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Invited review

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Ventilator-associated pneumonia in critically ill patients with COVID-19 infection, a narrative review

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Abstract:

COVID pneumonitis can cause patients to become critically ill. They may require intensive care and mechanical ventilation. Ventilator-associated pneumonia is a concern. This review aims to discuss the topic of ventilator-associated pneumonia in this group. Several reasons have been proposed to explain the elevated rates of VAP in critically ill COVID patients compared to non-COVID patients. Extrinsic factors include understaffing, lack of PPE and use of immunomodulating agents. Intrinsic factors include severe parenchymal damage, immune dysregulation, along with pulmonary vascular endothelial inflammation and thrombosis. The rate of VAP has been reported at 45.4%, with an ICU mortality rate of 42.7%. Multiple challenges to diagnosis exist. Other conditions such as acute respiratory distress syndrome, pulmonary oedema and atelectasis can present with similar features. Frequent growth of gram-negative bacteria has been shown in multiple studies, with particularly high rates of *pseudomonas aeruginosa*. The rate of invasive pulmonary aspergillosis has been reported at 4 ï 30%. We would recommend the use of invasive techniques when possible. This will enable de-escalation of antibiotics as soon as possible, decreasing overuse. It is also important to keep other possible causes of ventilator-associated pneumonia in mind, such as COVID-19 associated pulmonary aspergillosis, cytomegalovirus, etc. Diagnostic tests such as galactomannan and B-D-glucan should be considered. These patients may face a long treatment course, with risk of re-infection, along with prolonged weaning, which carries its own long-term consequences.

Introduction

The COVID-19 pandemic has taken the world by storm. Intensive care units (ICU) across the globe have been put under extreme pressure. Although the global COVID-19 pandemic has lasted over two years at this stage, VAP still poses a challenge to intensive care clinicians now. The estimated mortality rate of VAP in COVID patients is 42.7%2. An increase in the number of patients requiring intensive care has been shown. These patients go on to require invasive ventilation with prolonged ICU stays. As a result, these patients are at substantial risk for developing VAP. A pneumonia that occurs 48 hours post intubation or longer, is defined as VAP[1].

This review aims to discuss the topic of ventilator-associated pneumonia (VAP) in adult patients with COVID-19 pneumonitis requiring invasive mechanical ventilation. The risk factors, prevalence, diagnostic challenges, and aetiology will be detailed. Prevention, treatment, and stewardship will be examined. Weaning, reinfection and long-term outcomes of VAP in critically ill COVID patients will now be discussed.

Utilising the terms ñventilator-associated pneumonia,òñVAP,òñCOVIDòand ñICU,òa search was carried out to identify suitable publications to include in this review. The following databases were used: Pubmed, Embase, Annual Reviews, Biomedical Central Journals Complete, Cochrane database of systematic reviews, Cochrane database, and JAMA Network. Only articles written in English were included. This is intended to be a narrative review. It is not a meta-analysis.

Why do COVID patients develop VAP?

The risk of developing nosocomial infections in critically ill COVID patients is multifactorial. In terms of extrinsic factors, it has been proposed that a lack of adequate staffing and PPE (Personal Protective Equipment) at the beginning of the pandemic may have led to an increased rate of cross-contamination between patients, leading to higher rates of VAP compared to non-COVID patients23. They are also mechanically ventilated for longer and are more likely to require proning compared to non-COVID patients. It has been reported in some studies that this group of patients are proned twice as much as influenza patients45. Although proning may increase drainage of oral secretions, it has not been shown to reduce VAP6. The addition of immunomodulating agents such as corticosteroids, IL-6 antagonists and janus kinase inhibitors7 may further increase the risk of infection.

The RECOVERY TRIAL showed how corticosteroids decreased length of mechanical ventilation8. Although corticosteroids are sometimes described as a risk factor for VAP, the CoDEX trial displayed similar reduction in length of mechanical ventilation. There was no increase in rate of VAP9. Gragueb-Chatti et al demonstrated no increase in VAP or bloodstream infection in a multicentre study[10].

IL-6 antagonists are also postulated to create an immunosuppressive state. Yet, it has been shown that there may be some benefit to these agents before intubation. They

may decrease the need for intubation and mortality. Further research in this area is required11. Janus kinase inhibitors may be beneficial in reducing mortality if given in the initial one to two weeks of infection. Yet, further studies are needed12. Both IL-6 antagonists and Janus Kinase inhibitors may create an immunosuppressive state. Yet, as mentioned above, it has been suggested that both drugs may improve outcomes. At present, we can *speculate* that these drugs may cause immunosuppression and *potentially* lead to increased rates of VAP. Yet, further research is required in this area.

Grasselli et al demonstrated that COVID patients on ECMO had a rate of VAP of 35%. This was related to longer duration of stay in ICU and a higher mortality rate13. Luyt et al showed that COVID patients on ECMO had higher rates of VAP compared to influenza patients on ECMO. Although, the overall rate of bacterial coinfection was higher in the influenza population14.

In terms of intrinsic factors, the patients in question display more severe parenchymal damage, along with poor lung compliance compared to non-COVID patients, both of which are risk factors for VAP15. It is hypothesized that SARS-COV2 infection may cause an element of immunoparalysis16, along with immune dysregulation resulting in hyperinflammation and issues with lymphoid function171819. One study has shown that COVID patients that went on to develop VAP had a detectable change in their lung microbiome several weeks before. A decrease in their antibacterial immune defence was displayed20. Di Pascale et al found that the lung microbiome was significantly different in COVID-19 patients who developed *S. aureus* VAP compared to non-COVID patients. They found less diversity of bacteria, with *S. aureus*, *Streptococcus anginosus* and *Olsenella* making up the dominant growth21. It is theorised that SARS-COV2 infection may also cause pulmonary vascular endothelial inflammation and subsequent thrombosis2223242526. These factors combined create an environment suitable for bacterial growth.

In summary, extrinsic factors include staff shortages, lack of PPE23, treatment with immunomodulating agents71112 and ECMO1314. These may account for the increased rate of VAP in critically ill COVID patients compared to non-COVID patients. The effect of steroids is controversial, and has been shown in some studies to yield improved outcomes910. Intrinsic factors relating to the disease process itself are as follows. Lung parenchymal damage, poor compliance15, immune dysregulation1617181920, alterations in the lung microbiome21 and increased risk of thrombosis2223242526, may all play a role in creating a suitable environment for bacterial growth. All risk factors considered, VAP is a serious complication of COVID pneumonitis. It is associated with shock, bacteraemia and polymicrobial infections27. Therefore, it still poses challenges to clinicians28.

Prevalence

A recent meta-analysis in May 2021 found that the rate of VAP was elevated in COVID patients compared to non-COVID patients4. The rate of VAP was 45.4%. When broken down study by study, the range of VAP was 7.6% - 86%. These differences in rate of VAP may be attributable to differences in clinical settings, staffing, patient factors (such as reason for ICU admission, and disease severity), and the diagnostic criteria for VAP used in each study. The ICU mortality rate was 42.7% in critically ill COVID patients, but this was not necessarily attributable to VAP. The mean ICU LOS (length of stay) was 28.58 days. One point that was displayed on comparison of the different retrospective studies involved in the meta-analysis was how slight variations in the definition of VAP were present. One can see the difficulty this may pose when comparing different studies.

Fumagalli et al described a rate of VAP of approximately 50% as well, with a range of 21% to 64%. The first episode of VAP was usually detected between days 8 and 12 of invasive ventilation. Twelve to thirty days was the average length of mechanical ventilation. ICU mortality of COVID patients with VAP was like that of non-COVID patients with VAP, at approximately 40 - 55%36[29]. This is in keeping with 3.

Jain et al described the rate of VAP in COVID patients at 48.15%, with a mortality rate of 51.4%. There was an overall increased risk of VAP compared to non-COVID patients. Males had an increased risk of VAP 30. Blonz et al showed a rate of VAP of 48.9%, with a recurrence rate of 19.7%31. VAP has been shown to occur late in mechanical ventilation313233. Nseir et al described an association between VAP and an increased 28-day mortality in COVID patients. Yet, this was not any higher than patients with influenza or intubated for a non-viral reason34.

Challenges of diagnosis

It is important to note that some controversy does exist around the diagnosis of VAP. Sampling methods may vary depending on region28. An element of subjectivity regarding diagnosis may also be involved4. If a patient is cultured and fails to grow any microbe, they may not be included in many studies as VAP. Whereas a patient may never have any cultures sent due to other reasons, and they too will not be recorded as VAP. Many of the clinical signs that would indicate VAP are also shared with acute respiratory distress syndrome (ARDS), atelectasis, and pulmonary oedema. The administration of steroids or ECMO (Extra Corporeal Membrane Oxygenation) may mask a fever3. The Clinical Pulmonary Infection Score (CPIS) is a score that has been proposed to predict VAP. It considers temperature, leukocytes, tracheal secretions, PaO2:FiO2 ratio, imaging, and cultures35. Yet, it is not currently included in the most recent guidelines on treatment of VAP, as there is a risk of antibiotic overuse36.

There is conflicting evidence in relation to the use of invasive versus non-invasive diagnostic procedures. It has been reported that invasive diagnostic strategies, such as bronchoalveolar lavage (BAL), have been shown to reduce mortality, identify organ

failure earlier and reduce the overuse of antibiotics, when compared to non-invasive strategies37. Yet, no significant difference in patient outcomes were shown whether invasive versus non-invasive diagnostic strategies were implemented in a meta-analysis in 201438. It is important to note that invasive or distal strategies include BAL, protected specimen brush (PSB) and lung biopsy. Blind mini-BAL is not always guaranteed to obtain a distal sample. Therefore, it is classified as a non-invasive strategy37.

In critically ill COVID patients, performing BAL poses its own risks. This cohort of patients may display poor oxygenation and poor compliance due to ARDS. There is also a risk of viral transmission. One study showed a decrease in the use of BAL from 60% to 25% due to the pandemic39. Despite the aforementioned risks associated with invasive sampling, we would recommend the use of invasive techniques when possible. It is important to keep both patient and staff safety in mind. This will enable de-escalation of antibiotics as soon as possible, decreasing overuse.

C-reactive protein (CRP), procalcitonin and soluble triggering receptor expressed on myeloid cells (sTREM-1) are some of the biomarkers that have been suggested to be useful in the diagnosis of VAP in all patients. Yet, further studies are required40414243. Clinical assessment is still regarded as paramount. The use of routine monitoring of a specific biomarker is not recommended4445.

