Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Antimicrobial stewardship in the ICU in COVID-19 times: the known unknowns

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ABSTRACT

Since the start of the COVID-19 pandemic, there has been concern about the concomitant rise of antimicrobial resistance. While bacterial co-infections seem rare in COVID-19 patients admitted to hospital wards and intensive care units (ICUs), an increase in empirical antibiotic use has been described. In the ICU setting, where antibiotics are already abundantly—and often inappropriately—prescribed, the need for an ICU-specific antimicrobial stewardship programme is widely advocated. Apart from essentially warning against the use of antibacterial drugs for the treatment of a viral infection, other aspects of ICU antimicrobial stewardship need to be considered in view of the clinical course and characteristics of COVID-19. First, the distinction between infectious and non-infectious (inflammatory) causes of respiratory deterioration during an ICU stay is difficult, and the much-debated relevance of fungal and viral co-infections adds to the complexity of empirical antimicrobial prescribing. Biomarkers such as procalcitonin for the decision to start antibacterial therapy for ICU nosocomial infections seem to be more promising in COVID-19 than non-COVID-19 patients. In COVID-19 patients, cytomegalovirus reactivation is an important factor to consider when assessing patients infected with SARS-CoV-2 as it may have a role in modulating the patient immune response. The diagnosis of COVID-19-associated invasive aspergillosis is challenging because of the lack of sensitivity and specificity of the available tests. Furthermore, altered pharmacokinetic/pharmacodynamic properties need to be taken into account when prescribing antimicrobial therapy. Future research should now further explore the 'known unknowns', ideally with robust prospective study designs.

Introduction

Since the start of the COVID-19 (coronavirus disease 2019) pandemic, there has been concern about the concomitant rise of another—equally relevant but more chronic—pandemic, that of antimicrobial resistance [1]. While bacterial co-infections seem rare in COVID-19 patients admitted to hospital wards and intensive care units (ICUs) [2,3], an increase in empirical antibiotic use has been described in this group of patients [4]. In the ICU setting, where antibiotics are already abundantly—and often inappropriately—prescribed, the need for an ICU-specific antimicrobial stewardship (AMS) programme has been widely advocated [5,6]. This warning should be emphasised during the current COVID-19 pandemic [7]. Apart from essentially warning against the use of antibacterial drugs for the treatment of a viral infection, relevant aspects of ICU AMS need to be reconsidered in view of the clinical course and characteristics of patients admitted with COVID-19. In this paper, we describe how some of the established principles of ICU AMS (use of biomarkers, empirical treatment, pharmacokinetics/pharmacodynamics and treatment of ICU-acquired infections) may require adaptation in patients infected with SARS-

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Table 1
Antimicrobial recommendations in COVID-19 times

AMS domain	COVID-19 patients
Empirical therapy on ICU admission (community-acquired)	Refrain from empirical antibacterial therapy unless in septic shock
Empirical therapy during ICU admission (nosocomial)	Use PCT to decide upon starting antibacterial therapy. Regimen in septic patients to include coverage for Gram-positive pathogens and resistant Gram-negative pathogens in the right scenario. If *Candida auris* is identified in the centre, empirical coverage needs to be considered if bacterial infection is less likely Consider CAPA as nosocomial infection Perform appropriate diagnostics to establish CAPA upon clinical findings (Fig. 1)
Antimicrobial dosing	Consider altered PK/PD due to COVID-19: risk for both underdosing and overdosing (Fig. 2)
Management of CMV reactivation	Uncertainty: treatment of CMV reactivation should be considered on a case-by-case basis
Use of antifungals	Do not routinely use antifungal prophylaxis. Therapy to be started in some patients based on the proposed algorithm

COVID-19, coronavirus disease 2019; AMS, antimicrobial stewardship; ICU, intensive care unit; PCT, procalcitonin; CAPA, COVID-19-associated invasive pulmonary aspergillosis; PK/PD, pharmacokinetics/pharmacodynamics; CMV, cytomegalovirus.

CoV-2 (severe acute respiratory syndrome coronavirus 2), the virus that causes COVID-19. In this rapidly evolving pandemic, we are aware that the available knowledge is still limited. Therefore, in a field with lack of significant evidence for AMS strategies, we point to the need for more studies and suggest the direction of such research.

In this review, we want to focus on key aspects of AMS that are impacted most by COVID-19. This may relate to patient as well as organisational factors. These topics were not randomly selected but rather chosen by all authors based on the fact that they either lack definitive data and clear evidence or remain controversial. We identified the empirical use of antibacterials, pharmacokinetic changes in patients with COVID-19, use of biomarkers and opportunistic infections as most relevant for the clinician at the bedside (Table 1).

