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

Paul-Henri Wicky, Camille d’Humières, and Jean-François Timsit

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
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.

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 PaO2/FiO2 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...
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],

| Study [ref]        | Sample size | VAP incidence | Type of sample (%) | 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 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 |
| Uitjos 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’Humieres et al. [53] | 77        | 84.4/NA       | ETA/BAL, culture, PCR | 91                               | 57.4% failure at day7 |
| Beaucot 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.

**VAP crude incidence (%) and incidence density (expressed per 1000 mechanical ventilation days (whenever available).**
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; ESBL 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].

Acknowledgements

We would like to thank Celine Feger (MD) Emibiotech™ for her editorial assistance.

Financial support and sponsorship

None.

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, Shionogi, Thermostifer, advisory board in the past 5 years for Beckton-Dickinson, MSD, Pfizer, Gilead, Paratek, Nabriwa, Medimmune, Bayer Pharma and grant to his research unit from MSD, Pfizer, Thermostifer. P.H.W. and C.D. have no conflict of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of particular interest
- of outstanding interest

1. Rouze A, Martin-Loeches I, Povoa P, coVAPid study Group. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med 2021; 47:188–198.

An European multicenter retrospective cohort including 568 patients, comparing lower respiratory tract infections occurring in COVID-19, influenza and nonm ARDS. The incidence was higher in SARS-CoV-2 infections (50.5 versus 30.3 and 25.3%, respectively). Multidrug-resistant pathogens were isolated in 23.3%.

2. Nseir S, Martin-Loeches I, Povoa P, et al, coVAPid study group. Relationship between ventilator-associated pneumonia and mortality in COVID-19 patients: a planned ancillary analysis of the coVAPid cohort. Crit Care 2021; 25:177.

3. Povoa P, Martin-Loeches I, Nseir S. Secondary pneumonias in critically ill patients with COVID-19: risk factors and outcomes. Curr Opin Crit Care 2021; 27:468–473.

4. Vacheron C-H, Lepape A, Savée A, et al, REA-REZO Study Group. Increased incidence of ventilator-acquired pneumonia in coronavirus disease 2019 patients: a multicentric cohort study. Crit Care Med 2021. doi: 10.1097/ CCM.0000000000005287. [Epub ahead of print]

5. Rouze A, Martin-Loeches I, Povoa P, et al, coVAPid study group. Early bacterial identification among intubated patients with COVID-19 or influenza pneumonia: a European Multicenter Comparative Cohort Study. Am J Respir Crit Care Med 2021; 204:546–556.

6. García-Vidal C. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021; 27:83–88.

7. Pickens CO, Gao CA, Cuttica MJ, et al. Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia. Am J Respir Crit Care Med 2021; 204:921–932.

Among 179 patients of this single center study, 44.4% of patients developed VAP, with early BAL performed in the first 48 h, which diagnosed a superinfection in 21% patients, and of all VAP, 20.8% were because of difficult-to-treat pathogens. The authors used mPCR for microbiological confirmation.

8. Langford BJ, So M, Raybardon S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis, Clin Microbiol Infect 2021; 27:520–531.

9. Russell CD, Fairfield CJ, Drake TM, et al, ISARIC4CC investigators. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. Lancet Microbe 2021; 2:e354–e365.

10. Petit N, Nguyen CT, Lew AK, et al. Reducing the use of empiric antibiotic therapy in COVID-19 on hospital admission. BMC Infect Dis 2021; 21:516.

11. Grageub-Chati I, Lopez A, Hamdi D, et al. Impact of dexamethasone on the incidence of ventilator-associated pneumonia and blood stream infections in COVID-19 patients requiring invasive mechanical ventilation: a multicenter retrospective study. Ann Intensive Care 2021; 11:87.

12. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; 397:1637–1645.
How common is VAP after COVID-19? Wicky et al.

13. REMAP-CAP Investigators. Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021; 384:1491–1502.

14. Wicky PH, Niedermann MS, Timsit J-F. Ventilator-associated pneumonia in patients with COVID-19: a systematic review and meta-analysis. Antibiotics (Basel) 2021; 10:545.

