Management of pneumonia in critically ill patients

Catia Cillóniz,[1,2,3,4] Antoni Torres,[1,2,3,4] Michael S Niederman[5]

[1]Department of pneumology, Hospital Clinic of Barcelona, Spain
[2]August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
[3]University of Barcelona, Barcelona, Spain
[4]Biomedical Research Networking Centers in Respiratory Diseases (CIBERES), Barcelona, Spain
[5]Weill Cornell Medical College, Department of Pulmonary Critical Care Medicine, New York, NY, USA

Correspondence to:
MS Niederman
msn9004@med.cornell.edu

Cite this as: *BMJ* 2021;375:e065871
http://dx.doi.org/10.1136/bmj-2021-065871

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

ABSTRACT

Severe pneumonia is associated with high mortality (short and long term), as well as pulmonary and extrapulmonary complications. Appropriate diagnosis and early initiation of adequate antimicrobial treatment for severe pneumonia are crucial in improving survival among critically ill patients. Identifying the underlying causative pathogen is also critical for antimicrobial stewardship. However, establishing an etiological diagnosis is challenging in most patients, especially in those with chronic underlying disease; those who received previous antibiotic treatment; and those treated with mechanical ventilation. Furthermore, as antimicrobial therapy must be empiric, national and international guidelines recommend initial antimicrobial treatment according to the locationís epidemiology; for patients admitted to the intensive care unit, specific recommendations on disease management are available. Adherence to pneumonia guidelines is associated with better outcomes in severe pneumonia. Yet, the continuing and necessary research on severe pneumonia is expansive, inviting different perspectives on host immunological responses, assessment of illness severity, microbial causes, risk factors for multidrug resistant pathogens, diagnostic tests, and therapeutic options.

Introduction

Pneumonia is a major health problem, being associated with high morbidity and short and long term mortality. It is also the leading infectious disease cause of mortality among all ages worldwide.[1 2] Pneumonia in critically ill patients may present as pneumonia acquired in the community (community acquired pneumonia, CAP); pneumonia acquired in the hospital (hospital acquired pneumonia, HAP); or pneumonia related to mechanical ventilation (ventilator associated pneumonia, VAP). Severe pneumonia is associated with high short and long term mortality, and those who survive often have important sequelae such as alterations of lung function, reduction in mental and cognitive functions, weakness and reduction of motor function, and reduced functional autonomy.[3 4] Appropriate diagnosis of severe pneumonia is crucial to improve survival of critically ill patients. Identifying a pathogen is critical for antimicrobial stewardship in critically ill patients with severe pneumonia. However, in most patients, identifying the cause is challenging, especially in those with chronic underlying disease, those who received previous antibiotic therapy, and those treated with mechanical ventilation. Prompt and adequate antimicrobial treatment is crucial for the best outcomes in critically ill patients with severe pneumonia, and is a key focus of international guidelines for the management of pneumonia.[5–7]

In this article, we review current knowledge on the management of pneumonia in critically ill patients, including CAP and HAP, focusing on epidemiology, microbial etiology, pathogenesis, treatment, and prevention.

Sources and selection criteria

We searched databases from 2000 to 2021, including PubMed, Medline, the Cochrane Database of Systematic Reviews, and the Central Register of Controlled Trials (clinicaltrials.gov). We used both keywords and keyword combinations, including "pneumonia", "severe respiratory infection", "severe pneumonia", "pneumonia in critically ill", "community acquired pneumonia", "intensive care pneumonia", "hospital acquired pneumonia", "ventilator associated pneumonia", "management of pneumonia", "diagnosis of pneumonia", and "pneumonia therapy". We reviewed relevant titles and abstracts of this search and prioritized studies in English, considering meta-analyses, systematic reviews, international guidelines, randomized controlled trials (RCTs), and large, descriptive and observational studies. We include some additional, relevant articles published before 2000.

Defining severe pneumonia and its epidemiology

Severe community acquired pneumonia (SCAP)

Early identification of patients with SCAP is critical to provide rapid, definitive treatment and to avoid delay

in providing intensive care treatment, in an effort to reduce mortality.[8 9] Multiple scoring systems provide support in deciding the site of care, but most of these tools predict mortality risk, and not specifically the need for intensive care admission. Proper site of initial care is important, since both length of hospital stay and mortality of patients first admitted to the general ward and then transferred to the intensive care unit (ICU) are higher than for patients directly admitted to the ICU.[10 11]

The most widely accepted criteria for defining severe CAP are from the 2007 Infectious Disease Society of America/American Thoracic Society (ATS/IDSA) consensus guidelines on the management of CAP in adults[12] (box 1). ICU care is needed for those who require mechanical ventilation or vasopressor support of shock, or the presence of three of nine minor criteria. Several validation studies[13–17] of the minor criteria found that they were accurate for predicting need for ICU admission.

The number of patients requiring intensive care is growing, along with the rising number of individuals who are older, immunocompromised, or with underlying serious comorbidities. In 2018, a cross sectional study[18] showed a substantial increase in hospitalization for acute respiratory infections throughout the period 2003–15. The rise was more evident in the older population: ICU admission was reported to be 3.3 times higher in patients aged 85–89 and 5.8 times higher in patients ≥90, compared with younger populations.

A secondary analysis of a prospective, population based cohort study on hospitalized patients with CAP in the US found that 23% needed ICU admission, of whom 24% required invasive mechanical ventilation and 20% required non-invasive mechanical ventilation. The authors reported an incidence of CAP in the ICU of 145 cases per 100 000 adults per year.[19]

CAP is also a major cause of sepsis. In 2016, the third international consensus definition (Sepsis-3) defined sepsis as an increase in the Sequential Organ Failure Assessment (SOFA) score of two points or more, and recommended the use of the quick Sequential Organ Failure Assessment (qSOFA) score to identify patients at high risk of death and prolonged ICU stay among those with suspected infection, such as CAP.[20] Several studies evaluated the performance of qSOFA in a CAP population,[21–27] and showed that it was more accurate than other scores, such as CRB (confusion, respiratory rate, blood pressure), and SOFA in predicting mortality and ICU admission. In spite of early recognition and treatment of SCAP, short and long term mortality remain high (27–50%).[19]

Box 1: ATS/IDSA criteria for severe CAP

Minor criteria

- Respiratory rate ≥30 breaths/min
- PaO_2/FiO_2 ratio ≤250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level ≥20 mg/dL)
- Leukopenia (white blood cell count <4 ×10^9/L)
- Thrombocytopenia (platelet count <100 ×10^9/L)
- Hypothermia (core temperature <36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

Hospital acquired pneumonia (HAP)

HAP has an estimated annual incidence of five to 10 cases per 1000 hospital admissions globally, and is considered the second most common hospital acquired infection.[7] One subgroup, ventilator associated pneumonia (VAP), which occurs in patients on mechanical ventilation for at least 48 hours, affects 10–25% of all ventilated patients, with the risk being highest in the first 5–7 days of mechanical ventilation.[5 7] VAP remains a frequent nosocomial infection in the ICU, and causes significant morbidity. However, debate continues on attributable mortality rates, varying widely and being affected by diverse confounders.[28 29] With the implementation of recent, effective prevention strategies, however, incidence and mortality have been decreasing.[30–33] In addition to VAP, some patients with severe HAP deteriorate and then require mechanical ventilation for management, and this population is referred to as ventilated HAP (fig 1).

HAP develops after ≥48 hours of hospitalization and is classified as HAP in the ward, with a mortality rate of 13–28%. HAP in the ICU (non-ventilated ICU HAP) has a mortality of 15%, and VAP and ventilated HAP have a mortality rate of up to 28%.

In epidemiological studies, the average rate of VAP in the US is four cases per 1000 days of mechanical ventilation,[5 34] which represents half the rate reported in Europe: 9.5 cases per 1000 days of mechanical ventilation.[35] In recent years, the incidence of VAP has gradually declined in the US and in Europe, possibly in relation to the implementation of preventive care bundles.[36 37] However, the use of surveillance definitions developed by the Centers for Disease Control and Prevention (CDC) resulted in concern about the accuracy of the VAP definition, especially as rates dropped but mortality did not. These VAP definitions have recently been supplemented by ventilator associated event (VAE) reporting. The updated definitions include any condition that is associated with a decline in oxygenation. Incidence of VAP is greater than with the previous definition, although VAE may not always be the result of infection, and is of unclear significance as a measure of ICU quality of care. Furthermore, it is not widely used in Europe.[38]

In the US, some quality initiatives have a goal of "zero ventilator associated pneumonia" (ZERO-VAP)[38]; however, concerns about the ZERO-VAP target have been raised.[39] First, it is difficult to quantify and determine the eradication of a preventable disease

doi: 10.1136/bmj-2021-065871 | *BMJ* 2021;375:e065871 | the bmj

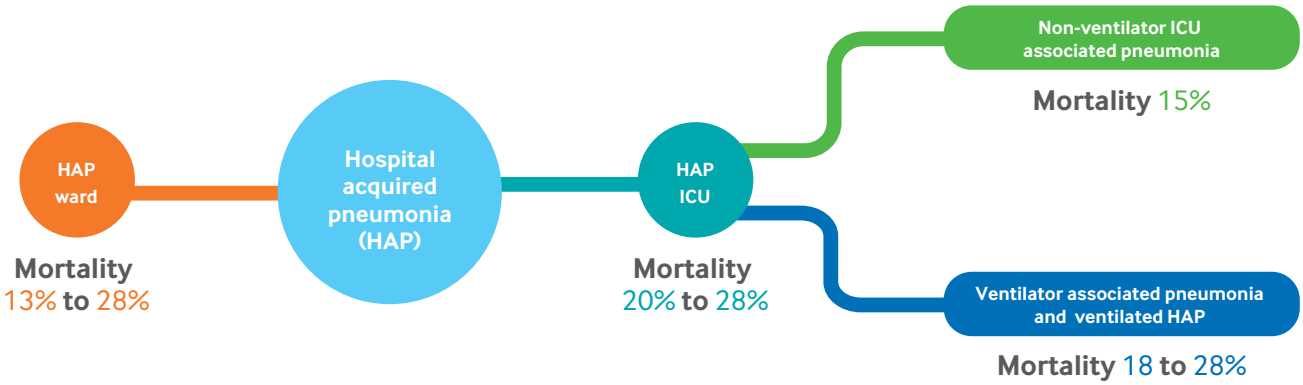

Fig 1 | Spectrum of hospital acquired pneumonia

without accurate and reliable diagnostic methods, and no gold standard exists for diagnosing VAP. Second, the CDC VAP definition can be manipulated, leading to an underestimation of occurrence of VAP. Third, monitoring adherence to long term prevention measures poses a notable challenge. To determine the efficacy of interventions in reducing VAP, innovative diagnostic markers and the application of improved research methods are needed.

HAP and VAP are considered leading causes of death from nosocomial infection.[4 28 40 41] Mortality in the US is approximately 13%,[5] but a recent prospective and multicenter observational study[42] indicated that 30 day mortality caused by VAP was 30% in Europe. Similarly, after analyzing data of 14 212 patients admitted to the ICU for more than 48 hours, a separate French observational study reported that the risk of 30 day mortality increased by 82% in patients with HAP and 38% in patients with VAP.[43] Compounding these findings is an analysis of non-inferiority endpoints by Talbot et al[44] that examined seven bacterial HAP/VAP datasets and reported that 28 day all-cause mortality was higher in ventilated HAP (28%), followed by VAP (18%) and non-ventilated HAP (15%). These results highlight the influence of patient related factors on outcomes, as reported in a previous, prospective observational study,[45] and underpin the impact of preventive measures.

Antibiotic resistance is a major concern in HAP/VAP globally, especially because of its association with prolonged length of hospital stay and higher mortality. Gram negative microorganisms are the pathogens that most frequently cause HAP/VAP.[46] In an observational, 24 hour point prevalence study[46] of 15 202 ICU patients from 1155 centers across 88 countries, infections caused by *Enterococcus* resistant to vancomycin, *Klebsiella* resistant to β-lactam antibioticsó including third generation cephalosporins and carbapenems, or *Acinetobacter* species resistant to carbapenemó were independently associated with a higher risk of death. These findings emphasize the importance of knowing local epidemiology and risk factors for multidrug resistant pathogens to target the most likely etiologic pathogens in patients with HAP/VAP.

New concepts in pneumonia pathogenesis

CAP and cardiovascular disease

In addition to its short term sequelae, CAP has long term implications for mortality that may be related to heart disease as a complication of pneumonia.[47] Approximately 8-25% of patients with CAP have been reported to experience at least one cardiac event during hospitalization,[48-50] including acute coronary syndrome, new or worsening heart failure, new or worsening arrhythmias, and acute stroke.[51 52] Such events are more commonly reported in patients with chronic cardiovascular disease, in severe cases of pneumonia, and in conditions related to pathogens, such as pneumococcus and influenza virus,[53-55] but they can also occur in patients without chronic cardiovascular disease.[56]

The pathogenesis of cardiac dysfunction in pneumonia is multifactorial, involving host factors, pathogens, and medication.[51 57 58] A great proportion of hospitalized CAP patients are older adults with comorbidities (chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus), who may have chronic endothelial dysfunction.[59-61] During the acute phase of pneumonia, inflammation occurs in the lungs, but a systemic inflammatory response also occurs that augments the release of pro-inflammatory cytokines, which could directly or indirectly injure the myocardium.[62]

Streptococcus pneumoniae (pneumococcus) is the most common bacterial pathogen in CAP, and clinical and animal data have shown that the organism can invade the myocardium directly and cause cardiac damage.[63] Pneumolysin, the most important virulence factor of pneumococcus, can also cause cardiomyocyte necroptosis[64] (a programmed mode of cell death that increases inflammation), which may result in cardiac damage.[65] Similarly, pneumococcal bacteremia is known to be a risk factor for cardiac events,[66] with the risk lasting for up to 10 years after the pneumonia episode.[62 66] Shenoy et al,[67] in an experimental study of pneumococcus, reported that cardiac damage

depends on the ability of a clinical isolate to cause high grade bacteremia, and pathological damage may depend on the pneumococcal strain. Respiratory viruses, identified using new molecular testing, are frequently reported as a cause of CAP, and they too can cause cardiac injury. A self-controlled case series reported an increase in the risk of myocardial infarction during the week after laboratory confirmed infection with influenza virus. This risk was six times higher when compared with the risk present during the year before or after infection. Importantly, an elevated incidence of acute myocardial infarction after influenza infection was observed in adults aged ≥65.[68] Compounding these findings is a time series analysis of English hospital admissions, in which a small yet strongly significant correlation was noted between weekly occurrence of new acute myocardial infarction or ischemic stroke hospitalization in older adults, especially in patients aged ≥65 with positive laboratory results for respiratory viruses (including influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, rhinovirus, and adenovirus).[69] Replication of respiratory viruses within the myocardium may lead to a cascade of inflammatory processes that causes fibrosis and, thereby, cardiac necrosis. It may also lead to alterations in lipid metabolism, by which the course of atherosclerosis would be accelerated, and serve as a possible mechanism for cardiac damage.[70 71] Several mechanisms have been suggested to help explain cardiac effects as sequelae of viral infection; however, we do not yet have complete understanding of the exact mechanisms, or the ideal approach to prevention.

VAP and the endotracheal tube

Endotracheal intubation allows pathogens to enter directly into the lower respiratory tract, interfering with normal lung defense mechanisms, with the endotracheal tube (ETT) becoming a reservoir for pathogenic microorganisms.[72] Biofilm formation on the tube has two important implications: (1) it causes intraluminal narrowing that may impede weaning from the ventilator, and (2) bacterial pathogens grow embedded and protected in an extracellular polymeric substance or matrix that makes them more resistant to antimicrobials,[73] and they serve as a nidus of endobronchial infection[74] that is difficult to eliminate.[75] Biofilm is detectable in approximately 95% of endotracheal tubes in ventilated patients, occurring within hours of endotracheal intubation.[76] The most frequent biofilm pathogens are *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcusaureus*, and *Klebsiella pneumoniae*, and colonization may be the first step toward VAP.[77 78] An observational study[79] reported that biofilm formation, after at least 24 hours, was less in both silicone coated polyvinyl chloride (PVC) and noble metal coated PVC ETTs than in uncoated PVC ETTs.