In patients receiving an IL-6 inhibitor, CRP may not be accurate. IL-6 is involved in the stimulation of CRP synthesis from hepatocytes4647. Initial studies demonstrated a low procalcitonin level in patients with SARS-COV2 infection alone4849. Yet, elevated procalcitonin has also been shown in severe SARS-COV2 infection50. Viral infection may also interfere with Interferon-gamma release, and this may cause an inaccurate procalcitonin level51. Rouzé et al demonstrated a slightly elevated procalcitonin in patients with bacterial coinfection versus patients without. Yet, not as elevated as in influenza patients with coinfection52. In diagnosis, procalcitonin has been described as a promising tool, requiring further evaluation5354.

In summary, biomarkers such as CRP and procalcitonin may show promise in the future. Yet, at present, further research is required in this area. Our recommendations are to use these biomarkers as adjuncts to diagnosis. Yet, clinical context is essential, and they should not be used in place of clinical acumen.

Aetiology

- *Bacteria*

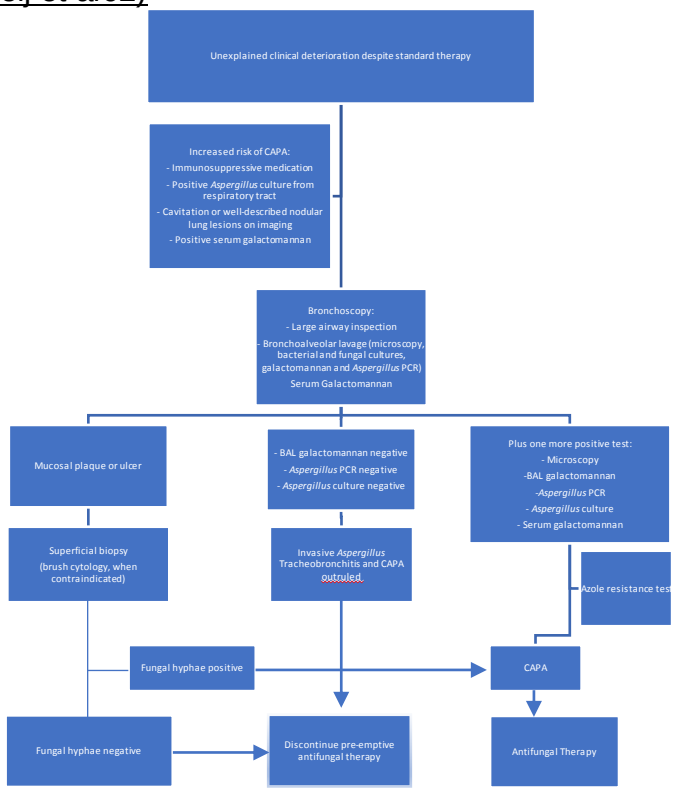
On review of the meta-analysis by Ippolito et al, the main bacteria grown included gram negative bacteria: *E. faecium*, *K. pneumonia*, *A. baumannii*, *P. aeruginosa*, *Enterobacter spp*., *E. coli*, along with *S. aureus*. This is in keeping with previous descriptions4. Fumagalli et al described how greater than 50% of bacteria grown were gram-negative3. Blonz et al showed how *Enterobacteriae* accounted for half of the microbiological growth and *pseudomonas* accounted for 15.1%31. Papazian et al36 described how the micro-organisms responsible for VAP can vary depending on multiple factors. These include the length of hospital and ICU stay, length of mechanical ventilation, local bacterial strains, and exposure to antimicrobials. Gram-negative bacteria include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species. *S. aureus* is the most common gram-positive bacteria. The bacteria that are usually isolated may not be related to intubation; they are related to the severity of underlying disease33. Increased use of empirical antibiotics due to the COVID-19 pandemic poses a threat of increased MDROs in the future, and we will discuss this later in the review55.

- *COVID-19 associated invasive pulmonary aspergillosis*

In comparison to bacteria, *Aspergillus* is rarely the causative agent of VAP in non-COVID patients, except for patients undergoing mechanical ventilation for influenza, or in the immunocompromised. Rouzé et al demonstrated a lower incidence of IPA (invasive pulmonary aspergillosis) in COVID patients compared to influenza patients (4.1% vs 10.2%, respectively). This may be due to the increased proportion of immunosuppression recorded in the influenza group. Yet, this was adjusted for. BAL was performed less frequently in the COVID group due to risk of viral transmission. This may have led to under recognition of aspergillosis. Finally, they concluded that the mechanism of entry into the lower respiratory tract and pulmonary lesions related to SARS-COV2 and influenza are different. This may account for the different rates of IPA. 56. Yet, *Aspergillus* infection may be underdiagnosed due to delay in diagnosis or lack of recognition57. Invasive pulmonary aspergillosis has become more prevalent as a cause of VAP in COVID patients versus non-COVID patients in general4. Fumagalli et al reported the incidence of COVID-19 associated invasive pulmonary aspergillosis ranged from 4-30%3. This is higher than the non-COVID population. Yet, further research is still required. One multicentre study in the UK describes how *Aspergillosis* may be underdiagnosed, when looking at critically ill non-COVID non-neutropenic patients. Up to 20% of VAP may in fact be IPA. They advised clinicians to practise a high level of suspicion, and utilise galactomannan whenever these patients undergo BAL[58]. It is also advised to acquire distal samples for culture, along with consecutive serum galactomannan indices. Galactomannan from BAL fluid has been shown to be promising in early identification and exclusion of COVID-19 associated invasive pulmonary aspergillosis. Yet, it must be used as an adjunct to the clinical picture. Galactomannan from ETA samples is yet to be validated59. B-D-glucan has been

shown to support the diagnosis of COVID-19 associated invasive pulmonary aspergillosis. Again, this must be utilised in conjunction with the clinical context. Two or more positive results have a greater diagnostic ability. Real time polymerase chain reaction (PCR) for *Aspergillus* DNA supports diagnosis6061. Lateral Flow Device (LFD) provides is method of detection of the *Aspergillus* antigen that can be achieved incredibly quickly62. Increased length of mechanical ventilation and steroid use increase the risk of *Aspergillus* infection63. To treat IPA, the current guidelines recommend the use of a triazole (Voriconazole or Isavuconazole) initially6457. Diagnosis and treatment is outlined in Figure 1. Currently, a phase 4 trial is ongoing looking at the use of prophylactic posaconazole for influenza patients. No results are available yet (https://clinicaltrials.gov/ct2/show/NCT03378479). There are three other antifungals that are currently undergoing trial. These include ibrexafungerp (https://clinicaltrials.gov/ct2/show/NCT03672292), olorofim (https://clinicaltrials.gov/ct2/show/NCT03583164), and fosmanogepix (https://clinicaltrials.gov/ct2/show/NCT04240886). Hopefully, these new medications can provide other treatment options in the future. It is important to note that antifungal resistance (triazole-resistance) is increasing. Therefore, techniques to identify these resistant strains may be crucial in choice of antifungal treatment, and for epidemiological data57. *Candida* has still not been identified as a VAP-causing agent at this point65.

Figure 1. Management of COVID-19 associated invasive pulmonary aspergillosis (adapted from Verweij et al62)



- *Viral*

Viruses such as RSV and influenza, amongst others, can be a cause of VAP[66][67]. HSV and CMV can cause reactivation pneumonia in immunocompromised patients[68]. Some studies have shown a benefit to treating viral reactivations with antivirals. Yet, further research is required[36]. Meyer et al showed that HSV reactivation in COVID patients is associated with increased 60-day mortality. Of the 153 critically ill COVID patients included in the study, they found a reactivation rate of 26.1% [69].

- *Other agents*

No reports of VAP caused by atypical bacteria were identified from our search. It appears that atypical bacteria are not a frequent cause of co-infection in COVID patients, and even less so a cause of VAP. *S. pneumoniae* is rarely seen. Yet, they should still be considered within the clinical context of each patient[56][57][58]. *Tuberculosis* (TB) is not a common cause of VAP. It is more likely to have been present before SARS-COV2 infection. TB patients are at higher risk of COVID infection, with a higher mortality rate[70]. Our search found no cases of VAP caused by *non-tuberculous mycobacteria.* Yet, two case reports of co-infection with mycobacteria in COVID patients were described in the literature (*M. simiae*[71] and *M. abscessus*[72]).

Prevention and infection control

From a nursing standpoint, good preventive measures are crucial in all intubated patients (COVID and non-COVID) [73]. Elevation of the head of bed, draining of subglottic secretions, and maintenance of endotracheal cuff pressure all decrease the risk of aspiration. Avoiding prolonged mechanical ventilation can be achieved by appropriate weaning. Daily interrupted sedation has been shown to decrease rates of VAP[74]. It is thought that this is secondary to an improved respiratory function and gag reflex. Daily evaluation for extubation should be carried out also. An effort should be made to reduce the pathogen load. Different techniques such as regular tooth brushing, and chlorhexidine mouthwash should be implemented[75]. These have been shown to decrease rates of VAP. Early enteral feeding within 48 hours has also been shown to reduce the rate of translocation of intestinal bacteria to the lungs[76]. Routine circuit changes have been shown to increase rates of VAP[77]. Suction of the endotracheal tube should be performed only when necessary and with good technique. Yet, subglottic suctioning has been described as under-utilised and is recommended in COVID patients receiving mechanical ventilation[78]. Two studies based in the non-intensive care setting have shown decreased rates of VAP with brief intubations during theatre. Nam et al. reported a 600% decrease in postoperative VAP in cardiac patients who underwent routine subglottic suctioning[79]. Yuzkat et al showed a decrease in rates of VAP post rhinoplasty surgery[80]. We could not find any literature comparing these preventative measures on the development of VAP between COVID and non-COVID patients. Sakano et al advise to continue incorporating the most up to date evidence

into ICU care bundles (as discussed in this paragraph). They make the solid point that the best way to avoid VAP is to avoid intubation in the first place[81].

The above-mentioned practices can be incorporated into care bundles aimed specifically at reducing rates of VAP82. These practices can be applied to all ventilated patients. Yet, in terms of nursing ventilated COVID patients, the following recommendations have been made. Oral intubation is preferred over nasal. A closed suctioning system should be used to drain and discard condensation. Head of bed elevation should be in place. A new circuit should be used with each patient. It should only be changed if necessary. HME filters should only be changed every 5 ï 7 days or when soiled83. Due to the challenges mentioned previously regarding the diagnosis of VAP, one cannot say with complete certainty if these preventative measures reduce the rate of VAP. The definition of VAP in different studies may vary84.