Empirical antibacterial therapy for COVID-19

Empirical antibiotics are often administered in severely-ill patients when a bacterial infection is suspected as the primary cause of the critical illness. Viral pneumonia can predispose to bacterial superinfections by causing structural damage to the lung tissue and weakening host immunity. In previous influenza pandemics, bacterial co-infections and superinfections were associated with excess mortality [8].

Severe COVID-19 infection presents with clinical, radiological and laboratory signs that mimic those of bacterial pneumonia, therefore initiation of empirical antibiotic treatment has been common practice. At the same time, different from our experience with influenza infection, it is clear that upon initial presentation to the hospital, bacterial infection is rarely present. Recent studies have reported that 60–98% of patients received empirical antibiotic treatment, whereas the prevalence of documented bacterial co-infection ranges from 1–8% depending on the setting, with higher numbers reported in patients admitted to the ICU [2,3,9,10]. Thus, this widespread empirical antibiotic use is not supported by contemporary data.

However, it is very challenging to diagnose bacterial superinfection in patients with COVID-19 for many reasons. The most prevalent radiological findings in these patients are ground-glass opacities, consolidation and a mix of these two features in a predominantly peripheral distribution [11]. There are no specific radiographic features that distinguish between viral and bacterial pneumonia, particularly the atypical bacterial pneumonias. As the viral infection progresses, so do the radiological findings, and the distinction between that and a superimposed infection is often difficult [12].

Furthermore, severe COVID-19 is accompanied by a profound systemic inflammatory reaction, reflected by elevated inflammatory markers such as C-reactive protein (CRP), ferritin and interleukin-6 (IL-6). Procalcitonin (PCT) is an inflammatory marker considered to rise more in bacterial compared with viral infections. However, in a recent systematic review and meta-analysis on the ability of PCT to distinguish bacterial from non-bacterial causes of community-acquired pneumonia, the pooled sensitivity and specificity was only 0.55 and 0.76, respectively, when using a cut-off value of 0.5 μg/L, concluding that they are too low to be of real clinical value [13]. In COVID-19, PCT levels have been shown to correspond to disease severity, with the highest values seen in patients requiring ICU care and with elevated values also associated with poor outcome [14,15]. Although the cut-off value of 0.5 μg/L does not seem useful, the specificity of PCT increases with increasing levels. Thus, in a patient presenting with double-digit PCT levels, a bacterial infection should be highly considered and managed accordingly. Further details on the utility of PCT are discussed below.

Therefore, based on the available evidence, we recommend not to initiate antimicrobials routinely in patients admitted to the emergency department or ICU with proven COVID-19. When superimposed infection is suspected, appropriate microbiological sampling is highly recommended whenever possible. Whereas one may be reluctant to sample intubated COVID-19 patients invasively, taking appropriate precautions during endotracheal aspirate sampling will minimise the risk of viral transmission.

However, for patients developing septic shock, empirical antibiotics are indicated and should be used according to standard antibiotic guidelines with the aim of providing as optimal antibiotic coverage as possible. The choice of antibiotic should be influenced by local antimicrobial susceptibility patterns as well as patient-related factors and immune status. In view of the emerging literature on the predominance of Gram-negative pathogens in ventilator-associated pneumonia (VAP) in ICU COVID-19 patients including multidrug-resistant pathogens, empirical coverage should include adequate therapy for such pathogens. Also, since centres have reported an increased incidence of Gram-positive bacteraemias with coagulase-negative staphylococci and *Enterococcus faecalis*, empirical coverage may be recommended in the right clinical scenario [16]. Once culture and susceptibility results are available, directed therapy with prompt de-escalation to a narrow-spectrum antibiotic, whenever possible, is recommended to complete the remaining duration of treatment. 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, CRP, fever, requirement for vasopressors etc. This may be even more difficult when patients are treated with immunomodulatory agents such as corticosteroids or tocilizumab. A fixed duration of therapy is therefore recommended depending on the site of infection and should be guided by available evidence indicating that a shorter duration of 5–8 days for hospital-acquired pneumonia, for example, is without disadvantages compared with older recommendations of 10–14 days [17].

Nosocomial infections in COVID-19: use of biomarkers as a tool in COVID-19

COVID-19 is characterised by inflammatory damage to endothelial tissues, particularly in the lung. It is thus logical to expect that a wide range of inflammatory markers are elevated in COVID-19 and that these parameters correlate with disease severity and outcomes [18]. This observation also holds true for PCT [14,19]. Recent evidence has questioned the traditional 'dogma' that PCT is able to distinguish between bacterial and viral infections [20,21] and suggests that it may more likely be a 'host response marker' rather than a specific determinant of the aetiology of infections. Still, as bacterial superinfections have the potential to complicate viral pneumonias and thus increase inflammatory activation, PCT might have a discriminatory potential.

