Pulmonary infections complicating acute respiratory distress syndrome

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Take home message: Pulmonary superinfections of ARDS patients considerably impact patients' prognosis. It is favored by altered local and systemic immune defenses. The poor outcome of ARDS with pulmonary superinfections is probably related to the lack of early accurate diagnostic methods and difficulties in optimizing therapy.

Abstract

Pulmonary infection is one of the main complications occurring in patients suffering from the acute respiratory distress syndrome (ARDS). Beside traditional risk factors, dysregulation of lung immune defences and microbiota may play an important role in ARDS patients. Prone positioning does not seem to be associated with a higher risk of pulmonary infection. Although bacteria associated with VAP in ARDS patients are similar to those in patients without ARDS, atypical pathogens (*Aspergillus*, herpes simplex virus and cytomegalovirus) may also be responsible for infection in ARDS patients. Diagnosing pulmonary infection in ARDS patients is challenging, and requires a combination of clinical, biological and microbiological criteria. The role of modern tools (e.g. molecular methods, metagenomic sequencing…) remains to be evaluated in this setting. One of the challenges of antimicrobial treatment is antibiotics diffusion into the lungs. Although targeted delivery of antibiotics using nebulization may be interesting, their place in ARDS patients remains to be explored. The use of extracorporeal membrane oxygenation in the most severe patients is associated with a high rate of infection and raises several challenges, diagnostic issues and pharmacokinetics/pharmacodynamics changes being at the top. Prevention of pulmonary infection is a key issue in ARDS patients, but there is no specific measure for these high-risk patients. Reinforcing preventive measures using bundles seems to be the best option.

Introduction

Acute respiratory distress syndrome (ARDS) regroups a wide range of diseases whose consequence is lung inflammation, alveolar damage and pulmonary edema [1]. Whatever the initial lung injury, patients with ARDS are prone to develop secondary pulmonary infection, namely ventilator-associated pneumonia (VAP). Recent data from the Center for Disease Control and Prevention suggest that VAP rates are not dropping in the US despite stateside prevention efforts [2]. VAP complicating ARDS appears to be a common problem, affecting between 20 and 40% patients [3][4]. This high frequency may be explained by traditional factors such as bronchial contamination due to endotracheal intubation, mechanical ventilation (MV) duration, but also because of impaired local (alveolar) and systemic defenses, and other specific and non-specific factors [5]. In this article, we will review specific challenges related to ARDS patients, namely specific risk factors, diagnostic challenges, unusual pathogens, issues with antimicrobial treatment and prevention of infection.

Pathophysiology

Immune defenses and respiratory microbiota

Patients with ARDS exemplify the apparently paradoxical immune state of critically ill patients, whereby activated immune cells mediate organ damage whilst manifesting impaired anti-microbial defenses [6]. Impaired cellular functions have been identified across both the innate and adaptive arms of the immune system [7, 8], and appear to be stereotyped rather than specific to any precipitating cause of ARDS [9]. This apparently paradoxical state is due to the ability of pro-inflammatory and tissue damage molecules to drive immune dysfunction [9, 10].

Dysfunctional immune cells are found in the lung as well as peripheral blood [9]. Interestingly, lung mucosal immune defects are protracted after the cure from primary inflammation, thus increasing the susceptibility to hospital-acquired pneumonia and ARDS for weeks after systemic inflammation [11]. Following experimental pneumonia, pulmonary macrophages and dendritic cells demonstrated prolonged suppression of immune functions which increased the susceptibility to secondary infection [12]. Expansion of immuno-modulatory regulatory T-cells (T_{reg}) is also seen, and may mediate impaired innate as well as adaptive immune function [13]. Patients with suspected VAP, including those with ARDS, demonstrated impaired phagocytic function of alveolar neutrophils, which interestingly appeared to be mediated by different mediators than those driving dysfunction in the peripheral blood [9]. Whilst we have a growing understanding of the mediators driving dysfunction, and the intracellular mechanisms which drive them [14], we do not as yet have proven therapies although there are multiple potential agents [7].

When aiming at modulating immunity during inflammation, it is important to differentiate innate and adaptive immune cells responses. While exhaustion and apoptosis seem to be central to lymphocyte defects observed in critically ill patients [15], some innate immune cells undergo reprogramming involving epigenetic reprogramming and increased cellular metabolism, a phenomena so called trained immunity, resulting in high production of inflammatory cytokines such as IL-6 and TNFα during secondary immune challenge [16]. While glucocorticoids are classically considered as immunosuppressive drugs, it has been shown that they can prevent the immune reprogramming observed after inflammatory response [16], thus limiting the susceptibility of ICU patients to respiratory complications such as pneumonia or ARDS and improving outcomes of patients with ARDS [17].

Part of the complexity of pulmonary super-infections arises from the interaction between the injured host with their pulmonary microbiome. Although considerably less

abundant and diverse than the better studied gastro-intestinal microbiome [18], the pulmonary microbiome is increasingly well defined and undergoes significant changes during critical illness and ARDS [19]. The major role of respiratory microbiota on mucosal immunity and respiratory functions in health suggest that its alterations could be involved in the respiratory complications observed in critically ill patients [20]. Indeed, mechanically ventilated patients experience a reduction in diversity of pulmonary microbes and an increase in enteric-type organisms, even in the absence of overt infection [21].

Early alterations of the lung microbiome, notably increased bacterial burden and biofilm formation, enrichment with gut-associated bacteria and loss of diversity, are associated with the risk of ARDS and the duration of MV support in critically ill patients [22]. Pre-existing dysbiosis, such as that induced by tobacco smoke, may also influence the development of ARDS following major trauma [23]. Alongside changes in bacterial species, it is common to find reactivation of latent herpesviridae such as herpes simplex virus (HSV) and cytomegalovirus (CMV) [24]. The drivers of these changes are incompletely understood but are multi-factorial, with possible mechanisms illustrated in Figure 1 [13, 22, 25]. Adding further complexity is the potential for microbes themselves to drive further immune dysfunction [26]. VAP should therefore be conceptualised as less a de-novo infection by an exogenous pathogen but rather a dysbiotic response to critical illness with overgrowth of specific genera of bacteria [27]. Appropriate antibiotic therapy targeting the dominant species, being those frequently detected by culture, is key in certain patients but risks exacerbating dysbiosis and further harm to the patient [28]. What remains to be proven is whether interventions to restore symbiosis, i.e. to increase bacterial diversity rather than only eliminating dominant species, can improve outcomes [27]. Although the experience of faecal transplantation in *Clostridium difficile* associated diarrhoea suggests that microbial transplantation may be an effective form of therapy [29], negative experience of probiotics in

pancreatitis and recent examples of ‘probiotic’ bacteria causing infections sound a note of caution [30, 31]. Developing effective therapies for respiratory dysbiosis will require tools to profile the host peripheral and pulmonary immune cell function and the pulmonary microbiome [8].

Hyperoxia as a risk factor for pulmonary infection

Hyperoxia is common in patients receiving MV for ARDS. A secondary analysis of the LUNG SAFE trial [32], reported that 30% of the 2005 analyzed patients had hyperoxia on day 1, and 12% had sustained hyperoxia. While two randomized controlled trials found beneficial effect of avoiding hyperoxia [33, 34], a recent large international multicenter trial demonstrated no effect of conservative oxygen therapy in a cohort of critically ill patients [35]. However, a subsequent sub-study raised the possibility of clinically important harm with conservative oxygen therapy in patients with sepsis [36].