Adequate staffing has also been shown to be essential. The nurse-to-patient ratio has been suggested as a good indicator for the level of staffing. This is not only for decrease in pathogen spread, but also in terms of adequate diagnosis and treatment of VAP8586. It is important to note that many ICUs around the world expanded outside their original setting. This occurred due to sudden high demand for ICU beds. Therefore, many critically ill patients received care outside of ICU. These patients showed an elevated mortality87.

Infection control plays a key role when treating COVID patients. We would advise specific antimicrobial surveillance studies for ICU[88]56. Diagnostic tests should be carried out when infection is suspected, not pre-emptively. Patients should be cared for in separate rooms89. It has been advised that healthcare workers should wear full PPE including visor and N95 facemask when caring for patients. All healthcare staff involved should be vaccinated against SARS-COV2. At present, it is not advised to routinely test staff for SARS-COV2 infection. Basic hand hygiene, infection control surveillance, disinfection of clinical areas, and separation of waste have all been advised89. Antimicrobial stewardship remains a key feature, as with non-COVID patients. The aim is to not only prevent viral transmission of COVID, but to also reduce the spread of other pathogens and multi-drug resistant organisms (MDROs)89.

Treatment

The initial empirical cover advised for VAP is as follows5369091: (Figure 2)

- Low risk of MDROs and low mortality risk: antibiotic monotherapy advised (e.g., ertapenem, ceftriaxone, cefotaxime, levofloxacin, moxifloxacin)
- High risk of MDROs +/- greater than 15% mortality risk with no septic shock: single gram-negative agent advised* +/-MRSA coverage.
- High risk of MDROs +/- greater than 15% mortality risk with septic shock: dual gram-pseudomonal therapy +/- MRSA coverage.

*if antibiotic shows antimicrobial activity for >90% of gram-negative bacteria in the ICU

Studies have reported the mean ICU mortality for COVID patients who develop VAP at 42.7%2. Yet, the exact attributable mortality is unknown. It is important to treat each individual patient within their own clinical context.

The efficacy and appropriateness of novel antibiotics against resistant gram-negative bacteria is shown in Table 1.

Figure 2. Advised empiric cover for VAP (adapted from Torres et al.[92]).

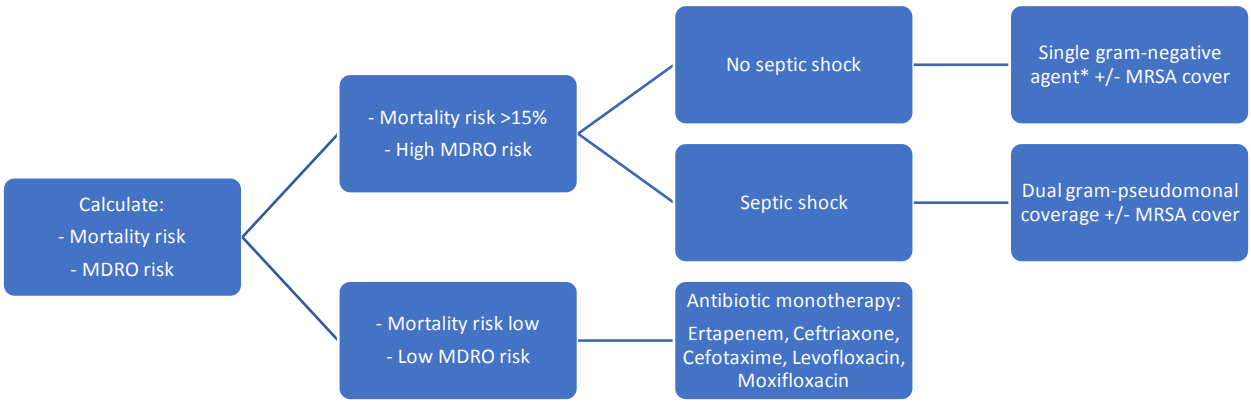


Table 1: Efficacy and appropriateness of novel antibiotics for gram-negative bacteria in ICU (adapted from Garduno et al.93)

Antibiotic	***Enterobacteriaes***			***MDR Pseudomonas***	***MDR Acinetobacter***
	KPC (Class A)	*NDM and other MBLs (Class B)*	*OXA-48 (Class D)*		
Ceftolozane-tazobactam					
Ceftazidime-avibactam				*Better than Ceftazidime alone*	
Imipenem-relebactam			*If Carbapenem sensitive*		
Meropenem-vaborbactam			*If Carbapenem sensitive*		
Aztreonam-avibactam					
Cefideroco					
Eravacycline					
Plazomicin					

Red: High resistance. Yellow: Moderate resistance. Green: Low resistance.
KPC: Klebsiella pneumoniae carbapenemase. NDM: New Delhi Metallobetalactamase. MBL: Metallobetalactamase. OXA-48: carbapenem hydrolysing oxacillinase. MDR: Multidrug resistant.

The efficacy of nebulised antibiotics has not been demonstrated at present. Many patients have concomitant bloodstream infections for which nebulised antibiotics alone would be inappropriate94. Apart from Colistin, no significant increase in efficacy has been shown when nebulised antibiotics are used as an adjunct to the intravenous route9596979899.

Stewardship

Risk factors for MDROs have been shown to be related to previous colonisation, ARDS occurring before VAP, septic shock and acute renal replacement therapy (RRT) before VAP5. Increased use of empirical antibiotics due to the COVID-19 pandemic poses a threat of increased MDROs in the future100. *Enterobacteriae* resistant to Cephalosporins have become more common. This is due to ESBL and AmpC B-lactamase expression101. Carbapenemase expression is also worrying. *P. aeruginosa* strains that are multi-drug resistant are also becoming more frequently detected102. 50-

67% *of Acinetobacter baumannii* strains grown from VAP are Carbapenem resistant103. It has been described how critically ill COVID patients are at increased risk of MDROs, and this can significantly influence outcome104. One study performed in a single centre showed approximately 77% of *K. pneumoniae* cultured from COVID patients in the ICU demonstrated multidrug resistance105.

Certain guidelines do not recommend administration of antibiotics in patients that have a negative culture but are clinically stable5. In this way, patients are exposed to less unnecessary antibiotics. This should decrease the risk of bacterial imbalance, that leads to infections such as *Clostridium difficile*. It should also decrease the development of MDROs. Yet, it is inevitably the clinicianôs decision whether the patient is at risk of deterioration, and if antibiotics should be commenced5. If antibiotics are administered before sampling, this may yield a false negative result. Papazian et al recommend re-evaluating every 48-72 hours, using the clinical course to decide when to stop antibiotics. This is in relation to VAP in all patients36. They also describe the use of a decreasing procalcitonin to stop antibiotics. If the procalcitonin is less than 0.5 ng/ml or it has reduced by 80% from its peak at 48-72 hours, this may indicate that it is appropriate to stop antibiotics106107. Yet, clinical judgement should still be utilised. As previously discussed, we would not recommend reliance on procalcitonin alone, and further research is required in this area. At present, it takes anywhere from 24 to 48 hours to culture bacteria. Broad spectrum empirical antibiotics are required during this time. Ideally, patients should only receive broad spectrum antibiotics for as short a duration as possible. Therapy should be targeted based on cultures. This should decrease the growth of MDROs. Certain methods such as PCR can identify bacteria and resistant strains quicker. Yet, it must be requested for specific pathogens. One example is the detection of *mecA* to detect MRSA108. There is currently a new diagnostic tool called the Unyvero system. This technique can identify the most common causative agents of VAP (20 bacteria and one fungus). It can also detect 19 markers of resistance. Results are available within 4 to 5 hours. At present, Unyvero may over detect. It can detect commensals, non-viable bacteria and pathogenic bacteria that have not reached pathogenic thresholds. Therefore, it may lead to the overuse of antibiotics. Although this technique does require further refinement, it does pose a potential improvement in VAP diagnosis in the future109110111112.

Antibiotic overtreatment may be a risk factor for developing VAP in COVID patients. An imbalance in the bodyôs natural flora may occur as a result. In the early days of the pandemic, it was thought that Azithromycin had some antiviral properties against SARS-COV2. This has now been disproven and is not recommended as empirical treatment anymore. Although, Blonz et al did find that the risk of polymicrobial VAP was reduced with the initiation of empirical antibiotics31. At present, empirical antibiotics are not routinely recommended for COVID patients without any evidence of bacterial infection, as this may lead to overuse, along with the development of MDROs 113. Combination therapy is advised when treating VAP, apart from patients in the early stages of VAP or without risk of MDROs. Therapy should be targeted based on cultures and is usually recommended for seven days36. Karolyi et al performed a study that showed how the results of a multiplex PCR were consistent with microbiological cultures. This may

provide an earlier bacterial identification in the future. They concluded that diagnosis may be made easier if both techniques are used together114.

Weaning and reinfection

Unsuccessful weaning has been associated with poorer outcomes. Elevated peak plateau pressures may increase the risk of unsuccessful weaning. Whereas higher compliance and lower driving pressures may reduce the risk. Positive end expiratory pressure, partial pressure of carbon dioxide, and P/F ratio (partial pressure of oxygen/fraction of inspired oxygen) appear to have no significant bearing on whether a patient is weaned successfully or not115. Protective mechanical ventilation is advised116. One article showed that patients extubated within two weeks had no pathogenic growth. Yet, these patients may only have been extubated as they did not develop VAP117. Tracheostomy placement has been shown to be safe and beneficial in this group of patients118119120121. Yet, a higher rate of tracheomalacia has been reported (5%)122. Tracheostomy has been shown to improve ICU capacity123. Although no difference in *mortality* has been shown between early and late tracheostomy insertion124, earlier tracheostomy placement has been shown to have better *overall outcomes*125. There may be a benefit in preserving muscle mass126.

Although Blonz et al showed a recurrence rate of 19.7%31, one study reports reinfection rates of 43% in critically ill COVID patients. This did influence prognosis. It was mentioned that hospital overburden at the start of the pandemic may be responsible for this127. Immune dysregulation may also be a factor128. MDROs are frequently seen in reinfection. Reinfection is associated with length of mechanical ventilation and ICU LOS. Early diagnosis plays a key role in identifying MDROs early, commencing adequate treatment and improving outcomes129.