Originally, the value of PCT in COVID-19 is three-fold. First, as discussed above, PCT may have a decisive role in the identification of patients in whom antibiotics may be safely withheld, particularly in an emergency department setting with non-critically-ill patients. This is an established use of PCT that can be 'applied' from its use in the management of other respiratory infections [22]. Second, serial measurements of PCT offers insight into the 'inflammatory dynamics' of patients, where secondary increases should trigger a work-up for bacterial superinfection [7]. Third, PCT guidance may be used once antibiotic therapy has been initiated to shorten the duration of treatment [23–25]. This is also an established use of PCT and may be part of an institutional AMS programme.

All these aspects of PCT guidance of antibiotic therapy have been successfully applied in patients with COVID-19. A study looking at the effects of an AMS intervention comprising institutional treatment guidelines in combination with frequent 'audit and feedback' (called the 'COVID-19 huddle') incorporated PCT guidance both for initiation and discontinuation of antibiotics [26]. The intervention was able to reduce antibiotic prescription significantly. In three other studies with similar PCT thresholds to withhold therapy, antibiotic use was safely reduced in patients with 'low' PCT values [27–29]. Incorporation of PCT into clinical decision-making might thus help to withhold or rapidly discontinue antibiotics when bacterial infection appears unlikely in the setting of low PCT values. Evidence for such a strategy was also provided by a retrospective multicentre analysis from the Netherlands where the effect of clinical guidelines including a PCT algorithm were examined [2]. Despite abundant antibiotic prescriptions on admission to the hospital, the duration of treatment was kept relatively short, with a median of 2 days.

In the ICU, the value of PCT to identify secondary infections was demonstrated in an analysis of 66 critically-ill patients [30]. While both CRP and PCT were variably elevated in many patients on initial presentation, secondary increases were clearly associated with superinfections complicating COVID-19. This effect was particularly distinctive for PCT.

Taken together, measurement of PCT on diagnosis of COVID-19 may influence the decision to initiate or withhold antibiotics. If PCT is low (<0.5 μg/L), it appears safe to not give antibiotics in the absence of overt organ failure. In the uncommon situation where this is unclear and antibiotics are started, a repeated measurement after 24–48 h is recommended. If PCT remains low, stopping antibiotics should be highly considered. If a bacterial co-infection is likely or proven and antibiotic therapy is started, repeated measurements every 48–72 h make sense to guide the duration of therapy. If PCT decreases by $>80\%$ from the initial value or falls below 0.5 μg/L, stopping antibiotics is reasonable.

Secondary increases of PCT during ICU admission should trigger a careful evaluation for infectious complications, including extrapulmonary sources (urinary tract, soft tissue and bloodstream infections).

It is unclear what effect immunomodulatory therapies (e.g. dexamethasone, but also IL-1- and IL-6-blocking agents) have on biomarkers. Such interventions are increasingly advocated for patients admitted to the ICU with severe COVID-19 pneumonia [31]. Earlier studies showed that while induction of CRP may be attenuated by corticosteroids, PCT appears to be unaltered [32]. In one study on the use of anakinra, an IL-1-blocking agent, in COVID-19, the decrease of PCT ($P = 0.001$) was more pronounced in the anakinra group [33]. Another study showed that tocilizumab treatment is associated with a reduction of CRP and PCT in COVID-19 infection [34]. Whether this reduction reflects the intended attenuation of a dysregulated immune reaction ('cytokine storm') or is a hallmark of serious immunosuppression is uncertain at this moment. It is also not clear whether the dynamics of CRP and PCT are suppressed in bacterial superinfections, jeopardising the indicative value of these parameters.

Nosocomial infections in COVID-19: invasive pulmonary aspergillosis

From early in the course of the COVID-19 pandemic there was concern about the emergence of invasive pulmonary aspergillosis (IPA), as viral pneumonias are known to increase patients' susceptibility to fungal co-infections [35]. Invasive fungal infections including aspergillosis were reported during the SARS-CoV-1 outbreak in 2002 [36,37]. Similarly, aspergillosis is known to complicate the course of severe influenza pneumonia and to increase morbidity and mortality in this population [38,39]. Following the onset of the COVID-19 pandemic, several reports emerged on IPA complicating severe COVID-19 disease and increasing mortality [40–45], including reports on azole-resistant aspergillus pneumonia [46]. In addition, reports on emerging *Candida auris* in the time of COVID-19 have emerged in countries where this fungus had not been previously reported [47]. Overuse and abuse of antifungal agents might be partly responsible.

COVID-19-associated pulmonary aspergillosis (CAPA) was coined to refer to invasive aspergillosis that complicates acute respiratory distress syndrome (ARDS) in patients with severe COVID-19 pneumonia. While bacterial pneumonia may be overdiagnosed in critically-ill COVID-19 patients, CAPA poses diagnostic challenges in clinical practice. Therefore, 1 year after the onset of the pandemic, it is necessary to address these two questions: how to differentiate colonisation from invasive disease in critically-ill COVID-19 patients; and what is the true incidence of CAPA?