Oxygen toxicity is mainly related to the formation of reactive oxygen species (ROS), especially during hypoxia/re-oxygenation and long exposure to oxygen. High level of inspired oxygen is responsible for denitrogenation phenomena and inhibition of surfactant production promoting expiratory collapse and atelectasis [37]. Absorption atelectasis occurs within few minutes after pure O_2 breathing. In mechanically ventilated patients, atelectasis seriously impairs cough reflex and mucus clearance resulting in abundant secretions in the lower airways and higher risk for VAP. Prolonged hyperoxia also impairs the efficacy of alveolar macrophages to migrate, phagocyte and kill bacteria, resulting in decreased bacterial clearance [38]. Hyperoxemia markedly increased the lethality of *Pseudomonas aeruginosa* in a mouse model of pneumonia [39]. Additionally, O_2 can cause pulmonary-specific toxic effect called hyperemic acute lung injury (HALI) (Figure 2).

Although earlier studies reported a link between high FiO2 and atelectasis, further studies are required to evaluate links between hyperoxia and mortality or VAP. In a single center cohort study of 503 patients, among whom 128 (28%) had VAP, multivariate analysis identified number of days spent with hyperoxemia [OR =1.1, 95% CI: (1.04–1.2) per day, P=0.004], as an independent risk factor for VAP. However, the study was retrospective, performed in a single centre, and the definition used for hyperoxia (at least one PaO_2 value >120 mmHg per day) could be debated [40].

In the recent HYPERS2S randomized controlled trial [34], the percentage of patients with atelectasis doubled in patients with hyperoxia compared with those with normoxia (12% *vs.* 6%, P=0.04). However, no significant difference was found in VAP rate between hyperoxia and control group (15% *vs.* 14%, P=0.78). However, VAP was not the primary outcome of this trial, and no clear definition of ICU-acquired pneumonia. Further well-designed studies are required to determine the relationship between hyperoxia and VAP.

Prone position as a risk factor for pulmonary infection

Prone position is recommended in patients with severe ARDS and is commonly used in this population. There is a rationale supporting a beneficial effect of prone position on the incidence of VAP, as it facilitates secretion drainage and allows atelectasis resolution. Previous human and animal studies have clearly showed a link between atelectasis and VAP, and reported that efficient secretion drainage might result in lower incidence of VAP [37]. On the other hand prone position might facilitate microorganisms dissemination, and increase microaspiration of contaminated secretions.

The results of studies on the relationship between prone position and VAP should be interpreted with caution, because of some limitations such as observational design, small

number of included patients and confounding factors. Five recent studies were performed in patients with protective lung MV, including 4 randomized controlled studies and one large observational cohort. Mounier et al. [41] reported no significant reduction of VAP incidence in a large cohort (n = 2409) of hypoxemic patients receiving prone position, as compared to those who did not receive this intervention (HR 1.64 (95% CI 0.7-3.8)). One randomized controlled trial reported reduced risk for VAP in multiple trauma patients who received intermittent prone position, as compared to those who did not (p = 0.048) [42]. However, the incidence of VAP was very high in the control group (89%), and the number of included patients was small (n = 40). Three other randomized controlled trials reported no significant relationship between prone position and VAP [4, 43, 44]. However, these studies lack of information on efficient preventive measures of VAP, such as the use of subglottic secretion drainage or continuous control of tracheal cuff pressure, and VAP was not their primary outcome. In summary, available data do not support a significant relationship between prone position and VAP, although it has demonstrated beneficial effects on mortality in severe ARDS.

Diagnostic challenges

The diagnosis of lung infections in patients with ARDS is challenging [45]. The diagnosis of pneumonia, the dominant respiratory infection of concern in ARDS, is ultimately a histopathological diagnosis which requires the presence of airspace inflammation and an infecting organism. However obtaining lung tissue for diagnosis is seldom practical nor desirable in ventilated patients [5]. The clinical features of systemic inflammation and localizing chest signs such as crepitations and bronchial breathing are non-specific and insensitive. Whilst radiological evidence of airspace infiltration is useful, the gold-standard of computed tomography is not practical for most patients leading practitioners to rely on

plain radiographs and ultrasound, and even computed tomography cannot always reliably distinguish between infective and non-infective causes of airspace infiltration [5, 45]. Use of clinical and radiographic criteria alone are likely to significantly over-estimate the rate of pneumonia and lead to excessive, potentially harmful, use of antibiotics [28]. It is also important to recall that pneumonia itself is the commonest precipitant of ARDS, which together with the bilateral radiographic alterations in ARDS patients, create an additional challenge for the ascertainment of a "new or worsening pulmonary infiltrate", a condition required for clinical diagnosis of VAP [5]. Another challenge is the distinction between ventilator-associated tracheobronchitis (VAT) and VAP. VAT is defined as a lower respiratory tract infection without involvement of the lung parenchyma (and therefore without new/progressive chest X-ray infiltrate). The distinction between VAT and VAP in ARDS patients remained challenging given the poor accuracy of chest radiograph to detect new infiltrates.

Obtaining samples from the lungs for microbiological culture is crucial to the establishment of infection. However, there is considerable variability in the timing and type of specimen obtained in practice [46]. The identification of infection can be complicated by colonisation of the proximal airways, which happens rapidly after intubation and is frequent in ARDS patients [5]. It is important to differentiate between colonisation (presence of bacteria, even at a high burden, in the respiratory tract without lung infection), a harmless phenomenon, and infection. Although protected deep lung sampling by broncho-alveolar lavage or protected specimen brush reduces the risk of false positives relative to endotracheal aspirate, this has not been convincingly demonstrated to alter outcomes although observational data suggests they can safely reduce antibiotic use [47]. Although false-positive results from proximal colonisation are a significant problem, intercurrent use of antibiotics is common in ARDS patients and increases the risk of false-negative culture. This is,

increasingly, being addressed by the use of culture-independent molecular technique, however the utility of the tools available is limited by their restricted range of organisms covered and the risk of over-sensitive detection of irrelevant organisms driving inappropriate use of antimicrobials [48–50]. Physicians should be aware of this particular point and therefore interpret with caution results of these tests. There are very few prospective studies demonstrating the impact of molecular diagnostics on patient management and the results of forthcoming trials are awaited. Antigen detection in the lower respiratory tract can also aid diagnosis, especially with organisms such as *Aspergillus* where culture and PCR are imperfect [51]. The value of *Aspergillus* Sp. and *Aspergillus fumigatus* PCR is promising but remained to be evaluated in ARDS patients. In patients with ARDS and bilateral radiographic infiltrates, there remains a question of which region to sample invasively. Whilst trials have not been undertaken to answer this question definitively, observational data suggests that in the presence of bilateral infiltrates, uni-lobe sampling is sufficient and minimizes risk of lavage volume and duration of bronchoscopy [52].