Long-term issues

It has been shown there is a high mortality rate in critically ill COVID patients three months post hospital discharge130. Ongoing symptoms were found in two thirds. Ten percent of these required home oxygen. Yet, hospital readmission rates were still low. Persistent symptoms were associated with the following independent risk factors: female gender, ICU LOS, ICU-acquired pneumonia, and ARDS. Of these, ICU-acquired pneumonia prevention could yield a potential reduction in mortality post discharge130.

Conclusion

In summary, the COVID-19 pandemic has tested ICUs globally. For several reasons, COVID patients are at high risk of developing VAP. Although the diagnosis of VAP remains controversial, and can vary from study to study, an elevated incidence has been shown in COVID patients. Through review of the major studies, it appears that the rate of VAP is between 7.6% - 86%[4]. The ICU mortality rate was 42.7% (not necessarily attributable to VAP)[2]. The mean ICU LOS was 28.58 days. Gram negative bacteria such as *pseudomonas* (15.1%), along with *S. aureus* were the most common organisms grown[4]. COVID-19 associated invasive pulmonary aspergillosis was reported at 4% to 30%[3]. Viruses were even less common. Atypical bacteria and TB were not reported as a cause of VAP. Preventive measures can be implemented through care bundles, and this may lead to a reduction in VAP. Treatment is recommended to begin with a broad empirical cover. Yet, this should be targeted based on microbial growth as soon as possible. MDROs are already increasing in frequency, and antibiotic stewardship will continue to play an essential role. Biomarkers such as procalcitonin show promising potential, but still require further evaluation. Drugs commonly used in the treatment of COVID patients such as dexamethasone, tocilizumab and janus kinase inhibitors considerably reduce CRP and procalcitonin. This causes another challenge in diagnosis47. New methods of early identification of microbes along with certain resistance patterns may result in improved diagnosis and treatment in the future. Ongoing trials of new medications and techniques are still yet to display any positive findings. Although our knowledge of this disease process is ever expanding, we still hold a pessimistic view for this group of patients. We would recommend the use of invasive techniques when possible. This will enable de-escalation of antibiotics as soon as possible, decreasing overuse. It is important to diagnose other possible causes of VAP, such as COVID-19 associated invasive pulmonary aspergillosis, CMV, etc. Utilization of other diagnostic tests such as galactomannan and B-D-glucan should be performed.

References

[1] Kalanuria, A.A., Zai, W. & Mirski, M. Ventilator-associated pneumonia in the ICU. *Crit Care* **18,** 208 (2014), available: https://doi.org/10.1186/cc13775 [accessed 24 Mar. 2022]

2 Ippolito M, Ramanan M, Bellina D, Catalisano G, Iozzo P, Di Guardo A, Moscarelli A, Grasselli G, Giarratano A, Bassetti M, Tabah A, Cortegiani A. Personal protective equipment use by healthcare workers in intensive care unit during the early phase of COVID-19 pandemic in Italy: a secondary analysis of the PPE-SAFE survey. Ther Adv Infect Dis. 2021 Feb 25;8:2049936121998562. doi: 10.1177/2049936121998562. PMID: 33717482; PMCID: PMC7922607, available: https://pubmed.ncbi.nlm.nih.gov/33717482/ [accessed 30 Dec. 2021]

3 Fumagalli, J., Panigada, M., Klompas, M., & Berra, L. Ventilator-associated pneumonia among SARS-CoV-2 acute respiratory distress syndrome patients. *Current opinion in critical care*, (2022) *28*(1), 74ï 82, available: https://doi.org/10.1097/MCC.0000000000000908 [accessed 30 Dec. 2021]

4 Ippolito M, Misseri G, Catalisano G, et al. Ventilator-Associated Pneumonia in Patients with COVID-19: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)*. 2021;10(5):545. Published 2021 May 7. doi:10.3390/antibiotics10050545, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8150614/ [accessed 30 Dec. 2021]

5 Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. doi: 10.1093/cid/ciw353. Epub 2016 Jul 14. Erratum in: Clin Infect Dis. 2017 May 1;64(9):1298. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1435. Erratum in: Clin Infect Dis. 2017 Nov 29;65(12):2161. PMID: 27418577; PMCID: PMC4981759, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981759/ [accessed 31 Dec. 2021]

6 Ayzac L, Girard R, Baboi L, Beuret P, Rabilloud M, Richard JC, Guérin C. Ventilator-associated pneumonia in ARDS patients: the impact of prone positioning. A secondary analysis of the PROSEVA trial. Intensive Care Med. 2016 May;42(5):871-878. doi: 10.1007/s00134-015-4167-5. Epub 2015 Dec 23. PMID: 26699917, available: https://link.springer.com/article/10.1007%2Fs00134-015-4167-5 [Accessed 31 Dec. 2021]

7 Limen RY, Sedono R, Sugiarto A, Hariyanto TI. Janus kinase (JAK)-inhibitors and coronavirus disease 2019 (Covid-19) outcomes: a systematic review and meta-analysis [published online ahead of print, 2021 Sep 29]. *Expert Rev Anti Infect Ther*. 2021;1-10. doi:10.1080/14787210.2021.1982695, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8500309/ [accessed 13 Jan. 2022]

8 RECOVERY Collaborative Group, Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T., Chadwick, D., Rege, K., Fegan, C., Chappell, L. C., Faust, S.

N., Jaki, T., Landray, M. J. Dexamethasone in Hospitalized Patients with Covid-19. *The New England journal of medicine*, (2021) *384*(8), 693ï 704, available: https://doi.org/10.1056/NEJMoa2021436 [accessed 31 Dec. 2021]

9 Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, Avezum A, Lopes RD, Bueno FR, Silva MVAO, Baldassare FP, Costa ELV, Moura RAB, Honorato MO, Costa AN, Damiani LP, Lisboa T, Kawano-Dourado L, Zampieri FG, Olivato GB, Righy C, Amendola CP, Roepke RML, Freitas DHM, Forte DN, Freitas FGR, Fernandes CCF, Melro LMG, Junior GFS, Morais DC, Zung S, Machado FR, Azevedo LCP; COALITION COVID-19 Brazil III Investigators. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020 Oct 6;324(13):1307-1316. doi: 10.1001/jama.2020.17021. PMID: 32876695; PMCID: PMC7489411, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489411/ [accessed 31 Dec. 2021]

[10] Gragueb-Chatti I, Lopez A, Hamidi D, Guervilly C, Loundou A, Daviet F, Cassir N, Papazian L, Forel JM, Leone M, Dellamonica J, Hraiech S. 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 May 31;11(1):87. doi: 10.1186/s13613-021-00876-8. PMID: 34057642; PMCID: PMC8165680. [accessed 13 Jan. 2022]

11 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, Spiga F, Savovic J, Tierney J, Baron G, Benbenishty JS, Berry LR, Broman N, Cavalcanti AB, Colman R, De Buyser SL, Derde LPG, Domingo P, Omar SF, Fernandez-Cruz A, Feuth T, Garcia F, Garcia-Vicuna R, Gonzalez-Alvaro I, Gordon AC, Haynes R, Hermine O, Horby PW, Horick NK, Kumar K, Lambrecht BN, Landray MJ, Leal L, Lederer DJ, Lorenzi E, Mariette X, Merchante N, Misnan NA, Mohan SV, Nivens MC, Oksi J, Perez-Molina JA, Pizov R, Porcher R, Postma S, Rajasuriar R, Ramanan AV, Ravaud P, Reid PD, Rutgers A, Sancho-Lopez A, Seto TB, Sivapalasingam S, Soin AS, Staplin N, Stone JH, Strohbehn GW, Sunden-Cullberg J, Torre-Cisneros J, Tsai LW, van Hoogstraten H, van Meerten T, Veiga VC, Westerweel PE, Murthy S, Diaz JV, Marshall JC, Sterne JAC. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021 Aug 10;326(6):499-518. doi: 10.1001/jama.2021.11330. PMID: 34228774; PMCID: PMC8261689, available: https://jamanetwork.com/journals/jama/fullarticle/2781880 [accessed 31 Dec. 2021]

12 Limen RY, Sedono R, Sugiarto A, Hariyanto TI. Janus kinase (JAK)-inhibitors and coronavirus disease 2019 (Covid-19) outcomes: a systematic review and meta-analysis [published online ahead of print, 2021 Sep 29]. *Expert Rev Anti Infect Ther*. 2021;1-10. doi:10.1080/14787210.2021.1982695, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8500309/ [accessed 13 Jan. 2022]

13 Grasselli G, Scaravilli V, Di Bella S, Biffi S, Bombino M, Patroniti N, Bisi L, Peri AM, Pesenti A, Gori A, Alagna L. Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome. Crit Care Med. 2017 Oct;45(10):1726-1733. doi: 10.1097/CCM.0000000000002652. PMID: 28777198, available: https://doi.org/10.1097/CCM.0000000000002652 [accessed 31 Dec. 2021]

