Ventilator-associated pneumonia among SARS-CoV-2 acute respiratory distress syndrome patients

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Purpose of review
We conducted a systematic literature review to summarize the available evidence regarding the incidence, risk factors, and clinical characteristics of ventilator-associated pneumonia (VAP) in patients undergoing mechanical ventilation because of acute respiratory distress syndrome secondary to SARS-CoV-2 infection (C-ARDS).

Recent findings
Sixteen studies (6484 patients) were identified. Bacterial coinfection was uncommon at baseline (<15%) but a high proportion of patients developed positive bacterial cultures thereafter leading to a VAP diagnosis (range 21–64%, weighted average 50%). Diagnostic criteria varied between studies but most signs of VAP have substantial overlap with the signs of C-ARDS making it difficult to differentiate between bacterial colonization versus superinfection. Most episodes of VAP were associated with Gram-negative bacteria. Occasional cases were also attributed to herpes virus reactivations and pulmonary aspergillosis. Potential factors driving high VAP incidence rates include immunoparalysis, prolonged ventilation, exposure to immunosuppressants, understaffing, lapses in prevention processes, and overdiagnosis.

Summary
Covid-19 patients who require mechanical ventilation for ARDS have a high risk (>50%) of developing VAP, most commonly because of Gram-negative bacteria. Further work is needed to elucidate the disease-specific risk factors for VAP, strategies for prevention, and how best to differentiate between bacterial colonization versus superinfection.

Keywords
acute respiratory distress syndrome, coronavirus disease 2019, SARS CoV-2, ventilator-associated pneumonia

INTRODUCTION
Critical care physicians worldwide face the challenge of managing patients with acute respiratory failure because of SARS CoV-2 pneumonia and Covid-related Acute Respiratory Distress Syndrome (C-ARDS). Most of the pathogenetic characteristics, clinical manifestations, and treatment strategies for C-ARDS are similar to ARDS due to other etiologies \([1]\) but some specific features do characterize the clinical course of C-ARDS. In particular, many centers have reported high rates of ventilator-associated pneumonia (VAP) complicating the course of C-ARDS. An increasing body of literature characterizes the incidence, risk factors, diagnostic features, and adequacy of treatment of VAP among C-ARDS patients undergoing mechanical ventilation. This article will summarize literature-to-date regarding VAP in C-ARDS patients.

METHODS
We performed a systematic search strategy using PubMed, EMBASE, and Web of Science for all studies of any design addressing VAP in adult patients affected by C-ARDS and requiring invasive
mechanical ventilation. Only studies with a definition of VAP based on the US Centers for Disease Control and Prevention’s National Healthcare Safety Network or European Center for Disease Control recommendations [2–4] were included. Additional articles were sought by checking the reference lists of included articles.

RESULTS
We identified 16 studies (2 studies investigated the same cohort), including 6484 C-ARDS patients requiring invasive mechanical ventilation, designed to investigate the incidence, risk factors, and clinical course of patients developing at least one episode of VAP (Table 1) [5,7,8–11,12,13,15,16,17,18,19–21]. The median observation period of included studies was 3 months (range 1–12 months) consistent with the high Covid-19 occupancy rates of ICUs worldwide.

INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA IN CORONAVIRUS DISEASE-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME
The incidence of VAP can be expressed either as an incidence proportion (number of new VAP cases/total number of patients studied) or as an incidence-density (total number of VAP episodes/total amount of days at risk). The baseline incidence-density of VAP before Covid-19 varied widely both within and between countries but on average ranged between 2 to 20 events per 1000 ventilator-days [22,23]. Differences in case mix, care patterns, staffing, and above all surveillance criteria are acknowledged among the reasons for incidence variability [24]. Rates are substantially higher within some populations; one study, for example, reported a raw incidence rate of at least one episode of microbiologically confirmed bacterial VAP of 29% among 339 patients with severe ARDS [25].

The incidence of VAP amongst patients with C-ARDS in our review also varied widely, ranging from 21 to 64% (pooled mean 50%). Only five studies (two multicenter and three single center) reported VAP incidence-densities. These ranged from 18 to 45 episodes per 1000 ventilator-days (pooled mean 27 episodes per 1000 ventilator-days) [11,12,16,20]. Gamberti et al. [8] identified late-onset VAP as a factor contributing to the prolonged duration of mechanical ventilation duration associated with C-ARDS. Many studies also reported recurrent VAP episodes (up to four events in a single patient) despite appropriate antimicrobial treatment. The first VAP episode typically occurred between the 8th and 12th day after initiation of invasive mechanical ventilation.