The diagnosis of IPA is particularly problematic in COVID-19 as evidenced by a wide range of reported incidences among ICU patients, from 3.3–30% in different case series [48,49]. IPA is well defined in patients with neutropenia, immunosuppression and organ transplantation using radiological diagnostic criteria (EORTC/MSG criteria as either proven, probable or possible) [50,51]. Likewise, the AspICU group proposed and validated an algorithm [52] for diagnosing IPA in non-neutropenic ICU patients, and introduced the term putative invasive pulmonary aspergillosis (PIPA) [53]. Applying these diagnostic criteria to COVID-19 ARDS may not be valid for a number of reasons [54]. First, characteristic radiological features of invasive mould disease (nodular lesions ± halo signs, cav-

itation) may not be present in COVID-19 ARDS and findings may overlap with superimposed infiltrates from viral or bacterial infections. Second, the aspergillus galactomannan (GM) test does not have the same sensitivity as in neutropenic patients; the sensitivity of GM in CAPA in one study was approximately 21% [55]. And third, the gold standard for IPA diagnosis is histopathological diagnosis, but lung biopsy has been considered unsafe in this pandemic. Bronchoscopy and bronchoalveolar lavage are not favoured in this population because of the risk of viral transmission to healthcare 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).

In a prospective Italian cohort, 30-day mortality was higher in patients with suspected CAPA [48]. Another prospective study from the UK revealed a trend towards lower mortality with antifungal therapy [49]. Hence, it is essential to establish the diagnosis and expedite treatment to reduce mortality. An expert panel proposed consensus criteria for a case definition of CAPA and provided up-to-date management recommendations for diagnosis and treatment [56]. They recommend to consider investigations for CAPA with any of the following clinical findings in COVID-19 patients with refractory respiratory failure for more than 5–14 days who are critically ill: refractory fever for >3 days or a new fever after a period of defervescence of longer than 48 h while on appropriate antibiotic therapy, in the absence of any other obvious causes; worsening respiratory status (e.g. tachypnoea or increasing oxygen requirement); haemoptysis; and pleural friction rub or chest pain. Imaging will not differentiate CAPA from ARDS complicating COVID-19. However, IPA should be highly considered when nodularities or lung cavitations are noted on lung computed tomography (CT). The panel recommend to collect lower respiratory tract samples for microbiological cultures in addition to the use of serum and/or bronchoalveolar lavage GM and PCR as well as 1-3 β-D-glucan if available. The latter tests have a low sensitivity but high specificity in non-neutropenic patients. We suggest a diagnostic and treatment algorithm as depicted in Fig. 1.

As mentioned earlier, the literature abounds with reports of case series and cohorts of patients with CAPA. Two prospective cohorts found the incidence of CAPA to be 14.1% and 27.7%, respectively, after a median of 4 (2–8) days from ICU admission [55,57]. A systematic review summarising 85 published cases found that the mean age at the time of presentation was 67 years and that the vast majority of patients were male (75.4%) and had no pre-existing immunocompromising conditions [58]. However, comorbidities such as type 2 diabetes mellitus, obesity, hypertension and chronic obstructive pulmonary disease (COPD) were fairly common. Leukopenia is another risk factor. White et al. found that use of corticosteroids and COPD were important for the development of CAPA in addition to mechanical ventilation [57]. One study found an increased risk with the use of azithromycin prior to ICU admission [59]. This needs to be verified in future studies. In a cohort from France where the AspICU algorithm was used, there were fewer cases of putative aspergillosis in COVID-19 ARDS patients compared with non-COVID-19 ARDS patients, but there was no difference in aspergillus colonisation between the two groups [60].

Therefore, it may be legitimate to ask whether CAPA really exists. How does CAPA differ from IPA generally described in ICU patients? How does it differ from influenza-associated invasive aspergillosis? After all, all share similar risk factors, contribute alike to mortality and morbidity, and deserve the same treatment. The difference lies in the diagnosis and the difficulty applying those criteria to CAPA. While more research is needed to define the real incidence of CAPA, to understand the risk factors in order to mitigate them, and to study treatment and outcomes, it is essential to further develop diagnostic criteria specific to COVID-19-associated invasive aspergillosis.

Cytomegalovirus (CMV) reactivation during COVID-19: should it be treated?

Severe COVID-19 manifests as viral pneumonia causing ARDS and as a heightened immune activation resulting in a 'cytokine storm' potentially leading to multiorgan failure. Elderly patients appear to be significantly more susceptible to complications of COVID-19 [61]. According to some observations, mortality from COVID-19 was greatest in cities and regions with a large proportion of elderly among their populations. Immunosenescence, which is a gradual decline in innate and acquired immunity seen in the elderly, could be contributing to the inability to control initial infection with SARS-CoV-2, resulting in severe disease and death [62,63].