15. Lupu C-E, Sahoun T, Goutier M, et al. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care 2020; 10:158.

16. The outcome of the 86% of patients developing VAP after COVID-19 ARDS under ECMO was assessed. A recurrence occurred in 79% of patients. Enterobacteriaceae accounted for 70% of causative pathogens, whereas Pseudomonas aeruginosa for 37%. The median time of 10 days for VAP after admission, was longer than in other studies.

17. Schmidt M, Brechtel N, Harri S, et al. Nosocomial infections in adult cardiac surgery patients supported by venoarterial extracorporeal membrane oxygenation. Clin Infect Dis 2012; 55:1633–1641.

18. Franchineau G, Luyt CE, Combes A, Schmidt M. Ventilator-associated pneumonia in extracorporeal membrane oxygenation-assisted patients. Ann Trans Med 2018; 6:427.

19. Weiss E, Zahar J-R, Alder J, et al. Elaboration of consensus clinical endpoints to evaluate antimicrobial treatment efficacy in future hospital-acquired Ventilator-associated bacterial pneumonia clinical trials. Clin Infect Dis 2019; 68:1912–1918.

20. Lupu CE, Boudadna L, Morris AC, et al. Pulmonary infections complicating ARDS. Intensive Care Med 2020; 46:2186–2183.

21. Maes M, Higginson E, Pereira-Dias J, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care 2021; 25:25.

22. Among 81 COVID patients of this prospective study, 49 patients were diagnosed with VAP, and a cumulated incidence of 28/1000 ventilator-days, higher than the 144 non-COVID controls (15/1000). A key interest of this study in the methods used to confirm the infection, using real-time PCR (TaqMan array) as an alternative of BAL culture.

23. Blonz G. Epidemiology and microbiology of ventilator-associated pneumonia in COVID-19 patients: a multicenter retrospective study in 188 patients in an ICU of an inundated French Region. Crit Care 2021; 25:72.

24. An hospital from an uninundated region reported the incidence of patients referred from overcrowded area during the first wave. The cumulated incidence of VAP was particularly elevated (33.7/1000 ventilator-days), and characterized by a high prevalence of recurrences (20%), and lung complications such as empyema (3.8%) and abscesses (1.4%).

25. Razai K. Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to coronavirus 19 disease. Critical Care 2020; 24:699.

26. A retrospective study reporting a higher incidence of VAP in 90 COVID-19 patients as compared with non-COVID patients (64 versus 44%). The incidence of MDR-related VAP was equivalent to other studies (23%).

27. Liti jos J-F, Bredin S, Lascamou J-B, et al. Increased susceptibility to intensive care unit-acquired pneumonia in severe COVID-19 patients: a multicentre retrospective cohort study. Ann Intensive Care 2021; 11:20.

28. Moretti M, Van Laethem J, Minini A, et al. Ventilator-associated bacterial pneumonia in SARS-CoV-2 pneumonia in 2019. A retrospective monocentric cohort study. J Infect Chemother 2021; 27:826–833.

29. Raujel M, Estrada J, Yoboung T, et al. Ventilator-associated pneumonia in COVID-19 patients: a retrospective cohort study. Antibiotics (Basel) 2021; 10:988.

30. Giacobbe DR. Incidence and prognosis of ventilator-associated pneumonia in critically ill patients with COVID-19: a multicenter cohort study. JAMA Intern Med 2021; 181:585–593.

31. Contou D, Cally R, Sarafit F, et al. Causes and timing of death in critically ill COVID-19 patients. Crit Care 2021; 25:79.

32. Patrucco F, Albera C, Bellocchia M, et al. SARS-CoV-2 detection on broncho-alveolar lavage: an Italian Multicenter experience. Respiratory 2020; 99:970–978.

33. Chang SH, Jiang J, Kon ZN, et al. Safety and efficacy of bronchoscopy in critically ill patients with coronavirus disease. Chest 2021; 159:870–872.

