Review article

Ventilator-associated pneumonia: pathobiological heterogeneity and diagnostic challenges

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Ventilator-associated pneumonia (VAP) affects up to 20% of critically ill patients and induces significant antibiotic prescription pressure, accounting for half of all antibiotic use in the ICU. VAP significantly increases hospital length of stay and healthcare costs yet is also associated with long-term morbidity and mortality. The diagnosis of VAP continues to present challenges and pitfalls for the currently available clinical, radiological and microbiological diagnostic armamentarium. Biomarkers and artificial intelligence offer an innovative potential direction for ongoing future research. In this Review, we summarise the pathobiological heterogeneity and diagnostic challenges associated with VAP.

Ventilator-associated pneumonia (VAP) is a nosocomial infection of the lung parenchyma that occurs after 48 h of tracheal intubation and mechanical ventilation[1–4]. Within the Intensive Care Unit (ICU), VAP is the most frequent nosocomial infection, impacting 20–36% of critically ill patients. Incidence rates vary, ranging from 2 to 16 episodes per 1000 ventilator days, and are influenced by factors such as diagnostic criteria, preventative measures, and patient and geographical variations[5–8]. Intubation is the primary risk factor, associated with more than 95% of pneumonis in the ICU; however, patients with reduced consciousness, trauma, older age and illness severity also have an increased risk[9–11].

Reported mortality rates for VAP span a wide range (24–76%); however, attributing mortality solely to VAP is complex due to the severity of underlying illnesses and diagnostic heterogeneity within ICU populations[12,13]. VAP can lead to the development of septic shock or acute respiratory distress syndrome if the treatment is delayed or inappropriate[14]. VAP results in substantial antibiotic prescription pressure, accounting for half of all antibiotics used in the ICU[15–20]. However, the prolific use of antibiotic therapy contributes to a vicious cycle of increasing multidrug-resistant (MDR) pathogens and mortality[21]. Treatment failure increases the risk of mortality and may occur in a third to two-thirds of VAP cases, with inappropriate antibiotic use the most common cause[22,23]. VAP increases hospital length of stay by an average of four to nine days and healthcare costs by £9000 per patient[3,18,24–26]. Despite preventative measures, there is a rising prevalence of MDR and persistently high mortality and healthcare costs associated with VAP. The pathobiological heterogeneity and diagnostic challenges associated with VAP remain of significant importance in global healthcare. In this review, we summarise the pathobiological heterogeneity and diagnostic challenges associated with VAP.

Pathobiology of VAP

The pathobiology of VAP is multi-factorial due to alterations in the usual protective airway defences and changes in the patient microbiological flora and immune responses. There are several predisposing factors in ICU patients and some present therapeutic opportunities (Fig. 1).

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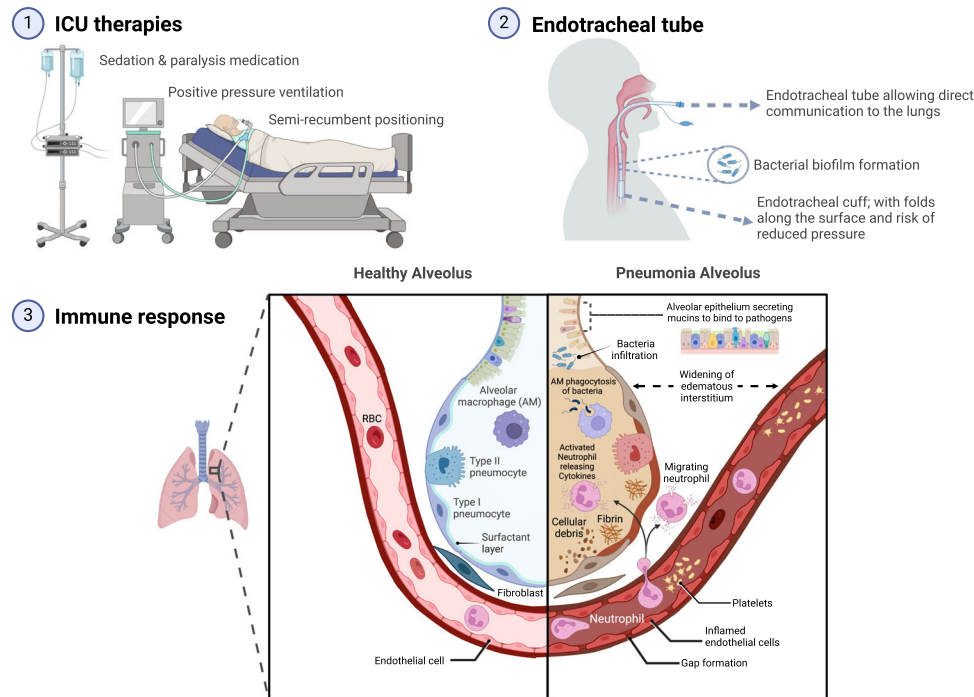
Fig. 1 | Mechanisms of ventilator-acquired pneumonia. 1 External factors associated with ICU therapies include mechanical ventilation, sedation and paralysis agents and semi-recumbent positioning; **2** Endotracheal tube prevents glottis closure and provides direct communication to the lungs, allowing microaspiration of secretions from the nasal sinuses and oropharynx. The endotracheal cuff is at risk of deflation, movement and small folds, allowing pooled secretions to leak. A bacterial biofilm can form around the endotracheal tube, which can then become dislodged by movement or suctioning; **3** In response to invading pathogens, alveolar macrophages and neutrophils' immune and inflammatory response lead to inflamed, oedematous and infected alveoli. Abbreviations: ICU = intensive care unit; AM = alveolar macrophages. Figure 1 was created with BioRender.com released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license (https://creativecommons.org/licences/by-nc-nd/4.0/deed.en).