The role of the microbiome in pneumonia pathogenesis

Multiple bacterial species are present in the healthy lung, which is not, as previously thought, sterile, and they comprise the "lung microbiome."[80] *Prevotella*, *Veillonella*, *Streptococcus*, *Fusobacterium,* and *Hemophilus* species are the most frequently reported bacterial pathogens in this microbiome, which is a dynamic community, with a constant equilibrium among species and in an interaction with lung immunity. In the healthy state, the microbiome comprises a diverse population of organisms, and they are present in a relatively low microbial load.

Acute infection and chronic pulmonary diseases, such as pneumonia, non-cystic fibrosis bronchiectasis,[81] chronic pulmonary obstructive disease (COPD),[82] or asthma[83] disturb the equilibrium of the healthy lung microbiome. This dysbiosis results in changes in microbial communities, often leading to less diversity and an increase in the microbial load.[84] The risk factors for dysbiosis that lead to bacteria such as pneumococcus to cause disease are only partially understood.[85]

In a longitudinal analysis of the lung microbiome in critically ill intubated patients, the authors observed that the biomass of the lung microbiome increased over time.[86] A progressive change also took place in community diversity, as bacterial taxa in the healthy lung are replaced with a less diverse group of organisms, including *Staphylococcus* spp, and *Acinetobacter* spp in patients with pneumonia.[87] In addition, a relation exists between the lung microbiome and lung immunity,[88 89] which shows that the enrichment of the lung microbiome with oral taxa was associated with inflammation in the lung (increased alveolar concentration of inflammatory cytokines, increased alveolar lymphocytes) and a distinct metabolomic profile.

Recently, it was proposed[88] that HAP is not only an acute condition caused by contamination of the lung by exogenous microorganisms, but also the result of a dysbiosis between the lung microbiome and mucosal immunity. This approach could lead to the implementation of new preventive methods to restore immune function, and novel therapies that allow for the manipulation of the lung microbiome instead of its elimination by antibiotics.

Diagnosis of pneumonia

Suspicion and clinical diagnosis of pneumonia in patients coming from the community rely on the presence of acute symptoms (≤7 days) of a lower respiratory tract infection that include cough, expectoration, fever, chills, and dyspnea, together with the presence of a new infiltrate on chest radiograph.[90] Typically, pneumonia symptoms may be less evident in older people, in whom the absence of fever was reported in approximately 30% of patients.[91] Similarly, individuals treated with antibiotics, steroids, and non-steroidal anti-inflammatory drugs may also present with less evident symptoms of lung infection.[92] Other conditions, such as pulmonary embolism, pulmonary edema, and lung cancer, may mimic pneumonia and present with fever and pulmonary infiltrates.[93] It is helpful and important to review prior chest radiographs, if

doi: 10.1136/bmj-2021-065871 | *BMJ* 2021;375:e065871 | thebmj

possible, to rule out other diseases. Rarely, after a negative chest radiograph, patients may receive a diagnosis of pneumonia by more sensitive methods such as a chest computed tomography (CT) scan.

VAP is usually suspected when patients have symptoms of fever or hypothermia, leukocytosis or leukopenia, and evidence of purulent secretions in an ETT or tracheostomy aspirate, in the setting of a new or progressive lung infiltrate. Data on clinical, radiological, and laboratory parameters often provide the basis for clinicians to initiate antimicrobial treatment in patients with VAP. Interestingly, a systematic review and meta-analysis (including 25 studies and data of 1639 patients)[94] that investigated performance of several diagnostic tests for VAP reported that sensitivity and specificity of physical examination findings for VAP were poor: fever (66.4% [95% confidence interval (CI) 40.7 to 85.0], 53.9% [95% CI 34.5 to 72.2]) and purulent secretions (77.0% [95% CI 64 to 85.9], 39.0% [95% CI 25.8 to 54.0]). The presence of infiltrates on chest radiographs had a sensitivity of 88.9% (95% CI 73.9 to 95.8%) and specificity of 26.1% (95% CI 15.1 to 41.4%); the endotracheal aspirate had a sensitivity of 75.7% (95% CI 51.5 to 90.1) and specificity of 67.9% (95% CI 40.5 to 86.8); and the clinical pulmonary infection score (CPIS) >6 had a sensitivity of 73.8% (95% CI 50.6 to 88.5) and specificity of 66.4% (95% CI 43.9 to 83.3). The study found poor specificity for the classic clinical indicators for VAP diagnosis, highlighting the need for a new diagnostic tool for this condition.

For pneumonia diagnosis, radiographic confirmation is essential. It provides important information on the site, extent, and associated features of pneumonia. The presence of pleural effusion or multilobar involvement serves as an indicator of severity.[6] Reported sensitivity and specificity of chest radiographs in CAP were 66% and 77%, respectively.[95] A standard chest radiograph for CAP consists of posteroanterior and lateral views. However, diagnostic performance of chest radiographs increases with the use of lateral projection images. Chest radiographs have some limitations, as shown by results obtained in a prospective and multicenter interventional study[96] that included 319 patients diagnosed with CAP who had a chest radiograph and thoracic CT scan at admission. In this study, no evidence of pneumonia was present on CT scans in 30% of patients diagnosed with CAP based on the clinical presentation and chest radiograph. Conversely, the CT scan identified up to 35% of pneumonia cases, which had not initially been caught by chest radiographs. These results underpin the potential importance of CT scans as a complementary tool to chest radiographs in diagnosing pneumonia. Further, CT scans could prove helpful in cases with non-specific radiographic findings; pulmonary complications such as empyema or cavitation; clinical suspicion of an underlying lesion such as lung carcinoma; and recurrent or non-resolving pneumonia.[97]

In VAP, clinicians often use chest radiographs to determine evidence of new infiltrates. Radiography is reported as the most widely employed imaging technique in diagnosing this condition.[98] However, chest radiographs are not sensitive or specific for VAP diagnosis.[99 100] Interestingly, lung ultrasound is a promising, non-invasive imaging tool for such diagnoses. A systematic review and meta-analysis[101] that included 12 studies with data of 1515 patients found that lung ultrasounds have a sensitivity and specificity of 88% and 89%, respectively, with an area under the curve (AUC) of 0.95. A separate systematic review and meta-analysis[102] showed that the emergence of sub-pleural consolidations on lung ultrasound in anterior lung regions had a specificity of 95% (95% CI 79% to 99%) on the eve of the day when clinical suspicion was present. On the day when clinical suspicion was present, the emergence of lobar/sub-lobar consolidations in anterior lung regions had a specificity of 100% (95% CI 87% to 100%) while the emergence of lobar/sub-lobar consolidations with dynamic air bronchograms had a specificity of 96% (95% CI 81% to 99%). These data suggest that lung ultrasounds are highly accurate in diagnosing VAP. However, applying this technique requires considerable expertise and practice, especially in mechanically ventilated patients.

Guideline recommendations[6] for microbiological diagnosis in patients with severe CAP include obtaining good quality sputum, blood, and pharyngeal swab samples to detect respiratory viruses in patients with severe illness. Molecular detection through polymerase chain reaction (PCR) is the gold standard for virus diagnosis.[103] Detecting viruses through antigen based assays is limited owing to low sensitivity (40-70%); in cases of negative results, although specificity ranges between 90% and 95%, testing cannot rule out a viral infection diagnosis.[103] Sputum is recommended to be collected before starting antibiotic treatment. Sensitivity for Gram staining of a sputum sample is approximately 80% in cases of pneumococcal pneumonia and 78% in pneumonia caused by *Staphylococcus*; specificity is 93-96%.[104 105] Results of respiratory samples must be interpreted with caution: the detected microorganism may form part of the normal flora or may be present as a result of colonization in the patient.[103] Also, urinary antigen detection testing of *S pneumoniae* and *L pneumophila* has good sensitivity and specificity, and should be performed in those with severe CAP. Finally, bronchoscopic samples such as bronchoalveolar lavage in intubated patients are easy to retrieve and provide information about organisms in the lower respiratory tract.

Debate continues about the best respiratory sampling method and the most accurate diagnostic approach for nosocomial pneumonia. The latest US guidelines[5] recommend non-invasive sampling (endotracheal aspiration) with semiquantitative cultures to diagnose VAP and non-VAP. However, with the aim of reducing antibiotic exposure, the latest European guidelines[7] recommend obtaining distal

quantitative cultures before antibiotic treatment in clinically stable patients with suspected VAP. Similarly, guidelines also recommend obtaining a sample from the lower respiratory tract (eg, distal or proximal quantitative or qualitative culture), even in patients with HAP, to narrow the initial spectrum of empirical antibiotic treatment. The recommendation includes retrieving lower respiratory samples before any change in antimicrobial treatment; as such a change significantly reduces the sensitivity and specificity of both qualitative and quantitative samples.

Molecular diagnostic methods that allow for the detection of multiple pathogens and antimicrobial resistance in a single sample could greatly facilitate VAP management, especially in patients with risk factors for multidrug resistant (MDR) bacteria. These methods are highly sensitive, and if a suspected MDR pathogen is absent with this testing, it is not likely to be present on culture, and antibiotic coverage of that pathogen can be stopped. For example, an RCT[106] investigated whether rapid automated polymerase chain reaction (rPCR) assays that detect meticillin resistant *S aureus* (MRSA) in bronchoalveolar lavage (BAL) samples could safely decrease the use of vancomycin or linezolid for suspected cases of MRSA pneumonia in mechanically ventilated patients (22 patients received antibiotic management based on the rPCR result and 23 other patients continued with routine care). It found that duration of anti-MRSA treatment for the initial suspected episode of MRSA pneumonia was significantly shorter in the intervention group (32 h *v* 72 h, P<0.001). Furthermore, hospital mortality was reported to be 14% and 39% in the intervention and routine care groups, respectively (P=0.06). Similarly, a separate experimental study sought to detect *S aureus* in endotracheal aspirate samples from mechanically ventilated patients using GeneXpert MRSA/*S aureus* endotracheal aspirate (ETA) assay in comparison with two PCR based methods (including GeneXpert) and three culture based methods. It found that the assays had both a sensitivity and specificity of 100% when compared with the other assays, underpinning the value of these new diagnostic techniques in the management of pneumonia. Nonetheless, clinical implementation of these techniques in routine clinical practice is difficult partly because of high costs and a lack of standardization. Also, because of the highly sensitive nature of these techniques, they cannot always distinguish colonization from infection.

The changing etiology of pneumonia

Severe CAP: the emerging role of viruses, community acquired MRSA, and selected Gram negative bacteria

In severe CAP, pneumococcus remains the most commonly identified bacterial pathogen.[59 107–109] However, the past decade has seen an increase in the use of molecular diagnostic techniques that facilitate detection of multiple viruses in one respiratory sample. As a result, respiratory viruses in severe CAP have been reported with increasing frequency.[110–112] Additionally, an increase in the age of patients hospitalized for pneumonia is important, as this population is more susceptible to severe viral infection.[60 113 114] Data from a systematic review and meta-analysis from Europe have shown a prevalence of respiratory viruses of between 20% and 25% of CAP cases[115 116]; these percentages are similar to those reported in studies from the US[110] and Asia.[111]

The US multicenter study,[110] which included 2259 adults with radiographic evidence of pneumonia and specimens available for etiological diagnosis, found that a viral cause was detected in 23% of cases, with rhinovirus and influenza virus being the most common. Bacterial pathogens were detected in 11%, while mixed viral and bacterial pathogens were in 3%. Among the 482 ICU patients included in this study, the most common group of microorganisms included respiratory viruses (22%), followed by bacterial pathogens (19%), and bacterial-viral co-infection (4%). A prospective, multicenter observational study[111] found that, of the 2649 non-immunocompromised adult patients with CAP, viruses were identified in 915 of the 1177 with an etiological diagnosis. Influenza was present in 581 patients, and non-influenza virus in 240. ICU admission occurred in 8.3% and 5.4% owing to influenza virus and non-influenza virus, respectively. Also, the 90 day mortality rates were 3.8% and 1.7%, respectively, with no significant differences.

Similarly, a prospective cohort study that compared the outcomes of hospitalized patients with CAP and influenza with those with and without bacterial co-infection[117] found that those with viral and bacterial co-infection had acute respiratory distress syndrome (ARDS) more frequently than those with pure viral CAP or bacterial CAP (21% viral and bacterial co-infection; 19% viral CAP; and 10% bacterial CAP; P<0.001). They also required ICU admission more often (32% viral and bacterial co-infection; 32% viral CAP; and 13% bacterial CAP; P<0.001) than those with bacterial pneumonia. Interestingly, 30 day mortality did not differ among groups (4% in viral and bacterial co-infection; 3% viral CAP; and 6% bacterial CAP [P=0.232]).

In the ICU, viruses often are present in combination with bacterial pathogens. In one observational study of 49 mechanically ventilated patients with CAP,[118] 49% of cases had a viral etiology, pure or mixed, with rhinovirus and adenovirus the most frequently detected. Sepsis can also complicate viral infections. A retrospective observational study[113] reported that 26% of ICU patients presented with viral sepsis and had an associated ICU mortality of 8%. Moreover, ARDS is another frequent complication in viral pneumonia.[119] One recent study found that respiratory viruses were the causal agent in 11% of mechanically ventilated patients with CAP and ARDS.[120] A prospective observational study[121] investigated the incidence of respiratory viruses in patients admitted to 16 Italian ICUs during the

2014-15 influenza season. It reported that the influenza A virus was the most frequently detected (83%), followed by human rhinovirus (12%), and RSV and influenza B virus (3% each). A prospective cohort study[122] from Australia and New Zealand reported an increase in ICU admissions resulting in pneumonia and sepsis during the winter and spring of 2017, with influenza virus strain H3N2 being predominant. This rise in ICU admissions was also higher than during the 2009 H1N1 pandemic.

Bacteria such as *S pneumoniae, H influenzae,* and *S aureus* constantly colonize the upper airways, with at least one of these bacteria colonizing approximately 20-50% of healthy individuals. Colonization can also synergize with viral infections to add to poor outcomes.[123 124] In influenza infections, colonization by *S pneumoniae* has been associated with an increased risk of ICU admission and mortality. Colonization by *S aureus* has been associated with an increased risk of mortality in adults, and MRSA co-infection has been associated with severe disease and mortality.[125 126]

However, it is uncertain whether co-detection represents either true co-infection (two or more pathogens that infect the patient at the same time and run the same time course) or sequential infection instead (eg, a preceding viral infection with some residual viral shedding and a secondary bacterial infection). Both scenarios pose a challenge in routine clinical practice. A prior influenza infection is well known to damage epithelial cells, thereby leading to a compromised barrier function of the airway and exposed surface receptors, and favors adhesion of bacteria. An experimental study[127] found that a prior influenza infection increased pneumococcal colonization of the murine nasopharynx and promoted a spread of bacteria into the lungs. It observed that influenza accelerated bacterial replication in vivo, and sialic acid was identified as a host derived metabolite stimulating pneumococcal proliferation. Recent findings regarding innate and adaptive immune system responses during co-infection with influenza virus and *S pneumoniae* or *S aureus* showed that the presence of both microorganisms resulted in dysregulated cytokine and chemokine production. This type of dysregulated production occurred after pattern recognition receptors recognized the pathogen and triggered dynamic changes in immune cell recruitment and activation.[128] A hyperactivated signaling pathway elicits a massive recruitment of immune cells and an overshooting of inflammatory processes, leading to severe lung damage. As a result of such injury, pathogens can penetrate more deeply into the tissue and uncontrolled replication of viral and bacterial pathogens can occur.[128] Also, suppressed immune reactions can take place, owing to lower pathogen clearance which occurs as a result of an inhibition of immune cells or signaling cascades by pathogens. All of these mechanism can explain increased morbidity and mortality in cases of influenza virus and bacterial co-infection.[128 129]

Community acquired MRSA (CA-MRSA) infections are reported globally and are associated with severe outcomes. The estimated incidence is approximately 0.51-0.64 cases per 100 000 inhabitants.[130] Clinical presentation of CA-MRSA includes necrotizing pneumonia, a severe form of pneumonia associated with abscess and cavity formation, and sometimes empyema. CA-MRSA has been reported in healthy, young adults with CAP and no exposure to healthcare settings and leads to poor clinical outcomes and high mortality, especially in those with post-influenza infection. Severe, necrotizing CA-MRSA pneumonia is thought to be caused by the exotoxin Panton-Valentine leukocidin (PVL).[131] PVL is a toxin that causes leukocyte destruction and tissue necrosis.

