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Early View

Invited review

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Please cite this article as: Boyd S, Nseir S, Rodriguez A, *et al*. Ventilator-associated pneumonia in critically ill patients with COVID-19 infection, a narrative review. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00046-2022).

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 – 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 “ventilator-associated pneumonia,” “VAP,” “COVID” and “ICU,” a 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*

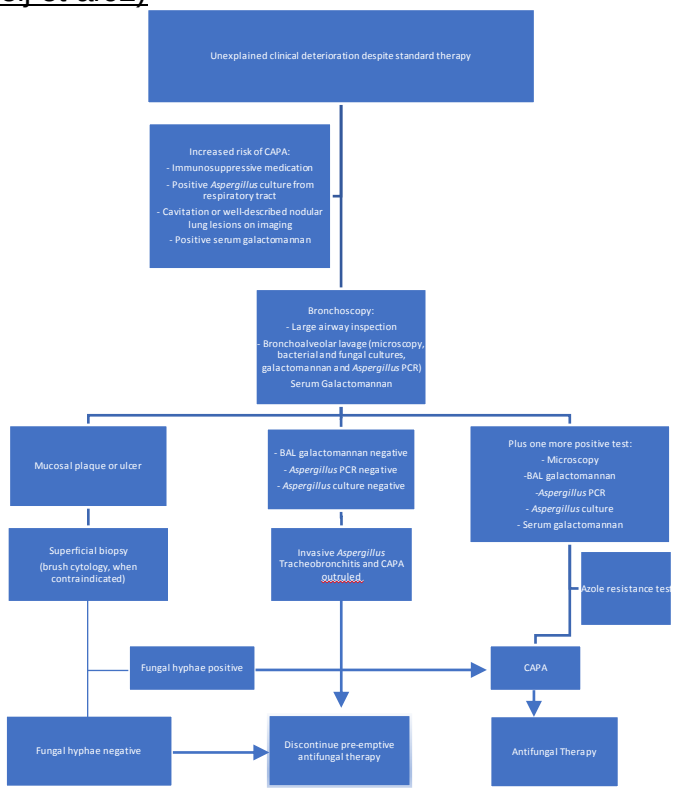
On review of the meta-analysis by Ippolito et al, the main bacteria grown included gram negative bacteria: *E. faecium*, *K. pneumonia*, *A. baumannii*, *P. aeruginosa*, *Enterobacter spp*., *E. coli*, along with *S. aureus*. This is in keeping with previous descriptions4. Fumagalli et al described how 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 – 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]).

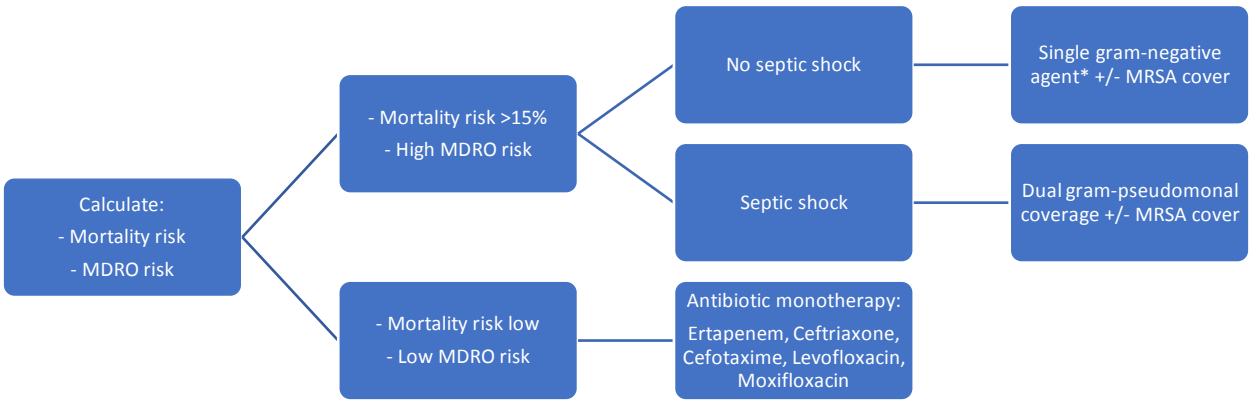


Table 1: Efficacy and appropriateness of novel antibiotics for gram-negative bacteria in ICU (adapted from Garduno et al.93)

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 clinician's 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 body's 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.

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