomodulatory therapy Regimen in septic patients should include cover-age for Gram positive pathogens and resistant Gram negative pathogens in the right scenario guided by the local epidemiology If *Candida auris* is identified in the centre, empiric coverage needs to be considered if bacterial infections are less likely
COVID associated invasive pulmonary aspergillosis (CAPA)	Consider CAPA as a nosocomial infection but do not routinely use antifungal prophylaxis Perform appropriate diagnostics to establish CAPA upon clinical findings Therapy should be started in some patients if they fulfill certain criteria
Management of CMV reactivation	Uncertainty: treatment of CMV reactivation should be considered on a case-by-case basis
Antimicrobial dosing	Consider altered Pk/Pd due to COVID-19: there is a risk for both underdosing and overdosing

ICU: intensive care unit; PCT: procalcitonin; PK/PD: Pharmacokinetics/pharmacodynamics

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