How common is ventilator-associated pneumonia after coronavirus disease 2019?

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Purpose of review
The first studies on COVID-19 patients with acute respiratory distress syndrome (ARDS) described a high rate of secondary bacterial ventilator-associated pneumonia (VAP). The specificity of VAP diagnoses in these patients are reviewed, including their actual rate.

Recent findings
Published studies described high rates of bacterial VAP among COVID-19 patients with ARDS, and these VAP episodes are usually severe and of specifically poor prognosis with high mortality. Indeed, Severe acute respiratory syndrome - coronavirus disease 19 (SARS-CoV2) infection elicits alterations that may explain a high risk of VAP. In addition, breaches in the aseptic management of patients might have occurred when the burden of care was heavy. In addition, VAP in these patients is more frequently suspected, and more often investigated with diagnostic tools based on molecular techniques.

Summary
VAP is frequented and of particularly poor prognosis in COVID-19 patients with ARDS. It can be explained by SARS-CoV-2 pathophysiology, and also breaches in the aseptic procedures. In addition, tools based on molecular techniques allow an early diagnosis and unmask VAP usually underdiagnosed by traditional culture-based methods. The impact of molecular technique-based diagnostics in improving antibacterial therapy and COVID-19 prognosis remain to be evaluated.

Keywords
antimicrobial stewardship, coronavirus disease 2019, molecular diagnostic, ventilator-associated pneumonia

INTRODUCTION

The outcome of acute respiratory distress syndrome (ARDS) because of COVID-19 is singularly worse when complicated with nosocomial pneumonia. Indeed, the relative risk of developing a lower respiratory tract infection (LRTI) has been reported to be 60% higher in these patients compared with patients with ARDS from other causes [1▪▪]. Their prognosis is characterized by an increased crude mortality and a prolonged duration of mechanical ventilation by about 70 and 40%, respectively [2].

INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA IN CORONAVIRUS DISEASE 2019 PATIENTS

The reported incidence of ventilator-associated pneumonia (VAP) in COVID-19 ARDS, ranges from 25 to almost 85%, and represents twice as many complications as in control ARDS patients without COVID-19 (Table 1) [3]. In COVID-19 patients, VAP occurred earlier than in other mechanically ventilated patients [4]. Despite a relatively low rate of bacterial coinfection [5,6,7▪], patients with COVID-19 pneumonia frequently receive antimicrobial therapy. Indeed, up to three out of four patients are treated with antimicrobials in the community setting [8]. In a large multicentric prospective cohort in the United Kingdom, 37% of patients were treated with antimicrobials before hospital admission, and 70.6% developed secondary infections, at least 48 h after admission [9]. Importantly, 85.2% received one or more ant-infective treatments at hospital despite the fact that significant bacteriological confirmation of co-infection was

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KEY POINTS

- Incidence of ventilator-associated pneumonia (VAP) is higher in COVID-19 invasively ventilated patients than in patients with other causes of ARDS.
- High VAP incidence is explained by COVID-19-associated immune alteration, pulmonary infarction, as well as the extensive use of immunosuppressive agents.
- VAP in COVID-19 patients is frequently associated with treatment failure, abscess, empyema, and recurrences.
- The use of multiplex PCR shortened the delay of bacterial identification and has been increasingly used during the COVID-19 pandemic. Its impact on appropriateness of antibacterial therapy and prognosis remains to be evaluated.

obtained in only 10% of the cases. This initial antimicrobial overuse has been suggested to increase the risk of VAP in patients who will require ICU admission, intubation, and mechanical ventilation [6,10].

PATHOPHYSIOLOGY OF CORONAVIRUS DISEASE 2019 ACUTE RESPIRATORY DISTRESS SYNDROME MAY EXPLAIN HIGH INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA

Some differences in the incidence should be analysed according to the following considerations (Fig. 1). First, key aspects of the physiopathology of Severe acute respiratory syndrome - coronavirus disease 19 (SARS-CoV2)-induced pneumonia, such as altered coagulation and inherent immunothrombosis, may also specifically support a higher risk for pulmonary infarction. Second, disease-associated immune impairment could at least partly explain the propensity of developing VAP, also potentially driven by the use of immunomodulator therapies. The use of dexamethasone (DXM) might favor the occurrence of VAP and its recurrences. However, in a multicenter cohort study conducted during the first and second wave of COVID-19, Gragueb-Chatti *et al.* [11] found that the cumulative incidence of VAP was not significantly different in patients treated with DXM or not. Although the use of antagonists of IL-6 receptors is associated with an increased risk of bacterial infections, large randomized studies did not unmask a significant increase of VAP risk [12,13]. However, adverse event reporting was reduced in both platform trials and the reported cases of VAP in IL-6 receptor antagonists and control group were surprisingly low. Third, as compared with other ARDS, the increased incidence of VAP may be partially because of less rigorous use of standard prevention strategies during COVID-19 waves, more prolonged duration of mechanical ventilation, prolonged use of sedation, and more frequent need for prone position [14].