Intensive care unit treatments and bacterial colonisation

The presence of an endotracheal tube (ETT) is a significant risk factor, as it breaches the natural protective barriers of the upper airway, allowing direct communication to the tracheobronchial tree[19,27] (Fig. 1). The ETT's high-volume, low-pressure protective cuff minimises gross aspiration but does not prevent micro aspirations. These phenomena include entrainment of pooled secretions, loss of cuff pressure and ETT movement[27–29]. The oropharynx, nasal sinuses and stomach are potential reservoirs of pooled secretions, which are susceptible to leaking below the cuff, resulting in silent micro-aspiration[2,15,30,31]. The ETT also causes epithelial damage and impedes cough, swallowing and mucociliary clearance mechanisms[27,32,33]. These mechanisms are further compromised by ICU therapies, such as sedation, paralysis, positive pressure ventilation and the influence of gravity associated with semi-recumbent positioning. Although necessary interventions, these ICU therapies can cause respiratory muscle weakness, mucociliary dysfunction and reduced airway humidification, which exacerbate the impairments to cough, tracheal mucus velocity and secretion clearance[12,27,32,34].

VAP is also related to bacterial biofilm formation, found on the ETT surface of 95% of mechanically ventilated patients[27,35–37] (Fig. 1). The biofilm acts as a reservoir for infective microorganisms, which can become dislodged, enter the distal airways and subsequently lead to VAP, with associations found between pathogens in tracheal secretions and the ETT biofilm[27,35–38]. Biofilm occurs within hours of intubation and is anticipated to precede VAP[36]. The longer the period of mechanical ventilation, the greater the risk of VAP[10].

Microbiology, local innate immunity and inflammation associated with VAP

Microbiology

VAP is often polymicrobial with an increasing prevalence of antibiotic-resistant bacteria[9]. The most prevalent pathogens causing VAP are gram-negative bacteria (mainly *Klebsiella, Acinetobacter, Pseudomonas, Escherichia coli* and other Enterobacteriaceae) and some gram-positive species such as *Staphylococcus aureus* and Enterococci[39,40]. Candida colonisation is also common, presenting a risk for fungal VAP[41]. Based on bacteriological data, VAP can be classified as either early or late-onset; early occurs between 48 and 96 hours after ICU admission and late-onset occurs after 96 h[42–44]. Early-onset VAP is more likely to be caused by bacteria which are antibiotic-sensitive, such as *Streptococcus* pneumonia, enteric gram-negative bacilli or methicillin-susceptible *Staphylococcus aureus*, and therefore usually hold better prognosis[44,45]. Late-onset VAP is more likely to be caused by MDR pathogens, such as *Pseudomonas aeruginosa, Acinetobacter baumanni*, methicillin-resistant *S. aureus*, and as such, are associated with higher morbidity and mortality[44–46]. However, the timing of onset is not the only risk for MDR, as patients with pre-admission immunosuppression, prior antibiotic use or recent hospitalisation are also at greater risk of MDR or atypical infections, with emerging studies reporting similar MDR prevalence regardless of timings of onset[44,45,47–50]. In non-neutropenic patients, multicenter studies suggest a prevalence of Aspergillus infection up to 12%, which may be an emerging problem in ICUs due to the increasing use of immunosuppressive therapies[51].

In early studies of patients with bacterial pneumonia, there is a reactivation of Cytomegalovirus, herpes simplex virus-1, and Epstein-Barr virus in up to 48% of patients, with an independent association

with mortality[52]. These worrying trends in bacterial, fungal and viral infections should trigger new prospective large registry studies to standardise the diagnosis, identify new therapeutic opportunities, improve adherence to culture results, and improve prescription practices that plague intensive care units[53].

The microbiome of the lung as a modulator of VAP

Although previously once considered sterile, the lungs are now recognised as hosting a diverse and dynamic microbiome that, under healthy conditions, maintains a symbiotic ecosystem and immune homoeostasis[54,55]. Numerous factors may cause microbiome dysbiosis during critical illness, including prior antibiotic use, mechanical ventilation or diet changes, which may exacerbate the risk of complications such as VAP[54]. Dysbiosis of the lung microbiota associated with VAP is linked to altered oropharyngeal microbiota, from which there is microaspiration or translocation to the lungs via the ETT, alongside gut-to-lung translocation and ICU-related factors such as antibiotic therapy[55]. Common ICU therapies, such as sedation and mechanical ventilation, impair cough reflexes and secretion clearance, decreasing bacterial elimination from the airways and increasing bacterial load[56,57]. During VAP, the lung microbiota becomes overwhelmed and dysbiotic, with low microbial diversity and high microbial burden[39,58,59].

The innate immune response of the lung parenchyma

For pneumonia to develop, microbes, typically bacteria, must first overcome mechanical barriers, such as cough, swallowing and the mucociliary escalator[37]. This is followed by tracheal and lung colonisation and expansion of pathobionts that exceed the lungs' capacity to maintain immune resistance and tissue resilience[59]. Alveolar macrophages (AMs) are a diverse phagocyte group in the lower respiratory tract. Under healthy conditions, AMs maintain alveolar homoeostasis and are the most abundant innate immune cells during local infection, providing the first line of defence against invading respiratory pathogens[60]. AMs adapt to provide phagocytosis and apoptosis of microbes. Furthermore, AMs orchestrate coordinated innate immune response of cytokine activity through NF-kB transcription, including interleukins (IL-1α, IL-1β, IL-6, IL-8) and tumour necrosis factor (TNF-a) that recruit neutrophils to the site of infection. AMs act as antigen-presenting cells, stimulating lymphocyte cells and triggering cellular and humoral responses, subsequently leading to inflammation of the lung parenchyma, leaking capillaries and exudative congestion[58,59].