14 Luyt CE, Sahnoun T, Gautier M, Vidal P, Burrel S, Pineton de Chambrun M, Chommeloux J, Desnos C, Arzoine J, Nieszkowska A, Bréchot N, Schmidt M, Hekimian G, Boutolleau D, Robert J, Combes A, Chastre J. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care. 2020 Nov 23;10(1):158. doi: 10.1186/s13613-020-00775-4. PMID: 33230710; PMCID: PMC7682692, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7682692/ [accessed 31 Dec. 2021]
15 Moretti, M., Van Laethem, J., Minini, A., Pierard, D., & Malbrain, M. Ventilator-associated bacterial pneumonia in coronavirus 2019 disease, a retrospective monocentric cohort study. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*, (2021) *27*(6), 826ï 833, available: https://doi.org/10.1016/j.jiac.2021.01.011 [accessed 01 Jan. 2022]
16 Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020 May 1;368(6490):473-474. doi: 10.1126/science.abb8925. Epub 2020 Apr 17. PMID: 32303591, available: https://www.science.org/doi/10.1126/science.abb8925?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 30 Dec. 2021]
17 Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. Cell Host Microbe. 2020 Jun 10;27(6):883-890.e2. doi: 10.1016/j.chom.2020.04.017. Epub 2020 May 4. PMID: 32407669; PMCID: PMC7196896, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7196896/ [accessed 31 Dec. 2021]
18 Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe. 2020 Jun 10;27(6):992-1000.e3. doi: 10.1016/j.chom.2020.04.009. Epub 2020 Apr 21. PMID: 32320677; PMCID: PMC7172841, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172841/ [accessed 31 Dec. 2021]
19 Luyt CE, Bouadma L, Morris AC, Dhanani JA, Kollef M, Lipman J, Martin-Loeches I, Nseir S, Ranzani OT, Roquilly A, Schmidt M, Torres A, Timsit JF. Pulmonary infections complicating ARDS. Intensive Care Med. 2020 Dec;46(12):2168-2183. doi: 10.1007/s00134-020-06292-z. Epub 2020 Nov 11. PMID: 33175277; PMCID: PMC7656898, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7656898/ [accessed 31 Dec. 2021]
20 Tsitsiklis A, Zha BS, Byrne A, Devoe C, Levan S, Rackaityte E, Sunshine S, Mick E, Ghale R, Jauregui A, Sarma A, Neff N, Serpa PH, Deiss TJ, Kistler A, Carrillo S, Ansel KM, Leligdowicz A, Christenson S, Jones N, Wu B, Darmanis S, Matthay MA, Lynch SV, DeRisi JL; COMET Consortium+, Hendrickson CM, Kangelaris KN, Krummel MF, Woodruff PG, Erle DJ, Rosenberg O, Calfee CS, Langelier CR. Impaired antibacterial

immune signaling and changes in the lung microbiome precede secondary bacterial pneumonia in COVID-19. medRxiv [Preprint]. 2021 Mar 26:2021.03.23.21253487. doi: 10.1101/2021.03.23.21253487. PMID: 33791731; PMCID: PMC8010763.
21 De Pascale G, De Maio F, Carelli S, De Angelis G, Cacaci M, Montini L, Bello G, Cutuli SL, Pintaudi G, Tanzarella ES, Xhemalaj R, Grieco DL, Tumbarello M, Sanguinetti M, Posteraro B, Antonelli M. Staphylococcus aureus ventilator-associated pneumonia in patients with COVID-19: clinical features and potential inference with lung dysbiosis. Crit Care. 2021 Jun 7;25(1):197. doi: 10.1186/s13054-021-03623-4. PMID: 34099016; PMCID: PMC8182737, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8182737/ [accessed 01 Jan. 2022]
22 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120-128. doi: 10.1056/NEJMoa2015432. Epub 2020 May 21. PMID: 32437596; PMCID: PMC7412750, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7412750/ [accessed 30 Dec. 2021]
23 Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020 Jun;46(6):1105-1108. doi: 10.1007/s00134-020-06059-6. Epub 2020 Apr 28. PMID: 32347323; PMCID: PMC7186535, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7186535/ [accessed 30 Dec. 2021]
24 Wicky PH, Niedermann MS, Timsit JF. Ventilator-associated pneumonia in the era of COVID-19 pandemic: How common and what is the impact? Crit Care. 2021 Apr 21;25(1):153. doi: 10.1186/s13054-021-03571-z. PMID: 33882991; PMCID: PMC8059113, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8059113/ [accessed 31 Dec. 2021]
25 Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098. doi: 10.1007/s00134-020-06062-x. Epub 2020 May 4. PMID: 32367170; PMCID: PMC7197634, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197634/ [accessed 31 Dec. 2021]
26 O'Donnell, J. S., Peyvandi, F., & Martin-Loeches, I. Pulmonary immuno-thrombosis in COVID-19 ARDS pathogenesis. *Intensive care medicine*, (2021) *47*(8), 899ï 902, available: https://doi.org/10.1007/s00134-021-06419-w [accessed 02 Jan. 2022]
27 Rouyer, M., Strazzulla, A., Youbong, T., Tarteret, P., Pitsch, A., de Pontfarcy, A., Cassard, B., Vignier, N., Pourcine, F., Jochmans, S., Monchi, M., & Diamantis, S. Ventilator-Associated Pneumonia in COVID-19 Patients: A Retrospective Cohort Study. *Antibiotics (Basel, Switzerland)*, (2021) *10*(8), 988, available: https://doi.org/10.3390/antibiotics10080988 [accessed 01 Jan. 2022]
28 Giacobbe D.R., Battaglini D., Enrile E.M., Dentone C., Vena A., Robba C., Ball L., Bartoletti M., Coloretti I., Di Bella S., et al. Incidence and Prognosis of Ventilator-

Associated Pneumonia in Critically Ill Patients with COVID-19: A Multicenter Study. *J. Clin. Med.* 2021;10:555. doi: 10.3390/jcm10040555, available: https://www.mdpi.com/2077-0383/10/4/555 [accessed 30 Dec. 2021]

[29] Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C. Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1998 Apr;157(4 Pt 1):1165-72. doi: 10.1164/ajrccm.157.4.9708057. PMID: 9563735, available: https://www.atsjournals.org/doi/10.1164/ajrccm.157.4.9708057?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 16 Mar. 2022]

30 Jain S, Khanna P, Sarkar S. Comparative evaluation of ventilator-associated pneumonia in critically ill COVID- 19 and patients infected with other corona viruses: a systematic review and meta-analysis. Monaldi Arch Chest Dis. 2021 Sep 28. doi: 10.4081/monaldi.2021.1610. Epub ahead of print. PMID: 34585556, available: https://monaldi-archives.org/index.php/macd/article/view/1610/1337 [accessed 31 Dec. 2021]

31 Blonz G, Kouatchet A, Chudeau N, Pontis E, Lorber J, Lemeur A, Planche L, Lascarrou JB, Colin G. Epidemiology and microbiology of ventilator-associated pneumonia in COVID-19 patients: a multicenter retrospective study in 188 patients in an un-inundated French region. Crit Care. 2021 Feb 18;25(1):72. doi: 10.1186/s13054-021-03493-w. PMID: 33602296; PMCID: PMC7891465, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7891465/ [accessed 31 Dec. 2021]

32 Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, Cuchet-Lourenço D, Lux J, Sharma-Hajela S, Ravenhill B, Hamed I, Heales L, Mahroof R, Soderholm A, Forrest S, Sridhar S, Brown NM, Baker S, Navapurkar V, Dougan G, Bartholdson Scott J, Conway Morris A. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021 Jan 11;25(1):25. doi: 10.1186/s13054-021-03460-5. Erratum in: Crit Care. 2021 Apr 6;25(1):130. PMID: 33430915; PMCID: PMC7797892, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7797892/ [accessed 31 Dec. 2021]

33 Esperatti M, Ferrer M, Theessen A, Liapikou A, Valencia M, Saucedo LM, Zavala E, Welte T, Torres A. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. Am J Respir Crit Care Med. 2010 Dec 15;182(12):1533-9. doi: 10.1164/rccm.201001-0094OC. Epub 2010 Aug 6. PMID: 20693381, available: https://www.atsjournals.org/doi/10.1164/rccm.201001-0094OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 31 Dec. 2021]

34 Nseir, S., Martin-Loeches, I., Povoa, P., Metzelard, M., Du Cheyron, D., Lambiotte, F., Tamion, F., Labruyere, M., Makris, D., Boulle Geronimi, C., Pinetonde Chambrun, M., Nyunga, M., Pouly, O., Mégarbane, B., Saade, A., Gomà, G., Magira, E., Llitjos, J. F., Torres, A., Ioannidou, I., é coVAPid study group. Relationship between ventilator-associated pneumonia and mortality in COVID-19 patients: a planned ancillary analysis of the coVAPid cohort. *Critical care (London, England)*, (2021) *25*(1), 177, available: https://doi.org/10.1186/s13054-021-03588-4 [accessed 01 Jan. 2022]

35 Schurink CAM, Nieuwenhoven CAV, Jacobs JA, Rozenberg-Arska M, Joore HCA, Buskens E, Hoepelman AIM, Bonten MJM. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med. 2004 Feb;30(2):217-224. doi: 10.1007/s00134-003-2018-2. Epub 2003 Oct 18. PMID: 14566455, available: https://link.springer.com/article/10.1007%2Fs00134-003-2018-2 [accessed 31 Dec. 2021]
36 Papazian, L., Klompas, M., & Luyt, C. E. Ventilator-associated pneumonia in adults: a narrative review. *Intensive care medicine*, (2020) *46*(5), 888ï 906, available: https://doi.org/10.1007/s00134-020-05980-0 [accessed 31 Dec. 2021]
37 Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stéphan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med. 2000 Apr 18;132(8):621-30. doi: 10.7326/0003-4819-132-8-200004180-00004. PMID: 10766680, available: https://www.acpjournals.org/doi/10.7326/0003-4819-132-8-200004180-00004?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 01 Jan. 2022]
38 Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst Rev. 2014 Oct 30;(10):CD006482. doi: 10.1002/14651858.CD006482.pub4. PMID: 25354013, available: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006482.pub4/full [accessed 01 Jan. 2022]
39 Wahidi MM, Shojaee S, Lamb CR, Ost D, Maldonado F, Eapen G, Caroff DA, Stevens MP, Ouellette DR, Lilly C, Gardner DD, Glisinski K, Pennington K, Alalawi R. The Use of Bronchoscopy During the Coronavirus Disease 2019 Pandemic: CHEST/AABIP Guideline and Expert Panel Report. Chest. 2020 Sep;158(3):1268-1281. doi: 10.1016/j.chest.2020.04.036. Epub 2020 May 1. PMID: 32361152; PMCID: PMC7252059, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252059/ [01 Jan. 2022]
40 Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med. 2004 Jan 29;350(5):451-8. doi: 10.1056/NEJMoa031544. PMID: 14749453, available: https://www.nejm.org/doi/10.1056/NEJMoa031544?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov [accessed 01 Jan. 2022]
41 Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, Aubry A, Trouillet JL, Bernard M, Chastre J. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med. 2008 Aug;34(8):1434-40. doi: 10.1007/s00134-008-1112-x. Epub 2008 Apr 18. PMID: 18421435, available: https://link.springer.com/article/10.1007%2Fs00134-008-1112-x [accessed 01 Jan. 2022]
42 Póvoa P, Martin-Loeches I, Ramirez P, Bos LD, Esperatti M, Silvestre J, Gili G, Goma G, Berlanga E, Espasa M, Gonçalves E, Torres A, Artigas A. Biomarker kinetics in the prediction of VAP diagnosis: results from the BioVAP study. Ann Intensive Care.