P aeruginosa, extended spectrum β-lactamase producing *Enterobacteriaceae* and MRSA (PES pathogens) form part of another important microorganism group that causes CAP. Such pathogens account for up to 6% of hospitalized patients with CAP and a microbiological diagnosis; however, current empirical therapy recommendations in guidelines do not target this pathogen group. In 2015, a prospective observational study[132] proposed the PES score to assess the risk of pneumonia owing to PES pathogens. The score showed modest accuracy in validation studies in the general population (AUC 0.81; 95% CI 0.74 to 0.88), ICU population (AUC 0.73; 95% CI 0.61 to 0.86) and in very old patients with CAP (AUC 0.64; 95% CI 0.58 to 0.71).[133] Other scores assessing the potential risk of MDR pathogens in patients with CAP have been published in the past 10 years[134-137] (fig 2).

A prospective, multicenter cohort study[138] assessed an antibiotic strategy based on risk factors for PES pathogens, independent of the site of pneumonia acquisition. Risk factors for PES pathogens included antibiotic therapy in the past 180 days; poor functional status (Barthel index <50 or performance status ≥3); hospitalization for >2 days within the past 90 days; occurrence of pneumonia ≥5 days after admission to an acute hospital; requirement for hemodialysis; and immunosuppression. In a multicenter cohort of 1089 patients (656 CAP, 238 healthcare associated pneumonia, 140 HAP and 55 VAP), patients with 0-1 risk factors for PES pathogens were to receive treatment with standard therapy (a β-lactam plus a macrolide), whereas patients with ≥2 risk factors for PES pathogens were proposed to receive appropriate therapy for HAP (a two or three drug regimen combining an antipseudomonal β-lactam with a quinolone or aminoglycoside plus optional linezolid or vancomycin). Approximately 83% of patients received treatment according to the proposed algorithm, and only 4% had inappropriate treatment. Basing the algorithm on risk factors for PES pathogens and disease severity instead of the site of pneumonia acquisition appeared to simplify antimicrobial treatment and improve the accuracy of empirical treatment. However, this algorithm requires validation in a large population. Table 1 describes the recommendations for therapy of

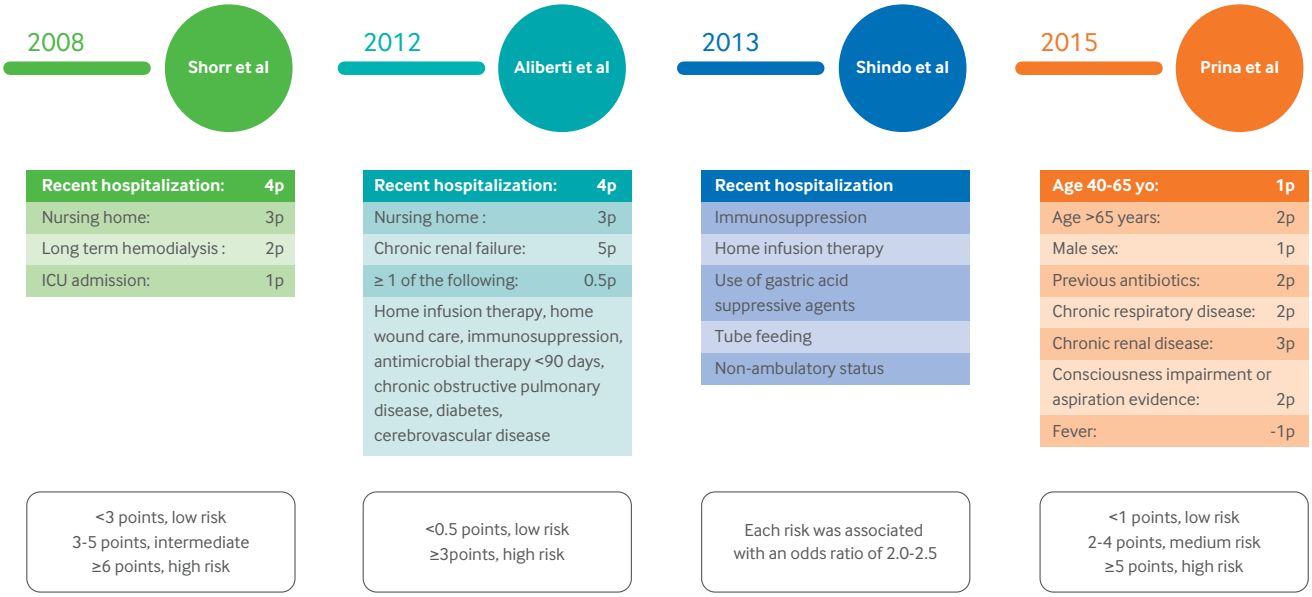

Fig 2 | Prediction of multidrug resistant pathogens in CAP

HAP/VAP proposed by current US and European guidelines, but the principles extend to patients with severe CAP as well, and were used in the algorithm cited above.

It is important to recognize that in patients with CAP, PES pathogens do not have a universal distribution. A limited number of centers have reported this group of pathogens,[132 133 139–142] so clinicians should consider local etiology and resistance patterns.

VAP: the role of MRSA and drug resistant Gram negative pathogens

In the past decade, studies from the US and Europe have reported an increase in the prevalence of MDR pathogens in VAP.[143–145] The most frequent MDR Gram negative pathogens were *P aeruginosa*, *Acinetobacter* spp, and extended spectrum β-lactamase producing *Enterobacteriaceae*. In addition, MRSA is the most frequent MDR Gram positive pathogen. These pathogen groups are associated with poor clinical outcomes, especially because of inappropriate or delayed initial antimicrobial treatment.[146–148]

Current guidelines from ATS/IDSA[5] and the European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Asociación Latinoamericana del Tórax[7] highlight the importance of administering prompt and adequate empirical treatments based on a patient's risk stratification for MDR pathogens and on local microbiological and antibiotic resistance data (table 2).

US guidelines[5] identify five risk factors associated with MDR pathogens: previous intravenous antibiotic treatment within 90 days; hospitalization for ≥5 days before the occurrence of VAP; septic shock at the time of VAP; ARDS preceding VAP; and the need for renal replacement treatment before VAP onset. Interestingly, a prospective cohort study[149] found that in using these risk factors for MDR pathogens, sensitivity was high, yet specificity was very low and overall performance poor, which could lead to excessive broad spectrum empirical antimicrobial treatment. Among the five risk factors, only antibiotic use in the past 90 days (negative predictive value of 79%) and ≥5 days of hospitalization (negative predictive value of 80%) before pneumonia were strongly associated with the presence of MDR

Table 1 | Empiric treatment according to US And European guidelines

Risk for MDR pathogens	US guidelines	European guidelines
Low	Single, narrow spectrum antibiotic with activity against non-resistant Gram negative microorganisms	**(≤15% mortality risk, low MDR risk)** Narrow spectrum antimicrobial with activity for meticillin susceptible *S aureus* and non-resistant Gram negatives: ertapenem, ceftriaxone, cefotaxime, moxifloxacin, levofloxacin
High	Dual antibiotic treatment against Gram negative microorganisms. MRSA coverage if >10-20% of *S aureus* isolates are MRSA	**(>15% mortality risk and/or high MDR risk)** No septic shock: monotherapy with broad spectrum agent active against >90% of likely Gram negative pathogens +/-MRSA (if > 25% of *S aureus* isolates are MRSA) Septic shock: combination therapy with anti-pseudomonal regimen +/-MRSA (if > 25% of *S aureus* isolates are MRSA)

Both guidelines agree on stratifying patients according to individual and local community risk factors for MDR pathogens.[6]

Table 2 | High risk of MDR pathogens in HAP/VAP	
European guidelines (2017)	US guidelines (2016)
Previous antibiotic treatment	Previous antibiotic treatment
≥5 days of hospitalization	≥5 days of hospitalization
Septic shock	Septic shock
Hospital settings with high rates of MDR pathogens (>25%)	ARDS before VAP
Previous colonization by MDR Pathogens	Acute renal replacement therapy before initiation of VAP
Mortality risk >15%	

VAP=ventilator associated pneumonia; ARDS=acute respiratory distress syndrome; HAP=hospital-acquired pneumonia; MDR=multidrug resistant.[4;6]

pathogens. The presence of ARDS preceding VAP had a negative predictive value of 71% for the presence of MDR pathogens. European guidelines[7] do not include renal replacement treatment or ARDS in the definition of patients at high risk for MDR microorganisms. For this reason, in addition to individual patient risk factors, European guidelines include hospital settings with high rates of MDR microorganisms (>25% of all ICU pathogens are MDR), local patterns of resistance, and prior colonization by MDR microorganisms as determinants of risk for such pathogens.

Treatment

CAP guideline recommendations

The ATS/IDSA CAP guidelines were published in 2019[6] and included changes from previous recommendations.[12] Most notably, the guidelines recommended eliminating the category of healthcare associated pneumonia (HCAP), to avoid overuse of empiric broad spectrum treatment. The incidence of resistant pathogens was low enough, even among those with severe CAP, and administering broad spectrum therapy for all those with HCAP led to its overuse. Patients with HCAP who faced high CAP mortality generally had clinical features and multiple comorbidities that affected survival, rather than the mere presence of risk factors for resistant pathogens. Furthermore, reports about adverse outcomes, such as an increase in infections related to *Clostridium difficile*, was associated with the overuse of broad spectrum antibiotics.[135 150 151]

Initial choice of antibiotic

For most patients with severe CAP, initial treatment includes the combination of a β-lactam plus a macrolide or fluroquinolone. For patients without MRSA and pseudomonal risk factors, the β-lactam could be cefotaxime, ceftriaxone, ampicillin-sulbactam, or ceftaroline.[6] For those with pseudomonal risk factors, pathogen coverage could be achieved with a β-lactam such as piperacillin/tazobactam, cefepime, ceftazidime, imipenem, or meropenem. In patients who have a β-lactam allergy, aztreonam is an alternative. Newer β-lactams with activity against more resistant Gram negative pathogens are discussed below.

How to select broad spectrum antibiotics

In severe CAP, evidence suggests that the combination of β-lactam plus macrolide significantly improves the prognosis of patients, compared with non-macrolide regimens.[152-155] A retrospective observational study reported that patients with severe pneumonia had lower rates of 14 day (8% *v* 27%, P=0.02) and 30 day (18% *v* 37%, P=0.05) mortality with combination therapy of β-lactam plus macrolides than with flouroquinolones.[154] Similarly,[153] a prospective multicenter observational study assessed 257 intubated patients with severe CAP, in which 20% of patients received monotherapy and the remaining 80% combination therapy. After the authors adjusted for severity, the use of macrolides was associated with lower ICU mortality (hazard ratio 0.48, CI 95% 0.23 to 0.97, P=0.04) when compared with patients receiving fluoroquinolones. The authors recommended combination therapy with macrolides in intubated patients with severe CAP. A meta-analysis that comprised 9850 critically ill patients with CAP[155] observed that combination therapy with a macrolide and β-lactam (21% *v* 24%; risk ratio 0.82; 95% CI 0.70 to 0.97; P=0.02) was associated with reduced mortality when compared with other regimens. A prospective cohort study that included 1131 patients with CAP[152] found that combination treatment based on pneumonia severity index (PSI) and CURB-65 score[12 22 23] did not significantly reduce 30 day mortality in either group. However, combination therapy based on the ATS/IDSA criteria significantly reduced 30 day mortality in patients with severe pneumonia (odds ratio (OR) 0.12, 95% CI 0.007 to 0.57), albeit not in cases of non-severe pneumonia (OR 1.85, 95% CI 0.51 to 5.40).

An advantage of combination therapy is its ability to cover atypical pathogens, as well as a potential benefit from the immunomodulatory effect of macrolides to attenuate bacterial virulence factors and an excessive systemic inflammatory response. An experimental study[156] found that macrolides inhibit pneumolysin production, even in macrolide resistant strains of pneumococcus. Pneumolysin promotes the extra-pulmonary spread of pneumococcus, which can, in turn, cause cardiac damage.[57] Furthermore, when used as a part of combination therapy,[157] macrolides reduced mortality in patients with severe CAP, especially in those with pneumococcal bacteremia.[158 159] A prospective, multicenter and international study analyzing 844 cases of pneumococcal bacteremia[159] found that combination therapy was associated with a lower 14 day mortality rate (23% *v* 55%, P=0.015).

Optimal treatment for MRSA

Unlike nosocomial MRSA, CA-MRSA is susceptible to clindamycin, TMP-SMX, and doxycycline.[160]

Clindamycin and linezolid can inhibit toxin production, which blocks bacterial protein synthesis.[160] According to the ATS/IDSA guideline recommendations,[6] antimicrobial therapy for MRSA should only be used when patients have risk factors for MRSA (prior respiratory isolation of MRSA; recent hospitalization [in the last 90 days], and use of parenteral antibiotics [in the last 90 days], and locally validated risk factors for MRSA). Clinicians should also obtain samples for cultures and perform nasal PCR testing to guide decisions regarding whether to de-escalate or continue treatment.[161 162]

Options for empirical therapy for MRSA include vancomycin 15 mg/kg/12 h (adjustments made based on levels) or linezolid 600 mg/12 h. In patients with severe necrotizing CAP, it may be necessary to add an anti-toxin to treatment, such as adding clindamycin to vancomycin or using linezolid (which also has anti-toxin activity) alone. Linezolid penetrates the lung better than vancomycin, but clinicians more commonly administer it in HAP and VAP than in CAP.

Antiviral agents

Viral pneumonia is recognized as a common cause of severe CAP, and many patients have mixed viral and bacterial infections. The ATS/ISDA guidelines recommend using anti-influenza treatment (oseltamivir) in all patients with documented severe influenza, regardless of symptom duration, although the benefit is greatest if given within the first 48 hours.[6] In addition, because of a high incidence of bacterial co-infections, antibiotic treatment is recommended in confirmed influenza infections, especially to cover for pneumococcus and *S aureus*. However, de-escalation of antibiotics is recommended in patients who show no evidence of bacterial co-infection and show clinical stability after 48-72 hours of antibiotic treatment.[6]

In patients with covid-19, bacterial pneumonia has sometimes been observed alongside viral pneumonia.[163 164] Most patients with lung infiltrates initially receive antibiotics, with discontinuation of such treatment occurring based on clinical assessment and serial measurements of biomarkers such as procalcitonin.[165 166] For hospitalized patients with covid-19, the antiviral agent remdesivir has shown some benefit, particularly during the early course of the disease, as have monoclonal antibodies (especially in early stage disease and outpatients).[167] Data from two large randomized controlled trials on the use of remdesivir in covid-19 showed varying results. The ACTT-1 trial[168] found that remdesivir was superior to placebo in shortening the time to recovery in hospitalized adults with covid-19, while the SOLIDARITY trial[169] reported no mortality benefit. Currently, remdesivir is recommended for patients with severe covid-19 who require oxygen therapy, excluding mechanical ventilation or extracorporeal membrane oxygenation.[170]

For other viral pneumonias in immune competent hosts, antiviral agents are not routinely administered.

Corticosteroids

Corticosteroids have immunomodulatory properties and are frequently used as adjunctive therapy in severe pneumonia because of their anti-inflammatory effects. Controversy still surrounds their use, but data from some studies have shown that the use of glucocorticoids reduces mortality in patients with severe CAP, especially in those with a high level of systemic inflammation.[171 172] However, this effect has yet to be seen in patients with non-severe pneumonia.

In a multicenter, randomized, double blind and placebo controlled trial study investigating the effect of corticosteroids on treatment failure in 120 patients with severe CAP (61 received methylprednisolone and 59 were control cases) and a high inflammatory response (initial levels of C reactive protein (CRP) >15 mg/dL), treatment failure was reported to be less frequent in the group receiving corticosteroids (13%) when compared with the placebo group (31%) (P=0.02). However, in-hospital mortality was similar between both groups (10% *v* 15%; P=0.37). The study concluded that the use of low dose corticosteroids (0.5 mg/kg every 12 hours for five days) decreased treatment failure in patients with severe CAP and a high inflammatory response, when compared with placebo.[171]

Another systematic review and meta-analysis,[172] including data from 1506 patients (748 patients were randomized to corticosteroids and 758 patients to placebo) from six trials reported that the use of corticosteroids in hospitalized patients with CAP reduced the time to clinical stability (adjusted difference, −1.03 days; 95% CI −1.62 to −0.43 days; P=0.001) and length of hospital stay (−1.15 days; 95% CI −1.75 to −0.55 days; P<0.001) by approximately one day without any effect on mortality (OR, 0.75; 95% CI 0.46 to 1.21; P=0.24). However, the authors also reported an increased risk for CAP related re-hospitalization (OR 1.85, 95% CI 1.03 to 3.32, P=0.04) and hyperglycemia (OR 2.15; 95% CI 1.60 to 2.90, P<0.001).