There may be an association between latent CMV infection and immunosenescence. The prevalence of latent CMV infection increases with age and in itself could be a major driver of immune senescence and inflammation [62,64,65]. Indeed, chronic CMV infection triggers an increase in CD8 differentiated T-cells accompanied by a decrease in naïve T-cells, potentially leading to immune modulation and immune deficiency seen with older age [66–68]. This may result in a decreased ability to fight other viruses, such as SARS-CoV-2 [62]. On another hand, CMV infection and reactivation is also accompanied by a rise in inflammatory markers, which may predict an increased vulnerability of the elderly population to the cytokine storm associated with COVID-19 [62].

CMV reactivation in COVID-19 may result from stress and from the use of IL-1 inhibitors, IL-6 inhibitors, glucocorticoids and other immunobiological therapies [69–71]. We reviewed the potential roles and interactions between CMV infection and/or reactivation and SARS-CoV-2 in critically-ill non-neutropenic patients. CMV reactivation is common in critically-ill ICU patients; it is usually associated with poor outcomes as well as increased morbidity and mortality [72–77]. CMV reactivation can present as viraemia and could include end-organ damage such as colitis and pneumonitis.

At this stage of the pandemic, very few studies have evaluated the incidence of CMV reactivation in COVID-19 patients, both in serum and the lungs. One study conducted by Le Balc'h et al. showed an incidence of CMV reactivation alone in 2 of 38 COVID-19 patients and of CMV co-reactivation with other herpesviruses in 7 of 38 patients [78]. A study by Paolucci et al. included 104 SARS-CoV-2-infected patients in ICUs and subintensive care units (sub-ICUs), of which 96.2% (100/104) were CMV-seropositive at the time of hospitalisation, but none had CMV reactivation [79]. However, the incidence of Epstein–Barr virus reactivation in this study was significant with an incidence of 95.2% in ICU patients and 83.6% in sub-ICU patients [79]. We found only one report of SARS-CoV-2 and CMV co-infection in a 93-year-old woman who had bilateral pneumonia and lymphocytopenia. The patient had CMV viraemia with elevated levels of CMV IgG (>180 U/mL) and IgM (38.7 U/mL). She received lopinavir/ritonavir and hydroxychloroquine but passed away 6 days after her admission, secondary to ARDS. A few reports described CMV end-organ damage in critically-ill COVID-19 patients, specifically colitis and other gastrointestinal involvement [70,80,81]. All three case reports describe patients who were treated with ganciclovir. Two of the patients were successfully treated and fully recovered from the infection, while one patient had partial resolution of symptoms with residual gastrointestinal inflammation after treatment [70,80,81].

CMV reactivation is well known in neutropenic patients and haematopoietic stem cell transplant recipients where treatment is highly recommended. However, despite the negative outcomes associated with CMV reactivation in non-neutropenic critical care pa-