In the event of pathogenic microbes overwhelming the local immune defences of the lung, the AMs and epithelial cells release additional cytokines, which facilitate the migration of neutrophils into the lung airspaces. In VAP positive for bacterial culture, there is a recruitment of neutrophils to the lungs, resulting in phagocytosis, degranulation, release of reactive oxygen species (ROS) and formation of neutrophil extracellular traps (NETs)[61–63]. NETs contain histones and antimicrobial peptides, which can kill invading pathogens associated with VAP[61–64]. Neutrophils and derived markers suggestive of a compartmentalised proinflammatory state can be used to diagnose bacterial pneumonia in VAP but require meticulous standardised bronchoalveolar lavage, and the resources and expertise are lacking in most centres, precluding its use in routine clinical practice[65].

Localised inflammation

Critical illness is a heterogeneous status of simultaneous proinflammation and immune suppression[66,67]. In addition, mechanical ventilation is known to induce a localised inflammatory response of pulmonary cytokine upregulation, termed biotrauma[68]. Biotrauma generates persistent local inflammation and may increase the VAP risk[68]. Determining the causal mediators of inflammation and their attributable contribution to VAP is often clinically challenging. However, recent studies have demonstrated a significant increase in pulmonary biomarkers interleukin-1 beta (IL-1β), IL-8, matrix metalloproteinase-8 (MMP-8), MMP-9 and human neutrophil elastase (HNE) and serum CRP and IL-6 in the instance of VAP[40,65,69]. Although neutrophils play an important role in the innate immune response to VAP, the release of NETs can also contribute to localised and persistent inflammation[61–64,70]. This persistent inflammation can lead to lung injury and increase the risk of mortality[61,70].

Histological definitions of VAP

VAP has been defined as the presence of consolidation with leucocyte accumulation in bronchioles and alveoli[14,71–73]. VAP has been categorised into four stages of severity[73]: early-stage bronchiolitis characterised by purulent mucus plugs with a proliferation of polymorphonuclear leucocytes (PMNL) within the bronchioles and bronchiolar wall. This is ensured by focal bronchopneumonia, with scattered neutrophilic infiltrates in the terminal bronchioles and alveoli. A confluent bronchopneumonia follows with focal infiltrates that extend into adjacent lobes. A lung abscess is the final step, with an extension of confluent bronchopneumonia, additional tissue necrosis, and the destruction of the surrounding lung architecture. Histological studies suggest that VAP is heterogeneous, with concurrent coexisting phases[14]. Early-phase pneumonia with capillary congestion and fibrinous exudate with PMNL in the alveolar spaces progresses to intermediate-phase pneumonia with alveoli containing fibrin, PMNL and a few erythrocytes. In the advanced phase, the macrophages engulf cellular debris when PMNL fills the alveoli, followed by a phase of resolution where the macrophagic activity of mononuclear cells eliminates inflammatory exudate.

Overall, VAP is a non-homogenous and diffuse process, often involving both lungs and mainly the lower lobes[14]. This histological pattern may be due to the distribution of bacteria from central to distal airways by the flow and volume generated by mechanical ventilation. However, this complex and dynamic presentation can explain why diagnostic methods are challenging.

Diagnosis of VAP

Despite significant work on diagnosing pneumonia and published international guidelines (Supplementary Information File), the definition and diagnosis of VAP remain controversial, with substantial variations in reference standards[17,19,25,37]. This confusion means that VAP incidence rates in the same patient cohort varied from 4% to 42% due to differing diagnostic criteria[4,11,44,74–78]. The diagnosis of VAP lacks sensitivity and specificity, forcing the clinician to balance the risks of unnecessary antibiotics against possible patient harm due to delayed therapy[8,17,19,79,80]. These diagnostic uncertainties and the absence of clear, accepted actionable evidence nationally and internationally lead to a reluctance to adhere to antimicrobial hygiene, adding to antibiotic pressure in VAP[53]. To reduce mortality, timely antimicrobial therapy is essential[8,79,80]. It is also imperative to diagnose other infections often wrongly attributed to pneumonia and identify confounders such as fluid overload and acute respiratory distress syndrome (ARDS). Hence, the diagnosis of VAP must be sensitive, specific and timely.

Histopathological examination of inflamed and infected lung tissue is considered the most accurate diagnostic tool for diagnosing VAP[37,81]. However, a lung biopsy is not practical or appropriate for the critically ill, and post-mortem examination is too late to influence treatment[25,37]. Clinical guidelines, therefore, attempt to amalgamate clinical, radiological and microbiological criteria to support the diagnosis of VAP[11,44,74–76] (Table 1)[17].

Clinical diagnosis of VAP: the pitfalls

Clinical examination is essential but has a sensitivity of 66.4% (95% CI 40.7–85.0) and specificity of 53.9% (95% CI 34.5–72.2) in the diagnosis of VAP[8]. Classical clinical features clinicians use for diagnosing VAP, such as fever, purulent secretions and leukocytosis, have a sensitivity of 69% and a specificity of 75% in post-mortem and prospective clinical

Table 1 | Clinical, Radiological and Microbiological Criteria for diagnosing VAP

Criteria	Description
Clinical	•Fever > 38 °C with no other cause AND •Leucocytosis or leukopenia AND at least one of the following; •New onset or change in sputum •Cough, dyspnoea or tachypnoea •Worsening gas exchange
Radiological	•Chest radiographs or computed tomograms with evidence of pulmonary infiltrates OR air bronchograms. If there is a pulmonary disease history, compare serial images.
Microbiological	•Positive quantitative culture from minimally contaminated lower respiratory tract specimen OR •Positive sputum culture or non-quantitative lower respiratory tract culture

studies[71]. These clinical features often formulate the foundation of VAP diagnosis, combined with radiological and microbiological investigations[37]. However, the preliminary signs of inflammation, including fever, tachycardia and leucocytosis, are nonspecific to VAP and can be seen in any process associated with the systemic inflammatory response of critical illness[19]. Although inconclusive and attributable to any condition that releases cytokines, fever and leucocytosis should prompt further clinical investigation[12,19,37].