2016 Dec;6(1):32. doi: 10.1186/s13613-016-0134-8. Epub 2016 Apr 14. PMID: 27076187; PMCID: PMC4830786, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4830786/ [accessed 01 Jan. 2022]
43 Salluh JIF, Souza-Dantas VC, Póvoa P. The current status of biomarkers for the diagnosis of nosocomial pneumonias. Curr Opin Crit Care. 2017 Oct;23(5):391-397. doi: 10.1097/MCC.0000000000000442. PMID: 28759466, available: https://oce-ovid-com.proxy.library.rcsi.ie/article/00075198-201710000-00007/HTML [accessed 01 Jan. 2022]
44 Martin-Loeches, I. , Rodriguez, A. & Torres, A. New guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia: USA vs. Europe. *Current Opinion in Critical Care,* (2018) *24* (5), 347-352. doi: 10.1097/MCC.0000000000000535, available: https://oce-ovid-com.proxy.library.rcsi.ie/article/00075198-201810000-00006/HTML [accessed 02 Jan. 2022]
45 Palazzo, S. J., Simpson, T., & Schnapp, L. Biomarkers for ventilator-associated pneumonia: review of the literature. *Heart & lung : the journal of critical care*, (2011) *40*(4), 293ï 298, available: https://doi.org/10.1016/j.hrtlng.2010.11.003 [accessed 02 Jan. 2022]
46 Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. 2002;22(10):1668ï 73, available: https://www.ahajournals.org/doi/full/10.1161/01.ATV.0000029781.31325.66 [accessed 13 Jan. 2022]
47 Kooistra, E.J., van Berkel, M., van Kempen, N.F. *et al.* Dexamethasone and tocilizumab treatment considerably reduces the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. *Crit Care* **25,** 281 (2021), available: https://doi.org/10.1186/s13054-021-03717-z [accessed 13 Jan. 2022]
48 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 Apr 28;323(16):1574-1581. doi: 10.1001/jama.2020.5394. Erratum in: JAMA. 2021 May 25;325(20):2120. PMID: 32250385; PMCID: PMC7136855, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136855/ [accessed 31 Dec. 2021]
49 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013; PMCID: PMC7092819, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7092819/ [accessed 31 Dec. 2021]

50 Heer RS, Mandal AK, Kho J, Szawarski P, Csabi P, Grenshaw D, Walker IA, Missouris CG. Elevated procalcitonin concentrations in severe Covid-19 may not reflect bacterial co-infection. Ann Clin Biochem. 2021 Sep;58(5):520-527. doi: 10.1177/00045632211022380. Epub 2021 Jun 18. PMID: 34018843, available: https://journals.sagepub.com/doi/10.1177/00045632211022380?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 31 Dec. 2021]
51 Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J Clin Microbiol. 2010 Jul;48(7):2325-9. doi: 10.1128/JCM.00655-10. Epub 2010 Apr 26. PMID: 20421436; PMCID: PMC2897488, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2897488/ [accessed 30 Dec. 2021]
52 Rouze A, Martin-Loeches I, Povoa P, Metzelard M, Du Cheyron D, Lambiotte F, Tamion F, Labruyere M, Boulle Geronimi C, Nieszkowska A, Nyunga M, Pouly O, Thille AW, Megarbane B, Saade A, Diaz E, Magira E, Llitjos JF, Cilloniz C, Ioannidou I, Pierre A, Reignier J, Garot D, Kreitmann L, Baudel JL, Fartoukh M, Plantefeve G, Beurton A, Asfar P, Boyer A, Mekontso-Dessap A, Makris D, Vinsonneau C, Floch PE, Weiss N, Ceccato A, Artigas A, Bouchereau M, Duhamel A, Labreuche J, Nseir S; 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 May 26;204(5):546ï 56. doi: 10.1164/rccm.202101-0030OC. Epub ahead of print. PMID: 34038699; PMCID: PMC8491267, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8491267/ [accessed 31 Dec. 2021]
53 Richards, O., Pallmann, P., King, C., Cheema, Y., Killick, C., Thomas-Jones, E., Harris, J., Bailey, C., & Szakmany, T. Procalcitonin Increase Is Associated with the Development of Critical Care-Acquired Infections in COVID-19 ARDS. *Antibiotics (Basel, Switzerland)*, (2021) *10*(11), 1425, available: https://doi.org/10.3390/antibiotics10111425 [accessed 01 Jan. 2022]
54 Côrtes, M. F., de Almeida, B. L., Espinoza, E., Campos, A. F., do Nascimento Moura, M. L., Salomão, M. C., Boszczowski, I., Freire, M. P., de Carvalho, L. B., Paranhos-Baccalà, G., Costa, S. F., & Guimarães, T. Procalcitonin as a biomarker for ventilator associated pneumonia in COVID-19 patients: Is it an useful stewardship tool?. *Diagnostic microbiology and infectious disease*, (2021) *101*(2), 115344, available: https://doi.org/10.1016/j.diagmicrobio.2021.115344 [accessed 01 Jan. 2022]
55 Cantón, Rafael; Gijón, Desirèe; Ruiz-Garbajosa, Patricia. Antimicrobial resistance in ICUs: an update in the light of the COVID-19 pandemic, Current Opinion in Critical Care: October 2020 - Volume 26 - Issue 5 - p 433-441 doi: 10.1097/MCC.0000000000000755, available: https://journals.lww.com/co-criticalcare/Fulltext/2020/10000/Antimicrobial_resistance_in_ICUs__an_update_in_the.2.aspx [accessed 01 Jan. 2022]
56 Rouzé, A., Lemaitre, E., Martin-Loeches, I. *et al.* Invasive pulmonary aspergillosis among intubated patients with SARS-CoV-2 or influenza pneumonia: a European multicenter comparative cohort study. *Crit Care* **26,** 11 (2022). https://doi.org/10.1186/s13054-021-03874-1, available: https://ccforum.biomedcentral.com/articles/10.1186/s13054-021-03874-1#citeas [accessed 13 Jan. 2022]

57 Mohamed A, Rogers TR, Talento AF. COVID-19 Associated Invasive Pulmonary Aspergillosis: Diagnostic and Therapeutic Challenges. J Fungi (Basel). 2020 Jul 22;6(3):115. doi: 10.3390/jof6030115. PMID: 32707965; PMCID: PMC7559350, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7559350/ [accessed 01 Jan. 2022]

[58] Loughlin L, Hellyer TP, White PL, McAuley DF, Conway Morris A, Posso RB, Richardson MD, Denning DW, Simpson AJ, McMullan R. Pulmonary Aspergillosis in Patients with Suspected Ventilator-associated Pneumonia in UK ICUs. Am J Respir Crit Care Med. 2020 Oct 15;202(8):1125-1132. doi: 10.1164/rccm.202002-0355OC. PMID: 32609533; PMCID: PMC7560800. [accessed 15 Mar. 2022]

59 Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, Spriet I, Verbeken E, Van Wijngaerden E. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med. 2008 Jan 1;177(1):27-34. doi: 10.1164/rccm.200704-606OC. Epub 2007 Sep 20. PMID: 17885264, available: https://www.atsjournals.org/doi/10.1164/rccm.200704-606OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 01 Jan. 2022]

60 Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, Caliendo AM, Castagnola E, Cruciani M, Cuenca-Estrella M, Decker CF, Desai SR, Fisher B, Harrison T, Heussel CP, Jensen HE, Kibbler CC, Kontoyiannis DP, Kullberg BJ, Lagrou K, Lamoth F, Lehrnbecher T, Loeffler J, Lortholary O, Maertens J, Marchetti O, Marr KA, Masur H, Meis JF, Morrisey CO, Nucci M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Racil Z, Roilides E, Ruhnke M, Prokop CS, Shoham S, Slavin MA, Stevens DA, Thompson GR, Vazquez JA, Viscoli C, Walsh TJ, Warris A, Wheat LJ, White PL, Zaoutis TE, Pappas PG. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020 Sep 12;71(6):1367-1376. doi: 10.1093/cid/ciz1008. PMID: 31802125; PMCID: PMC7486838, accessed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7486838/ [accessed 01 Jan. 2022]

61 Talento AF, Dunne K, Joyce EA, Palmer M, Johnson E, White PL, Springer J, Loeffler J, Ryan T, Collins D, Rogers TR. A prospective study of fungal biomarkers to improve management of invasive fungal diseases in a mixed specialty critical care unit. J Crit Care. 2017 Aug;40:119-127. doi: 10.1016/j.jcrc.2017.03.025. Epub 2017 Mar 30. PMID: 28384600, available: https://www.sciencedirect.com/science/article/abs/pii/S0883944116310243?via%3Dihub [accessed 01 Jan. 2022]

62 Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis.
Verweij PE, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, Calandra T, Chiller T, Clancy CJ, Cornely OA, Depuydt P, Koehler P, Lagrou K, de Lange D, Lass-Flörl C, Lewis RE, Lortholary O, Liu PL, Maertens J, Nguyen MH, Patterson TF,

Rijnders BJA, Rodriguez A, Rogers TR, Schouten JA, Wauters J, van de Veerdonk FL, Martin-Loeches I.
Intensive Care Med. 2021 Aug;47(8):819-834. doi: 10.1007/s00134-021-06449-4, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8220883/ [accessed 13 Jan. 2022]
63 Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, Hallek M, Jung N, Klein F, Persigehl T, Rybniker J, Kochanek M, Böll B, Shimabukuro-Vornhagen A. COVID-19 associated pulmonary aspergillosis. Mycoses. 2020 Jun;63(6):528-534. doi: 10.1111/myc.13096. Epub 2020 May 15. PMID: 32339350; PMCID: PMC7267243, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267243/ [accessed 02 Jan. 2022]
64 Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-e60. doi: 10.1093/cid/ciw326. Epub 2016 Jun 29. PMID: 27365388; PMCID: PMC4967602, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4967602/ [accessed 01 Jan. 2022]
65 Fàbregas N, Torres A, El-Ebiary M, Ramírez J, Hernández C, González J, de la Bellacasa JP, de Anta J, Rodriguez-Roisin R. Histopathologic and microbiologic aspects of ventilator-associated pneumonia. Anesthesiology. 1996 Apr;84(4):760-71. doi: 10.1097/00000542-199604000-00002. PMID: 8638829, available: https://pubs.asahq.org/anesthesiology/article/84/4/760/35442/Histopathologic-and-Microbiologic-Aspects-of [accessed 31 Dec. 2021]
66 Loubet, P., Voiriot, G., Houhou-Fidouh, N., Neuville, M., Bouadma, L., Lescure, F. X., Descamps, D., Timsit, J. F., Yazdanpanah, Y., & Visseaux, B. Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*, (2017) *91*, 52ï 57, available: https://doi.org/10.1016/j.jcv.2017.04.001 [accessed 31 Dec. 2021]
67 van Someren Gréve, Juffermans, N. P., Bos, L. D. J., Binnekade, J. M., Braber, A., Cremer, O. L., de Jonge, E., Molenkamp, R., Ong, D. S. Y., Rebers, S. P. H., Spoelstra-de Man, A. M. E., van der Sluijs, K. F., Spronk, P. E., Verheul, K. D., de Waard, M. C., de Wilde, R. B. P., Winters, T., de Jong, M. D., & Schultz, M. J. (2018). Respiratory Viruses in Invasively Ventilated Critically Ill Patients-A Prospective Multicenter Observational Study. *Critical Care Medicine*, *46*(1), 29ï 36, available: https://doi.org/10.1097/CCM.0000000000002752 [accessed 31 Dec. 2021]
68 Luyt CE, Combes A, Deback C, Aubriot-Lorton MH, Nieszkowska A, Trouillet JL, Capron F, Agut H, Gibert C, Chastre J. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. Am J Respir Crit Care Med. 2007 May 1;175(9):935-42. doi: 10.1164/rccm.200609-1322OC. Epub 2007 Jan 18. PMID: 17234903, available: https://www.atsjournals.org/doi/10.1164/rccm.200609-1322OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 31 Dec. 2021]