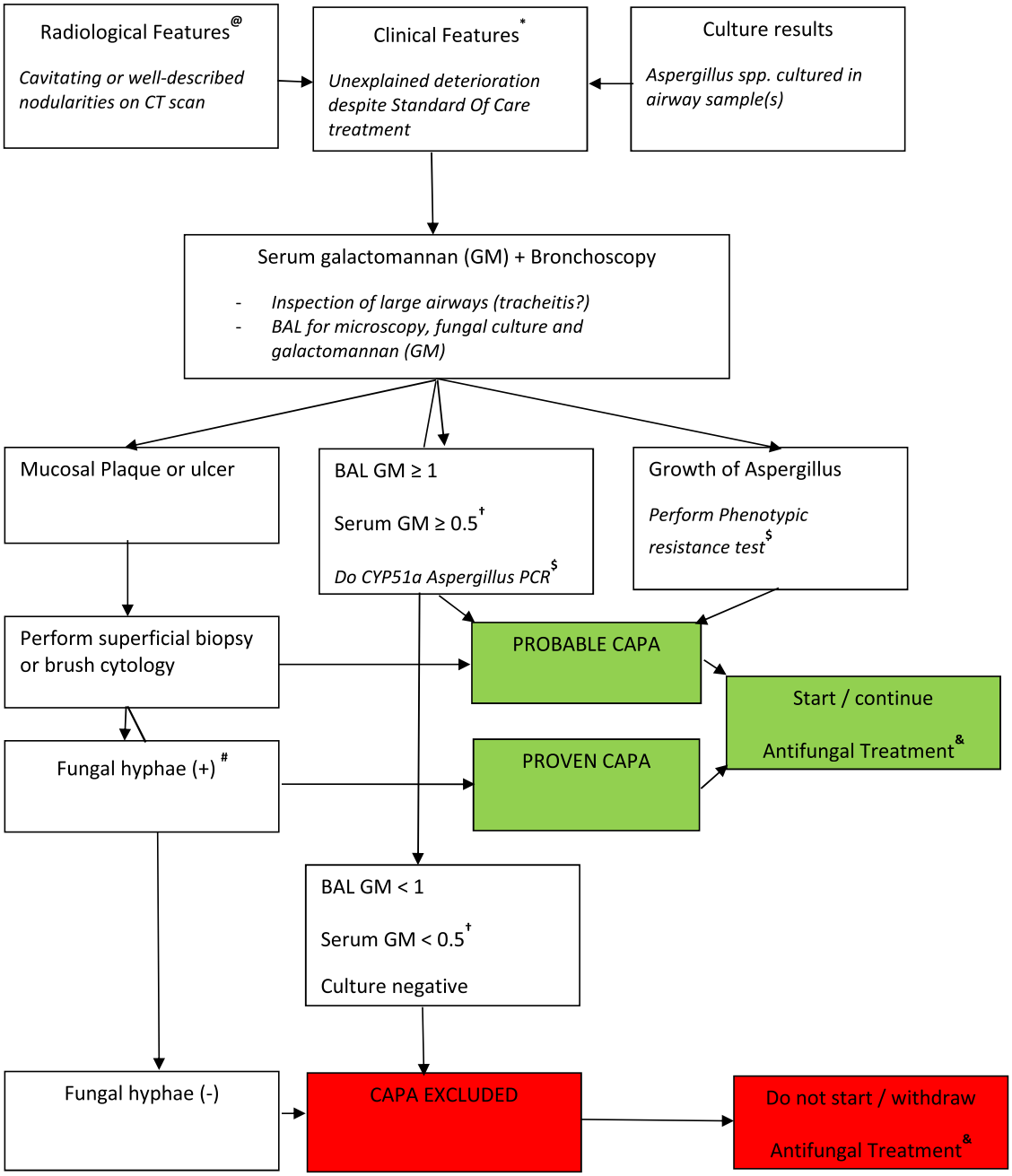

Fig. 1. Flowchart depicting a diagnostic and therapeutic algorithm (taken from Dutch SWAB Guideline addendum, unpublished data, reprinted with permission). [@] This does not mean that lung CT should be standard of care for all ICU patients with COVID-19. Instead, the flow diagram is meant to be used when a CT is done during routine patient care and shows cavitating or well-described nodular lung lesions. [*] The standard of care of COVID-19 is likely to change in the future but for now it includes thromboembolic prophylaxis, therapy with dexamethasone and exclusion of pulmonary embolism by CT. Other causes of clinical respiratory deterioration may also need to be have been excluded (pneumothorax, atelectasis, progressive pulmonary fibrosis). [$] If there is growth of *Aspergillus*, phenotypic resistance testing can be used, e.g. with VIPcheck™ on site or at a mycology reference laboratory. In culture-negative but GM-positive BAL samples, CYP51A *Aspergillus* PCR can be used to exclude the presence of the two most frequent resistance mutations conferring azole resistance (TR_{34}/TR_{46} pattern). [#] Formally, only when septate hyphae of 2.5–4.5 μm in diameter are seen AND the presence of *Aspergillus* DNA is also documented, the infection is classified as proven CAPA. However, the presence of hyphae compatible with *Aspergillus* suffices to start antifungal therapy. [†] Serum GM is generally negative but increases the probability of CAPA if positive in combination with positive BAL GM. [&] It is recommended to start antifungal therapy as early as possible. If BAL test results are available the same day, these can be awaited before antifungal therapy is started. If not immediately available, it is recommended to consider starting antifungal therapy pre-emptively while awaiting test results. CT, computed tomography, ICU, intensive care unit; COVID-19, coronavirus disease 2019; GM, galactomannan; BAL, bronchoalveolar lavage; CAPA, coronavirus-associated pulmonary aspergillosis.

tients, there seems to be little data about the benefit of treating CMV reactivation in these patients, especially in light of the adverse events associated with the treatment options.