The host response makes up the crucial second component of any infection syndrome, and therefore host biomarkers can be of use in diagnosing infection in ARDS. Laboratory haematological features of inflammation, including leucocytosis, neutrophilia and elevated C-reactive protein are not specific to infection, and can occur in sterile precipitants of ARDS [53]. The inflammatory response in pneumonia is highly compartmentalized and alveolar cytokines and other alveolar markers are the most discriminant for pneumonia (Table 1) [54]. Notably, although alveolar cytokines demonstrated excellent assay performance, measurement of pulmonary cytokines did not alter antimicrobial prescribing in a recent randomised trial [55]. This illustrates that the challenges in diagnosis lie not only with the technology, but also the behavioural response to results.

Peripheral blood markers have the advantage of avoiding the need for bronchoscopic sampling and are therefore easier to obtain, however they are generally less able to discriminate pneumonia from other infections and many lack sensitivity and or specificity for infection (Table 1).

In summary, the diagnosis of pulmonary infection in ARDS is challenging, existing techniques are imperfect and risk both inadequate and over-treatment. A combination of clinical, biological and radiological assessment, combined with microbiological sampling from the lungs remains the current gold standard (Figure 3). The development of molecular diagnostics focusing on both host and pathogen offers great promise, but their impact on patient management and outcomes remains to be convincingly demonstrated.

Epidemiology of nosocomial pulmonary infections in ARDS patients

The most common bacterial causes of VAP include *Enterobacterales*, *Pseudomonas aeruginosa*, *Staphylococcus au*reus, and *Acinetobacter* among the general population of mechanically ventilated patients [56]. The pathogens associated with VAP in ARDS are similar to those seen among non-ARDS patients who develop VAP (Figure 4) [4, 52, 57]. Moreover, patients with ARDS undergoing ECMO demonstrate the same breakdown of pathogens with *Pseudomonas aeruginosa* and *Staphylococcus aureus* predominating [58]. One important element, regardless of the specific causative bacteria seen in VAP, is that antibiotic resistance is increasing in VAP as well as in other nosocomial infections. In 2017, the Tigecycline Evaluation and Surveillance Trial described important European changes in antimicrobial susceptibility between 2004 and 2014, with increases in the rates of ESBL-positive *Escherichia coli* (from 8.9 to 16.9%), MDR *Acinetobacter baumannii* complex (from 15.4 to 48.5%), ESBL-positive *Klebsiella pneumoniae* (from 17.2 to 23.7%), and methicillin-

298 resistant *Staphylococcus aureus* (MRSA) (from 27.5 to 28.9%) [59]. Similar worrisome
299 trends for bacterial susceptibility to available antimicrobials have been reported by other
300 investigators as well [60, 61]. Most worrisome is the increasingly recognized presence of
301 resistance to new antibiotics specifically developed to treat VAP [62].

302 Prior antibiotic exposure and subsequent changes in the host's airway microbiome due
303 to dysbiosis seem to drive the prevalence of antibiotic-resistant bacterial causes of VAP
304 (Figure 5) [22, 63]. Presence of invasive devices such as endotracheal tubes and antibiotic
305 administration promote pathogenic bacterial colonization due to the overwhelming of local
306 defenses resulting in the development of an intermediate respiratory infection termed VAT
307 [64]. VAT represents a compartmentalized host response associated with a better overall
308 prognosis compared to VAP, but VAT can prolong duration of MV and ICU length of stay
309 [65]. If the aforementioned response is not compartmentalized progression to VAP is likely
310 and potentially other organ failure to include the ARDS may occur [66].

311 One of the major fears concerning nosocomial pulmonary infections in ARDS at the
312 present and into the future is the increasing presence of novel pathogens and infections with
313 microorganisms for which limited treatment options exist. As we increasingly treat older and
314 more immunocompromised hosts with ARDS the likelihood for emergence of novel
315 pathogens and infection with pan-resistant microorganisms will increase. Early identification
316 of such emerging pathogens in ARDS is critical. The importance of early identification of
317 novel pathogens is necessary to facilitate epidemiologic surveillance, curtailing pathogen
318 spread, and providing early treatment as illustrated by recent nosocomial outbreaks of middle
319 eastern respiratory syndrome coronavirus, SARS-CoV-2 and pan-resistant *Escherichia coli*
320 [67–70]. In the future, metagenomic next-generation sequencing should allow earlier and
321 more targeted treatments for novel pathogens causing ARDS or complicating the course of
322 patients with ARDS. Such technology will allow earlier pathogen identification and accelerate

the workup and treatment for both infectious and noninfectious causes of diseases complicating ARDS [71].

Atypical causes of respiratory infections in ARDS patients

Although the majority of respiratory infections in ARDS patients are caused by bacteria, ICU-induced immunoparalysis may induce infection with unusual pathogens

Although invasive pulmonary aspergillosis (IPA) has been reported mainly in immunocompromised patients, lower respiratory tract colonization with *Aspergillus* has been associated more frequent in ARDS than in other patients invasively ventilated in ICU [72]. The mechanism of damage involves the combination of alveolar damage (induced by ARDS) and a dysregulation of the local immune response, together with sepsis-induced immunosuppression, innate immunity and antigen presentation impairment, accounting for the development of IPA in previously colonized patients [15, 73]. Co-infection with influenza has been reported as a risk factor for IPA [74]. Contou et al. reported isolation of *Aspergillus* in the lower respiratory tract in almost 10% of patients with ARDS (50% had putative or proven IPA) [75]. An important finding from this study was that median time between initiation of MV and first sample positive for *Aspergillus* spp was only 3 days. Moreover, a post-mortem study in ARDS patients found that 10% of deceased patients had IPA manifestations [76]. If *Aspergillus* is identified as a pathogen in an immunocompetent patient, it is recommended to screen for any kind of immunosuppression (humoral, cellular or combined, complement, …).

Viruses may also be responsible for infection in ARDS patients. Because of immunoparalysis following the initial pro-inflammatory response to aggression, latent viruses such as herpesviridae may reactivate in ICU patients [7]. HSV and CMV are frequently

recovered in lung or blood of ICU patients (up to 50%, depending on the case-mix), their reactivation being associated with morbidity and mortality [24, 77, 78]. However, the exact significance of these reactivations is debated: these viruses may have a true pathogenicity and cause lung involvement [24, 79], thereby having a direct role in morbidity/mortality observed with their reactivation; or they may be bystanders, their reactivation being only secondary to disease severity or prolonged ICU stay. To date, the answer is not known; data regarding a potential benefice of antiviral treatment being controversial. For HSV, the most recent randomized control trial found no increase in ventilator-free days in patients having received acyclovir, but a trend towards lower 60-day mortality rate (hazard ratio for death within 60 days post randomization for the acyclovir group vs control was 0.61 (95% CI, 0.37–0.99, p =0.047) [80]. For CMV, 2 recent RCTs were performed: the first one showed that valganciclovir prophylaxis in CMV-seropositive patients was associated with lower rate of CMV reactivation as compared to placebo, but not with better outcome [81]; and the second one showed that, as compared to placebo, ganciclovir prophylaxis did not lead to lower Il-6 blood level at day 14, but patients having received ganciclovir had trend towards lower duration of MV [82]. Besides latent viruses, respiratory viruses (rhinovirus, influenza, adenovirus…) have been recently made responsible for nosocomial infection in ventilated or non-ventilated patients [83]. However, like herpesviridae, their true impact on morbidity/mortality is not known.