Cough, sputum production, tachypnoea and hypoxia
In critically unwell patients, the cough may be suppressed by sedation, positive pressure ventilation, artificial airway or disease progression (e.g., traumatic brain injury or stroke)[37,82,83]. A high burden of purulent tracheal secretions may suggest lower respiratory tract infection, yet in intubated patients, and this may be due to a suppression of cough reflex, bacterial colonisation upon airway devices and impaired mucociliary clearance[18,27]. Tracheal secretions may have other potential sources, such as tracheobronchitis and may be exacerbated by smoking history or underlying respiratory diseases[15,19,84]. As outlined in international guidelines, a change in subjective sputum characteristics (such as colour or consistency) contributes to the diagnosis of VAP[44,85].

Tachypnoea and dyspnoea as an aid to VAP diagnosis have limited utility in the ICU as these features can be masked by sedation and ventilatory support. In the spontaneously breathing ICU patient, breathlessness may be multi-factorial and driven by other causes that may mimic the broad symptoms of pneumonia, such as delirium, pain, agitation or respiratory muscle weakness. Changes to oxygenation, ventilation and gas exchange may signify an inflammatory process of the lung parenchyma pointing towards a VAP but can be a feature of a non-infective aetiology, such as ARDS[37]. VAP and ARDS are both associated with hypoxaemia; however, their diagnosis has significant overlap and direct association, with pneumonia being the leading cause of ARDS, whilst ARDS also increases the risk of VAP[74].

Radiological diagnosis of VAP
Radiological investigations aim to identify the presence of alveolar inflammation and secretions. Pneumonia results in new or progressive infiltrates, resulting in an air-bronchogram due to alveolar opacification and air-filled bronchi with lobar and sub-lobar consolidation[37]. Areas of pulmonary opacities, areas of increased attenuation described as ground-glass infiltrates and the appearance of an air-bronchogram are all features of pneumonia on imaging[86].

Radiological investigations also aid the differentiation between VAP and ventilator-associated tracheobronchitis (VAT). VAT presents with similar clinical and laboratory criteria to VAP yet is distinguished by the absence of pulmonary infiltrates on imaging as it does not involve the lung parenchyma[44,87,88]. VAT and VAP are closely related, as

VAT is often a precursor to VAP[15,89]. Early recognition and differentiation between subtypes of ventilator-associated respiratory infections by radiological examination provides an opportunity for earlier, targeted intervention and antibiotic therapy[89]. Techniques such as computed tomography (CT), plain chest X-ray (CXR) or lung ultrasound (LUS) are usually combined with clinical criteria to support a diagnosis of VAP[11,15,75].

Computed tomography
CT is the gold examination standard, providing a three-dimensional anatomical and pathological orientation without anatomy overlap and high resolution of different tissue densities[25,37,90,91]. Although helpful, CT is not routinely utilised to diagnose VAP in ICU patients due to transportation risks, the requirement for additional sedation and paralysis to facilitate CT and the radiation burden[15,37,90,92]. In our quaternary referral hospital, with trained staff performing intrahospital transfers to CT, up to 30% of patients are reported to have adverse events due to the transfer, in line with published literature[93–95]. Hence, it is reserved for VAP with diagnostic difficulties[15].

Chest X-ray
In a recent UK survey, over 75% of ICU consultants reported they would request a CXR if clinically indicated by an acute change in clinical symptoms suspicious of VAP[17]. CXRs are portable and enable bedside imaging, avoiding the risks associated with CT transfer. However, although relatively inexpensive and practical, the interpretation of CXR imaging is often challenging in critically ill ICU patients due to the overlap of other common pathologies which present with lung infiltrates, such as pulmonary contusions, atelectasis, pulmonary oedema or ARDS[12,15]. CXR provides an isolated, two-dimensional image of a complex three-dimensional structure in which several tissues overlay one another, making interpretation challenging[96,97]. CXR findings should be compared to previous imaging to establish new or progressive changes[75]. The optimal approach for CXR requires posterior-anterior and lateral images in the erect posture[96], which is impossible in the critically ill patient, necessitating an anterior-posterior view[96]. Imaging quality and interpretation are also confounded by factors such as body habitus, inspiration stage, disease progression and artefacts[98].

A recent systematic review reported that CXR had a sensitivity of 88.9% (95% CI 73.9–95.8) and a specificity of 26.1% (95% CI 15.1–41.4) with a significant discrepancy in interpretation, increasing the likelihood of late or missed diagnosis[8]. A comparison of CT and CXR suggested poor cross-validation between CXR and CT chest, with less than 45% of opacities on CT observed on CXR and 26.9% vice versa[15,86,98]. CXR may still be considered a valuable adjunct for diagnosing VAP[12,25].

Lung ultrasound
Lung Ultrasound (LUS) provides a rapid, point-of-care, noninvasive bedside assessment with no radiation risk[78,99,100]. LUS has minimal operator dependence and high interobserver agreement after training and at different levels of expertise; however, visualisation can be challenging in patients with obesity, subcutaneous emphysema and chest wall oedema[100]. Increasing evidence supports the use of LUS for detecting and monitoring VAP, identified by subpleural consolidation or dynamic bronchogram[99,101,102]. Equally, such features are associated with any source of lung consolidation and are not specific to VAP alone[78,101]. When combined with clinical signs and symptoms, LUS provides earlier and superior diagnostic performance than CXR in critically ill mechanically ventilated patients, including those with VAP[103–106]. Although the results of small-scale observational studies are promising for LUS, there has been minimal application to its benefit on patient outcomes. Earlier diagnosis using LUS, rather than CXR, has been associated with reduced ventilator-free days yet has not been shown to expedite VAP resolution nor improve antibiotic-free days or