Moreover, there is an unclear benefit from treating this condition on mortality and morbidity in the ICU [82]. Adverse events of CMV treatment include acute kidney injury and bone marrow suppression, among others. In the setting of COVID-19, it is not yet clear whether CMV reactivation is widely prevalent and whether it might contribute to the severity of disease. Unfortunately, treatment of CMV reactivation in critically-ill COVID-19 patients may lead to further complications, especially in the context of existing lymphopenia and sepsis. Therefore, treatment of CMV reactivation

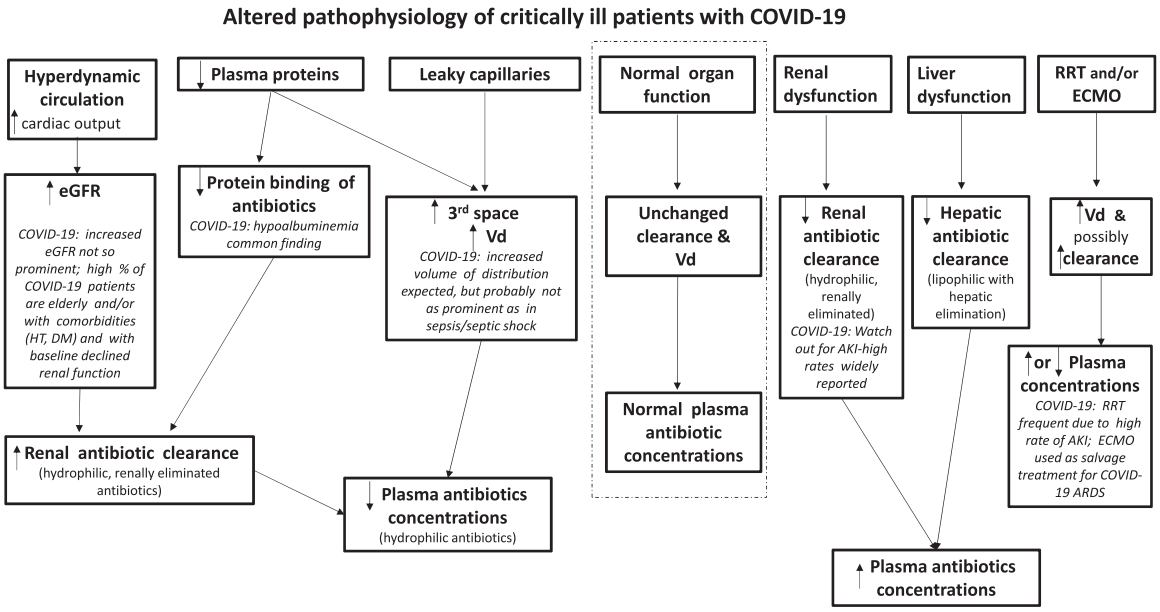

Fig. 2. Pharmacokinetics/pharmacodynamic (PK/PD) alterations in COVID-19 patients. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HT, hypertension; RRT, renal replacement therapy; Vd, volume of distribution.

should be considered on a case-by-case basis weighing the risks versus benefits of therapy.

CMV reactivation might be an important factor to consider in COVID-19 patients as it may have a role in modulating the 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. Data are currently scarce and further research is needed to assess the incidence and outcomes of CMV reactivation on morbidity and mortality in the context of COVID-19 to help guide recommendations for therapy and follow-up.

Pharmacokinetic/pharmacodynamic (PK/PD) alterations in COVID-19 patients

Just like other patients in the ICU, the PKs of multiple drugs may be severely affected in patients with COVID-19. The most important contributors to PK changes in critically-ill patients are changes in the volume of distribution (V_d), protein binding and drug clearance (Fig. 2) [83–97].

Increases in the V_d have been described in small patient series reporting on the PKs of antivirals and other drugs and it can be expected that this is also the case for many antibiotics. Use of extracorporeal techniques may add to this risk, as well as obesity, which is a common feature of patients with severe COVID-19 disease [87]. On the other hand, fluid administration in patients with COVID-19 may be less aggressive compared with sepsis and septic shock, resulting in smaller changes in V_d.

Protein binding of antimicrobials is also affected. Hypoalbuminaemia is a common finding in patients with COVID-19. In a large series of ICU patients, hypoalbuminaemia was very common in patients who did not survive [88] and has been identified as a risk factor for mortality in a study from China [85]. Renal clearance is the main route of elimination for many antibiotics used in the ICU. In COVID-19 patients, kidney function may be altered for many reasons. Patients with COVID-19 often have co-morbidities; a large study from Italy found that hypertension and cardiovascular disease were most common, with chronic kidney disease (CKD) only present in 3% of patients. On the other hand, a Spanish study reported CKD in 6.7% of patients (9.7% in the >65 years age cohort), while another study from the UK reported end-stage renal failure in 13% of COVID-19 ICU admissions [86,91]. Acute kidney injury (AKI) has been widely reported in hospitalised patients with COVID-19 and seems to be multifactorial, but its pathophysiology is not fully elucidated. It typically develops throughout the hospital stay and is most frequently reported in patients with severe disease and in those with lower estimated glomerular filtration rate (eGFR) at presentation [90]. Reported incidences are variable [91], but an AKI incidence of up to 76% in ICU patients has been reported as well as the need for renal replacement therapy (RRT) for as high as more than one-quarter of ICU patients [89,92].