34. Mingote A, Mimone F, Remiotti M, et al. Pneumonia in COVID-19 critically ill patients by BioFire FilmArray pneumonia plus panel. J Microbiol Methods 2021; 186:106259.

35. Kolenda C, Ranc A-G, Boisset S, et al. Assessment of respiratory bacterial coinfections among severe acute respiratory syndrome coronavirus 2-positive patients hospitalized in intensive care units using Commercial Culture and BioFire FilmArray Pneumonia Plus Essay. Open Forum Infect Dis 2020; 7:7a9a484.

36. Maataoui N, Chemali L, Patrizi J, et al. Impact of rapid multiplex PCR on management of antibiotic therapy in COVID-19-positive patients hospitalized in intensive care unit. Eur J Clin Microbiol Infect Dis 2021; 40:2227–2334.

The authors described the impact of multiplex PCR panel on antibiotic use for HAP/VAP affecting COVID-19 patients admitted in ICU. Positive results tested in initiation or adaptation of antibiotics in 44% of cases, and withdrawal in 19% when the test was negative, 24% remaining antibiotic-free when the PCR was negative.

37. de Maeyer T, Vanden Branden JF, et al. Molecular testing for acute respiratory infections in intensive care unit-hospitalized COVID-19 patients: Conventional culture vs BioFire FilmArray pneumonia Plus panel. J Microbiol Methods 2021; 186:106259.

38. Combe C, Bouscary D, et al. Ventilator-associated pneumonia in critically ill patients with ventilator-associated pneumonia or ventilated hospital-acquired pneumonia. Critical Care 2020; 24:386.

39. Monard G, Pehlivan J, Ager M, et al. ADAPT study group. Multicenter evaluation of a syndromic rapid multiplex PCR test for early adaptation of antimicrobial therapy in adult patients with pneumonia. Crit Care 2020; 24:434.

40. Timsit JF, Bissett M, Rendaux M, et al. Effect of previous antimicrobial therapy on the accuracy of the main procedures used to diagnose nosocomial pneumonia in patients who are using ventilation. Chest 1995; 108:1036–1040.

41. Buetti N, Rucilded S, de Montmollin E, et al. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-control study from the multicenter OUTCOMEREA network. Intensive Care Med 2021; 47:180–187.

42. Grasselli G, Scarcagli V, Mangioni D, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest 2021; 160:454–465.

43. Camellini E, Moy A-C, Dudoignon E, et al. Performance of a multiplex polymerase chain reaction panel for identifying bacterial pathogens causing pneumonia in critically ill patients with COVID-19. Diagn Microbiol Infect Dis 2021; 99:115183.

44. Ackermann M, Verleden SE, Kuehnlein M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesisis in Covid-19. N Engl J Med 2020; 383:120–128.

45. Beaucote V, Boulanger C, Troillet JA, et al. Long abscesses in critically ill coronavirus disease 2019 patients with ventilator-associated pneumonia: A French monocenter retrospective study. Crit Care Explor 2021; 3:e0482.

46. Among 161 patients with COVID-19 in this single-center study, 119 (73%) were diagnosed with VAP. Among these patients, aspergillus was isolated from 32% of species, and Entrobacteriacae for 42%. Nevertheless, the test was negative, 24% remaining antiobiotic-free when the PCR was negative.

47. The authors described the impact of multiplex PCR panel on antibiotic use for HAP/VAP affecting COVID-19 patients admitted in ICU. Positive results tested in initiation or adaptation of antibiotics in 44% of cases, and withdrawal in 19% when the test was negative, 24% remaining antibiotic-free when the PCR was negative.

48. The authors described the impact of multiplex PCR panel on antibiotic use for HAP/VAP affecting COVID-19 patients admitted in ICU. Positive results tested in initiation or adaptation of antibiotics in 44% of cases, and withdrawal in 19% when the test was negative, 24% remaining antibiotic-free when the PCR was negative.