In summary, HSV and CMV may cause viral disease in ARDS patients, and respiratory viruses may be responsible for hospital-acquired pneumonia, however the true impact of these viral infections on outcomes remains to be determined.

Specificity of pulmonary infections in ECMO patients

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is now part of the management of refractory ARDS [84, 85]. These very sick patients are at high risk for developing typical ICU-related nosocomial infections (e.g. VAP or bloodstream infections), in addition to ECMO-specific infections, including localized infections at peripheral cannulation insertion sites. Bizzarro *et al* reported a high prevalence rate of nosocomial infection of 21 % in a large international registry of ECMO patients [86], pulmonary infection being the most frequently reported. This high prevalence may be explained by underlying comorbidities, concomitant critical illness, prolonged mechanical support, MV and ICU stay as well as impairment of the immune system by the extracorporeal circuitry through the endothelial dysfunction, coagulation cascade, and pro-inflammatory mediators release [87]. While the rate of pulmonary infection on ECMO has not been thoroughly compared with a population with same critical illness but in absence of ECMO, VAP was reported in 32 out of 92 patients receiving ECMO (87% VV-ECMO) by Grasseli *et al* [88]. Among 220 patients who underwent VA-ECMO for >48 hours and for a total of 2942 ECMO days, 142 (64%) developed 222 nosocomial infections, corresponding to a rate of 75.5 infectious episodes per 1000 ECMO days. VAP was the main site of infection with 163 episodes occurring in 120 patients after a median ± standard deviation of 7 ± 12 days [89]. VAP and resistant organisms are therefore common in that population [88–90]. Duration of ECMO has been frequently associated with a higher incidence of VAP [89, 91], even if a causal relationship is impossible to establish. Indeed, longer ECMO runs could be a direct consequence of infectious complications rather than a risk factor. However, it seems clear that ECMO patients who acquired VAP had longer durations of MV and ECMO support and a higher overall ICU mortality [88, 89, 91] . Similarly, immunocompromised patients and older age were consistently found as risk factors associated with infections on ECMO [89, 92]. The clinical diagnosis of pulmonary infection in ECMO patients is challenging, since they may have signs

of systemic inflammatory response, possibly triggered by the ECMO itself, whereas fever could be absent if the temperature is controlled by heat exchanger on the membrane. In addition, the common application of an ultra-protective ventilation aiming to rest the lung on VV-ECMO and frequent pulmonary edema on VA-ECMO make difficult the interpretation of new infiltrates on chest-X ray, which are commonly used to suspect a VAP. Beyond the diagnosis challenge of pulmonary infection on ECMO, the changes of pharmacokinetics/pharmacodynamics (PK/PD) of antimicrobial agents could also contribute to delay appropriate antimicrobial treatment and consequently increase the burden of infections. An increase of the volume of distribution by ECMO, as well as the severity of the underlying illness and drugs clearance impairment through renal or liver dysfunctions complicates the management of antibiotics and antifungal therapies [93]. While waiting for large in vivo studies aiming to report the respective PK/PD of antimicrobial agents on ECMO, avoiding lipophilic agents (i.e more likely sequestrated on the ECMO membrane) [93] and therapeutic drug monitoring are warranted.

Antimicrobials and the lung

Apart from bacteraemias/fungaemias, most infections are in interstitial or tissue spaces and hence efficacy of a drug should be related to drug concentrations and actions in those tissues [94]. Drugs will cross body membranes (move from intravenous compartment into tissue compartments) if there is an intrinsic “carrier mechanism”, or if the compound is either a small molecule or is lipophilic [95].

Hydrophilic antimicrobials are found in extravascular lung water, but for relevant lung tissue penetration the lipophilic drugs are most important [94–97]. Large molecules like vancomycin, teicoplanin, aminoglycosides, colistin will have poor lung tissue concentrations when given intravenously (ELF/plasma concentration ratio << 1) [95, 96]. Betalactams

penetrate into lung parenchyma better than other hydrophobic antibiotics [96]. ELF/Plasma concentration ratio for glycylcyclines (e.g. tigecycline) is around 1. Lipophilic compounds such as macrolides, ketolides, quinolones, oxazolidinones, antifungals and antivirals will have good lung tissue concentrations (ELF/plasma concentration ratio > 1) after intravenous administration [97]. Oxazolidinones (linezolid), glycylcyclines (tigecycline) and sulfonamides (cotrimoxazole) may be effective in the treatment of MDR pathogens; however there is no ARDS specific lung PK (ELF/plasma concentration) data for these drugs. Although newer antimicrobials (ceftolazone-tazobactam, meropenem-vaborbactam, plazomicin) have activity against drug-resistant gram-negative pathogens, there are limited alternatives against drug resistant *Acinetobacter baumaniii* such as cefiderocol which is undergoing phase 3 clinical trials.

The advent of newer generation of delivery devices and MDR organisms have led to a renewed interest in the field of nebulized antimicrobials [98], although recent trials in pneumonia have failed to demonstrate clinical benefits [99, 100]. ARDS is often associated with multiple organ dysfunction syndrome. Hence, the possibility of achieving high intrapulmonary concentrations with limited systemic side effects is appealing. Although recent well conducted RCTs argued against systematic use of nebulized antimicrobials in nosocomial pneumonia [99, 100] it may still have a place in treatment of severe lung infections due to MDR bacteria. In this view, selecting the correct antimicrobial formulation and dosing (Table 2) is an essential first step, as well as the best device, namely vibrating mesh nebulizer [101]. Clinical PK data available for some nebulized antibacterial, antiviral and antifungals confirm high pulmonary and low systemic exposure [102]. Sputum PK studies report high variability and are difficult to interpret [102]. However, lung deposition of nebulized antimicrobials is influenced by many factors, including specific ventilator settings. Ventilator settings and procedures usually recommended for improving aerosol delivery (high

tidal volume, low respiratory rate and low inspiratory flow, systematic changes of expiratory filters…) are difficult to implement in patients with ARDS, at least those with the most severe forms. ARDS is a heterogeneous lung condition causing inhomogeneous ventilation distribution potentially affecting drug delivery at the affected site. Increased lung inflammation can also increase systemic concentrations by increased diffusion across the alveolo-capillary barrier, thus influencing the nebulized drug dosing [103]. Further PK studies investigating nebulized antimicrobial in ARDS are required for recommending dosing regimens in this condition.

Areas of investigation such as pulmonary nanomedicine and targeted delivery using intracorporeal nebulization catheter whilst still investigational has the potential to overcome many of these barriers and enhance lung tissue antimicrobial concentrations [104].

Prevention of pulmonary infections in ARDS patients

Nosocomial infections may contribute to the mortality related to ARDS given that such infections are responsible for worsening hypoxemia and causing sepsis. As such, the prevention of these infections must be reinforced to avoid straining the prognosis of patients suffering from ARDS. However, interpreting the VAP prevention literature is this context is challenging because 1) no studies have been conducted purposely in ARDS patients 2) several preventive measures have been shown to reduce the rate of pulmonary infection but many less have demonstrated an impact on patient prognosis [105]. That being said, the general strategy for preventing pulmonary infection applies also in ARDS patients. However some preventive measures deserve a special focus in the context of ARDS patients (Figure 6): 1) oral care with chlorhexidine is suspected to worsen the respiratory failure; 2) Selective digestive

decontamination (SDD) deserves to be discussed in such high risk patients as it has been proven to be effective in reducing mortality in ICU patients and likely lowers VAP rates.