Data from two randomized clinical trials[173 174] support the use of hydrocortisone as adjunctive therapy in patients with septic shock. The randomized Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock trial [173] included 3658 patients with septic shock undergoing mechanical ventilation (1832 patients randomized to hydrocortisone group and 1826 to the placebo group). The participants received either hydrocortisone at a dose of 200 mg per day or placebo for seven days or until death or ICU discharge. The authors reported that the use of hydrocortisone in this population did not result in a lower 90 day mortality when compared with patients who received placebo (OR, 0.95; 95% CI 0.82 to 1.10; P=0.50). A multicenter, double blind and randomized trial[174] evaluating the effect of hydrocortisone plus fludrocortisone treatment against a placebo in 1241 patients with septic shock (614 randomized to hydrocortisone plus fludrocortisone and 627 to placebo) reported that 90

day all-cause mortality was lower in patients who received hydrocortisone plus fludrocortisones (43% *v* 49%, P=0.03).

Conversely, several studies observed that the use of corticosteroids in influenza may be associated with a significantly higher mortality rate possibly resulting from superinfection.[175-177] Despite these concerns, recent studies of severe covid-19 pneumonia with respiratory failure have shown a mortality benefit, particularly in the controlled, open label Randomized Evaluation of COVID-19 Therapy trials, which included the administration of 6 mg of dexamethasone daily for 10 days[178] in patients on oxygen or mechanical ventilation.

The ESCAPe trial (NCT01283009) investigated the use of methylprednisolone (20 days of treatment: seven days (40 mg/day), seven days (20 mg/day), and six days (12 mg/day and 4 mg/day) versus placebo in 583 critically ill adult patients with CAP, with the primary study outcome being 60 day mortality. The mean age of patients was 68.8 years and mean PSI was 124 patients. Of these, 96% were male and 33% were on ventilation. With respect to 60 day mortality, the results showed no differences in superiority between methylprednisolone and placebo (OR 0.90; 95% CI 0.58 to 1.40, P=0.635).[179]

Current recommendations in international guidelines on the use of corticosteroids as adjunctive therapy are to not administer them routinely in patients with either non-severe CAP or severe influenza pneumonia. However, corticosteroids may prove valuable in patients with severe pneumonia with refractory septic shock or a high systemic inflammatory response, as well as in those with pneumococcal CAP with meningitis.[6]

Immunoglobulin treatment

Some studies have shown lower levels of circulating immunoglobulins in patients admitted to ICU with severe pneumonia when compared with non-ICU patients, as well as an association between these lower levels of immunoglobulins and increased mortality.[180 181] These data suggest a possible role of immunoglobulins in adjunctive treatment for severe CAP.

In a single center observational study[182] investigating the role of immunoglobulin levels (IgG, IgA, IgM) in 362 patients with CAP (172 ward and 190 ICU) and their impact on outcomes, IgG2 levels <301 mg/dL were associated with worse prognosis. Furthermore, low concentrations of IgG2 were an independent marker of ICU admission and mortality. Similarly, a separate single center observational study[181] reported that IgM concentrations were inversely associated with severity and a protective factor against mortality in cases of severe influenza CAP.

The efficacy of immunoglobulins was investigated as an adjunctive therapy in mechanically ventilated patients with severe CAP and septic shock.[183] In an observational study of 1324 patients receiving immunoglobulins as adjunctive therapy and 6940 controls, no significant association was seen between adjunctive therapy and mortality. Similarly, another post hoc subgroup analysis of data from a retrospective cohort study including 960 patients with sepsis and septic shock found no association between the use of low dose IgG immunoglobulins as adjunctive therapy and decreased ICU (21% *v* 18%, P=0.185) or in-hospital mortality (34% *v* 31%, P=0.066).[184]

Additionally, a double blind phase II study[185] published data on 160 patients with severe pneumonia and requiring invasive mechanical ventilation, who were randomized to trimodulin (a polyclonal antibody preparation containing IgM, IgA, and IgG) or placebo for five consecutive days. Treatment with trimodulin did not increase ventilator-free days when compared with patients in the placebo group (median days 11 *v* 8, P=0.173). Interestingly, the authors observed that a subset of patients with elevated CRP and/or lower IgM levels had reduced mortality and an increase in ventilator-free days, with trimodulin treatment.

VAP guideline recommendations

In the past decade, the increased incidence of MDR pathogens reported in VAP has complicated management, and infection caused by these organisms has been associated with worse outcomes.[147 148] Local epidemiology and susceptibility information should guide empiric treatment for VAP, in conjunction with a careful assessment of patients' risk factors for MDR pathogens.[5] Risk factors for MDR pathogens differ between US[5] and European[7] guidelines; however, when considering empiric therapy, local bacteriology and resistance patterns remain important, as does prior antibiotic treatment (table 2).

Combination therapy: why and when

In general, local antibiotic susceptibility patterns and the likelihood of MDR, Gram negative, or mixed Gram positive and Gram negative infections guide the choice between monotherapy and combination therapy.

According to US guidelines,[5] if the patient has no risk factors for specific MDR pathogens, such as *P aeruginosa* or MRSA, and receives treatment in an ICU with a low prevalence of MDR microorganisms (<10%), the use of a single, narrow spectrum antibiotic with activity against non-resistant Gram negative microorganisms is recommended (weak recommendation, low quality evidence). Following European guidelines, the use of narrow spectrum antibiotics active against non-resistant Gram negative microorganisms is recommended for patients with a low risk of both MDR microorganisms and mortality who receive treatment in an ICU with a low prevalence of MDR microorganisms (<25%) (weak recommendation, very low quality evidence).[7]

The use of dual antibiotic treatment is recommended in patients presenting with a high risk of MDR pathogens. A systematic review and meta-analysis [186] compared monotherapy and combination therapy

as empiric treatment for patients with VAP. The study included data of 41 trials and 7015 patients. No significant differences were noted in mortality between both regimens. The authors reported that the ceftazidime-aminoglycoside combination was inferior to meropenem (relative risk (RR) 0.70; 95% CI 0.53 to 0.93). Mortality and treatment failure rates for monotherapy and combination regimen were similar (RR for mortality with monotherapy, 0.94; 95% CI 0.76 to 1.16; and RR for treatment failure with monotherapy 0.88; 95% CI 0.72 to 1.07). The authors highlighted the small proportion of VAP cases caused by MDR pathogens as possibly explaining the lack of benefits of combination therapy. A randomized controlled trial[187] comparing empiric monotherapy with meropenem versus ciprofloxacin plus meropenem for suspected VAP showed no significant differences in 28 day mortality between groups (RR 1.05, 95% CI, 0.78 to 1.42, P=0.74). Furthermore, no differences were noted regarding length of ICU and hospital stay, treatment response, and emergence of antibiotic resistant bacteria. However, the study excluded patients known to be colonized or infected with *Pseudomonas* or MRSA. Interestingly, the authors analyzed cases (n=56) that had infection caused by *Pseudomonas* species, *Acinetobacter* species, and MDR Gram negative bacilli. They observed a higher likelihood of adequate initial therapy (84.2% *v* 18.8%, P=0.001) and microbiological clearance (64.1% *v* 29.4%, P=0.05) when a combination regimen of meropenem plus ciprofloxacin was administered to those with resistant organisms, compared with monotherapy. Similarly, a systematic review,[188] including data from 12 randomized controlled trials and 3571 patients with VAP, found no significant difference in all-cause mortality (OR 0.97, 95% CI 0.73 to 1.30), clinical recovery (OR 0.88, 95% CI 0.56 to 1.36), and length of ICU stay (mean difference 0.65, 95% CI 0.007 to 1.23) between monotherapy and combination therapy. However, the authors acknowledged that these data may not be generalizable to all patient groups, given that the study did not identify patients with an increased risk of MDR bacteria. Additionally, in cases caused by MDR bacteria, results from observational studies[189-192] showed combination regimens including broad spectrum β-lactam with an aminoglycoside increased the percentage of appropriately treated cases when compared with monotherapy or a combination regimen of a β-lactam and fluoroquinolone.

US guidelines recommend the use of dual antibiotic treatment against Gram negative microorganisms for patients with a high risk of an MDR microorganism; those with lung disease; and those treated in an ICU with either an unknown or high prevalence of MDR pathogens (>10%) (weak recommendation, low quality evidence). If the patient is also at risk for an MRSA infection, treatment for this pathogen is added. Conversely, European guidelines recommend a broader spectrum approach in empiric antibiotic treatment if the patient is in an ICU with a high prevalence of MDR microorganisms (>25%) and/or at high risk of MDR microorganisms and mortality. Specific choices are then guided by the hemodynamic status of the patient. In individuals with no septic shock at diagnosis, monotherapy is considered adequate, provided that the agent is active against >90% of common Gram negative organisms in the ICU setting. Broad spectrum, multidrug treatment is recommended for patients with septic shock. However, this therapy should provide coverage for *P aeruginosa*, *Enterobacteriaceae* with extended spectrum β-lactamases, and *A baumannii* (if highly prevalent in the ICU) (strong recommendation, low quality evidence). The rationale for combination therapy is to provide sufficiently broad spectrum coverage to make appropriate treatment more likely than with monotherapy. In addition, combination therapy could eradicate organisms more quickly than monotherapy, being associated with a survival advantage over monotherapy for patients with septic shock and a mortality risk >25%.[7 193]

Treatment for MDR pathogens: MRSA, Pseudomonas, Acinetobacter

Use of empiric anti-MRSA antimicrobials should be decided based on epidemiological data. The ATS/ISDA guidelines[5] suggest their use if >10-20% of *S aureus* isolates are MRSA, whereas European guidelines[7] suggest use if >25% of *S aureus* isolates are MRSA. For patients with a high risk of MDR pathogens or those treated in an ICU setting with >10% of Gram negative pathogens resistant to the best monotherapy option, European guidelines[7] suggest the use of two anti-pseudomonal agents from two separate classes.

The US guidelines[5] divide high risk patients into two main groups: (1) patients with a high risk of MDR pathogens and no septic shock who can receive a single broad spectrum agent active against >90% of Gram negative-likely microorganisms, and (2) patients with a high risk of MDR pathogens and septic shock who should receive a dual anti-pseudomonal regimen, with coverage for *Acinetobacter* spp and ESBL-producing *Enterobacteriaceae* if such pathogens are prevalent in the local antibiogram.

In recent years, new therapeutic options have become available for HAP/VAP, especially targeting MDR pathogens:

1. Ceftazidime-avibactam (CEF/AVI) is a combination of a third generation cephalosporin with a non-β-lactam β-lactamase inhibitor. CEF/AVI is active against a variety of β-lactamases, including Ambler Class A (*K pneumoniae* carbapenemases and ESBL-type enzymes), Ambler Class C, and some Ambler-class D serine enzymes (eg, oxacillinase oxa-48). However, it is not active against metallo-β-lactamases or Acinetobacter oxa-like carbapenemases. Ceftazidime-avibactam received approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in HAP/VAP. The combination regimen was shown to be non-inferior to meropenem in a randomized

controlled trial of carbapenem resistant, non-*Enterobacteriaceae* pneumonia.[194]

2. Ceftolozane-tazobactam (CEF/TAZ) is a cephalosporin and β-lactamase inhibitor with in vitro activity against multidrug resistant *P aeruginosa* and ESBL-producing *Enterobacteriaceae*. Results from a randomized controlled double blind, non-inferiority trial including 726 mechanically ventilated patients with Gram negative nosocomial pneumonia[195] compared CEF/TAZ (2 g ceftolozane plus 1 g tazobactam infused for 1 hour every 8 hours) (362 subjects in the ceftolozane-tazobactam group) with meropenem (1 g infused for 1 hour every 8 hours) (364 subjects in the meropenem group). In the study, both drugs were equivalent and well tolerated in mechanically ventilated patients with Gram negative nosocomial pneumonia. However, CEF/TAZ had a mortality advantage in those with ventilated HAP and those with previously unsuccessful antibiotic treatment for the current nosocomial pneumonia episode. This new antibiotic has received approval by the FDA and EMA for HAP treatment.[196 197]

3. Meropenem-vaborbactam is a combination agent containing an existing β-lactam antibiotic (meropenem) with a cyclic boronate non-β-lactamase inhibitor (vaborbactam) and is active against Gram negative microorganisms, including those with extended spectrum β-lactamases and *K pneumoniae* carbapenemases. However, it is not active against metallo-β-lactamase and oxacillinase producing strains. Although not approved for VAP, meropenem-vaborbactam showed an advantage for clinical recovery, when compared with the best available therapy (usually colistin), in a trial that included mechanically ventilated patients with carbapenem resistant *Enterobacteriaceae*.[198]

4. Imipenem-relebactam (IR) is a combination agent containing an existing β-lactam antibiotic (imipenem-cilastatin) with non-β-lactam β-lactamase inhibitor (relebactam) and is active against Gram negative microorganisms, including Ambler class C, extended spectrum β-lactamases and *K pneumoniae* carbapenemases. However, it is not active against metallo-β-lactamase and oxacillinase producing strains. In a phase III trial that compared IR with piperacillin-tazobactam in 537 patients with nosocomial pneumonia, with half of the patients being mechanically ventilated, both therapies were equivalent in clinical recovery and mortality.[199] Survival was, however, higher in the subgroup of those mechanically ventilated at baseline when they received IR.[199]

5. Cefiderocol is a siderophore cephalosporin that binds to iron and enters the bacterial cell, using the iron transport system. It is active against a wide range of carbapenem resistant pathogens including *Enterobacteriaceae, P aeruginosa,* and *Acinetobacter baumanii*. It is also active against *Stenotrophomonas maltophilia*. Cefiderocol is approved for nosocomial pneumonia, including VAP, but has shown no survival advantage or higher recovery rates when compared with meropenem. In a separate study, patients with VAP had a lower survival than with the best available therapy.[200 201]

Using pharmacokinetic/pharmacodynamic principles to optimize dosing

Applying pharmacokinetic/pharmacodynamic (PK/PD) principles to antibiotic dosing and delivery regimens may improve the outcomes of patients with pneumonia. Drugs that kill bacteria in a concentration dependent fashion (aminoglycosides) have their efficacy maximized in relation to how high a high peak concentration they achieve, relative to minimum inhibitory concentration (MIC) of the target pathogen, in the serum and at the site of infection. This can be optimized when the entire 24 hour dose is administered as a single infusion.[185 194] Conversely, β-lactams (penicillins, cephalosporins, carbapenems) reach their optimal bactericidal effect in relation to how long the concentration stays above the MIC of the target pathogen and this can be optimized by using a prolonged or continuous infusion.[131 195] For example, continuous infusion of vancomycin was associated with better outcomes,[202 203] while higher doses and a continuous infusion of linezolid led to improved outcomes, especially in patients with ARDS and infections caused by resistant pathogens.[204 205]

Aerosolized antibiotics

Aerosolized antibiotics can deliver higher antibiotic concentrations in the lung parenchyma and have less systemic toxicity than intravenous treatment, yet no recommendations call for their use as routine adjunctive therapy in VAP. Three randomized trials have investigated the use of adjunctive nebulized antibiotics in patients with VAP[206-209]: the IASIS trial (aerosolized adjunctive amikacin and fosfomycin in patients with VAP and suspected MDR, Gram negative bacteria); the INHALE trial (inhaled amikacin as adjunctive therapy in patients with VAP and suspected MDR, Gram negative bacteria); and the VAPORISE trial (inhaled tobramycin as adjunctive therapy in patients with VAP). All three studies showed negative results for improved clinical outcomes or mortality.

In 2019, results from a meta-analysis by the ATS/IDSA HAP guideline committee, which included nine studies of inhaled antibiotics for VAP treatment,[210] showed that the use of inhaled antibiotics was beneficial in treating VAP caused by difficult-to-treat microorganisms. The ATS/IDSA guidelines[5] therefore recommend adding inhaled antibiotics to systemic antibiotics in cases of Gram negative pneumonia caused by MDR microorganisms. Inhaled colistin should be used instead of polymyxin B. Inhaled antibiotics are also recommended as a last resort for patients with VAP and sensitive or resistant microorganisms who are not responding to treatment. European guidelines[7] do not recommend the use of inhaled antibiotics until more data have become available.