Table 2 | A summary table of the advantages and disadvantages of clinical, radiological and microbiological assessment tools for the diagnosis of VAP

	Advantages	Disadvantages
Bedside Clinical Symptoms	•Inexpensive •Rapid, bedside assessment •Any clinician/grade •Foundation of clinical suspicion	•Nonspecific to the cause of infection •Overlap with many disease processes •Confounded by ICU imposed factors •Inconclusive
Radiological Diagnosis	**CT**	
	•3D imaging •High resolution of different densities •Accurate	•Radiation risk •Transfer risks •Time delay •Cost
	CXR	
	•Portable enabling a bedside assessment •Rapid •Pragmatic •Inexpensive	•2D imaging only •Patient positioning limited •Difficult interpretation •Overlap with many disease processes •Benefits from comparison images
	Lung Ultrasound	
	•Portable enabling a bedside assessment •Rapid •Inexpensive •Minimal radiation •Dynamic exploration	•Specialist training •Limitations include body habitus and subcutaneous emphysema •Not a recognised or validated assessment tool
Microbiological Diagnosis	**Non-invasive techniques**	
	•Simple •Safe •Rapid/efficient to obtain a sample •Obtained by a breadth of ICU staff groups •Does not require extensive training	•Cross-contamination risk •Unable to isolate lower respiratory tract
	Invasive techniques	
	•Targets the lower respiratory tract, therefore, more specific	•Not routinely available over 24 h •Requires specialist training •Risk of patient instability
	Qualitative techniques	
	•Simple •Quicker and more efficient than quantitative methods	•Not specific to the exact organism
	Quantitative techniques	
	•Specific •Allows for targeted antibiotic therapy	•Timely •Costly •Laboratory resources •Expertise required

When diagnosing CAP, numerous scoring tools insist, including the PSI (pneumonia severity index)[163], CURB-65 (confusion; urea > 7 mM; respiratory rate ≥ 30 breaths·min−1; blood pressure < 90 mmHg systolic or ≤ 60 mmHg diastolic; aged ≥ 65 years old)[164] and the mATS (modified American Thoracic Society rule)[165]. Each is considered useful for predicting the need for intensive care unit treatment and mortality associated with pneumonia; however, their use in VAP diagnosis is not supported[166].

mortality[104]. Although there is increasing utility in the ICU, LUS is not currently recognised as a validated assessment tool in published guidelines for diagnosing VAP and requires further large-scale validation studies in critically ill patients on cost-effectiveness and patient outcomes.

Microbiological diagnosis of VAP

Accurate diagnosis techniques that identify the responsible infectious organisms are required to guide the most appropriate treatment regime[19,37]. A UK survey identified that all ICU consultants seek microbiology confirmation before the commencement of antibiotics for VAP, yet there is wide variation in techniques, availability and expertise[17]. The optimal method of microbiological diagnosis is a further source of controversy[19,37,75,107].

Endotracheal aspirates. the most prominent method for aetiological diagnosis of VAP is noninvasive techniques, specifically endotracheal aspirates (ETA)[108,109]. ETA is a simple, safe and efficient technique that can be performed by most ICU staff[19]. Although it avoids oropharyngeal contamination, it cannot differentiate from colonising organisms in the airway devices, leading to inconclusive results[12,19]. While evidence suggests ETA has high false favourable rates and is associated with increased antibiotic use, the quantitative analysis provides a reliable alternative to invasive techniques[19,107]. A recent systematic review and meta-analysis concluded that ETA had a sensitivity of 75.7% (95% CI 51.5–90.1) and specificity of 67.9% (95% CI 40.5–86.8) for the diagnosis of VAP[8]. Despite this, national guidelines advocate noninvasive ETA sampling based on its comparable outcomes with invasive techniques, including mortality, length of stay and duration of mechanical ventilation[74,76]. Although the accuracy of ETA remains controversial, ETA imposes minimal risk due to its simple, noninvasive nature[19,76].

Bronchoalveolar lavage (BAL). The invasive techniques that are commonly used to obtain distal airway samples by a fibreoptic bronchoscope include bronchoalveolar lavage (BAL) and protected specimen brushing (PSB)[19,75,107,108]. BAL and PSB bypass the upper airway contamination to collect samples from the lower respiratory tract[75,107,108]. BAL and PSB methods are only routinely available in some hospitals and require specialist training[15,25]. BAL and PSB result in a loss of positive end-expiratory pressure, risks of accidental extubation, bronchospasm and hypoxia, with the additional need for sedation or neuromuscular blocking agents[12].

Non-directed (without a bronchoscope) bronchial lavage techniques (NBL) allow cultures to be obtained without the complexities and risks accompanied by using a bronchoscope[110,111]. NBL is a safe and inexpensive method that can be performed by a range of clinicians, including respiratory therapists or physiotherapists, increasing routine availability[110,111]. NBL techniques have comparable diagnostic accuracy to BAL and PSB[112].

Evidence suggests no reduction in mortality, duration of mechanical ventilation or ICU length of stay when BAL and PSB were compared to ETA in patients with VAP[8,25,108,113]. PSB is claimed to have a sensitivity of 61.4% [95% CI 43.7–76.5] and specificity of 76.5% [95% CI 64.2–85.6], while BAL has a sensitivity of 71.1% [95% CI 49.9–85.9] and specificity of 79.6% [95% CI 66.2–85.9][8]. It is important to note that the reliability of such results is confounded by the lack of local, national, and international reference standards[25]. Because of the controversial evidence and risk of false positive and false negative results, findings should be interpreted cautiously[8].