There is no single preventive measure that will completely avert pulmonary infection in patient suffering from ARDS and patients must be approached with a package or bundle of preventive measure [106] provided that an early weaning strategy is part of the bundle [107]. Other preventive measures and notably some expensive medical devices such as automated endotracheal tube cuff pressure monitoring or endotracheal tube allowing subglottic secretion drainage have not been proven effective on patient's outcomes (mortality, duration of MV, antibiotic use) but could be dedicated to these high risk patients. However, translating research into an efficient bundle of care to prevent pulmonary infection remains a challenge and behavioral approaches to implement the measures are as important as the measures themselves [108].

Chlorhexidine-gluconate (CHG) use for oral care in ICU patients may be harmful despite previous consistent data showing its beneficial effect in preventing VAP [109]. Oral mucosa adverse events with 2% (w/v) CHG mouthwash in ICU are frequent but often transient. Adverse events described were erosive lesions, ulcerations, plaque formation (which are easily removed), and bleeding mucosa in 29 of 295 patients (9.8%) who received 2% (w/v) CHG [110]. A systematic review and meta-analysis by Labeau et al. in 2011 evaluated the effect of oral decontamination with CHX [109]. Twelve studies were included (n=2,341). Overall, CHX use resulted in a significant risk reduction of VAP (RR=0.67, 95% CI=0.55–0.94, p=0.02). Favorable effects were more pronounced in subgroup analyses for 2% CHX (RR=0.53, 95% CI=0.31–0.91) and for cardiosurgical patients (RR=0.41, 95% CI=0.17–0.98). However, a recent meta-analyses suggested that oral CHG paradoxically increased the risk of death, which may have resulted from toxicity of aspirated CHG in the

lower respiratory tract [111]. Consequently, it remains unclear whether using CHG for oral care affects outcomes in critically ill patients.

Selective digestive decontamination (SDD) remains definitely a matter of controversy [112]. On one hand it reduces the mortality in mechanically ventilated patients, on the other hand it use is limited by the potential of inducing more bacterial resistance. However, in ARDS patients at high risk of mortality with high level of bacterial resistance SDD deserves to be evaluated.

The better understanding of ARDS phenotype may offer an opportunity to develop more selective preventive measures in the future.

Conclusion

Pulmonary superinfections of ARDS patients considerably impact patients' prognosis. It is favored by altered local and systemic immune defenses.

The poor outcome of ARDS with pulmonary superinfections is probably related to the lack of early accurate diagnostic methods and difficulties in optimizing therapy. This article reviewed the available knowledge and revealed areas for future investigations in pathophysiology, diagnosis, treatment and prevention.

Potentials for improvements are numerous in all the fields:

Pathophysiology:

To improve knowledges about the host factors (both systemic and local) favoring superinfections.

To identify early the disequilibrium between the host and the microbiota that may promote pneumonia in ARDS patients.

Diagnosis:

To identify early criteria for suspicion of VAP and VAT.

To determine the appropriate time to perform bacteriological samples. In particular develop morphological way to unmask areas of pneumonia at the bedside.

To identify new diagnostic tests providing accurate and early diagnosis of pneumonia.

To develop accurate early methods of pathogens identification and to distinguish patients infected and simply colonized (especially for viruses and fungi).

Therapy:

To evaluate the impact of new molecular methods in diagnosing pneumonia in ARDS patients and improve prognosis.

To evaluate the impact of TDM monitoring of antimicrobials on the prognosis of ARDS patients with pneumonia.

To develop non-antibiotic therapies in the future, including vaccines, monoclonal antibodies and phage therapy.

Prevention:

Evaluate the benefit on antimicrobial consumption and prognosis of the use of SDD in ARDS patients in ICUs with a high level of bacterial resistance.

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Figure legends

Figure 1: Mechanisms which lead to altered microbiota in lungs and hence lead to infection. Abbreviations: ETT, endotracheal tube; TNF, yumor necrosis factor; IL, interleukin.

Figure 2: Mechanisms for the relationship between hyperoxia and ventilator-associated pneumonia. Abbreviations: VAP, ventilator-associated pneumonia; HALI, hyperoxic acute lung injury

Figure 3: Graphical representation of the combined assessment of clinical, radiological, laboratory evaluation of host response and microbiological data for the diagnosis of pneumonia as a proxy for histopathological examination.

Figure 4: Annual Epidemiological Report for 2016 Healthcare-associated infections in intensive care units (https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2016-HAI_0.pdf (Accessed 21 February 2020)) and the PROSEVA Trial [4]. Bar graphs depicting the percentages of the most frequently isolated microorganisms in ICU-acquired pneumonia episodes for 2016 (red bars) and for patients with acute respiratory distress syndrome (ARDS) (blue bars). Total number of isolates 16, 869 and 112 respectively.

Figure 5: Venn diagram showing the relationship and overlap for ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) with the acute

respiratory distress syndrome (ARDS). Respiratory microbiome dysbiosis is also demonstrated as a prerequisite for most cases of VAP and VT.

Figure 6: Prevention of pulmonary infections in ARDS patients: from highly recommended preventive measures to a cautious or even a not recommended use

Table 1. Summary of host-based biomarkers for diagnosis of pneumonia in ARDS

Marker	Performance
Alveolar	
Interleukin-1/Interleukin-8	Validated in multi-centre cohort [54] but did not influence practice in an RCT [55]
sTREM-1	Initial report but not validated in follow-up study [113, 114]
Exhaled breath markers	Experimental with technical variation currently limiting implementation [115]
Pentraxin-3	Meta-analysis suggested alveolar levels superior to plasma levels with moderate diagnostic performance, no RCT testing influence on practice [116]
Combination 'bio-score'	May be superior to individual markers, but remains to be validated [117]
Peripheral blood	
C-reactive protein	May be useful predictor of VAP, but non-specific and raised in both sterile and infective inflammation [118]
Procalcitonin	Lacks sensitivity for diagnosis of pneumonia but can significantly shorten antibiotic duration [118]
Pro-adrenomedullin	Limited utility in diagnosis of pneumonia but useful as marker of severity [118]
Pentraxin-3	Less effective as a diagnostic than alveolar levels [116]
Presepsin	No reports in VAP
Neutrophil CD64	Role in pneumonia uncertain [8]
Monocyte HLA-DR	Markers of monocyte deactivation and predictor of infection, but poor discriminant value for diagnosis of infection [8]

Abbreviations: ARDS, acute respiratory distress syndrome. RCT, randomized controlled trial. sTREM, soluble triggering receptor expressed on myeloid cells. VAP, ventilator-associated pneumonia. HLA, human leukocyte antigen.