Augmented renal clearance (ARC), on the other hand, has been identified as a cause of increased elimination of antibiotics, leading to subtherapeutic concentrations [93]. Patients presenting with COVID-19 have some clinical features that could be linked to ARC, such as fever and hyperinflammation. At this moment, published data on the incidence of ARC in COVID-19 patients are scarce. A recent study by Tomasa-Irriguible et al. documented ARC in nearly 40% of a small group of COVID-19 patients admitted to the ICU [94]; unfortunately, no details on the clinical characteristics related to ARC were reported. ARC was an uncommon finding in a small series of 20 patients in whom therapeutic drug monitoring (TDM) of β-lactam antibiotics was reported [95]; the median measured creatinine clearance was 98 mL/min. It should be taken into consideration that ARC might not be that prominent in COVID-19 cohorts as a high percentage of patients are elderly and, apart from the effect of possible co-morbidities, the aging process itself may cause a decline in renal function [96,97]. Finally, use of extracorporeal techniques is often required, with continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) as primary techniques [87], both of which are known to impact the PKs of antibiotics. ECMO poses particular challenges such as drug sequestration and hypoalbuminemia, all resulting in an increased V_d for many antibiotics.

A few studies have reported on antibiotic concentrations in patients with COVID-19. One small study from France described high inter-individual variability of β-lactam antibiotic concentrations despite similarities in clinical features [95]. The authors also reported a high risk of toxicity and recommend using TDM. Toxi-

city was a particular concern in patients at the later stages of antimicrobial therapy.

The question then is how can we improve dosing? Basic principles of antimicrobial dosing remain the same in patients with infections complicating COVID-19, and both the pathogen and the host should be considered important when selecting the appropriate dose. As explained above, the V_d may be higher and drug clearance variable, putting patients at risk both for underdosing and overdosing, and strategies should be aligned to this risk profile.

In order to increase target attainment, a variety of strategies including extended and continuous infusion of selected antibacterials as well as use of a loading dose is mandatory when using these infusion strategies. Renal function should be closely monitored to early 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; in a very recent meta-analysis, although two-thirds of patients with severe COVID-19 had laboratory finding of renal damage (increased creatinine, haematuria, proteinuria), the majority did not fulfil AKI criteria [98,99]. Also, where available, TDM is recommended to optimise dosing, both to monitor toxicity and the efficacy of drugs. As reduced kidney function and AKI may be more prevalent in patients with COVID-19 compared with sepsis from other causes, TDM is of particular relevance for antibiotics with potential toxicity such as vancomycin or aminoglycosides.

Considering that COVID-19 patients might typically develop severe nosocomial infections such as VAP and bacteraemia, the importance of antimicrobial dosing cannot be overestimated. Moreover, the involved pathogens may have limited susceptibility to commonly used antimicrobials. Several reports have pointed towards an increased risk of multidrug-resistant infections [7]. This is partly due to increased antibiotic use as well as compromised infection prevention strategies during the COVID-19 pandemic.

In summary, COVID-19 patients are at high risk for PK changes, and while inadequate concentrations may be encountered, some have a risk for higher concentrations and associated toxicity. Also considering that nosocomial pathogens with higher minimum inhibitory concentrations (MICs) may be more often encountered with VAP as a typical complicating infection, leniency towards higher concentrations for many antimicrobials is justified. When RRT is required, antibiotic dosing strategies should be adapted to the RRT modality, duration and membrane used. This often poses challenges, particularly when intermittent or sustained low-efficiency daily dialysis (SLEDD) techniques are used, as PKs vary considerably during episodes of on and off RRT. Finally, TDM is of particular importance, while development of population PK and PK/PD models specifically dedicated to COVID-19 patients might be useful [100].

Conclusions

During the current COVID-19 pandemic, AMS in the ICU setting is challenging. Distinction between infectious and non-infectious (inflammatory) causes of respiratory deterioration during the ICU stay is difficult, and the much-debated relevance of fungal and viral co-infections adds to the complexity. Apart from general recommendations to withhold antibacterial therapy for COVID-19 patients on admission unless patients are haemodynamically unstable, general AMS principles regarding starting, adapting and stopping antimicrobial treatment remain relevant. However, circumstances specific to COVID-19 patients need to be taken into account, especially related to altered PK/PD properties in these patients. Finally, the value of biomarkers such as PCT for the decision to start antibacterial therapy for nosocomial infections later on in the course of the ICU stay seems to be more promising in COVID-19 than in non-COVID-19 patients. Co-infections with fungi and reactivation of other viruses warrant attention, although the implications for therapy are not clear at this stage. Overuse of antifungal agents is discouraged in an era of emerging antifungal resistance except in scenarios where invasive infections are likely. Future research should now further explore these 'known unknowns', ideally with robust prospective study designs.

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