Crude mortality rates among the whole population of critically ill SARS-CoV-2-positive patients ranged between 30 and 40%. The average duration of mechanical ventilation was 12–30 days. In a single meta-analysis including 20 studies drawn from 12 countries, the pooled crude mortality rate for patients with C-ARDS disease who developed VAP was 43% [26]. This compared with a crude mortality rate of 40–55% amongst ARDS non-Covid patients with VAP [27,28]. Previous studies conducted in non-COVID patients identified VAP attributable mortality rate about 10% [29].

MICROBIOLOGY
Microorganisms associated with VAP also vary between studies. In most locations, Gram-negative bacteria have been reported to be the predominant microorganisms (>70% in most series) followed by Gram-positives (mostly Staphylococcus aureus). As most cases of Covid-related VAP are diagnosed more than 7 days from initiation of invasive mechanical ventilation (late VAP), patients are at increased risk for multidrug-resistant (MDR) bacterial strains.

A number of studies reported on COVID-19-Associated Pulmonary Aspergillosis (CAPA). The incidence of CAPA ranged from 4 to 30% [30,31] and varied depending on the sensitivity of Aspergillus diagnostic tests and the use of immunosuppressive therapies for COVID-19 (e.g. anti-IL-6 and/or steroids). One survey limited to Europe estimated a combined incidence of possible, probable, and proven CAPA of 15% of ICU C-ARDS patients [32]. The potential clinical significance of CAPA was highlighted in a study by White et al. [33], who reported more than 50% mortality among patients developing CAPA, none of whom received antifungal therapy. Studies were inconsistent in the criteria adopted for CAPA diagnosis, hence it is
| First author | Ref | Type of study | Location | Number of patients | Admission PaO\(_2\)/FiO\(_2\) (mmHg) | VAP incidence (%) | Time to first VAP (days) | Duration of MV (days) | Mortality (%) | VAP criteria | Pathogens |
|--------------|-----|-------------|----------|-------------------|-------------------------------|------------------|------------------------|---------------------|--------------|-------------|-----------|
| Bardi [5\*]  | SR  | Spain      | 140      | 124 [69–156]      | 21                             | –                | –                      | 36                  | –            | NHSN-CDC 2008 | PsAe 38\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | SaAu 24\% |
| Razazi [6\*] | SR  | France     | 90       | 120 [92–163]      | 64                             | 8 [5–12]         | 30 [19–45]            | 40                  | –            | ECDC        | GN 72\%   
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GNNF 41\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GP 3\%    |
| Buetti [7\*] | SR  | Switzerland| 48       | –                 | 69                             | –                | –                      | 25                  | –            | –           | –         |
| Gamberini [8\*] | MP | Italy (15 ICUs) | 391     | 94 [75–119]      | 65                             | > 7              | 14 [9–19]             | 36                  | –            | ECDC        | –         |
| Schmidt [9\*] | MP  | Europe (149 ICUs) | 2101   | 154 [106–223]    | 58                             | –                | 12 [7–17]             | 31                  | –            | –           | –         |
| Luyt [10\*]  | SR  | France     | 50       | –                 | 85                             | 10 [8–16]        | 45 [27–62]            | 34                  | –            | ECDC        | GN 70\%   
|              |     |             |          |                   |                               |                 |                        |                     |              |             | PsAe 37\% |
| Grasselli [11\*] | MR | Italy (8 ICUs) | 774     | 123 [90–174]    | 50                             | 12 [7–21]        | 24 [14–39]           | 30                  | –            | ECDC        | GN 64\%   
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GP 36\%   |
| Blonz [12\*] | SR  | France     | 188      | 150 [73–150]     | 49                             | 10               | 22 [16–36]           | 28                  | –            | ECDC        | –         |
| Masure [13\*] | SR  | UK         | 81       | –                 | 48                             | 9                | 14 [10–23]           | 38                  | –            | ECDC        | –         |
| Neir/Rouze [14,15\*] | MR | Europe (36 ICUs) | 568    | –                 | 51                             | 9 [6–13]         | 15 [9–23]            | 29                  | –            | ATS/IDSA 2005 | GN >80\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | PsAE 25\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | SaAu 13\%  |
| Giacobbe [16\*] | MR | Italy (7 ICUs) | 586    | –                 | 29                             | 10 [6–17]        | –                      | 46                  | –            | ECDC        | –         |
| Moretti [17] | SR  | Belgium    | 39       | 172 [153–235]     | 54                             | 12 [7–19]        | 21 [10–31]           | 44                  | –            | NHSN-CDC 2017 | GN >85\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | PsAe 18\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | SaAu 7\%   |
| Illlias [18\*] | MR | France (7 ICUs) | 176    | –                 | 52                             | 9 [6–14]         | 17 [10–28]           | 31                  | –            | CPIS\*      | –         |
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GN 70\%   
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GNNF 20\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GP 28\%   |
| Suarez-de-laRica [19] | SR | Spain | 107     | –                 | 33                             | –                | –                      | 69                  | –            | NHSN-CDC 2017 | PsAe 31\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | SaAu 23\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | Keb 26\%  |
| Pickens [20] | SP  | USA        | 179      | –                 | 44                             | 11               | 13 [18.5]            | 19                  | –            | Clinical Criteria & Microbiology | GN >50\%  
|              |     |             |          |                   |                               |                 |                        |                     |              |             | GP >50\%  |
| Roger [21]   | MP  | France (29 ICUs) | 966   | 112 [81–159]     | 43                             | –                | –                      | 18                  | –            | ECDC        | –         |