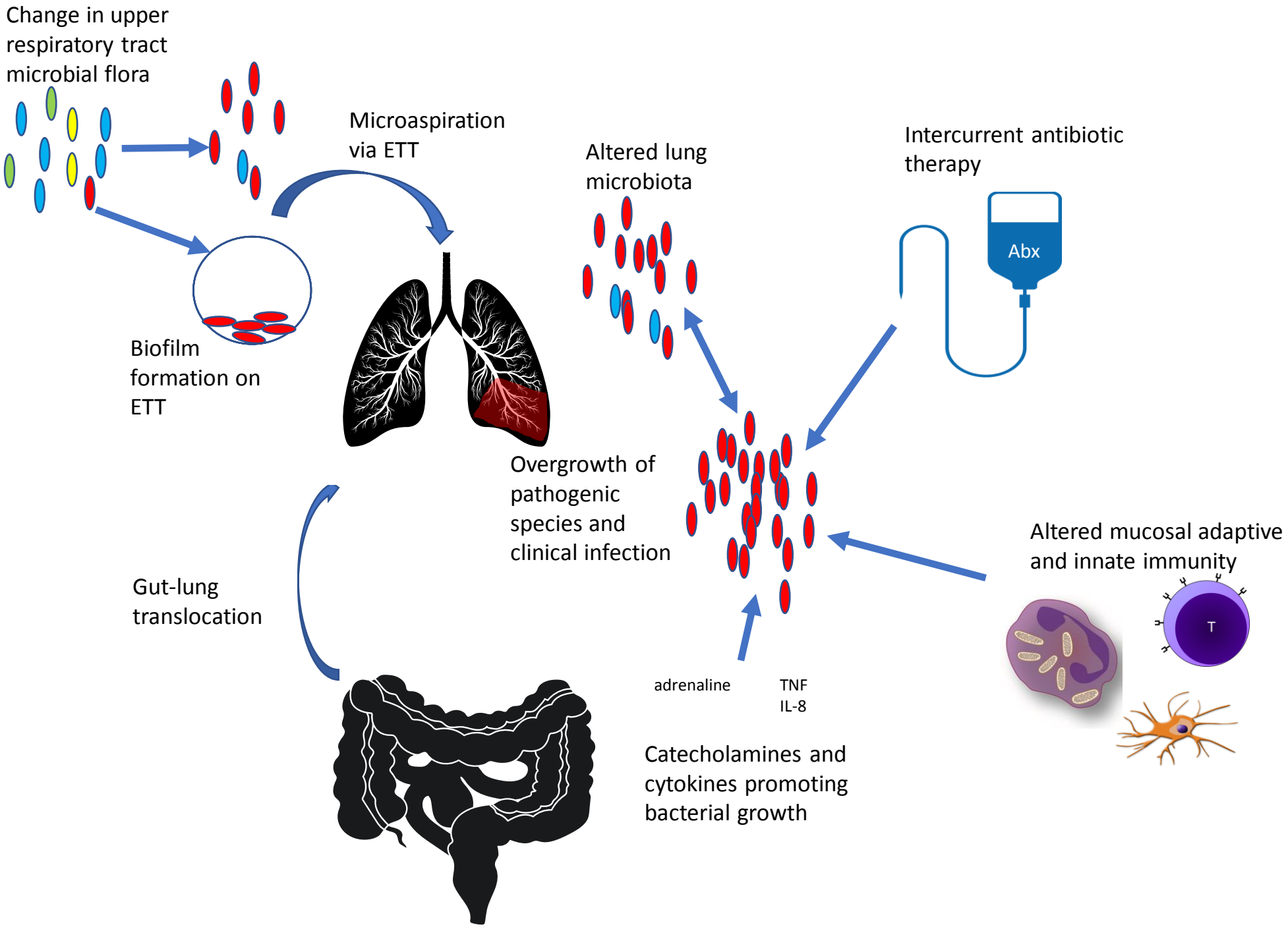
Table 2. Suggested dose for antimicrobials that may be proposed both IV and aerosolized.

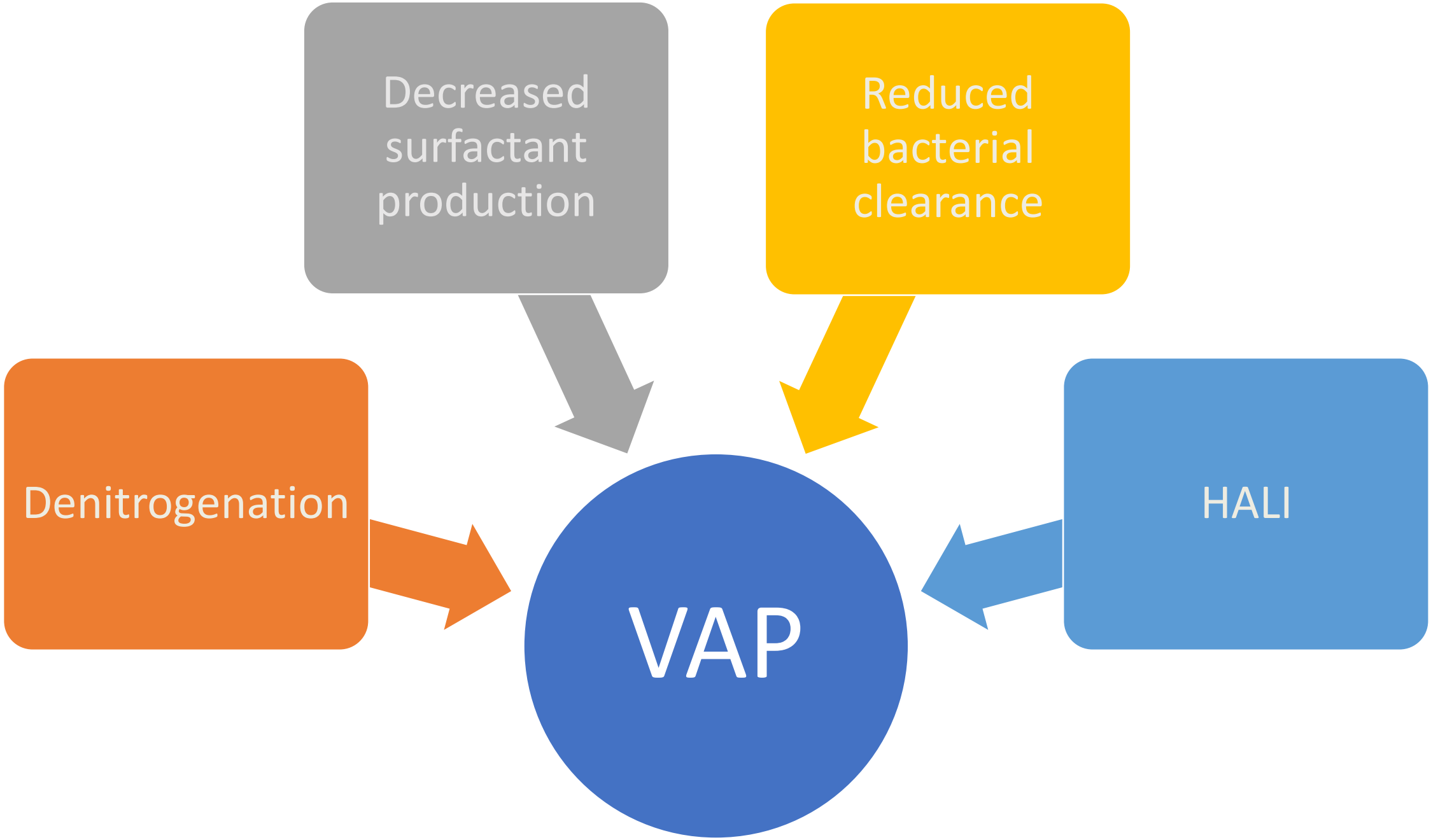
Drug	Suggested IV dose for ARDS lung infections (with Normal CrCl)	Notes	Suggested inhaled dose
Penicillins			
Ampicillin	2 gm 6 hourly (q6h)		1 g q 12h [119]
Ampicillin-sulbactam			3 g q 8h [120]
Cephalosporins			
Ceftazidime	2 gm 6-8 hourly		250 mg q 12h [121, 122] 15 mg/kg q 3 h [123]
Carbapenems			
Meropenem	1 gm 4- 6 hourly		Not recommended (no data)
Imipenem	500 mg – 1000 mg 6 hourly		50 mg q 6h [124]
Quinolones			
Moxifloxacin	400 mg daily		Not recommended (no data)
Ciprofloxacin	400 mg 8 hourly		Not recommended (no data in ventilated patients)
Levofloxacin	750 mg daily up to 500 mg 12 hourly		240 mg q 12 h [125]
Sulfonamide			
Trimethoprim/sulfamethoxazole	8- 10 mg trimethoprim/kg/day		Not recommended (no data)
Glycopeptide			
Vancomycin	30mg/kg loading	Keep Serum level 20-25 mg/L	120 mg q8 h [126,