Treatment duration for CAP and HAP

Data from two meta-analyses showed that short course antibiotic therapy (five to seven days) may be adequate in treating patients with CAP.[211 212] In the first meta-analysis of 19 randomized controlled trials including data of 4861 patients and irrespective of severity of pneumonia, the authors did not find any differences regarding clinical recovery rates between short (≤6 days) and long course treatments (≥7 days).[211] Furthermore, short course treatment was associated with fewer, serious adverse events (RR=0.73; 95 CI 0.55 to 0.97) and potentially lower mortality than long course treatment (RR=0.52; 95% CI 0.33 to 0.82). A second meta-analysis analyzing data from seven randomized controlled trials including 3021 patients[212] showed that short course antibiotic treatment (five days) in adults with bacterial CAP achieved clinical responses similar to those observed in patients receiving long course antibiotic therapy (7 to 14 days). The authors also reported that all-cause mortality did not differ in relation to duration of antibiotic treatment, and short course antibiotic therapy was associated with a lower rate of adverse effects.

According to the ATS/IDSA guidelines,[6] a patient's clinical stability should guide duration of antibiotic treatment, with it being no less than five days. The guidelines also state that longer courses of antibiotics are recommended in cases of pneumonia complicated by meningitis, endocarditis, and other deep seated infections. In cases of infection by other, less common pathogens, guidelines do not specify duration of treatment.[6]

For patients with VAP, US guidelines[5] recommend a seven day course of antibiotic treatment. Depending on the rate of improvement of clinical, radiological, and laboratory parameters; however, some patients may require a shorter or longer duration of antibiotics. European guidelines[7] recommend a 7-8-day course of antibiotic treatment in patients who are not immunodeficient, do not present with cystic fibrosis or other pulmonary complications (empyema, lung abscess, cavitation, or necrotizing pneumonia); received appropriate treatment initially; do not have a highly resistant pathogen (*P aeruginosa,* carbapenem resistant *Acinetobacter* spp, carbapenem resistant *Enterobacteriaceae)*; and respond well to antibiotic treatment.

Biomarkers

Biomarkers provide information about host response to infection and pharmacological intervention; however, heterogeneous immunological and inflammatory responses in patients with pneumonia make their universal use challenging.[213 214] Biomarkers, such as (CRP), procalcitonin (PCT), lymphocytes, red blood cell distribution, interleukin-6, pro-adrenomedullin, N-terminal pro-B-type natriuretic peptide, soluble triggering receptor expressed on myeloid cells-1, copeptin, and soluble form of urokinase-type plasminogen activator receptor have been studied.[214-222]

In clinical practice, CRP, PCT, and, more recently, lymphocytes are the most frequently used biomarkers to guide duration of antibiotic treatment and prognosis in pneumonia.

CRP is a major acute phase protein produced by macrophages in response to any type of inflammation, including bacterial and viral infections. It is released between four and six hours after acute injury, peaking at around 36-48 hours. However, CRP has low specificity in pneumonia diagnosis, as levels can be high owing to other clinical causes, such as neoplasia or autoimmune diseases.[223]

PCT is a peptide precursor of the hormone calcitonin that is synthesized in the thyroid gland. It increases during inflammatory and infectious diseases, primarily as an acute phase reactant produced in the liver. In healthy individuals, plasma concentrations of PCT are very low (<0.1 ng/mL); however, levels rise with bacterial infections.[223]

Although no PCT threshold has been found to discriminate specifically between viral and bacterial infection for adults hospitalized with CAP,[224] higher levels suggest an increased probability of bacterial infection.

Interestingly, results from secondary analyses of data from two prospective longitudinal cohorts [225] reported that the time from symptom onset in pneumonia to initial healthcare presentation may affect levels of CRP and PCT. The study included 541 patients with CAP, divided into two groups based on the time to symptoms: early presenters (<3 days since symptom onset) and late presenters (>3 days). In the study, CRP and PCT were lower in early presenters, suggesting that the time to presentation may influence the interpretation of these biomarkers. The authors also propose considering CRP as possibly a more useful biomarker in patients with a longer duration of symptoms; in patients with symptoms lasting ≤48 hours, PCT might hold better utility.

In patients with CAP, PCT has been studied as a tool to reduce duration of antibiotic treatment. Several RCTs have used serial PCT measurements to determine duration of antibiotic treatment, showing reduced treatment duration. However, control group participants who received standard treatment had antibiotic treatment courses lasting much longer than seven days[226-229] and exceeding guideline recommendations.

Current international guidelines recommend initiating antimicrobial treatment based on clinical suspicion in radiographically confirmed CAP and not on the basis of PCT levels.[6] Interestingly, studies have reported a correlation between higher levels of CRP and PCT and an increased risk of complications, admission to ICU, and short term mortality.[216 230-232]

A large meta-analysis of 26 studies on duration of antibiotic treatment in respiratory infections (CAP, HAP, VAP, exacerbations of COPD, and bronchitis)[233] found that treatment duration guided by PCT was associated with a reduction of 2.4 days of treatment (5.7 *v* 8.1 days, P<0.001). Further, lower mortality was observed in the group that received PCT guided

antibiotic treatment (OR 0.83, 95% CI 0.70 to 0.99, P=0.037). These benefits applied to patients with both CAP and VAP in the ICU. The recommendation set forth in European HAP/VAP guidelines[7] is to use serial PCT measurements in conjunction with clinical assessment to shorten duration of antibiotic treatment in pneumonia cases that required a prolonged course of treatment.

More recently, a study[213] investigated the value of lymphocytes as a biomarker of severity and found that lymphopenia conferred an increased risk of severity in patients with CAP, and that adding lymphocyte count to the CURB-65 score improved predictions of 30 day mortality. Another study from China[234] reported that the combination of PO_2/FiO_2 and lymphocyte count predicted mortality and ICU admission in hospitalized patients with influenza pneumonia. The authors found that the likelihood of severe influenza pneumonia was high in patients with PO_2/FiO_2 ≤250 or peripheral blood lymphocyte count $<0.8\times10^9$/L. Lymphocyte count was also studied as a biomarker in ICU acquired pneumonia (ICU-AP). A study from Spain of 473 patients reported that lymphocytopenia was an independent predictor of 90 day mortality in non-immunocompromised patients.[235] Lymphocyte count is simple and a non-costly biomarker that could prove useful, especially in hospitals where other biomarkers are not available; utility of this biomarker has been shown in severe CAP and in immunocompromised patients with ICU-AP.

Despite the promising value of CRP and PCT, limitations remain to biomarker use in daily practice. Biomarkers should be viewed as an adjunctive tool in clinical evaluations and decision making processes related to site of care and treatment duration.

Pneumonia prevention

CAP prevention focuses on vaccinations, and not so much on those at risk of severe pneumonia. This discussion will center on VAP and measures aimed at reducing the incidence of infection and improving the clinical course, with emphasis on interrupting disease pathogenesis. Currently, preventing colonization with pathogenic bacteria and modification of aspiration remain at the forefront of VAP prevention measures. Some of the most studied preventive measures in VAP include head-of-bed elevation, decreased duration or avoidance of mechanical ventilation, early mobilization, endotracheal tube cuff design, aspiration of subglottic secretions, oral care, and the use of probiotics.

Ventilated patients in the supine position (head elevation between 0° and 10°) have an increased risk of aspiring gastric contents when compared with patients in a semi-recumbent position (head of bed elevation between 30° and 45°).[236-238] In 2016, a review and meta-analysis[238] including eight RCTs comprising 759 patients compared a supine position with a semi-recumbent position. The authors found that the semi-recumbent position significantly reduced the risk of suspected VAP when compared with supine position (14% *v* 40%, RR 0.36; 95% CI 0.25 to 0.50). However, no significant difference was found in the occurrence of microbiologically confirmed VAP. A retrospective cohort study including 5539 patients undergoing mechanical ventilation for at least three days[239] reported that head-of-bed elevation, as well as measures such as sedative infusion interruptions, spontaneous breathing trials, and thromboprophylaxis, was associated with less time to extubation. The lateral Trendelenburg and semi-recumbent position were compared in a RCT[240] that included 395 patients (194 patients in the Trendelenburg position and 201 in the semi-recumbent position). The study showed that the semi-recumbent position was associated with a higher incidence of VAP than the lateral Trendelenburg position (4% *v* 0.5%; RR 0.13; 95% CI 0.02 to 1.03; P=0.04). No differences were seen in microbiologically confirmed VAP and mortality. However, this trial was stopped early due to adverse events in patients randomized in the lateral Trendelenburg position.

Head-of-bed elevation to a semi-recumbent position is a frequent intervention practiced as a preventive measure against VAP.[241 242]

Micro-aspiration of oropharyngeal secretions owing to invasive mechanical ventilation is the main risk factor for VAP.[243-245] Avoiding mechanical ventilation,[246-249] decreasing the time of intubation,[250] and spontaneous breathing trials[251 252] are effective measures in preventing VAP. Various investigators have evaluated the benefits of modifying shapes and materials of the endotracheal tube cuff as it relates to minimizing fluid leakage into the lungs via the cuff and preventing VAP. Cuffs made from materials such as polyurethane have undergone testing and are shown to fit the shape of the trachea better and thus reduce the flow of fluids to the lungs. In contrast with conventional cylindrical cuffs, newer cuffs are conical in shape and approach the tracheal wall evenly and uniformly at the point of maximum cuff diameter. Nonetheless, results from RCTs and meta-analysis do not support the conclusion that these innovations prevent VAP better than traditional materials and forms.[253-256]

Suctioning of subglottic secretions that pool above the endotracheal tube cuff is associated with lower VAP rates; however, controversy exists about its value in decreasing duration of mechanical ventilation, length of ICU stay, and ventilator associated events.[257-262] A recent systematic review and meta-analysis[263] that included 20 studies (nine systematic reviews and meta-analyses and 20 RCTs) found that drainage of subglottic secretions significantly reduced the incidence of VAP (RR 0.56; 95% CI 0.48 to 0.63, I^2=0%, P=0.841) and mortality (RR 0.88; 95% CI 0:80 to 0:97, I^2=0%, P=0.888). More high quality studies are needed to elucidate the potential contribution of this intervention in ventilated patients. Interestingly, a meta-analysis that investigated the influence of subglottic secretion drainage on the causative microorganisms of VAP

found a significant association between subglottic secretion drainage and decreased VAP caused by Gram positive cocci and *Hemophilus influenzae* (OR 0.29, 95% CI 0.18 to 0.48; P<0.001). However, no significant differences were seen in VAP caused by non-fermentative bacteria and enterobacteria.[264]

Selective digestive decontamination (SDD) is a prophylactic antibiotic strategy that controls the overgrowth of pathogens in the gut, especially those that are Gram negative and multidrug resistant, using topical oral and gastric antibiotics such as tobramycin, polymyxins, and amphotericin B, along with initial intravenous antibiotics. Previous studies[265 266] of ICU settings with low levels of antibiotic resistance observed that SDD and selective oropharyngeal decontamination (SOD) were associated with improved clinical outcomes. One study[267] reported that SDD was more effective than SOD for preventing infection.

The main concerns surrounding the use of SDD is the increased risk of antibiotic resistance[268] and the effect that antibiotic use may have on patients without bacterial infections. A study[269] showed that the use of SDD resulted in the selection of four resistance genes. It concluded that these results showed a limited risk of SDD in antibiotic resistance. Further, in ICU settings where moderate-to-high prevalence rates of antibiotic resistance pathogens exist, the use of SDD was not observed to be associated with decreased infection rates.[270] In a randomized clinical trial of decontamination strategies for mechanically ventilated patients in the ICU, the SDD strategy was reported not to add more benefit than standard care in ICU settings with a high prevalence of antibiotic resistant microorganisms.[270]

In ICU settings with a low prevalence of antibiotic resistant microorganisms, the SDD strategy was associated with less antibiotic resistance and with improved clinical outcomes. More studies are required in ICU settings with a higher prevalence of resistant microorganisms.

Additionally, the use of chlorhexidine for oral hygiene in patients under mechanical ventilation has been reported to reduce the risk of VAP.[271-274] An RCT[275] found that use of chlorhexidine 2%, in comparison with chlorhexidine 0.2%, was more effective as a preventive measure for VAP and in reducing oropharyngeal colonization. A Cochrane systematic review and meta-analysis reported that more evidence was needed regarding the use of chlorhexidine and its relation with reducing infection, mortality, and length of stay in the ICU.[274] Also, results from observational studies and a meta-analysis of RCTs showed an association between the use of chlorhexidine and increased mortality risk.[239 276-278] The micro-aspiration of chlorhexidine may cause ARDS[273 279] and could explain this harmful association. The use of chlorhexidine was also reported to be associated with adverse effects such as damage to oral mucosa (ie, erosive oral lesions, ulcerations, white or yellow plaques, and bleeding mucosa)[280] and hypersensitivity effects.[281 282] Additionally, a reported decrease in susceptibility to chlorhexidine is concerning.[283]

Finally, as part of SDD, short term and prophylactic systemic antibiotic treatment may be effective alone in patients who are urgently intubated after cardiac arrest or neurological injury. The use of 24-48 hour systemic antibiotic treatment may eradicate organisms that are aspirated during the intubation process and prevent the onset of VAP in the ensuing 48 hours.[284 285]

Emerging approaches to management

Investigations in metagenomics based on next generation sequencing (NGS) may significantly improve the diagnosis and treatment of pneumonia, especially in severe cases.[286-288] NGS allow for more accurate and rapid detection of multiple pathogens in a single assay. Plasma microRNA signatures have also emerged as a tool capable of predicting disease severity, being recently reported as a good marker of severity and deterioration of ICU patients with a diagnosis of covid-19.[289] Indeed, this technology may help clinicians provide more personalized management[290] in severe cases of pneumonia. Furthermore, evidence is growing for the value of technology, such as the Filmarray pneumonia test. This is a multiplex PCR assay that can detect the most commonly identified pathogens in pneumonia and their resistance patterns. Data on pathogen resistance have been recently published in a sub-study of the PROGRESS trial (a prospective and multicenter randomized trial).[291] The study included 56 patients with CAP and no risk factors for MDR pathogens, as well as another 34 patients with risk factors for MDR pathogens. Specifically, the pneumonia assay had a detection rate of 72%, whereas conventional microbiological testing had a rate of 10% (P<0.001). These results underpin the value of this new diagnostic test and its potential implementation in clinical practice in the future.

Guidelines

In formulating this review, we considered guidelines on the management of CAP, HAP, and VAP from the Infectious Diseases Society of America and the American Thoracic Society,[5 6] the European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Asociacion Latinoamericana del Torax.[5 7 12] Key recommendations are summarized above, and include likely pathogens, recommended diagnostic testing, choice of initial antimicrobial treatment, duration of treatment, use of adjunctive therapy, and prevention of pneumonia.

In patients with severe CAP, initial treatment is with the combination of a macrolide or fluoroquinolone, with a β-lactam. The β-lactam is chosen based on the presence of pseudomonal risk factors, and additional coverage for MRSA is also decided based on the presence of specific risk factors. Patients with documented influenza should receive oseltamivir,

Questions for future research

- What is the value of molecular diagnostic testing in the definitive microbial diagnosis of severe pneumonia? What is its role in de-escalating antimicrobial treatment?
- How do we identify severe cases of pneumonia, early in the course of illness?
- How do we complement the combination of biomarkers and severity scores with clinical judgment to improve the identification of severe pneumonia?
- What are the characteristics of patients with severe CAP who might benefit from corticosteroids or other anti-inflammatory therapies?
- Can new antimicrobial agents help us more effectively manage patients who are infected with MDR pathogens?
- Is short course antibiotic treatment necessary in patients with severe viral pneumonia?

with the addition of antibiotics. Treatment is for a minimum of 5-7 days and duration may be guided by biomarkers such as procalcitonin. Adjunctive therapy with corticosteroids is not routinely recommended, but may have benefit for selected patients. Prevention is focused on vaccination of at-risk populations.

HAP/VAP remains a diagnostic challenge, and existing guidelines differ on the value of bronchoscopic samples, cultured quantitatively. Recommendations for therapy are to treat all patients for *P aeruginosa* and other Gram negatives pathogens, with coverage for MDR pathogens and MRSA, based on individual risk factors and the frequency of these pathogens in a given ICU. Newer agents and inhaled antibiotics may have a role for some highly resistant pathogens. Most patients will need combination treatment, and duration of therapy can be as short as seven days if initial therapy is accurate, the pathogen is not highly resistant, and the patient has responded well to therapy. Prevention is focused on available interventions such as head-of-bed elevation, prevention of aspiration, and a focus on decreased duration or avoidance of mechanical ventilation, early mobilization, and endotracheal tube cuff design.