Data are expressed either as median [IQR] or mean (SD). ATS, American Thoracic Society; CPIS, Clinical Pulmonary Infection Score; ECDC, European Center for Disease Control; GN, Gram-negative; GNNF, Gram-negative nonfermenting; GP, Gram-positive; IDSA, Infectious Disease Society of America; Kib, Klebsiella; MP, multicenter prospective; MR, multicenter retrospective; MV, mechanical ventilation; NHSN-CDC, National Healthcare Safety Network Center for Disease Control; PaO\(_2\)/FiO\(_2\), partial pressure of oxygen to fraction of inspired oxygen fraction ratio; PsAe, Pseudomonas aeruginosa; Ref, reference; SR, single-center retrospective; SaAu, Staphylococcus aureus; VAP, ventilator-associated pneumonia.

\*Suspicion of a VAP is based on a CPIS greater than 6; suspected ICU-acquired pneumonia were subjected to a tracheobronchial aspirate or bronchoalveolar lavage with semiquantitative culture.
impossible to quantify the burden of care attributable to CAPA. However, the current evidence suggests a high prevalence of Aspergillus pneumonia among SARS-COV-2-positive critically ill patients compared with the whole population of ICU-admitted patients. Patients affected by CAPA show a high mortality rate [34].

The clinical implication of viral coinfection remains to be determined. At present, it seems that most viral coinfections do not lead to worse outcomes. However, reactivation or co-infection with a Herpesviridae family virus (e.g. cytomegalovirus or herpes simplex virus) has been described even in absence of immunosuppressive factors [35,36]. Maes et al. [13*], while measuring SARS-CoV-2 viral loads in bronchoalveolar fluid of C-ARDS patients, reported that 42% of samples were positive for Herpesviridae organisms. Previous studies in non-SARS-CoV-2-infected ICU immunocompetent patients found an association between cytomegalovirus reactivation and poorer outcomes [37]; however, it remains unclear whether cytomegalovirus reactivation plays a causative role or if it is just a surrogate for identifying patients with severe disease. Future studies are needed to elucidate the outcome and benefits of antiviral prophylaxis or treatment for cytomegalovirus reactivation.

**RISK FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA IN COVID-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME**

Multiple elements might contribute to the high rate of VAP observed in C-ARDS patients. Potential risk factors for developing VAP among C-ARDS patients are schematically illustrated in Fig. 1.

**Disease-related risk factors**

Three features of C-ARDS might contribute to the high reported incidence of VAP.
SARS-CoV-2 pathogenesis
SARS-CoV-2 infection has been associated to a certain degree of ‘immunoparalysis’. The severity of SARS-CoV-2 pneumonia is associated with the degree of lymphopenia and to the burden of the cytokine release syndrome attracting T cells into lung tissue [38]. SARS-CoV-2 can infect human circulating monocytes and macrophages leading to these cells’ deaths, thus inducing immunoparalysis of the host, which may facilitate SARS-CoV-2 infection progression [39]. Other authors have hypothesized that pulmonary vascular endothelial inflammation and subsequent thrombosis might make the lung parenchyma a favorable substrate for bacterial growth and prevent antimicrobial penetration [40,41*].