Qualitative vs quantitative microbiological analysis

BAL, PSB and ETA can be analysed quantitatively or qualitatively[108]. Quantitative analysis provides a threshold count of bacterial growth, allowing differentiation between infection and colonisation, whereas qualitative analysis identifies the presence or absence of pathogenic cultures (107). The rationale for using quantitative cultures of respiratory secretions sampled from patients with suspected VAP is to differentiate infectious organisms from simple colonisation and to optimise antibiotic therapy[19,108]. In early studies, evaluating a rapid multiplex PCR test for timely decision-making, bacterial resistance detection and antimicrobial treatment adaptation in adult patients was associated with antibiotic de-escalation. These findings should be welcomed in VAP, as they can reduce antibiotic prescription pressure

Table 3 | The Clinical Pulmonary Infection Score (CPIS)[122]

Body temperature≥ 36.5 or ≤ 38.4 = 0 point ≥ 38.5 or ≤ 38.9 = 1 point ≥ 39 or < 36.5 = 2 point	Pulmonary infiltration in chest X-ray No infiltration = 0 point Diffuse infiltration = 1 point Localised infiltration = 1 points
Leucocyte count, microscopy ≥ 4000 or ≤ 11.000 = 0 point < 4000 or > 11.000 = 1 point Rod form ≥ % 50 = Add 1 point	Progression in pulmonary infiltration Radiographic progression (-) = 0 point Radiographic progression (+) (After the exclusion of HF and ARDS) = 2 points
Tracheal secretion Tracheal secretion (−) = 0 point Tracheal secretion with less purulence = 1 point Abundant purulent secretion = 2 points	Pathogenic bacteria in tracheal aspirate culture No or few pathogenic bacteria = 0 point Moderate or high levels of pathogenic bacteria = 1 point For pathogenic bacteria to be seen in Gram staining, add 1 point
Oxygenation PaO_2/FiO_2, mmHg > 240 or ARDS (ARDS: $PaO_2/FiO_2 < 200$, $PaO_2/FiO_2 < 200$, PAWP ≤ 18 mmHg and bilateral acute infiltration) = 0 point PaO_2/FiO_2, mmHg ≤ 240 or ARDS = 2 points	Total (> 6 is accepted as pneumonia)

In the original work by Pugin et al., CPIS was reported to have a sensitivity of 93% and specificity of 96% for diagnosing VAP[122,123]. However, compared to quantitative cultures obtained by BAL and histology, the specificity and sensitivity of CPIS appeared to be low[123]. The individual components of the CPIS rely on subjective evaluation of clinical factors, each with questionable accuracy, such as progression of pulmonary infiltrates or purulent secretions, leading to a reduction in interrater reliability[12].

ARDS acute respiratory distress syndrome; *HF* heart failure; *PaO2* partial pressure of oxygen; *FiO2* fraction of inspired oxygen; *PAWP* pulmonary artery wedge pressure.

Table 4 | A summary table detailing biomarkers PCT, sTREM-1, CRP and proinflammatory cytokines

Biomarker	Summary
Procalcitonin (PCT)	PCT is an acute-phase reactant primarily produced by the liver in response to bacterial infections. PCT is a prohormone secreted into serum from neuroendocrine cells in the lungs or intestine as part of the systemic inflammatory response. PCT is a calcitonin precursor secreted by the C cells of the thyroid gland and K cells of the lung. In healthy individuals, PCT is normally undetectable (< 0.01 ng/mL) but detectable in patients with systemic, bacterial-induced inflammation. When stimulated by endotoxin, PCT is rapidly produced by parenchymal tissue throughout the body. PCT is a potentially valuable diagnostic test for the diagnosis of VAP.
Soluble triggering receptors expressed on myeloid cells type 1 (sTREM-1)	Triggering receptor expressed on myeloid cells (TREM-1) has been studied as a biological marker of microbial infection. TREM-1 is a glycoprotein member of the immunoglobulin superfamily strongly expressed on the neutrophils and monocytes infiltrating tissues invaded by bacteria or fungi. TREM-1 triggers the secretion of proinflammatory mediators through a signalling pathway and functions as an amplifier of the inflammatory response. In response to infection, soluble TREM-1 (sTREM-1) is either secreted or shed and can be measured in body fluids. sTREM-1 is almost undetectable in patients with non-microbial inflammation. It is important to note that sTREM-1 is also elevated in non-infectious inflammation aetiology.
C-reactive protein (CRP)	CRP is a nonspecific biological marker of inflammation synthesised in the liver. CRP synthesis occurs rapidly in response to infection and falls quickly once the stimulus is removed. In healthy individuals, serum CRP levels are low. In response to infection, trauma, surgery or cancer, serum CRP levels can rise rapidly and sharply. Serum CRP is an efficient way to determine inflammation.
Proinflammatory cytokines	Inflammatory cytokines and neutrophils, as an immune response to pneumonia, may act as innate immune markers of VAP and inflammation in bronchial alveolar lavage (BAL). Proinflammatory cytokines in BAL, including pulmonary interleukin (IL)–8 and IL-1β, have been associated with VAP. IL-8 is a proinflammatory chemokine produced by macrophages and epithelial cells in the early phases of injury to recruit neutrophils and other immune cells to the site of infection and inflammation. IL-1β is a proinflammatory cytokine crucial for host defence against infection and injury.

PCT procalcitonin; *sTREM–1* soluble triggering receptors expressed on myeloid cells type 1; *CRP* C reactive protein; *BAL* bronchial alveolar lavage; *IL* interleukin.

in ICU settings[114–117]. In the UK ICU setting, only up to 30% of intensive care units have access to quantitative reporting services for VAP. Additionally, clinicians in over a quarter of these units are inadequately trained in performing the procedure[17].

However, these findings should be interpreted with caution, as there is still no overall evidence that quantitative cultures reduce mortality, ICU length of stay, period of mechanical ventilation or rates of antibiotic change compared to qualitative cultures in patients with VAP[74,108]. Quantitative cultures may also be challenging in low- and middle-income countries. Guidelines recommend that semi-quantitative cultures diagnose VAP as it require fewer laboratory resources and expertise and provides more rapid results than quantitative cultures[44].