Conclusions

Despite advances in diagnosis, management, antimicrobial therapy, and prevention, pneumonia continues to have a major impact on healthcare systems worldwide. The emergence of multidrug resistant pathogens, the increasing age of the population, the increased number of patients with multiple comorbidities and polypharmacy are some of the challenges that clinicians face in the management of critically ill patients with pneumonia. Despite some differences in the international guidelines for the management of CAP and HAP/VAP, following these recommendations will ensure better outcomes for patients admitted to the ICU with pneumonia.

Patient involvement: no patients were directly involved in the creation of this article.

Contributors: CC, AT, and MN contributed equally to the design, development, and writing of this manuscript and guarantee authenticity of its authorship.

Provenance and peer review: commissioned; externally peer reviewed.

Competing interests: We have read and understood the *BMJ* policy on declaration of interests and declare the following interests: AT has participated in advisory boards for Pfizer. MN has participated in advisory boards for Pfizer, Merck, Bayer, Gilead, and Abbvie.

1 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-22. doi: 10.1016/S0140-6736(20)30925-9
2 Torres A, Cilloniz C, Niederman MS, et al. Pneumonia. *Nat Rev Dis Primers* 2021;7:25. doi: 10.1038/s41572-021-00259-0
3 Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness?*Curr Opin Crit Care* 2018;24:35-40. doi: 10.1097/MCC.0000000000000476
4 Sangla F, Legouis D, Marti P-E, et al. One year after ICU admission for severe community-acquired pneumonia of bacterial, viral or unidentified etiology. What are the outcomes?*PLoS One* 2020;15:e0243762. doi: 10.1371/journal.pone.0243762
5 Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;63:e61-111. doi: 10.1093/cid/ciw353
6 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45-67. doi: 10.1164/rccm.201908-1581ST
7 Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 2017;50:1700582. doi: 10.1183/13993003.00582-2017
8 Woodhead M, Welch CA, Harrison DA, Bellingan G, Ayres JG. Community-acquired pneumonia on the intensive care unit: secondary analysis of 17 869 cases in the ICNARC Case Mix Programme Database. *Crit Care* 2006;10(Suppl 2):S1 doi: 10.1186/cc4927.
9 Phua J, Ngerng WJ, Lim TK. The impact of a delay in intensive care unit admission for community-acquired pneumonia. *Eur Respir J* 2010;36:826-33. doi: 10.1183/09031936.00154209
10 Renaud B, Santin A, Coma E, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. *Crit Care Med* 2009;37:2867-74. doi: 10.1097/CCM.0b013e3181b02dbb
11 Restrepo MI, Mortensen EM, Rello J, Brody J, Anzueto A. Late admission to the ICU in patients with community-acquired pneumonia is associated with higher mortality. *Chest* 2010;137:552-7. doi: 10.1378/chest.09-1547
12 Mandell LA, Wunderink RG, Anzueto A, et al, Infectious Diseases Society of America, American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl 2):S27-72. doi: 10.1086/511159
13 Phua J, See KC, Chan YH, et al. Validation and clinical implications of the ATS/IDSA minor criteria for severe community-acquired pneumonia. *Thorax* 2009;64:598-603. doi: 10.1136/thx.2009.113795
14 Liapikou A, Ferrer M, Polverino E, et al. Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. *Clin Infect Dis* 2009;48:377-85. doi: 10.1086/596307
15 Kontou P, Kuti JL, Nicolau DP. Validation of the Infectious Diseases Society of America/American Thoracic Society criteria to predict severe community-acquired pneumonia caused by Streptococcus pneumoniae. *Am J Emerg Med* 2009;27:968-74. doi: 10.1016/j.ajem.2008.07.037
16 Brown SM, Jones BE, Jephson AR, Dean NC, Infectious Disease Society of America/American Thoracic Society 2007. Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med* 2009;37:3010-6. doi: 10.1097/CCM.0b013e3181b030d9
17 Chalmers JD, Taylor JK, Mandal P, et al. Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. *Clin Infect Dis* 2011;53:503-11. doi: 10.1093/cid/cir463

18 Laporte L, Hermetet C, Jouan Y, et al. Ten-year trends in intensive care admissions for respiratory infections in the elderly. *Ann Intensive Care* 2018;8:84. doi: 10.1186/s13613-018-0430-6
19 Cavallazzi R, Furmanek S, Arnold FW, et al. The burden of community-acquired pneumonia requiring admission to ICU in the United States. *Chest* 2020;158:1008-16. doi: 10.1016/j.chest.2020.03.051
20 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801-10. doi: 10.1001/jama.2016.0287
21 Ranzani OT, Prina E, Menéndez R, et al. New sepsis definition (Sepsis-3) and community-acquired pneumonia mortality. A validation and clinical decision-making study. *Am J Respir Crit Care Med* 2017;196:1287-97. doi: 10.1164/rccm.201611-2262OC
22 Chen YX, Wang JY, Guo SB. Use of CRB-65 and quick Sepsis-related Organ Failure Assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study. *Crit Care* 2016;20:167. doi: 10.1186/s13054-016-1351-0
23 Kolditz M, Scherag A, Rohde G, Ewig S, Welte T, Pletz M, CAPNETZ Study Group. Comparison of the qSOFA and CRB-65 for risk prediction in patients with community-acquired pneumonia. *Intensive Care Med* 2016;42:2108-10. doi: 10.1007/s00134-016-4517-y
24 Tokioka F, Okamoto H, Yamazaki A, Itou A, Ishida T. The prognostic performance of qSOFA for community-acquired pneumonia. *J Intensive Care* 2018;6:46. doi: 10.1186/s40560-018-0307-7
25 Müller M, Guignard V, Schefold JC, Leichtle AB, Exadaktylos AK, Pfortmueller CA. Utility of quick sepsis-related organ failure assessment (qSOFA) to predict outcome in patients with pneumonia. *PLoS One* 2017;12:e0188913. doi: 10.1371/journal.pone.0188913
26 Kim MW, Lim JY, Oh SH. Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. *Scand J Clin Lab Invest* 2017;77:486-92. doi: 10.1080/00365513.2017.1344298
27 Zhou H, Lan T, Guo S. Prognostic prediction value of qSOFA, SOFA, and admission lactate in septic patients with community-acquired pneumonia in emergency department. *Emerg Med Int* 2020;2020:7979353. doi: 10.1155/2020/7979353
28 Melsen WG, Rovers MM, Groenwold RHH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis* 2013;13:665-71. doi: 10.1016/S1473-3099(13)70081-1
29 Forel JM, Voillet F, Pulina D, et al. Ventilator-associated pneumonia and ICU mortality in severe ARDS patients ventilated according to a lung-protective strategy. *Crit Care* 2012;16:R65. doi: 10.1186/cc11312
30 Burja S, Belec T, Bizjak N, Mori J, Markota A, Sinkovič A. Efficacy of a bundle approach in preventing the incidence of ventilator associated pneumonia (VAP). *Bosn J Basic Med Sci* 2018;18:105-9.
31 Su KC, Kou YR, Lin FC, et al. A simplified prevention bundle with dual hand hygiene audit reduces early-onset ventilator-associated pneumonia in cardiovascular surgery units: An interrupted time-series analysis. *PLoS One* 2017;12:e0182252. doi: 10.1371/journal.pone.0182252
32 Dudeck MA, Edwards JR, Allen-Bridson K, et al. National Healthcare Safety Network report, data summary for 2013, device-associated module. *Am J Infect Control* 2015;43:206-21. doi: 10.1016/j.ajic.2014.11.014
33 Metersky ML, Wang Y, Klompas M, Eckenrode S, Bakullari A, Eldridge N. Trend in ventilator-associated pneumonia rates between 2005 and 2013. *JAMA* 2016;316:2427-9. doi: 10.1001/jama.2016.16226
34 Giuliano KK, Baker D, Quinn B. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control* 2018;46:322-7. doi: 10.1016/j.ajic.2017.09.005
35 Healthcare-associated infections in intensive care unitsó Annual Epidemiological Report for 2017. 2017; https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-intensive-care-units-annual-epidemiological-1
36 Álvarez-Lerma F, Palomar-Martínez M, Sánchez-García M, et al. Prevention of ventilator-associated pneumonia: the multimodal approach of the Spanish ICU "Pneumonia Zero" program. *Crit Care Med* 2018;46:181-8. doi: 10.1097/CCM.0000000000002736
37 Pileggi C, Mascaro V, Bianco A, Nobile CGA, Pavia M. Ventilator bundle and its effects on mortality among ICU patients: a meta-analysis. *Crit Care Med* 2018;46:1167-74. doi: 10.1097/CCM.0000000000003136
38 Álvarez Lerma F, Sánchez García M, Lorente L, et al, Sociedad Española de Medicina Intensiva, Sociedad Española de Enfermería Intensiva. Guidelines for the prevention of ventilator-associated pneumonia and their implementation. The Spanish "Zero VAP" bundle. *Med Intensiva* 2014;38:226-36. doi: 10.1016/j.medin.2013.12.007
39 Colombo SM, Palomeque AC, Li Bassi G. The zero VAP sophistry and controversies surrounding prevention of ventilator-associated pneumonia. *Intensive Care Med* 2020;46:368-71. doi: 10.1007/s00134-019-05882-w
40 Magill SS, Edwards JR, Bamberg W, et al, Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198-208. doi: 10.1056/NEJMoa1306801
41 Micek ST, Chew B, Hampton N, Kollef MH. A case-control study assessing the impact of nonventilated hospital-acquired pneumonia on patient outcomes. *Chest* 2016;150:1008-14. doi: 10.1016/j.chest.2016.04.009
42 Herkel T, Uvizl R, Doubravska L, et al. Epidemiology of hospital-acquired pneumonia: Results of a Central European multicenter, prospective, observational study compared with data from the European region. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2016s6;160:448-55. doi: 10.5507/bp.2016.014
43 Ibn Saied W, Mourvillier B, Cohen Y, et al, OUTCOMEREA Study Group. A comparison of the mortality risk associated with ventilator-acquired bacterial pneumonia and nonventilator ICU-acquired bacterial pneumonia. *Crit Care Med* 2019;47:345-52. doi: 10.1097/CCM.0000000000003553
44 Talbot GH, Das A, Cush S, et al, Foundation for the National Institutes of Health Biomarkers Consortium HABP/VABP Project Team. Evidence-based study design for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *J Infect Dis* 2019;219:1536-44. doi: 10.1093/infdis/jiy578
45 Esperatti M, Ferrer M, Giunta V, et al. Validation of predictors of adverse outcomes in hospital-acquired pneumonia in the ICU. *Crit Care Med* 2013;41:2151-61. doi: 10.1097/CCM.0b013e31828a674a
46 Vincent JL, Sakr Y, Singer M, et al, EPIC III Investigators. Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA* 2020;323:1478-87. doi: 10.1001/jama.2020.2717
47 Restrepo MI, Reyes LF, Anzueto A. Complication of community-acquired pneumonia (including cardiac complications). *Semin Respir Crit Care Med* 2016;37:897-904. doi: 10.1055/s-0036-1593754
48 Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012;125:773-81. doi: 10.1161/CIRCULATIONAHA.111.040766
49 Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis* 2007;45:158-65. doi: 10.1086/518849
50 Viasus D, Garcia-Vidal C, Manresa F, Dorca J, Gudiol F, Carratalà J. Risk stratification and prognosis of acute cardiac events in hospitalized adults with community-acquired pneumonia. *J Infect* 2013;66:27-33. doi: 10.1016/j.jinf.2012.09.003
51 Aldás I, Menéndez R, Méndez R, et al, Grupo NEUMONAC, Anexo. Grupo NEUMONAC. Early and late cardiovascular events in patients hospitalized for community-acquired pneumonia. *Arch Bronconeumol (Engl Ed)* 2020;56:551-8. doi: 10.1016/j.arbr.2020.07.003
52 Tralhão A, Póvoa P. Cardiovascular events after community-acquired pneumonia: a global perspective with systematic review and meta-analysis of observational studies. *J Clin Med* 2020;9:414. doi: 10.3390/jcm9020414
53 Violi F, Cangemi R, Falcone M, et al, SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in Pneumonia) Study Group. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. *Clin Infect Dis* 2017;64:1486-93. doi: 10.1093/cid/cix164
54 Aliberti S, Ramirez JA. Cardiac diseases complicating community-acquired pneumonia. *Curr Opin Infect Dis* 2014;27:295-301. doi: 10.1097/QCO.0000000000000055
55 Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med* 2019;380:171-6. doi: 10.1056/NEJMra1808137
56 Corrales-Medina VF, Taljaard M, Yende S, et al. Intermediate and long-term risk of new-onset heart failure after hospitalization for pneumonia in elderly adults. *Am Heart J* 2015;170:306-12. doi: 10.1016/j.ahj.2015.04.028
57 Anderson R, Nel JG, Feldman C. Multifaceted role of pneumolysin in the pathogenesis of myocardial injury in community-acquired pneumonia. *Int J Mol Sci* 2018;19:1147. doi: 10.3390/ijms19041147
58 Postma DF, Spitoni C, van Werkhoven CH, van Elden LJR, Oosterheert JJ, Bonten MJM. Cardiac events after macrolides or fluoroquinolones in patients hospitalized for community-acquired pneumonia: post-hoc analysis of a cluster-randomized trial. *BMC Infect Dis* 2019;19:17. doi: 10.1186/s12879-018-3630-7
59 Cillóniz C, Polverino E, Ewig S, et al. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013;144:999-1007. doi: 10.1378/chest.13-0062
60 Cillóniz C, Dominedò C, Ielpo A, et al. Risk and prognostic factors in very old patients with sepsis secondary to community-acquired pneumonia. *J Clin Med* 2019;8:961. doi: 10.3390/jcm8070961