	Same dose per day (divided or continuous infusion)		127]
Aminoglycosides			
Gentamicin	7mg/kg loading dose	Used primarily to sterilize blood	80 mg q8h [126, 127]
Tobramycin	7mg/kg loading dose	Used primarily to sterilize blood	300 mg q12 h [128]
Amikacin	25-30 mg/kg loading dose	Used primarily to sterilize blood	25mg/kg/day [123] 40 mg/kg/day [129] 400 mg q12h [100]
Polymyxins			
Colistin	4mg/kg loading then 500mg 6hourly (33.33mg colistin =1 million Units)		4 MIU q 8h [129]
Phosphonic acid derivative			
Fosfomycin	4g 6-8 hourly	Never alone	120 mg fosfomycin q12h [99]
Monobactam			
Aztreonam	1g 6 hourly		75 mg q 8h [130]

Available literature suggested adverse reaction with inhaled co-amoxiclav, Piperacillin tazobactam and ceftriaxone. No human data actually exist with other nebulized antibiotics.

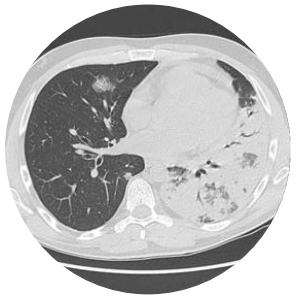
Abbreviations: IV, intravenous. ARDS, acute respiratory distress syndrome. CrCl, creatinine clearance. MIU, million international units.


Change in upper respiratory tract microbial flora
Microaspiration via ETT
Biofilm formation on ETT
Altered lung microbiota
Intercurrent antibiotic therapy
Abx
Overgrowth of pathogenic species and clinical infection
Altered mucosal adaptive and innate immunity
T
Gut-lung translocation
adrenaline
TNF
IL-8
Catecholamines and cytokines promoting bacterial growth

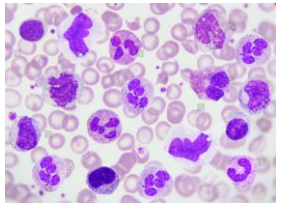

Decreased surfactant production
Reduced bacterial clearance
Denitrogenation
HALI
VAP

Clinical
Auscultatory findings
(rales, crepitations, bronchial breathing)
Purulent sputum
Deteriorating gas exchange

Radiological
Diffuse or lobar
infiltrates
Bronchograms



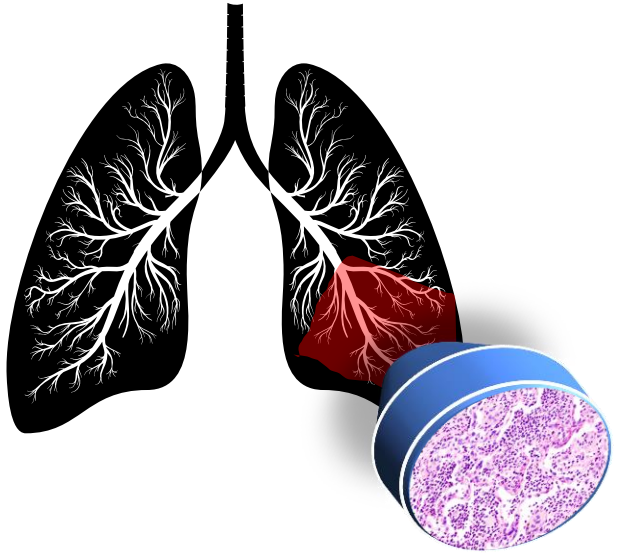
Laboratory assessment of host inflammation
Altered white cell and
neutrophil number
C-reactive protein
Procalcitonin
Alveolar cytokine levels