https://www.sciencedirect.com/science/article/abs/pii/S0272523118300935?via%3Dihub [accessed 01 Jan. 2022]
95 Kollef MH, Ricard JD, Roux D, Francois B, Ischaki E, Rozgonyi Z, Boulain T, Ivanyi Z, János G, Garot D, Koura F, Zakynthinos E, Dimopoulos G, Torres A, Danker W, Montgomery AB. A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial. Chest. 2017 Jun;151(6):1239-1246. doi: 10.1016/j.chest.2016.11.026. Epub 2016 Nov 24. PMID: 27890714, available: https://journal.chestnet.org/article/S0012-3692(16)62463-7/fulltext [accessed 01 Jan. 2021]
96 Niederman MS, Alder J, Bassetti M, Boateng F, Cao B, Corkery K, Dhand R, Kaye KS, Lawatscheck R, McLeroth P, Nicolau DP, Wang C, Wood GC, Wunderink RG, Chastre J. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis. 2020 Mar;20(3):330-340. doi: 10.1016/S1473-3099(19)30574-2. Epub 2019 Dec 19. PMID: 31866328, available: https://doi.org/10.1016/S1473-3099(19)30574-2 [accessed 01 Jan. 2021]
97 Zampieri FG, Nassar AP Jr, Gusmao-Flores D, Taniguchi LU, Torres A, Ranzani OT. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care. 2015 Apr 7;19(1):150. doi: 10.1186/s13054-015-0868-y. PMID: 25887226; PMCID: PMC4403838, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4403838/ [accessed 01 Jan. 2022]
98 Liu D, Zhang J, Liu HX, Zhu YG, Qu JM. Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis. Int J Antimicrob Agents. 2015 Dec;46(6):603-9. doi: 10.1016/j.ijantimicag.2015.09.011. Epub 2015 Oct 19. PMID: 26607337, available: https://www.sciencedirect.com/science/article/abs/pii/S0924857915003325?via%3Dihub [accessed 01 Jan. 2022]
99 Valachis A, Samonis G, Kofteridis DP. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis. Crit Care Med. 2015 Mar;43(3):527-33. doi: 10.1097/CCM.0000000000000771. PMID: 25493971, available: https://doi.org/10.1097/CCM.0000000000000771 [accessed 01 Jan. 2022]
100 Cantón, Rafael; Gijón, Desirèe; Ruiz-Garbajosa, Patricia. Antimicrobial resistance in ICUs: an update in the light of the COVID-19 pandemic, Current Opinion in Critical Care: October 2020 - Volume 26 - Issue 5 - p 433-441 doi: 10.1097/MCC.0000000000000755, available: https://journals.lww.com/co-criticalcare/Fulltext/2020/10000/Antimicrobial_resistance_in_ICUs__an_update_in_the.2.aspx [accessed 01 Jan. 2022]
101 Russo A, Giuliano S, Ceccarelli G, Alessandri F, Giordano A, Brunetti G, Venditti M. Comparison of Septic Shock Due to Multidrug-Resistant Acinetobacter baumannii or Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae in Intensive Care Unit Patients. Antimicrob Agents Chemother. 2018 May 25;62(6):e02562-17. doi:

10.1128/AAC.02562-17. PMID: 29555630; PMCID: PMC5971575, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5971575/ [accessed 31 Dec. 2021]
102 Denis JB, Lehingue S, Pauly V, Cassir N, Gainnier M, Léone M, Daviet F, Coiffard B, Baron S, Guervilly C, Forel JM, Roch A, Papazian L. Multidrug-resistant Pseudomonas aeruginosa and mortality in mechanically ventilated ICU patients. Am J Infect Control. 2019 Sep;47(9):1059-1064. doi: 10.1016/j.ajic.2019.02.030. Epub 2019 Apr 6. PMID: 30962023, available: https://www.ajicjournal.org/article/S0196-6553(19)30144-0/fulltext [accessed 31 Dec. 2021]
103 Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med. 2011 Dec 15;184(12):1409-17. doi: 10.1164/rccm.201102-0349OC. Epub 2011 Sep 15. PMID: 21920919, available: https://www.atsjournals.org/doi/10.1164/rccm.201102-0349OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed. 31 Dec. 2021]
104 Suarez-de-la-Rica A, Serrano P, De-la-Oliva R, Sánchez-Díaz P, Molinero P, Falces-Romero I, Ferrando C, Rello J, Maseda E. Secondary infections in mechanically ventilated patients with COVID-19: An overlooked matter? Rev Esp Quimioter. 2021 Aug;34(4):330-336. doi: 10.37201/req/031.2021. Epub 2021 Mar 23. PMID: 33764004; PMCID: PMC8329574, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8329574/ [accessed 01 Jan. 2022]
105 Ghanizadeh, A., Najafizade, M., Rashki, S., Marzhoseyni, Z., & Motallebi, M. Genetic Diversity, Antimicrobial Resistance Pattern, and Biofilm Formation in *Klebsiella pneumoniae* Isolated from Patients with Coronavirus Disease 2019 (COVID-19) and Ventilator-Associated Pneumonia. *BioMed research international*, *2021*, 2347872, available: https://doi.org/10.1155/2021/2347872 [accessed 01 Jan. 2022]
106 Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsey AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maraviĺ -Stojkoviĺ V, Verduri A, Beghé B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis. 2018 Jan;18(1):95-107. doi: 10.1016/S1473-3099(17)30592-3. Epub 2017 Oct 13. PMID: 29037960, available: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30592-3/fulltext [accessed 01 Jan. 2022]
107 Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, González Del Castillo J, Jensen JU, Kanizsai PL, Kwa ALH, Krueger S, Luyt CE, Oppert M, Plebani M, Shlyapnikov SA, Toccafondi G, Townsend J, Welte T, Saeed K. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med. 2019 Aug 27;57(9):1308-1318. doi: 10.1515/cclm-2018-1181. PMID: 30721141, available: https://www.degruyter.com/document/doi/10.1515/cclm-2018-1181/html [accessed 01 Jan. 2022]

108 Thomas LC, Gidding HF, Ginn AN, Olma T, Iredell J. Development of a real-time Staphylococcus aureus and MRSA (SAM-) PCR for routine blood culture. J Microbiol Methods. 2007 Feb;68(2):296-302. doi: 10.1016/j.mimet.2006.09.003. Epub 2006 Oct 12. PMID: 17046087, available: https://www.sciencedirect.com/science/article/abs/pii/S0167701206002685?via%3Dihub [accessed 01 Jan. 2022]
109 Jamal W, Al Roomi E, AbdulAziz LR, Rotimi VO. Evaluation of Curetis Unyvero, a multiplex PCR-based testing system, for rapid detection of bacteria and antibiotic resistance and impact of the assay on management of severe nosocomial pneumonia. J Clin Microbiol. 2014 Jul;52(7):2487-92. doi: 10.1128/JCM.00325-14. Epub 2014 Apr 30. PMID: 24789196; PMCID: PMC4097734, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097734/ [accessed 01 Jan. 2022]
110 Gadsby NJ, McHugh MP, Forbes C, MacKenzie L, Hamilton SKD, Griffith DM, Templeton KE. Comparison of Unyvero P55 Pneumonia Cartridge, in-house PCR and culture for the identification of respiratory pathogens and antibiotic resistance in bronchoalveolar lavage fluids in the critical care setting. Eur J Clin Microbiol Infect Dis. 2019 Jun;38(6):1171-1178. doi: 10.1007/s10096-019-03526-x. Epub 2019 Mar 11. PMID: 30859358, available: https://link.springer.com/article/10.1007%2Fs10096-019-03526-x [accessed 01 Jan. 2022]
111 Kunze N, Moerer O, Steinmetz N, Schulze MH, Quintel M, Perl T. Point-of-care multiplex PCR promises short turnaround times for microbial testing in hospital-acquired pneumonia--an observational pilot study in critical ill patients. Ann Clin Microbiol Antimicrob. 2015 Jun 13;14:33. doi: 10.1186/s12941-015-0091-3. PMID: 26071191; PMCID: PMC4469099, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4469099/ [01 Jan. 2022]
112 Papan C, Meyer-Buehn M, Laniado G, Nicolai T, Griese M, Huebner J. Assessment of the multiplex PCR-based assay Unyvero pneumonia application for detection of bacterial pathogens and antibiotic resistance genes in children and neonates. Infection. 2018 Apr;46(2):189-196. doi: 10.1007/s15010-017-1088-y. Epub 2017 Oct 31. PMID: 29086343, available: https://link.springer.com/article/10.1007%2Fs15010-017-1088-y [accessed 01 Jan. 2022]
113 Pickens CO, Gao CA, Cuttica MJ, Smith SB, Pesce LL, Grant RA, Kang M, Morales-Nebreda L, Bavishi AA, Arnold JM, Pawlowski A, Qi C, Budinger GRS, Singer BD, Wunderink RG; NU COVID Investigators. Bacterial Superinfection Pneumonia in Patients Mechanically Ventilated for COVID-19 Pneumonia. Am J Respir Crit Care Med. 2021 Oct 15;204(8):921-932. doi: 10.1164/rccm.202106-1354OC. PMID: 34409924; PMCID: PMC8534629, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8534629/ [accessed 31 Dec. 2021]
114 Karolyi M, Pawelka E, Hind J, Baumgartner S, Friese E, Hoepler W, Neuhold S, Omid S, Seitz T, Traugott MT, Wenisch C, Zoufaly A. Detection of bacteria via multiplex PCR in respiratory samples of critically ill COVID-19 patients with suspected HAP/VAP in the ICU. Wien Klin Wochenschr. 2021 Dec 9:1ï 6. doi: 10.1007/s00508-021-01990-0. Epub ahead of print. PMID: 34882256; PMCID: PMC8656439, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8656439/ [accessed 01 Jan. 2022]