Acute respiratory distress syndrome severity
Patients admitted to the ICU that require invasive mechanical ventilation secondary to SARS-CoV-2 infection meet the criteria for at least moderate but most frequently severe ARDS according to the Berlin definition criteria. The average PaO$_2$/FiO$_2$ ratio at ICU admission ratio among the studies analyzed was 95–170 mmHg. Many patients with disease of this severity require high levels of sedation to reduce their oxygen consumption and to help with ventilator tolerance. Others also require neuromuscular blocking agents to facilitate adequate ventilation and oxygenation. Both of these pharmacological interventions are usually continued well beyond the first 48 h after endotracheal intubation contributing to increased risk of VAP [42].

Among the ARDS rescue therapies, prone positioning has been widely adopted in C-ARDS patients both to treat hypoxemia and possibly to mitigate ventilator-induced lung injury. Although prone positioning may improve drainage of secretions from the oral cavity, data from a sub-analysis of the PROSEVA trial showed that prone positioning does not reduce VAP incidence [43].

Extracorporeal membrane oxygenation (ECMO) has been used, whenever available, to treat patients with the most severe cases of C-ARDS that are unresponsive to other rescue therapies. Grasselli et al. [44] showed an incidence of VAP of 35% in critically ill patients undergoing venovenous ECMO. The study also highlighted that VAP in ECMO patients is associated with longer duration of ICU stay and lower survival rate (40% in patients with VAP compared with 27% in other patients). Luyt et al. [10**] did a single-center analysis comparing the characteristics of 50 patients with Covid-related ARDS versus 45 patients with influenza-related ARDS on ECMO. The authors reported that patients with C-ARDS requiring ECMO had a lower rate of bacterial coinfection at ICU admission (18 versus 40%) but a higher incidence of VAP (86 versus 62%). In the C-ARDS group, VAP recurred in 79% of patients despite appropriate antimicrobial therapy.

Patients with C-ARDS tend to be ventilated for longer than ARDS patients without COVID-19. Among patients enrolled in the LUNG SAFE survey [45], a large observational study in ARDS patients gathered before the COVID-19 pandemic, median duration of mechanical ventilation was 8 days (interquartile range, 4–15 days), whereas patients with C-ARDS require longer periods of mechanical ventilation, with a median of 10 days (interquartile range, 6–17 days). The duration of mechanical ventilation is an independent risk factor for VAP. Furthermore, severity of disease and quantity and duration of corticosteroid use increase the risk for critical illness myopathy and prolonged dependence on mechanical ventilation. Finally, VAP itself tends to prolong duration of mechanical ventilation [8**,11**,14] leading to a vicious circle between duration of mechanical ventilation, VAP incidence, and further prolongation of mechanical ventilation.

Ventilator-associated pneumonia diagnosis
There is substantial overlap between the cardinal clinical signs of SARS-CoV-2 pneumonia, ARDS, and bacterial pneumonia. All are associated with pulmonary infiltrates, impaired oxygenation, fever, and abnormal white blood cell counts. The airways and endotracheal tubes of patients on mechanical ventilation rapidly become colonized with potentially pathogenic organisms frequently leading to positive cultures. Clinically, this makes it very difficult to differentiate between true bacterial superinfection and bona fide cases of VAP versus bacterial colonization alone superimposed on ARDS. Clinicians should preferentially rely on trajectory changes to diagnose VAP (new and progressive deterioration in oxygenation, new fever, new leukocytosis, change in secretions) but even these dynamic changes are nonspecific and potentially attributable to progression of ARDS, nonpulmonary infection, thromboembolic disease, fluid shifts, and/or drug reactions rather than VAP. This makes it likely that estimates of the incidence of VAP based primarily on new positive cultures overestimate the true incidence of VAP.

Treatment-related risk factors

Empirical antibiotic overtreatment
Antimicrobial therapy exposure is associated with a shift in patients’ commensal flora towards more
pathogenic organisms. In addition, antimicrobials exert selection pressure favoring the emergence of MDR bacterial strains.