61 Bermejo-Martin JF, Martín-Fernandez M, López-Mestanza C, Duque P, Almansa R. Shared features of endothelial dysfunction between sepsis and its preceding risk factors (aging and chronic disease). *J Clin Med* 2018;7:400. doi: 10.3390/jcm7110400
62 Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. *Lancet* 2013;381:496-505. doi: 10.1016/S0140-6736(12)61266-5
63 Brown AO, Millett ERC, Quint JK, Orihuela CJ. Cardiotoxicity during invasive pneumococcal disease. *Am J Respir Crit Care Med* 2015;191:739-45. doi: 10.1164/rccm.201411-1951PP
64 Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. *Nature* 2015;517:311-20. doi: 10.1038/nature14191
65 Beno SM, Riegler AN, Gilley RP, et al. Inhibition of necroptosis to prevent long-term cardiac damage during pneumococcal pneumonia and invasive disease. *J Infect Dis* 2020;222:1882-93. doi: 10.1093/infdis/jiaa295
66 Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up. *BMJ* 2017;356:j413. doi: 10.1136/bmj.j413
67 Shenoy AT, Beno SM, Brissac T, Bell JW, Novak L, Orihuela CJ. Severity and properties of cardiac damage caused by Streptococcus pneumoniae are strain dependent. *PLoS One* 2018;13:e0204032. doi: 10.1371/journal.pone.0204032
68 Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018;378:345-53. doi: 10.1056/NEJMoa1702090
69 Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of English data for 2004-2015. *Clin Infect Dis* 2018;67:8-17. doi: 10.1093/cid/cix1144
70 Sellers SA, Hagan RS, Hayden FG, Fischer WA2nd. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses* 2017;11:372-93. doi: 10.1111/irv.12470
71 Naghavi M, Wyde P, Litovsky S, et al. Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-deficient mice. *Circulation* 2003;107:762-8. doi: 10.1161/01.CIR.0000048190.68071.2B
72 Sommerstein R, Merz TM, Berger S, Kraemer JG, Marschall J, Hilty M. Patterns in the longitudinal oropharyngeal microbiome evolution related to ventilator-associated pneumonia. *Antimicrob Resist Infect Control* 2019;8:81. doi: 10.1186/s13756-019-0530-6
73 Ciofu O, Tolker-Nielsen T. Tolerance and resistance of *Pseudomonas aeruginosa* biofilms to antimicrobial agentsó How *P aeruginosa* can escape antibiotics. *Front Microbiol* 2019;10:913. doi: 10.3389/fmicb.2019.00913
74 Souza LCD, Mota VBRD, Carvalho AVDSZ, Corrêa RDGCF, Libório SA, Lopes FF. Association between pathogens from tracheal aspirate and oral biofilm of patients on mechanical ventilation. *Braz Oral Res* 2017;31:e38. doi: 10.1590/1807-3107bor-2017.vol31.0038
75 Fernández-Barat L, Motos A, Panigada M, et al. Comparative efficacy of linezolid and vancomycin for endotracheal tube MRSA biofilms from ICU patients. *Crit Care* 2019;23:251. doi: 10.1186/s13054-019-2523-5
76 Feldman C, Kassel M, Cantrell J, et al. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. *Eur Respir J* 1999;13:546-51. doi: 10.1183/09031936.99.13354699
77 Danin PE, Girou E, Legrand P, et al. Description and microbiology of endotracheal tube biofilm in mechanically ventilated subjects. *Respir Care* 2015;60:21-9. doi: 10.4187/respcare.02722
78 Fernández-Barat L, Torres A. Biofilms in ventilator-associated pneumonia. *Future Microbiol* 2016;11:1599-610. doi: 10.2217/fmb-2016-0040
79 Thorarinsdottir HR, Kander T, Holmberg A, Petronis S, Klarin B. Biofilm formation on three different endotracheal tubes: a prospective clinical trial. *Crit Care* 2020;24:382. doi: 10.1186/s13054-020-03092-1
80 Man WH, de Steenhuijsen Piters WAA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol* 2017;15:259-70. doi: 10.1038/nrmicro.2017.14
81 Woo TE, Lim R, Heirali AA, et al. A longitudinal characterization of the Non-Cystic Fibrosis Bronchiectasis airway microbiome. *Sci Rep* 2019;9:6871. doi: 10.1038/s41598-019-42862-y
82 Wang Z, Maschera B, Lea S, et al. Airway host-microbiome interactions in chronic obstructive pulmonary disease. *Respir Res* 2019;20:113. doi: 10.1186/s12931-019-1085-z
83 Sharma A, Laxman B, Naureckas ET, et al. Associations between fungal and bacterial microbiota of airways and asthma endotypes. *J Allergy Clin Immunol* 2019;144:1214-1227.e7. doi: 10.1016/j.jaci.2019.06.025
84 Martin-Loeches I, Dickson R, Torres A, et al. The importance of airway and lung microbiome in the critically ill. *Crit Care* 2020;24:537. doi: 10.1186/s13054-020-03219-4
85 Wu BG, Segal LN. The lung microbiome and its role in pneumonia. *Clin Chest Med* 2018;39:677-89. doi: 10.1016/j.ccm.2018.07.003
86 Kelly BJ, Imai I, Bittinger K, et al. Composition and dynamics of the respiratory tract microbiome in intubated patients. *Microbiome* 2016;4:7. doi: 10.1186/s40168-016-0151-8
87 Zakharkina T, Martin-Loeches I, Matamoros S, et al. The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with occurrence of pneumonia. *Thorax* 2017;72:803-10. doi: 10.1136/thoraxjnl-2016-209158
88 Roquilly A, Torres A, Villadangos JA, et al. Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia. *Lancet Respir Med* 2019;7:710-20. doi: 10.1016/S2213-2600(19)30140-7
89 Segal LN, Clemente JC, Tsay J-CJ, et al. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. *Nat Microbiol* 2016;1:16031. doi: 10.1038/nmicrobiol.2016.31
90 Antoni Torres CC. *Clinical Management of Bacterial Pneumonia | Antoni Torres | Springer.* 1st ed. Springer, 2015, https://www.springer.com/gp/book/9783319220611 doi: 10.1007/978-3-319-22062-8.
91 Cilloniz C, Ceccato A, San Jose A, Torres A. Clinical management of community acquired pneumonia in the elderly patient. *Expert Rev Respir Med* 2016;10:1211-20. doi: 10.1080/17476348.2016.1240037
92 Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet* 2015;386:1097-108. doi: 10.1016/S0140-6736(15)60733-4
93 Black AD. Non-infectious mimics of community-acquired pneumonia. *Pneumonia (Nathan)* 2016;8:2. doi: 10.1186/s41479-016-0002-1
94 Fernando SM, Tran A, Cheng W, et al. Diagnosis of ventilator-associated pneumonia in critically ill adult patients-a systematic review and meta-analysis. *Intensive Care Med* 2020;46:1170-9. doi: 10.1007/s00134-020-06036-z
95 Laursen CB, Sloth E, Lambrechtsen J, et al. Diagnostic performance of chest Radiograph for the diagnosis of community acquired pneumonia in acute admitted patients with respiratory symptoms. *Scand J Trauma Resusc Emerg Med* 2013;21:A21 doi: 10.1186/1757-7241-21-S2-A21.
96 Claessens YE, Debray MP, Tubach F, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am J Respir Crit Care Med* 2015;192:974-82. doi: 10.1164/rccm.201501-0017OC
97 Franquet T. Imaging of community-acquired pneumonia. *J Thorac Imaging* 2018;33:282-94. doi: 10.1097/RTI.0000000000000347
98 Ferreira-Coimbra J, Ardanuy C, Diaz E, et al. Ventilator-associated pneumonia diagnosis: a prioritization exercise based on multi-criteria decision analysis. *Eur J Clin Microbiol Infect Dis* 2020;39:281-6. doi: 10.1007/s10096-019-03720-x
99 Klompas M. Does this patient have ventilator-associated pneumonia?*JAMA* 2007;297:1583-93. doi: 10.1001/jama.297.14.1583
100 Chastre J, Luyt C-E. Does this patient have VAP?*Intensive Care Med* 2016;42:1159-63. doi: 10.1007/s00134-016-4239-1
101 Long L, Zhao H-T, Zhang Z-Y, Wang G-Y, Zhao H-L. Lung ultrasound for the diagnosis of pneumonia in adults: A meta-analysis. *Medicine (Baltimore)* 2017;96:e5713. doi: 10.1097/MD.0000000000005713
102 Staub LJ, Biscaro RRM, Maurici R. Emergence of alveolar consolidations in serial lung ultrasound and diagnosis of ventilator-associated pneumonia. *J Intensive Care Med* 2021;36:304-12. doi: 10.1177/0885066619894279
103 Torres A, Lee N, Cilloniz C, Vila J, Van der Eerden M. Laboratory diagnosis of pneumonia in the molecular age. *Eur Respir J* 2016;48:1764-78. doi: 10.1183/13993003.01144-2016
104 Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2004;39:165-9. doi: 10.1086/421497
105 Fukuyama H, Yamashiro S, Kinjo K, Tamaki H, Kishaba T. Validation of sputum Gram stain for treatment of community-acquired pneumonia and healthcare-associated pneumonia: a prospective observational study. *BMC Infect Dis* 2014;14:534. doi: 10.1186/1471-2334-14-534
106 Paonessa JR, Shah RD, Pickens CI, et al. Rapid detection of methicillin-resistant Staphylococcus aureus in BAL: a pilot randomized controlled trial. *Chest* 2019;155:999-1007. doi: 10.1016/j.chest.2019.02.007

107 Said MA, Johnson HL, Nonyane BAS, et al, AGEDD Adult Pneumococcal Burden Study Team. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta‐analysis of diagnostic techniques. *PLoS One* 2013;8:e60273. doi: 10.1371/journal.pone.0060273
108 Walden AP, Clarke GM, McKechnie S, et al, ESICM/ECCRN GenOSept Investigators. Patients with community acquired pneumonia admitted to European intensive care units: an epidemiological survey of the GenOSept cohort. *Crit Care* 2014;18:R58. doi: 10.1186/cc13812
109 Vallés J, Diaz E, Martín‐Loeches I, et al. Evolution over a 15‐year period of the clinical characteristics and outcomes of critically ill patients with severe community‐acquired pneumonia. *Med Intensiva* 2016;40:238‐45. doi: 10.1016/j.medin.2015.07.005
110 Jain S, Self WH, Wunderink RG, et al, CDC EPIC Study Team. Community‐acquired pneumonia requiring hospitalization among US adults. *N Engl J Med* 2015;373:415‐27. doi: 10.1056/NEJMoa1500245
111 Zhou F, Wang Y, Liu Y, et al, CAP‐China Network. Disease severity and clinical outcomes of community‐acquired pneumonia caused by non‐influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP‐China Network. *Eur Respir J* 2019;54:1802406. doi: 10.1183/13993003.02406‐2018
112 Kuypers J. Impact of rapid molecular detection of respiratory viruses on clinical outcomes and patient management. *J Clin Microbiol* 2019;57:e01890. doi: 10.1128/JCM.01890‐18
113 Cillóniz C, Dominedò C, Magdaleno D, Ferrer M, Gabarrús A, Torres A. Pure viral sepsis secondary to community‐acquired pneumonia in adults: risk and prognostic factors. *J Infect Dis* 2019;220:1166‐71. doi: 10.1093/infdis/jiz257
114 Cavallazzi R, Ramirez JA. Influenza and viral pneumonia. *Clin Chest Med* 2018;39:703‐21. doi: 10.1016/j.ccm.2018.07.005
115 Alimi Y, Lim WS, Lansbury L, Leonardi‐Bee J, Nguyen‐Van‐Tam JS. Systematic review of respiratory viral pathogens identified in adults with community‐acquired pneumonia in Europe. *J Clin Virol* 2017;95:26‐35. doi: 10.1016/j.jcv.2017.07.019
116 Burk M, El‐Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community‐acquired pneumonia: a systematic review and meta‐analysis. *Eur Respir Rev* 2016;25:178‐88. doi: 10.1183/16000617.0076‐2015
117 Abelenda‐Alonso G, Rombauts A, Gudiol C, et al. Influenza and bacterial coinfection in adults with community‐acquired pneumonia admitted to conventional wards: risk factors, clinical features, and outcomes. *Open Forum Infect Dis* 2020;27:ofaa066 doi: 10.1093/ofid/ofaa066.
118 Karhu J, Ala‐Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community‐acquired pneumonia. *Clin Infect Dis* 2014;59:62‐70. doi: 10.1093/cid/ciu237
119 Short KR, Kroeze EJBV, Fouchier RAM, Kuiken T. Pathogenesis of influenza‐induced acute respiratory distress syndrome. *Lancet Infect Dis* 2014;14:57‐69. doi: 10.1016/S1473‐3099(13)70286‐X
120 Cilloniz C, Ferrer M, Liapikou A, et al. Acute respiratory distress syndrome in mechanically ventilated patients with community‐acquired pneumonia. *Eur Respir J* 2018;51:1702215. doi: 10.1183/13993003.02215‐2017
121 Piralla A, Mariani B, Rovida F, Baldanti F. Frequency of respiratory viruses among patients admitted to 26 Intensive Care Units in seven consecutive winter‐spring seasons (2009‐2016) in Northern Italy. *J Clin Virol* 2017;92:48‐51. doi: 10.1016/j.jcv.2017.05.004
122 Burrell A, Huckson S, Pilcher DV, ANZICS. ANZICS. ICU admissions for sepsis or pneumonia in Australia and New Zealand in 2017. *N Engl J Med* 2018;378:2138‐9. doi: 10.1056/NEJMc1717178
123 Cillóniz C, Civljak R, Nicolini A, Torres A. Polymicrobial community‐acquired pneumonia: An emerging entity. *Respirology* 2016;21:65‐75. doi: 10.1111/resp.12663
124 Almeida ST, Paulo AC, Froes F, de Lencastre H, Sá‐Leão R. Dynamics of pneumococcal carriage in adults: a new look at an old paradigm. *J Infect Dis* 2021;223:1590‐600. doi: 10.1093/infdis/jiaa558
125 Palacios G, Hornig M, Cisterna D, et al. Streptococcus pneumoniae coinfection is correlated with the severity of H1N1 pandemic influenza. *PLoS One* 2009;4:e8540. doi: 10.1371/journal.pone.0008540
126 Centers for Disease Control and Prevention (CDC). Severe methicillin‐resistant Staphylococcus aureus community‐acquired pneumonia associated with influenza—Louisiana and Georgia, December 2006‐January 2007. *MMWR Morb Mortal Wkly Rep* 2007;56:325‐9.
127 Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. *Cell Host Microbe* 2014;16:55‐67. doi: 10.1016/j.chom.2014.06.005
128 Wilden JJ, Jacob JC, Ehrhardt C, Ludwig S, Boergeling Y. Altered signal transduction in the immune response to influenza virus and S. pneumoniae or S. aureus co‐infections. *Int J Mol Sci* 2021;22:5486. doi: 10.3390/ijms22115486
129 Aguilera ER, Lenz LL. Inflammation as a modulator of host susceptibility to pulmonary influenza, pneumococcal, and co‐infections. *Front Immunol* 2020;11:105. doi: 10.3389/fimmu.2020.00105
130 Vardakas KZ, Matthaiou DK, Falagas ME. Incidence, characteristics and outcomes of patients with severe community acquired‐MRSA pneumonia. *Eur Respir J* 2009;34:1148‐58. doi: 10.1183/09031936.00041009
131 He H, Wunderink RG. Staphylococcus aureus pneumonia in the community. *Semin Respir Crit Care Med* 2020;41:470‐9. doi: 10.1055/s‐0040‐1709992
132 Prina E, Ranzani OT, Polverino E, et al. Risk factors associated with potentially antibiotic‐resistant pathogens in community‐acquired pneumonia. *Ann Am Thorac Soc* 2015;12:153‐60. doi: 10.1513/AnnalsATS.201407‐305OC
133 Cilloniz C, Dominedo C, Peroni HJ, et al. Difficult to treat microorganisms in patients aged over 80 years with community‐acquired pneumonia: the prevalence of PES pathogens. *Eur Respir J* 2020;56:2000773. doi: 10.1183/13993003.00773‐2020
134 Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic‐resistant bacteria by select risk factors for health care‐associated pneumonia. *Arch Intern Med* 2008;168:2205‐10. doi: 10.1001/archinte.168.20.2205
135 Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug‐resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012;54:470‐8. doi: 10.1093/cid/cir840
136 Park SC, Kim EY, Kang YA, et al. Validation of a scoring tool to predict drug‐resistant pathogens in hospitalised pneumonia patients. *Int J Tuberc Lung Dis* 2013;17:704‐9. doi: 10.5588/ijtld.12.0723
137 Shindo Y, Ito R, Kobayashi D, et al. Risk factors for drug‐resistant pathogens in community‐acquired and healthcare‐associated pneumonia. *Am J Respir Crit Care Med* 2013;188:985‐95. doi: 10.1164/rccm.201301‐0079OC
138 Maruyama T, Fujisawa T, Ishida T, et al. A therapeutic strategy for all pneumonia patients: a 3‐year prospective multicenter cohort study using risk factors for multidrug resistant pathogens to select initial empiric therapy. *Clin Infect Dis* 2019;68:1080‐8. doi: 10.1093/cid/ciy631
139 Aliberti S, Cilloniz C, Chalmers JD, et al. Multidrug‐resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax* 2013;68:997‐9. doi: 10.1136/thoraxjnl‐2013‐203384
140 Cillóniz C, Dominedò C, Nicolini A, Torres A. PES pathogens in severe community‐acquired pneumonia. *Microorganisms* 2019;7:49. doi: 10.3390/microorganisms7020049
141 Ishida T, Ito A, Washio Y, et al. Risk factors for drug‐resistant pathogens in immunocompetent patients with pneumonia: Evaluation of PES pathogens. *J Infect Chemother* 2017;23:23‐8. doi: 10.1016/j.jiac.2016.09.002
142 Kobayashi D, Shindo Y, Ito R, et al. Validation of the prediction rules identifying drug‐resistant pathogens in community‐onset pneumonia. *Infect Drug Resist* 2018;11:1703‐13. doi: 10.2147/IDR.S165669
143 Micek ST, Wunderink RG, Kollef MH, et al. An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Crit Care* 2015;19:219. doi: 10.1186/s13054‐015‐0926‐5
144 Cillóniz C, Dominedò C, Torres A. An overview of guidelines for the management of hospital‐acquired and ventilator‐associated pneumonia caused by multidrug‐resistant Gram‐negative bacteria. *Curr Opin Infect Dis* 2019;32:656‐62. doi: 10.1097/QCO.0000000000000596
145 Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug‐resistant Gram negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. *Microb Drug Resist* 2016;22:412‐31. doi: 10.1089/mdr.2015.0220
146 Watkins RR, Van Duin D. Current trends in the treatment of pneumonia due to multidrug‐resistant Gram negative bacteria. F1000Res. 2019 Jan 30;8:F1000 Faculty Rev‐121.
147 Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug‐resistant, extensively drug‐resistant and pandrug‐resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268‐81. doi: 10.1111/j.1469‐0691.2011.03570.x
148 Bassetti M, Righi E, Vena A, Graziano E, Russo A, Peghin M. Risk stratification and treatment of ICU‐acquired pneumonia caused by multidrug‐resistant/extensively drug‐resistant/pandrug‐resistant bacteria. *Curr Opin Crit Care* 2018;24:385‐93. doi: 10.1097/MCC.0000000000000534
149 Ekren PK, Ranzani OT, Ceccato A, et al. Evaluation of the 2016 Infectious Diseases Society of America/American Thoracic Society guideline criteria for risk of multidrug‐resistant pathogens in patients with hospital‐acquired and ventilator‐associated pneumonia in the ICU. *Am J Respir Crit Care Med* 2018;197:826‐30. doi: 10.1164/rccm.201708‐1717LE