MODIFICATION OF DIAGNOSTIC STRATEGIES DURING CORONAVIRUS DISEASE 2019 PANDEMICS

Furthermore, the particularly high incidence of VAP should somehow be understood in light of the diagnostic criteria that are used, including the extensive use of new molecular methods. Indeed, VAP suspicion become very common, as patients with SARS-CoV2 ARDS often remain febrile, with prolonged alteration of PaO_2/FiO_2 ratio. In those patients mechanically ventilated, with a high level of positive airway pressure, profoundly sedated, and who received paralytic agents, hemodynamic alteration and vasopressor need are also frequent. The worsening of hemodynamic or oxygenation status are generally considered as the most reliable criteria for suspecting VAP [15▪▪]. Also, clinical criteria are usually fickle, and fever can be subdued especially with corticosteroids or extracorporeal membrane oxygenation (ECMO) [16–18]. Moreover, defining a new or worsening pulmonary infiltrate is of particular difficulty in patients with ARDS [19].

The heterogeneity of sample techniques may also have an impact [20▪▪,21▪▪,22▪,23–27] (Table 1). Fiberoptic bronchoscopy for bronchoalveolar lavage (BAL) during the COVID-19 pandemic has been variously performed. This procedure is at high risk of generating aerosol, thus carrying a potential hazard of exposure to the virus. Consequently, it has been scarcely used during the first pandemic wave [28]. Then, because of the reportedly low risk of virus dissemination, bronchoscopy has been more extensively used in intubated COVID-19 patients as compared with other ARDS patients [29], also because COVID-19 patients with ARDS have frequent atelectasis [30], related to obstructive mucosal secretions [31,32]. The extensive use of bronchoscopy may have led to an overuse of bacteriological sampling, eventually contributing to overdiagnosis of VAP. Indeed, Maes *et al.* [20▪▪] showed that patients with COVID-19 were more likely to be investigated for suspicion of VAP than other mechanically ventilated patients.

The generalization of molecular diagnostics methods can also explain an increase in the incidence of diagnosed VAP [33,34]. Throughout the pandemic, diagnostic strategies changed towards a wider use of multiplex PCR (mPCR) techniques, which thus became preferred compared with the culture-based gold standard. They initially represented a key advantage in the laboratory setting

Table 1. Main recent studies describing ventilator-associated pneumonia in coronavirus disease 2019 patients

Study [ref]	Sample size	VAP incidence[a]	Type of sample (%), technique	Antibiotics at ICU admission (%)	VAP-associated complications
Rouze *et al.* [1▪▪]	568	36/NA	ETA (70.9) BAL (29.1), Culture	88.5	23% MDR, paradoxically lower than in other ARDS
Garcia-Vidal [6]	144	25/NA	NA	74.4	NA
Pickens [7▪]	179	44.4/NA	BAL (100), culture, PCR	NA	NA
Gragueb-Chatti *et al.* [11]	151	60/26	ETA/BAL, culture	73	37% recurrence, 68% with same pathogen
Luyt *et al.* [15▪▪]	50	86/NA	ETA/BAL, culture	100	VAP under ECMO 66% had more than 1 recurrence, 38% polymicrobials
Maes *et al.* [20▪▪]	81	48/28	ETA/BAL, culture, PCR	94	NA
Blonz [21▪▪]	188	48.9/33.7	ETA/BAL, culture	89.9	20% multiple VAP, 3.6% empyema, 1.4% abscess
Razazi *et al.* [22▪]	90	64/NA	ETA/BAL, culture	100	25% recurrences with 23% MDR
Llitjos *et al.* [23]	176	52/NA	NA	92	21% recurrences
Moretti *et al.* [24]	39	54/NA	ETA/BAL, culture	NA	NA
Rouyer *et al.* [25]	79	53/NA	ETA/BAL, culture	NA	28% of recurrences, 17% clinical success at day 7
Giacobbe [26]	586	29/NA	NA	95	NA
Contou *et al.* [27]	73	64/NA	ETA/BAL, culture	100	Among 73 deaths in ICU (mortality 48%) 23% recurrences with 21% MDR
Grasselli *et al.* [44]	774	50/11.7	ETA/BAL, culture	NA	NA
D'Humières *et al.* [53]	77	84.4/NA	ETA/BAL, culture, PCR	91	57.4% failure at day7
Beaucoté *et al.* [47▪]	161	73/NA	ETA/BAL, culture	23	14% abscess on CT, polymicrobial