Azithromycin was hypothesized to have an antiviral activity against SARS-CoV-2 during the early months of the pandemic, and was thus, widely administered by both outpatient and inpatient providers to patients with either possible or confirmed SARS-CoV-2 infection. Randomized controlled trial data have since demonstrated the futility of azithromycin to reduce the duration of SARS-CoV-2 symptoms and risk of hospitalization [46**,47,48]. In addition, during the early months of the pandemic, the Surviving Sepsis Campaign [47] suggested administering empirical antibiotic therapy to patients with severe C-ARDS in order to treat/prevent bacterial coinfection. Accordingly, in many cohorts, the rate of antimicrobial therapy at the time of ICU admission is very high (>90%) despite lack of evidence for bacterial coinfection [48–51].

Among the studies included in the present review, the documented incidence of bacterial coinfection upon admission was low, ranging from 1 to 21% [11**,18*,20] with prevalence of Gram-positive organisms including Streptococcus spp. and methicillin-susceptible S. aureus [20]. Rouze et al. [52] performed a large scale (>1000 patients) comparison between viral–bacterial coinfection in patients with respiratory failure because of SARS-CoV-2 versus influenza virus. Severity of disease was similar between groups with about 70% patients intubated within 48 h from hospital admission and a high percentage (85–90%) of patients received empirical antimicrobial therapy in both groups. Bacterial coinfection was detected in 10 versus 33% of patients, respectively in the SARS-CoV-2 and influenza groups.

In summary, the current literature evidence does not support the use of broad-spectrum antibiotic therapy at ICU admission in C-ARDS patients based exclusively on the severity of the disease without evidence of bacterial coinfection.

Use of corticosteroids and immunomodulatory agents

After publication of the RECOVERY trial [53] and confirmation of its results in a subsequent meta-analysis [54], systemic steroid administration has become the mainstay of the treatment of C-ARDS among patients requiring respiratory support, from supplemental oxygen alone up to invasive mechanical ventilation. The use of steroids has sometimes been cited as a risk factor for developing VAP. However, the CoDEX trial reported a shorter duration of mechanical ventilation among the patients treated with high-dose dexamethasone and similar incidence of VAP (13%) as compared with patients receiving standard care [55]. In the C-ARDS literature, there is no evidence that corticosteroid therapy is associated with an increased incidence of VAP.

Immunosuppressive therapies (particularly IL-6 antagonists) have been also proposed and tested as a potential strategy to modulate the disproportionate inflammatory response triggered by SARS-CoV-2 infection. IL-6 antagonists cause a transient but long lasting (about 4 weeks) immunosuppressive state, which might favor the occurrence of bacterial superinfections, such as VAP. Given the inconsistency of data regarding outcomes of patient receiving anti-IL-6, a prospective meta-analysis of published data and ongoing trials was recently published by the WHO REACT working group [56]. This analysis suggested a possible benefit of treating with IL-6 antagonists among patients hospitalized with C-ARDS, decreasing both the requirement for invasive mechanical ventilation and mortality at 28 days. However, once patients are intubated, it seems that there are no benefits of starting IL-6 antagonist therapy. More definitive evidence is required to understand the effect of IL-6 antagonists among the patients during mechanical ventilation.

Pandemic logistics-related risk factors

Staffing

The SARS-CoV-2 pandemic spread quickly to several countries overwhelming hospital capacity in many regions [57]. Many healthcare systems were understaffed and unable to provide an effective response to the pandemic. Imbalance between workload and resources and reduced personnel might affect patients’ outcomes, and infectious disease prevention strategies might be inadvertently missed [58]. Before the most recent pandemic, Schwab et al. [59] detected a linear negative association between the nurse-to-ventilated-patient ratio and the risk for nosocomial infection occurrence (bloodstream infections and VAP).

Bundles

Previous literature has demonstrated the efficacy of combining multiple prevention measures in order to reduce VAP incidence, including: regular hand hygiene, use of noninvasive ventilation, head of bed elevation, daily interruption of sedation and assessment of readiness to wean, regular oral care, maintaining endotracheal cuff pressure at at least 20 cmH₂O, removal of condensate from ventilator circuits, avoidance of gastric overdistention,
avoidance of stomach acid suppressants, and use of sterile water to rinse respiratory equipment. Indeed, VAP prevention bundles are low tech and low cost, yet they can have a substantial impact on VAP rates. However, in a scenario of inadequate nurse-to-ventilated-patient ratio, use of underexperienced staff, and possible shortages of personal protective equipment, it is likely that the implementation and optimization of VAP prevention bundles suffered. Even in adequately resourced centers, however, VAP rates can be high. Blonz et al. [12*], for example, analyzed VAP incidence in C-ARDS patients in an ICU with adequate capacity relative to bed requests and an adequate nurse:patient ratio. Despite the adequacy of ICU and personnel capacity, the authors detected a 50% incidence of at least one microbiologically confirmed VAP episode.

**DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA IN COVID-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME**

Diagnosing VAP in patients with C-ARDS is a considerable challenge. Detecting new infiltrates on top of patients’ baseline infiltrates is elusive and it is often very difficult to know whether to attribute changes in opacities to progression of ARDS, pulmonary edema, atelectasis, or pneumonia. Clinicians are advised to consider patients’ concurrent clinical signs and trajectories while recognizing that these too are neither sensitive nor specific. Corticosteroid therapy or ECMO support might mask hyperpyrexia and other inflammatory changes. We advise microbiologic sampling in patients with a constellation of concurrent, new, progressive, and persistent findings, such as new fever after a period of normothermia accompanied by worsening oxygenation, new hypotension, new leukocytosis, and increases in airway secretions. Individually, these signs are not diagnostic but if present and persistent, a time-limited trial of antimicrobial therapy is reasonable.

From a ventilatory standpoint, development of VAP is characterized by worsening of both intrapulmonary shunt, usually measured as increase in either PEEP or fraction of inspired oxygen, and/or increase of dead space fraction measured as rise of the ventilatory ratio (minute ventilation to arterial pCO₂), and/or decrease of lung compliance. Accurate daily monitoring of gas exchange and lung mechanics might produce timely detection of pulmonary superinfection.

Regarding the microbiological surveillance for VAP, quantitative culture might add information to differentiate between VAP and airways colonization. Quantitative multiarray real-time PCR represents a possible adjunctive test that may render rapid results (3-4 h), detect viral superinfection, and possibly identify the presence of selected drug-resistant bacteria.

Procalcitonin (PCT) is often used as a biochemical marker to identify bacterial superinfection but the accuracy of this assay in this setting is limited. Studies from the outset of the pandemic [60,61] reported low PCT levels (<0.5 ng/ml) among C-ARDS patients at ICU admission. Patients with severe C-ARDS, however, can have high PCT levels without bacterial coinfection [62]. Variation in PCT levels might be blunted during viral infection because of the viral driven interferon-γ release, thus limiting the usefulness of PCT to identify bacterial infection [63]. Interestingly Rouze et al. [52], investigating incidence of coinfection among C-ARDS and influenza-related ARDS found that procalcitonin was marginally higher in patients coinfected with SARS-CoV-2 and bacteria [0.9 (0.3–4.3) versus 0.5 (0.2–1.5)] but less so compared with those coinfected with influenza and bacteria [6.4 (1.4–50.2) versus 1.5 (0.5–9.8)].

**TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA IN CORONAVIRUS DISEASE-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME**

The mainstay of VAP treatment remain timely and appropriate antibiotics. These are best informed through lower respiratory tract sampling via bronchoalveolar lavage or endotracheal aspirate. Empiric therapy uninformed by cultures is likely to lead to antibiotic overuse [20]. C-ARDS patients with VAP are at high risk of infection with MDR pathogens because of their prolonged hospitalizations and frequent exposure to antimicrobials. Clinicians should, therefore, have a low threshold for broad-spectrum therapy informed by local ecology, duration of hospitalization, and patients’ prior microbiologic testing. For patients with signs of septic shock, empiric combination therapy, and or use of a newer generation cephalosporin-beta-lactamase inhibitor combination or carbapenem-beta-lactamase inhibitor should be considered to increase the probability of active initial coverage. The high rate of recurrent VAP raises the question of whether there is possible advantage to prolonging antibiotic treatment beyond 7 days; however, we are not aware of data supporting this hypothesis. Trends of PCT levels are of unknown value for determining the timing of both initiation and discontinuation of antibacterials in C-ARDS.

**CONCLUSION**

Patients developing ARDS following infection by SARS-CoV-2 and requiring invasive mechanical
ventilation are exposed to a high risk (>50%) of developing at least one episode of VAP along the course of their critical illness. VAP might be caused by a variety of Gram-positive and negative bacteria depending on geographic locations. Disease, treatment, diagnostic challenges, and pandemic logistic-related risk factors all have contributed to the high incidence of VAP in C-ARDS patients. Despite recent promising studies, current diagnostics criteria, and treatment strategies largely reflect those adopted in the pre-SARS-CoV-2 era.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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