Scoring systems for the diagnosis of VAP
The clinical, radiological and microbiological assessment tools discussed need to provide a definitive diagnosis of VAP, each presenting its strengths and weaknesses, as summarised in Table 2. Scoring systems are frequently used in numerous areas of medical practice to overcome the pitfalls and controversy of individual diagnostic

methods, enabling clinicians to simplify and quantify complex clinical situations[118]. Scoring systems can provide an efficient and standardised method of assessment, diagnosis, risk stratification and outcome prediction in acute and emergency care medicine[119,120].

Clinical pulmonary infection score
The Clinical Pulmonary Infection Score (CPIS) is the most relevant scoring system for VAP and has been widely documented[12,44,121,122]. CPIS combines clinical, radiological and microbiological criteria into a pragmatic scoring system to provide a single, quantifiable result. The tool calculates a score of 0 to 12, with a score equal to or greater than six, signifying a high likelihood of VAP (Table 3)[44,122,123].

The main limitation is the variation in reference standards and modifications in the CPIS criteria, with varied opinions of sensitivity and specificity compared to bronchoscopic BAL, non-bronchoscopic BAL and post-mortem histology[44,123]. A CPIS score greater than six signifying VAP has a sensitivity of 73.8% (95% CI 50.6–88.5) and a specificity of 66.4% (95% CI 43.9–83.3)[8]. CPIS seem to provide benefits in monitoring and early detection and as an early warning system, as it potentially allows early antimicrobial therapy[75,124]. Although a
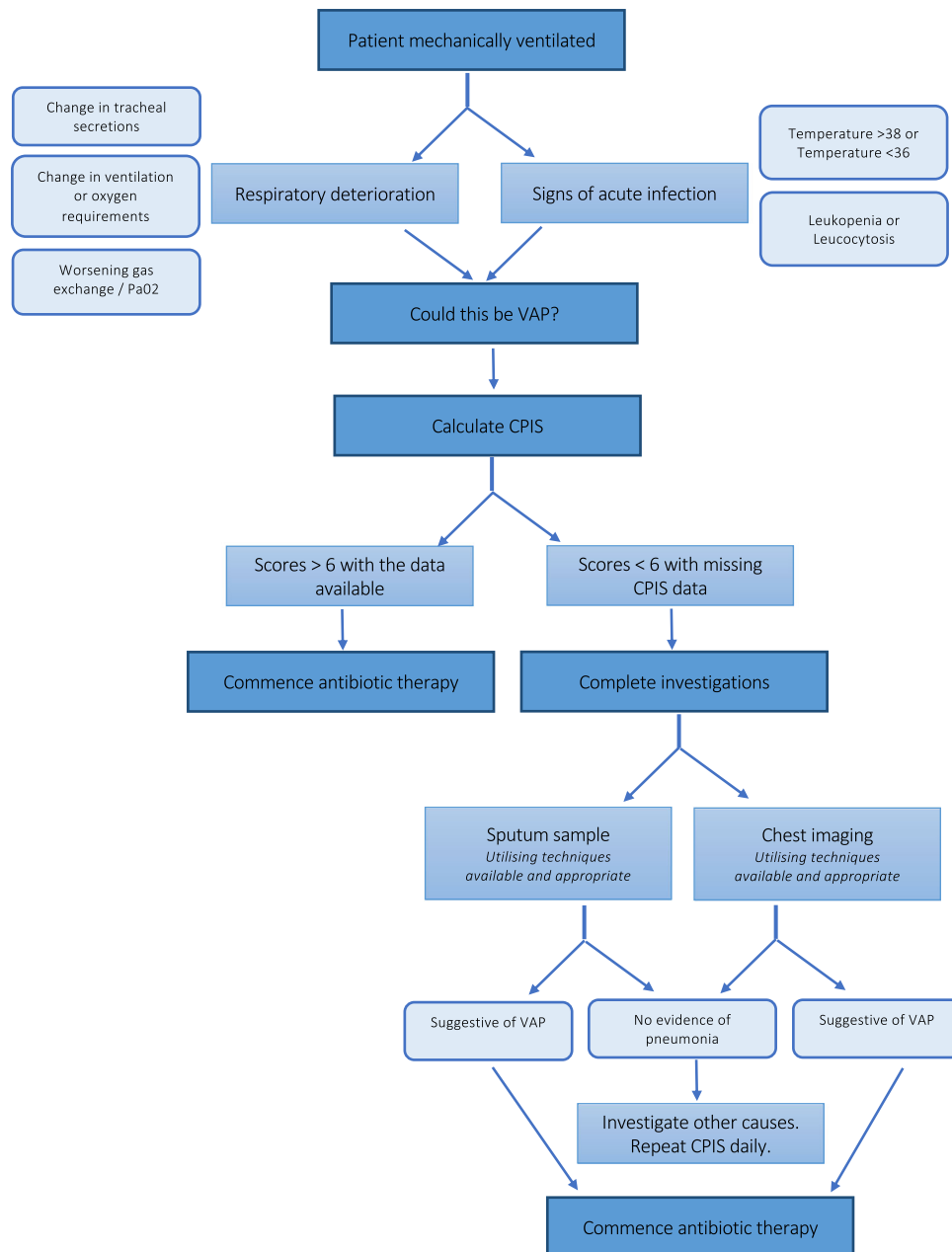
Fig. 2 | A simple, pragmatic ventilator-acquired pneumonia (VAP) diagnostic algorithm. An algorithm for the diagnosis of VAP has been outlined; firstly, using clinical symptoms and features of infection and respiratory deterioration to inform initial suspicion in ventilated patients and to prompt completion of the Clinical Pulmonary Infection Score (CPIS). If uncertainty remains regarding the diagnosis of VAP due to missing data from the CPIS, clinicians are then prompted to complete sputum sampling and chest imaging using available methods to determine diagnosis. Antibiotic therapy is recommended on confirmed diagnosis of VAP.

pragmatic combination of frequently available criteria, the accuracy and reliability of CPIS are controversial. The widespread use of the CPIS as a diagnostic tool for VAP should be adopted with caution and in the context of clinical research[8,121,123,125].