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ETA, endotracheal aspirates; MDR, multidrug-resistant; NA, nonavailable.
[a]VAP crude incidence (%) and incidence density (expressed per 1000 mechanical ventilation days (whenever available).

to limit healthcare workers exposition to the virus [35], by providing rapid identification of bacteria and selected resistance mechanisms while avoiding Gram stain examination and other manual tests. The accuracy of available panels is low for some pathogens, and those techniques are only able to identify a limited number of pathogens [36]. Inversely, a positive PCR with negative cultures does not definitely demonstrate a respiratory infection. This discrepancy has been analysed in recent retrospective studies, and frequent misdiagnoses were identified with bacterial identification and negative cultures or positive cultures under the traditional diagnostic thresholds [37,38,39▪▪]. Only two studies used systematic molecular assays for the diagnosis of pulmonary superinfections [20▪▪,39▪▪]. Pickens [7▪] investigated the impact of systematic BAL using a mPCR panel, and showed a VAP incidence of 44%, after 48 h of invasive ventilation. In only 7 patients out of 79, the qualitative culture was negative and the diagnosis only based on the positivity of the mPCR assay. Similar findings were observed by Maes *et al.* [20▪▪] with a semi-quantitative household mPCR. In Bichat hospital, mPCR was used on clinical indication for suspicion of hospital-acquired pneumonia or VAP in mechanically ventilated patients with COVID-19 ARDS, and was positive for 48 episodes. However, for 5 of these episodes, the cultures remained negative (11%), and for 18 other episodes, the culture was positive but below the quantitative thresholds (10^4 CFU/ml for BAL and 10^3 CFU/ml for mini-BAL) [39▪▪]. As for non-COVID patients [40,41], the significance of a positive mPCR test with negative culture (or below the threshold) remained speculative. It could correspond to a false-positive result that may artificially increase the incidence of VAP. But it might also represent a true positive, if new antimicrobials have been started for treatment of a new sepsis before bacteriological samples, and thus artefactually led to a negative culture [42].

IS IT REALLY AN ISSUE ?

VAP diagnosed in COVID-19 patients is frequently associated with bloodstream infections [21▪▪,43],