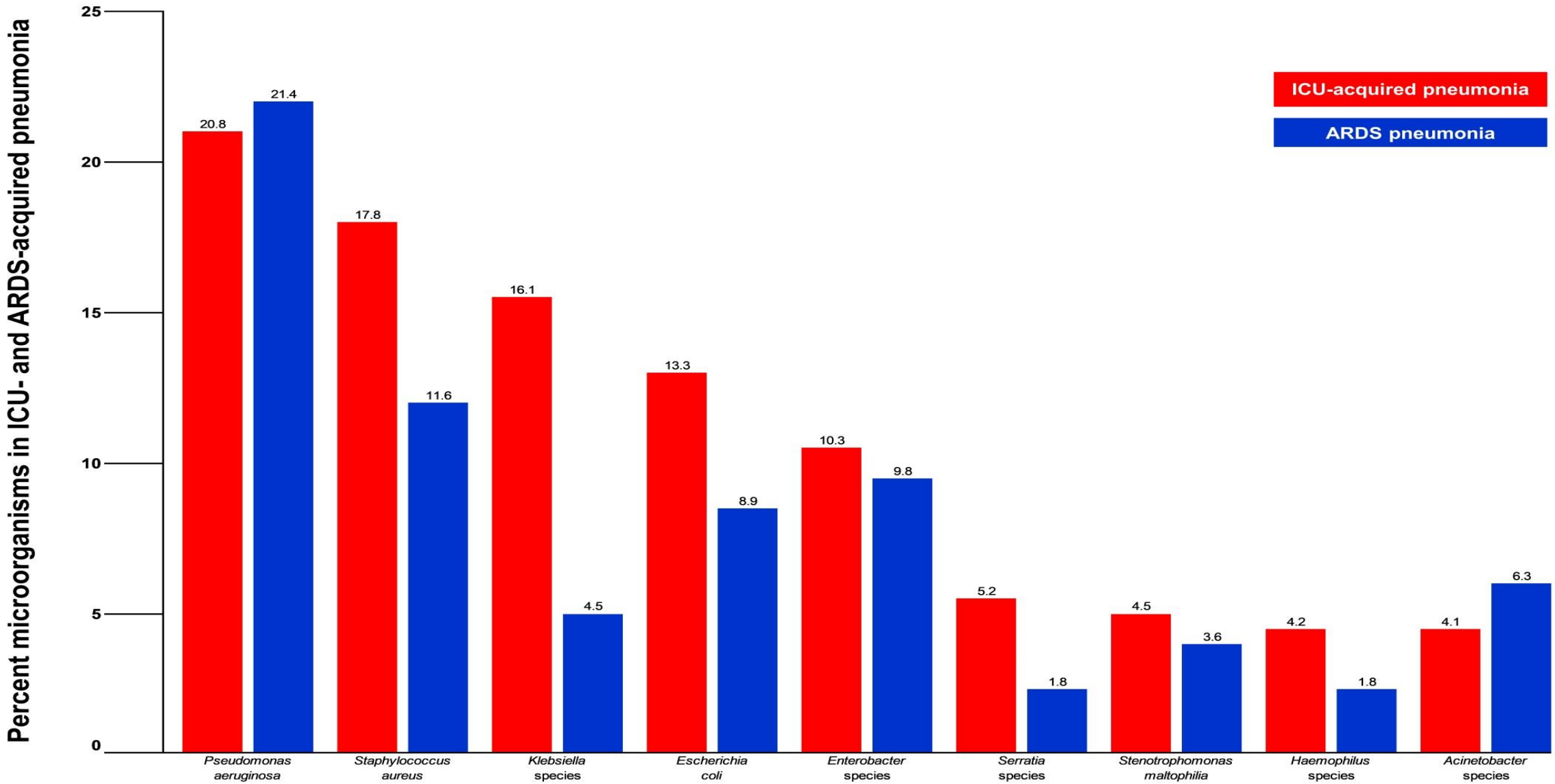


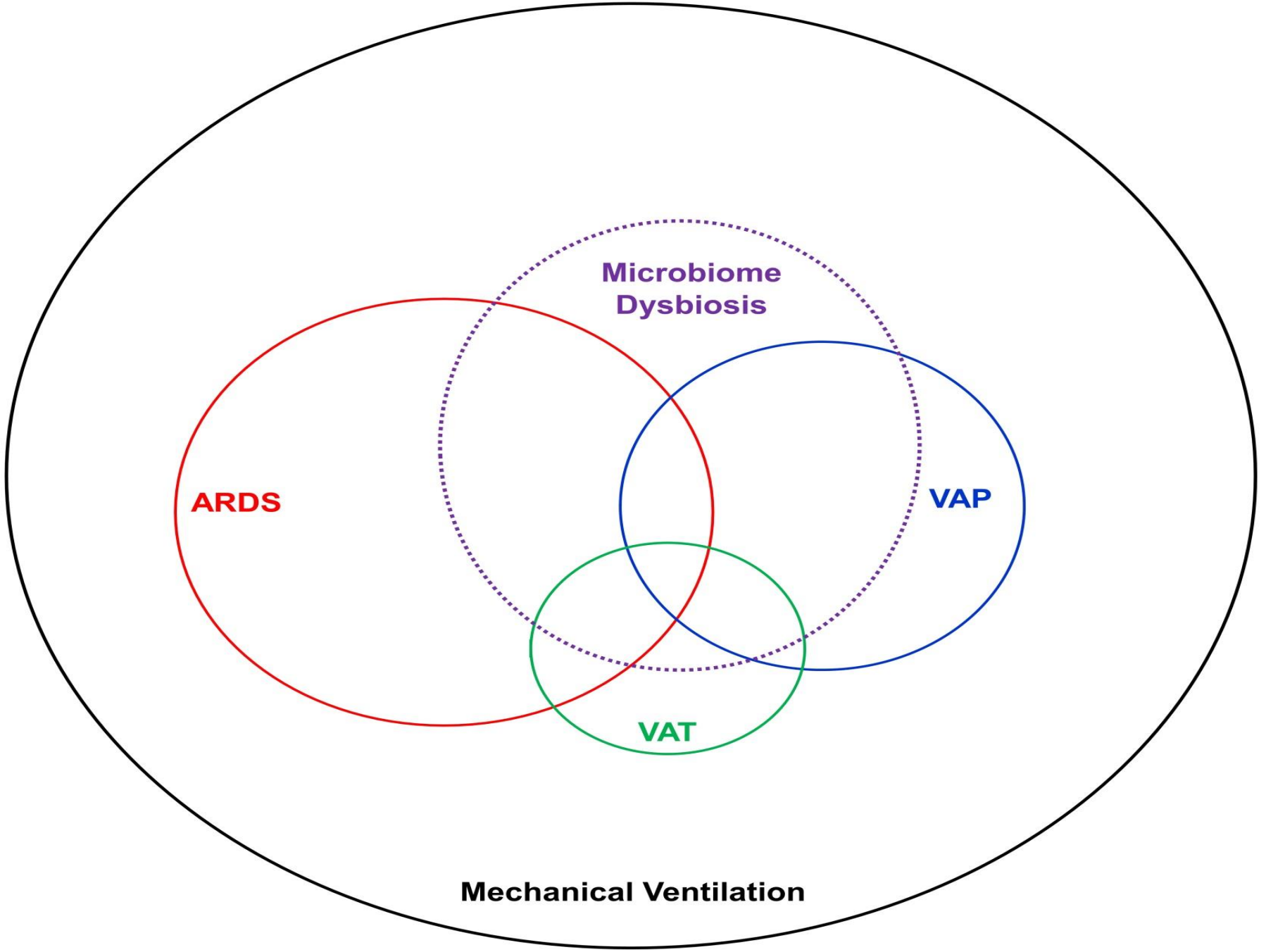
Microbiological
Culture
PCR-based detection
Antigen-based detection

Combined evaluation as proxy for histological diagnosis

Pneumonia:
a histo-pathological diagnosis




Percent microorganisms in ICU- and ARDS-acquired pneumonia
25
20
15
10
5
0
ICU-acquired pneumonia
ARDS pneumonia
20.8
21.4
17.8
11.6
16.1
4.5
13.3
8.9
10.3
9.8
5.2
1.8
4.5
3.6
4.2
1.8
4.1
6.3
Pseudomonas aeruginosa
Staphylococcus aureus
Klebsiella species
Escherichia coli
Enterobacter species
Serratia species
Stenotrophomonas maltophilia
Haemophilus species
Acinetobacter species


Microbiome
Dysbiosis
ARDS
VAP
VAT
Mechanical Ventilation

RECOMMENDED:

Pulmonary infection prevention bundle provided that an early weaning strategy is part of the bundle

POSSIBLY USEFUL although expensive:

- **Automated endotracheal tube cuff pressure monitoring**
- **Subglottic secretion drainage**

TO BE CONSIDERED:

Selective oral and digestive decontamination

MAYBE HARMFUL:

Oral care with chlorhexidine