Biomarkers for the diagnosis of VAP
The use of biomarkers in ICU has increased significantly in recent years to provide an objective and quantifiable characteristic of a biological process[126,127]. Biomarkers indicate a normal or pathological process or a pharmacological response[126]. The WHO defines a biomarker as any substance or process that can be measured in the body or by its products[128]. Biomarkers are usually proteins detected in any biological sample, including serum, bronchoalveolar lavage fluid and exhaled breath condensate, therefore acting as a potential diagnostic method for numerous infections, including VAP[126,127,129,130].

Many biological markers have been studied to improve the rapidity and performance of current diagnostic procedures of VAP, with almost 200 different biomarkers related to infectious diseases being reported[53,65,130–138]. There is increased recognition that procalcitonin (PCT), a soluble triggering receptor expressed on myeloid cells (sTREM-1), C-reactive protein (CRP) and proinflammatory cytokines such as IL-8 and IL-1β, may be elevated in non-infectious and infectious inflammatory causes (see Table 4)[65,76,127]. However, they are inconsistent in diagnosing VAP, altered by antibiotic usage and with variable sensitivities and specificities[127,137,139–147]. They are helpful for early identification of infection, timely initiation of antimicrobial therapy, and prompt evaluation of treatment course or duration. However,

currently, an ideal biomarker has to be identified. Recent guidelines, therefore, do not recommend using biomarkers for diagnosing VAP, although suggestive that they may offer guidance on the duration of therapy[76,148]. The utility of biomarkers as predictors of VAP has yet to be demonstrated.

Bringing the multimodal diagnosis with Artificial Intelligence

Artificial intelligence (AI) is a rapidly growing concept, offering many innovative and sophisticated possibilities within modern healthcare[149,150]. With the increased availability of electronic health records, AI can process and interpret vast and complex data, which is opportunistic for disease identification, outcome prediction, and phenotyping within the field of VAP[149,150]. AI uses supervised, semi-supervised or unsupervised machine learning to interpret complex information confounding variables and pre-existing conditions to support diagnosis and disease identification[150]. Previous studies have demonstrated the benefit of AI for successful image interpretation, including CT scan analysis for COVID-19-induced pneumonia and traumatic brain injury[150,151]. AI can potentially expedite and enhance CT or CXR interpretation and aid decision-making without microbial sampling, yet further validation is required in clinical practice models[152–156].

AI has also enabled algorithms to cluster symptoms to establish phenotypes and endophenotypes to predict deterioration in COVID-19, ARDS, pneumonia, and sepsis. In small studies, automated machine learning for VAP prediction was deemed superior to the CPIS for patients at high risk of VAP just 24 hours after intubations[150,157]. Although offering huge potential to alleviate practitioner decision-making, diagnostic uncertainty and potential treatment delay, further research and investment are required before the widespread implementation of AI in acute care medicine. In a recent systematic review, over 95% of AI studies in the ICU have been retrospective[149]. Prospective clinical trials are needed to improve their validity, usability, and trustworthiness. Secondly, there remain concerns regarding data privacy and the safety of information sharing[150]. Further resources, investment, and research are required before widespread implementation for the diagnosis, prognosis, and guided clinical management of VAP.

Healthcare inequalities—VAP in low-income countries

Healthcare-associated infections are a serious problem in low-income and middle-income countries, affecting a quarter of hospitalised patients[158]. The pooled incidence of VAP is greater in lower-income and middle-income countries than in high-income countries[159]. However, reporting and surveillance vary significantly in developing countries, with limited prevention interventions[160]. In many areas of low and middle-income with rapidly growing economies, such as across Asia, more people are accessing healthcare due to increasing provision, yet with a lack of regulation and stewardship of infection prevention and control and antibiotic stewardship[159]. In developing countries, VAP is associated with high mortality rates and increased ICU length of stay, contributing to an additional burden of scarce resources and excess costs[160,161]. In developing countries, the costs attributable to VAP are 5 times greater than in other patients[161]. Innovation with AI may reduce the cost of these patients.

Conclusion

The diagnosis of VAP continues to present a clinical conundrum[125]. With a variance in diagnostic methods and reference standards, the existing literature offers a limited comparison to measure VAP's progression and treatment response. Although considered a definitive marker, histological diagnosis is not viable for investigation for diagnosis and prognosis of VAP in ICU.

With limited consensus in clinical research, a pragmatic approach to diagnosis is required, encompassing clinical expertise and experience with the breadth of clinical information available. A combination of the available clinical, radiological and microbiological methods should be sought after and collectively evaluated, with an appreciation of the advantages and disadvantages of each diagnostic method (as outlined in Table 2)[162]. Future clinical studies should investigate the antibiotic pressures caused by the VAP and its diagnosis in critically ill patients. A suggested algorithm to aid a pragmatic clinical diagnosis of VAP is demonstrated in Fig. 2. Clinical tests should ensure the least possible harm, considering the risks of time delay, invasive procedures and location beyond the specialist care of the ICU environment. Rapid bedside testing of sensitive and specific pulmonary cytokines would benefit from further exploration to improve antibiotic stewardship and diagnostics.

Further research in the diagnosis of VAP with new investigations and existing usage of data with AI may provide a holistic and pragmatic approach.

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Author contributions

Competing interests

Additional information