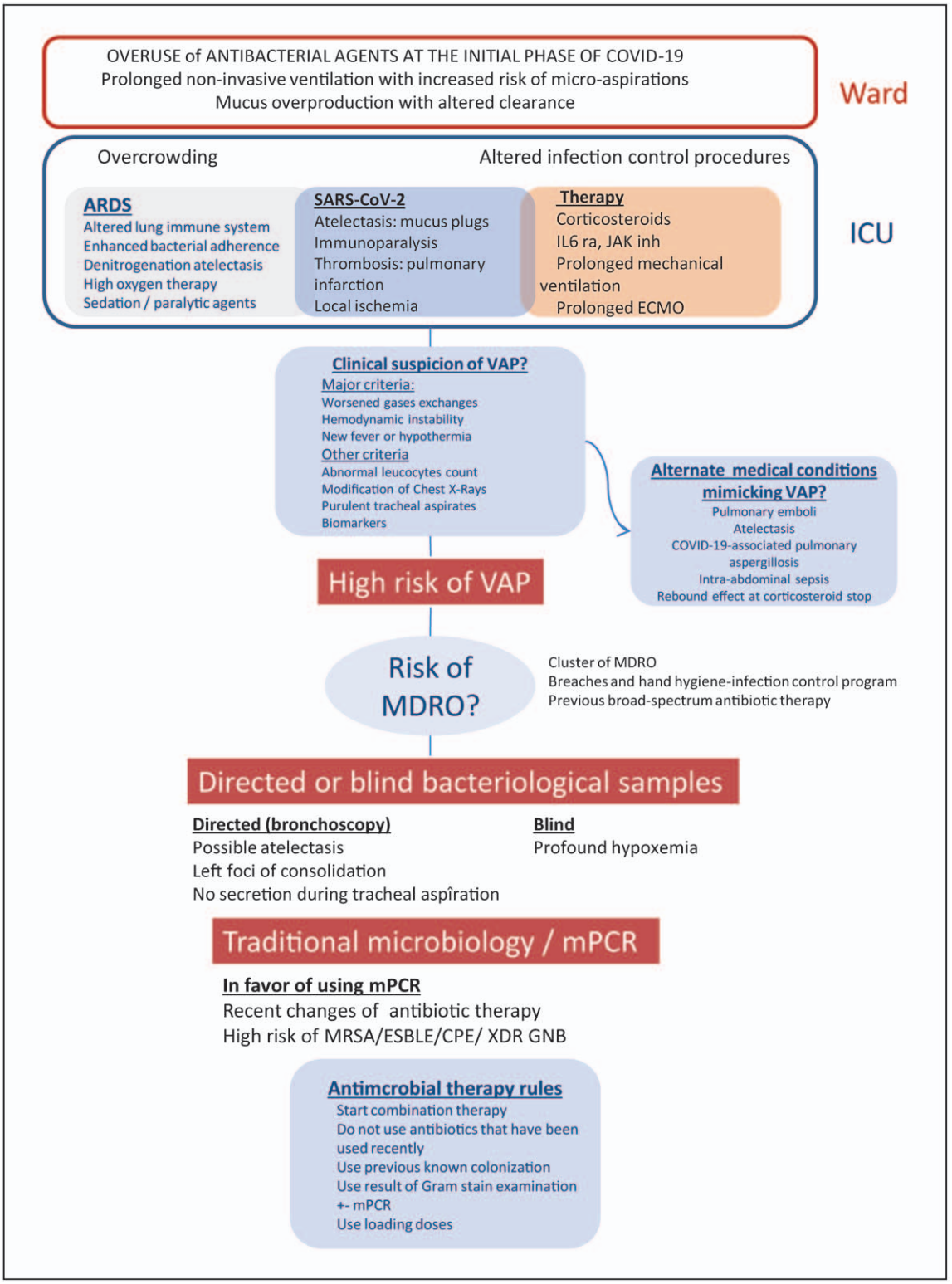

FIGURE 1. Ventilator-associated pneumonia in coronavirus disease 2019 patients with acute respiratory distress syndrome: potential pathophysiology, diagnostic and therapeutic strategies. ARDS, acute respiratory distress syndrome; CPE, carbapenemase producer enterobacterales; ESBLE extended Beta-lactamases producer enterobacterales; IL6 ra, IL-6 receptor antagonist; JAK, Janus kinase; MDRO, multidrug-resistant organisms; mPCR multiplex PCR; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS-CoV2, Severe acute respiratory syndrome - coronavirus disease 19; VAP, ventilator-associated pneumonia; XDR GNB, extensively resistant Gram-negative bacteria.

and is associated with a poor prognosis [1▪▪,15▪▪,21▪▪,44]. This particular severity argues against an overdiagnosis in available studies, which did not describe a specifically increased mortality.

The percentage of treatment failures and reported complications (Table 1) is a strong argument for the use of rapid and very sensitive diagnostic tests with a reduced turn-around time [45]. The mPCR panels also enable us to detect the presence of multi-resistant bacterial strains, and thus avoid the overuse of wide-spectrum molecules [40]. The association with lung perfusion abnormalities [46] raised the problem of impaired antibiotic diffusion, and eventually support the need to rely on therapeutic drug monitoring. In Table 1, we summarize the most frequent complications observed in the main studies.

The true impact of VAP on outcome also remains unclear. No significant association with attributable overmortality has been reported so far [1▪▪]. Still, COVID-19-associated and steroid-induced immunomodulation also implies superinfection because of other opportunistic pathogens. Patients treated with dexamethasone had reduced ICU length of stay, more ventilator-free days but similar mortality regardless of the timing of administration [48]. A true concern also exists about fungal superinfections that could be associated with lung abscesses. Screening for such diagnostic is warranted as they could occur in up to one-third of COVID-19 patients [49]. Consequently, alternative causes should be investigated that might be linked with an impaired prognosis, such as respiratory virus-related nosocomial co-infections [50].

CONCLUSION

In conclusion, the diagnosis of VAP remains challenging in COVID-19 patients with ARDS. The reported incidence is higher than that observed in other mechanically ventilated patients with or without ARDS. Poor infection control practices, local and systemic immune alterations, and extensive use of corticosteroids and immunosuppressive agents probably explain this result much more than an oversensitive diagnostic approach. Rapid molecular assays are instrumental in the timeliness and appropriateness of adequate antibiotic prescriptions [51]. Nonetheless, well conducted studies are needed to evaluate the impact of rapid diagnostic tests in the appropriateness of antimicrobial therapy in order to improve the prognosis of COVID-19 patients with ARDS [52].

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Conflicts of interest

J.F.T. is the principal investigator of the MULTICAP trial comparing a strategy with and without multiplex PCR for severe CAP (Projet Hospitalier de Recherche Clinique, French Ministry of Health, PHRC 16-0595, NCT03452826). Outside of the submitted work, J.F.T. reports lecture for MSD, Pfizer, Shionoghi, Thermofisher, advisory board in the past 5 years for Beckton-Dickinson, MSD, Pfizer, Gilead, Paratek, Nabriva, Medimune, Bayer Pharma and grant to his research unit from MSD, Pfizer, Thermofischer. P.H.W. and C.D. have no conflict of interest to declare.

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- ▪ of special interest
- ▪▪ of outstanding interest

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