115 Zhao H, Su L, Ding X, Chen H, Zhang H, Wang J, Long Y, Zhou X, Zhang S. The Risk Factors for Weaning Failure of Mechanically Ventilated Patients With COVID-19: A Retrospective Study in National Medical Team Work. Front Med (Lausanne). 2021 Aug 31;8:678157. doi: 10.3389/fmed.2021.678157. PMID: 34532326; PMCID: PMC8438164, available: https://www.frontiersin.org/articles/10.3389/fmed.2021.678157/full [accessed 13 Jan. 2022]
116 Kondili E, Makris D, Georgopoulos D, Rovina N, Kotanidou A, Koutsoukou A. COVID-19 ARDS: Points to Be Considered in Mechanical Ventilation and Weaning. J Pers Med. 2021 Oct 28;11(11):1109. doi: 10.3390/jpm11111109. PMID: 34834461; PMCID: PMC8618434, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8618434/ [accessed 13 Jan. 2022]
117 Paparoupa M, Aldemyati R, Roggenkamp H, Berinson B, Nörz D, Olearo F, Kluge S, Roedl K, de Heer G, Wichmann D. The prevalence of early- and late-onset bacterial, viral, and fungal respiratory superinfections in invasively ventilated COVID-19 patients. J Med Virol. 2021 Dec 24. doi: 10.1002/jmv.27548. Epub ahead of print. PMID: 34951498, available: https://onlinelibrary.wiley.com/doi/10.1002/jmv.27548 [accessed 13 Jan. 2022]
118 Sood RN, Palleiko BA, Alape-Moya D, Maxfield MW, Holdorf J, Uy KF. COVID-19 Tracheostomy: Experience in a University Hospital With Intermediate Follow-up. J Intensive Care Med. 2021 Dec;36(12):1507-1512. doi: 10.1177/08850666211043436. Epub 2021 Oct 29. PMID: 34713733; PMCID: PMC8600586, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8600586/ [accessed 13 Jan. 2022]
119 Long SM, Feit NZ, Chern A, Cooley V, Hill SS, Rajwani K, Schenck EJ, Stiles B, Tassler AB. Percutaneous and Open Tracheostomy in Patients With COVID-19: The Weill Cornell Experience in New York City. Laryngoscope. 2021 Dec;131(12):E2849-E2856. doi: 10.1002/lary.29669. Epub 2021 Jun 9. PMID: 34037983; PMCID: PMC8242792, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8242792/ [accessed 13 Jan. 2022]
120 Tetaj N, Maritti M, Stazi G, Marini MC, Centanni D, Garotto G, Caravella I, Dantimi C, Fusetti M, Santagata C, Macchione M, De Angelis G, Giansante F, Busso D, Di Lorenzo R, Scarcia S, Carucci A, Cabas R, Gaviano I, Petrosillo N, Antinori A, Palmieri F, D'Offizi G, Ianniello S, Campioni P, Pugliese F, Vaia F, Nicastri E, Ippolito G, Marchioni L, Icu Covid-Study Group. Outcomes and Timing of Bedside Percutaneous Tracheostomy of COVID-19 Patients over a Year in the Intensive Care Unit. J Clin Med. 2021 Jul 28;10(15):3335. doi: 10.3390/jcm10153335. PMID: 34362118; PMCID: PMC8347124, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8347124/ [accessed 13 Jan. 2022]
121 COVIDTrach collaborative. COVIDTrach: a prospective cohort study of mechanically ventilated patients with COVID-19 undergoing tracheostomy in the UK. BMJ Surg Interv Health Technol. 2021 Jul;3(1):e000077. doi: 10.1136/bmjsit-2020-000077. Epub 2021 Jul 8. PMID: 34282409; PMCID: PMC8275367, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8275367/ [accessed 13 Jan. 2022]
122 Guarnieri M, Andreoni P, Gay H, Giudici R, Bottiroli M, Mondino M, Casella G, Chiara O, Morelli O, Conforti S, Langer T, Fumagalli R. Tracheostomy in Mechanically

Ventilated Patients With SARS-CoV-2-ARDS: Focus on Tracheomalacia. Respir Care. 2021 Dec;66(12):1797-1804. doi: 10.4187/respcare.09063. Epub 2021 Sep 21. PMID: 34548406, available: http://rc.rcjournal.com/content/66/12/1797.short [accessed 13 Jan. 2022]
123 Krowsoski L, Medina BD, DiMaggio C, Hong C, Moore S, Straznitskas A, Rogers C, Mukherjee V, Uppal A, Frangos S, Bukur M. Percutaneous Dilational Tracheostomy at the Epicenter of the SARS-CoV-2 Pandemic: Impact on Critical Care Resource Utilization and Early Outcomes. Am Surg. 2021 Nov;87(11):1775-1782. doi: 10.1177/00031348211058644. Epub 2021 Nov 12. PMID: 34766508, available: https://journals.sagepub.com/doi/10.1177/00031348211058644?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [accessed 13 Jan. 2022]
124 Ferro A, Kotecha S, Auzinger G, Yeung E, Fan K. Systematic review and meta-analysis of tracheostomy outcomes in COVID-19 patients. Br J Oral Maxillofac Surg. 2021 Nov;59(9):1013-1023. doi: 10.1016/j.bjoms.2021.05.011. Epub 2021 May 18. PMID: 34294476; PMCID: PMC8130586, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8130586/ [accessed 13 Jan. 2022]
125 Prats-Uribe A, Tobed M, Villacampa JM, Agüero A, García-Bastida C, Tato JI, Rodrigáñez L, Holguera VD, Hernández-García E, Poletti D, Simonetti G, Villarraga V, Meler-Claramonte C, Sánchez Barrueco Á, Chiesa-Estomba C, Casasayas M, Parente-Arias P, Mata-Castro N, Rello J, Castro P, Prieto-Alhambra D, Vilaseca I, Avilés-Jurado FX; TraqueoCOVID SEORL Group. Timing of elective tracheotomy and duration of mechanical ventilation among patients admitted to intensive care with severe COVID-19: A multicenter prospective cohort study. Head Neck. 2021 Dec;43(12):3743-3756. doi: 10.1002/hed.26863. Epub 2021 Sep 15. PMID: 34524714; PMCID: PMC8652734, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8652734/ [accessed 13 Jan. 2022]
126 Damanti S, Cristel G, Ramirez GA, Bozzolo EP, Da Prat V, Gobbi A, Centurioni C, Di Gaeta E, Del Prete A, Calabrò MG, Calvi MR, Borghi G, Zangrillo A, De Cobelli F, Landoni G, Tresoldi M. Influence of reduced muscle mass and quality on ventilator weaning and complications during intensive care unit stay in COVID-19 patients. Clin Nutr. 2021 Aug 16:S0261-5614(21)00375-7. doi: 10.1016/j.clnu.2021.08.004. Epub ahead of print. PMID: 34465493; PMCID: PMC8364854, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8364854/ [accessed 13 jan. 2022]
127 Suarez-de-la-Rica A, Serrano P, De-la-Oliva R, Sánchez-Díaz P, Molinero P, Falces-Romero I, Ferrando C, Rello J, Maseda E. Secondary infections in mechanically ventilated patients with COVID-19: An overlooked matter? Rev Esp Quimioter. 2021 Aug;34(4):330-336. doi: 10.37201/req/031.2021. Epub 2021 Mar 23. PMID: 33764004; PMCID: PMC8329574, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8329574/ [accessed 13 Jan. 2022]
128 Guillon A, Hiemstra PS, Si-Tahar M. Pulmonary immune responses against SARS-CoV-2 infection: harmful or not? Intensive Care Med. 2020 Oct;46(10):1897-1900. doi: 10.1007/s00134-020-06170-8. Epub 2020 Jul 17. PMID: 32681297; PMCID: PMC7366461, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7366461/ [accessed 13 Jan. 2022]

129 Grasselli, G., Cattaneo, E. & Florio, G. Secondary infections in critically ill patients with COVID-19. *Crit Care* **25,** 317 (2021), available: https://doi.org/10.1186/s13054-021-03672-9 [accessed 13 Jan. 2022]
130 Martin-Loeches I, Motos A, Menéndez R, Gabarrús A, González J, Fernández-Barat L, Ceccato A, Pérez-Arnal R, García-Gasulla D, Ferrer R, Riera J, Lorente JÁ, Peñuelas Ó, Bermejo-Martin JF, Gonzalo-Calvo D, Rodríguez A, Barbé F, Aguilera L, Amaya-Villar R, Barberà C, Barberán J, Blandino Ortiz A, Bustamante-Munguira E, Caballero J, Carbajales C, Carbonell N, Catalán-González M, Galbán C, Gumucio-Sanguino VD, de la Torre MDC, Díaz E, Gallego E, García Garmendia JL, Garnacho-Montero J, Gómez JM, Jorge García RN, Loza-Vázquez A, Marín-Corral J, Martínez de la Gándara A, Martínez Varela I, Lopez Messa J, Albaiceta GM, Novo MA, Peñasco Y, Ricart P, Urrelo-Cerrón L, Sánchez-Miralles A, Sancho Chinesta S, Socias L, Solé-Violan J, Tamayo Lomas L, Vidal P, Torres A. ICU-Acquired Pneumonia Is Associated with Poor Health Post-COVID-19 Syndrome. J Clin Med. 2021 Dec 31;11(1):224. doi: 10.3390/jcm11010224. PMID: 35011967; PMCID: PMC8746263, available: https://www.mdpi.com/2077-0383/11/1/224/htm [accessed 13 Jan. 2022]