150 Webb BJ, Sorensen J, Jephson A, Mecham I, Dean NC. Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. *Eur Respir J* 2019;54:1900057. doi: 10.1183/13993003.00057-2019

151 Ewig S, Kolditz M, Pletz MW, Chalmers J. Healthcare-associated pneumonia: is there any reason to continue to utilize this label in 2019?*Clin Microbiol Infect* 2019;25:1173-9. doi: 10.1016/j.cmi.2019.02.022

152 Ito A, Ishida T, Tachibana H, Tokumasu H, Yamazaki A, Washio Y. Azithromycin combination therapy for community-acquired pneumonia: propensity score analysis. *Sci Rep* 2019;9:18406. doi: 10.1038/s41598-019-54922-4

153 Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010;36:612-20. doi: 10.1007/s00134-009-1730-y

154 Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of beta-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. *Antimicrob Agents Chemother* 2007;51:3977-82. doi: 10.1128/AAC.00006-07

155 Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med* 2014;42:420-32. doi: 10.1097/CCM.0b013e3182a66b9b

156 Anderson R, Steel HC, Cockeran R, et al. Comparison of the effects of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones, on the production of pneumolysin by Streptococcus pneumoniae in vitro. *J Antimicrob Chemother* 2007;60:1155-8. doi: 10.1093/jac/dkm338

157 Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med* 2014;42:420-32. doi: 10.1097/CCM.0b013e3182a66b9b

158 Waterer GW. Monotherapy versus combination antimicrobial therapy for pneumococcal pneumonia. *Curr Opin Infect Dis* 2005;18:157-63. doi: 10.1097/01.qco.0000160906.02308.3c

159 Baddour LM, Yu VL, Klugman KP, et al, International Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* 2004;170:440-4. doi: 10.1164/rccm.200311-1578OC

160 Siddiqui AH, Koirala J. Methicillin Resistant Staphylococcus Aureus. In: *StatPearls*. StatPearls Publishing, 2021, https://www.ncbi.nlm.nih.gov/books/NBK482221/.

161 Baby N, Faust AC, Smith T, Sheperd LA, Knoll L, Goodman EL. Nasal methicillin-resistant *Staphylococcus aureus* (MRSA) PCR testing reduces the duration of MRSA-targeted therapy in patients with suspected MRSA pneumonia. *Antimicrob Agents Chemother* 2017;61:e02432. doi: 10.1128/AAC.02432-16

162 Woolever NL, Schomberg RJ, Cai S, Dierkhising RA, Dababneh AS, Kujak RC. Pharmacist-driven MRSA nasal PCR screening and the duration of empirical cancomycin therapy for suspected MRSA respiratory tract infections. *Mayo Clin Proc Innov Qual Outcomes* 2020;4:550-6. doi: 10.1016/j.mayocpiqo.2020.05.002

163 Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLoS One* 2021;16:e0251170. doi: 10.1371/journal.pone.0251170

164 Feldman C, Anderson R. The role of co-infections and secondary infections in patients with COVID-19. *Pneumonia (Nathan)* 2021;13:5. doi: 10.1186/s41479-021-00083-w

165 Han J, Gatheral T, Williams C. Procalcitonin for patient stratification and identification of bacterial co-infection in COVID-19. *Clin Med (Lond)* 2020;20:e47. doi: 10.7861/clinmed.Let.20.3.3

166 Drewett GP, Smibert OC, Holmes NE, Trubiano JA. The use of procalcitonin as an antimicrobial stewardship tool and a predictor of disease severity in coronavirus disease 2019 (COVID-19). *Infect Control Hosp Epidemiol* 2021;1-3. doi: 10.1017/ice.2021.28.

167 National Institutes of Health. Information on covid-19 treatment, prevention and research. Covid-19 treatment guidelines.https://www.covid19treatmentguidelines.nih.gov/

168 Beigel JH, Tomashek KM, Dodd LE, et al, ACTT-1 Study Group Members. Remdesivir for the treatment of covid-19-final report. *N Engl J Med* 2020;383:1813-26. doi: 10.1056/NEJMoa2007764

169 Pan H, Peto R, Henao-Restrepo AM, et al, WHO Solidarity Trial Consortium. Repurposed antiviral drugs for covid-19-interim WHO Solidarity Trial results. *N Engl J Med* 2021;384:497-511. doi: 10.1056/NEJMoa2023184

170 Remdesivir. https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/remdesivir/

171 Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015;313:677-86. doi: 10.1001/jama.2015.88

172 Briel M, Spoorenberg SMC, Snijders D, et al, Ovidius Study Group, Capisce Study Group, STEP Study Group. Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data meta-analysis. *Clin Infect Dis* 2018;66:346-54. doi: 10.1093/cid/cix801

173 Venkatesh B, Finfer S, Cohen J, et al, ADRENAL Trial Investigators and the Australian-New Zealand Intensive Care Society Clinical Trials Group. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797-808. doi: 10.1056/NEJMoa1705835

174 Annane D, Renault A, et al, Brun-Buisson C, CRICS-TRIGGERSEP Network. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018;378:809-18. doi: 10.1056/NEJMoa1705716

175 Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016;3:CD010406. doi: 10.1002/14651858.CD010406.pub2

176 Moreno G, Rodríguez A, et al, Reyes LF, GETGAG Study Group. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med* 2018;44:1470-82. doi: 10.1007/s00134-018-5332-4

177 Cao B, Gao H, Zhou B, et al. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. *Crit Care Med* 2016;44:e318-28. doi: 10.1097/CCM.0000000000001616

178 Horby P, Lim WS, Emberson JR, et al, RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19-6 preliminary report. *N Engl J Med* 2021;384:693-704. doi: 10.1056/NEJMoa2021436

179 VA Office of Research and Development. CSP #574 -Evaluate the safety and efficacy of methylprednisolone in hospitalized veterans with severe community-acquired pneumonia. clinicaltrials.gov; 2020. https://clinicaltrials.gov/ct2/show/results/NCT01283009

180 de la Torre MC, Torán P, Serra-Prat M, et al. Serum levels of immunoglobulins and severity of community-acquired pneumonia. *BMJ Open Respir Res* 2016;3:e000152. doi: 10.1136/bmjresp-2016-000152

181 Justel M, Socias L, Almansa R, et al. IgM levels in plasma predict outcome in severe pandemic influenza. *J Clin Virol* 2013;58:564-7. doi: 10.1016/j.jcv.2013.09.006

182 de la Torre MC, Palomera E, Serra-Prat M, et al. IgG2 as an independent risk factor for mortality in patients with community-acquired pneumonia. *J Crit Care* 2016;35:115-9. doi: 10.1016/j.jcrc.2016.05.005

183 Tagami T, Matsui H, Fushimi K, Yasunaga H. Intravenous immunoglobulin use in septic shock patients after emergency laparotomy. *J Infect* 2015;71:158-66. doi: 10.1016/j.jinf.2015.04.003

184 Iizuka Y, Sanui M, Sasabuchi Y, et al. Low-dose immunoglobulin G is not associated with mortality in patients with sepsis and septic shock. *Crit Care* 2017;21:181. doi: 10.1186/s13054-017-1764-4.

185 Welte T, Dellinger RP, Ebelt H, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). *Intensive Care Med* 2018;44:438-48. doi: 10.1007/s00134-018-5143-7

186 Aarts MAW, Hancock JN, Heyland D, McLeod RS, Marshall JC. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2008;36:108-17. doi: 10.1097/01.CCM.0000297956.27474.9D

187 Heyland DK, Dodek P, Muscedere J, Day A, Cook D, Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med* 2008;36:737-44. doi: 10.1097/01.CCM.0B013E31816203D6

188 Arthur LE, Kizor RS, Selim AG, van Driel ML, Seoane L. Antibiotics for ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2016;10:CD004267.

189 Chamot E, Boffi El Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for Pseudomonas aeruginosa bacteremia. *Antimicrob Agents Chemother* 2003;47:2756-64. doi: 10.1128/AAC.47.9.2756-2764.2003

190 Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for Pseudomonas aeruginosa ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med* 2007;35:1888-95. doi: 10.1097/01.CCM.0000275389.31974.22

191 Martínez JA, Cobos-Trigueros N, Soriano A, et al. Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms. *Antimicrob Agents Chemother* 2010;54:3590-6. doi: 10.1128/AAC.00115-10
192 Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother* 2010;54:1742-8. doi: 10.1128/AAC.01365-09
193 Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. *Crit Care Med* 2010;38:1651-64. doi: 10.1097/CCM.0b013e3181e96b91
194 Torres A, Rank D, Melnick D, et al. Randomized trial of ceftazidime-avibactam vs meropenem for treatment of hospital-acquired and ventilator-associated bacterial pneumonia (REPROVE): analyses per US FDA-specified end points. *Open Forum Infect Dis* 2019;6:ofz149. doi: 10.1093/ofid/ofz149
195 Kollef MH, Novček M, Kivistik Ü, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2019;19:1299-311. doi: 10.1016/S1473-3099(19)30403-7
196 Approval Letter ZERBAXA. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/206829Orig1s008ltr.pdf
197 Approval letter ZERBAXA. https://www.ema.europa.eu/en/documents/variation-report/zerbaxa-h-c-3772-ii-0020-epar-assessment-report-variation_en.pdf
198 Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther* 2018;7:439-55. doi: 10.1007/s40121-018-0214-1
199 Titov I, Wunderink RG, Roquilly A, *et al.* A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis* 2020 Aug 12:ciaa803 doi: 10.1093/cid/ciaa803.
200 Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2021;21:213-25. doi: 10.1016/S1473-3099(20)30731-3
201 Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021;21:226-40. doi: 10.1016/S1473-3099(20)30796-9
202 Flannery AH, Bissell BD, Bastin MT, Morris PE, Neyra JA. Continuous versus intermittent infusion of vancomycin and the risk of acute kidney injury in critically ill adults: a systematic review and meta-Analysis. *Crit Care Med* 2020;48:912-8. doi: 10.1097/CCM.0000000000004326
203 Hao J, Chen H, Zhou J-X. Continuous versus intermittent infusion of vancomycin in adult patients: A systematic review and meta-analysis. *Int J Antimicrob Agents* 2016;47:28-35. doi: 10.1016/j.ijantimicag.2015.10.019
204 Soraluce A, Barrasa H, Asín-Prieto E, et al. Novel population pharmacokinetic model for linezolid in critically ill patients and evaluation of the adequacy of the current dosing recommendation. *Pharmaceutics* 2020;12:54. doi: 10.3390/pharmaceutics12010054
205 Taubert M, Zoller M, Maier B, et al. Predictors of inadequate linezolid concentrations after standard dosing in critically ill patients. *Antimicrob Agents Chemother* 2016;60:5254-61. doi: 10.1128/AAC.00356-16
206 Kollef MH, Ricard J-D, Roux D, et al. A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram negative ventilator-associated pneumonia: IASIS trial. *Chest* 2017;151:1239-46. doi: 10.1016/j.chest.2016.11.026
207 Niederman MS, Chastre J, Corkery K, Fink JB, Luyt C-E, García MS. BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. *Intensive Care Med* 2012;38:263-71. doi: 10.1007/s00134-011-2420-0
208 Stokker J, Karami M, Hoek R, Gommers D, van der Eerden M. Effect of adjunctive tobramycin inhalation versus placebo on early clinical response in the treatment of ventilator-associated pneumonia: the VAPORISE randomized-controlled trial. *Intensive Care Med* 2020;46:546-8. doi: 10.1007/s00134-019-05914-5
209 Niederman MS, Alder J, Bassetti M, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. *Lancet Infect Dis* 2020;20:330-40. doi: 10.1016/S1473-3099(19)30574-2
210 Sweeney DA, Kalil AC. Why don't we have more inhaled antibiotics to treat ventilator-associated pneumonia? *Clin Microbiol Infect* 2019;25:1195-9. doi: 10.1016/j.cmi.2019.04.018
211 Tansarli GS, Mylonakis E. Systematic review and meta-analysis of the efficacy of short-course antibiotic treatments for community-acquired pneumonia in adults. *Antimicrob Agents Chemother* 2018;62:e00635. doi: 10.1128/AAC.00635-18
212 Lan S-H, Lai C-C, Chang S-P, Lu L-C, Hung S-H, Lin W-T. Five-day antibiotic treatment for community-acquired bacterial pneumonia: A systematic review and meta-analysis of randomized controlled trials. *J Glob Antimicrob Resist* 2020;23:94-9. doi: 10.1016/j.jgar.2020.08.005
213 Bermejo-Martin JF, Cilloniz C, Mendez R, et al, NEUMONAC group. Lymphopenic community acquired pneumonia (L-CAP), an immunological phenotype associated with higher risk of mortality. *EBioMedicine* 2017;24:231-6. doi: 10.1016/j.ebiom.2017.09.023
214 Bermejo-Martin JF, Almansa R, Martin-Fernandez M, Menendez R, Torres A. Immunological profiling to assess disease severity and prognosis in community-acquired pneumonia. *Lancet Respir Med* 2017;5:e35-6. doi: 10.1016/S2213-2600(17)30444-7
215 Luo Q, Ning P, Zheng Y, Shang Y, Zhou B, Gao Z. Serum suPAR and syndecan-4 levels predict severity of community-acquired pneumonia: a prospective, multi-centre study. *Crit Care* 2018;22:15. doi: 10.1186/s13054-018-1943-y
216 Zhou H, Guo S, Lan T, Ma S, Zhang F, Zhao Z. Risk stratification and prediction value of procalcitonin and clinical severity scores for community-acquired pneumonia in ED. *Am J Emerg Med* 2018;36:2155-60. doi: 10.1016/j.ajem.2018.03.050
217 Legramante JM, Mastropasqua M, Susi B, et al. Prognostic performance of MR-proadrenomedullin in patients with community acquired pneumonia in the Emergency Department compared to clinical severity scores PSI and CURB. *PLoS One* 2017;12:e0187702. doi: 10.1371/journal.pone.0187702
218 Gilbert DN. Role of procalcitonin in the management of infected patients in the intensive care unit. *Infect Dis Clin North Am* 2017;31:435-53. doi: 10.1016/j.idc.2017.05.003
219 Julián-Jiménez A, González Del Castillo J, Candel FJ. Usefulness and prognostic value of biomarkers in patients with community-acquired pneumonia in the emergency department. *Med Clin (Barc)* 2017;148:501-10.
220 Keramat F, Ghasemi Basir HR, Abdoli E, Shafiei Aghdam A, Poorolajal J. Association of serum procalcitonin and C-reactive protein levels with CURB-65 criteria among patients with community-acquired pneumonia. *Int J Gen Med* 2018;11:217-23. doi: 10.2147/IJGM.S165190
221 Spoorenberg SMC, Vestjens SMT, Voorn GP, et al, Ovidius study group. Course of SP-D, YKL-40, CCL18 and CA 15-3 in adult patients hospitalised with community-acquired pneumonia and their association with disease severity and aetiology: A post-hoc analysis. *PLoS One* 2018;13:e0190575. doi: 10.1371/journal.pone.0190575
222 Méndez R, Méndez R, Aldás I, et al. Community-acquired pneumonia patients at risk for early and long-term cardiovascular events are identified by cardiac biomarkers. *Chest* 2019;156:1080-91. doi: 10.1016/j.chest.2019.06.040
223 Khan F, Owens MB, Restrepo M, Povoa P, Martin-Loeches I. Tools for outcome prediction in patients with community acquired pneumonia. *Expert Rev Clin Pharmacol* 2017;10:201-11. doi: 10.1080/17512433.2017.1268051
224 Self WH, Balk RA, Grijalva CG, et al. Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. *Clin Infect Dis* 2017;65:183-90. doi: 10.1093/cid/cix317
225 Méndez R, Menéndez R, Cilloniz C, et al. Initial inflammatory profile in community-acquired pneumonia depends on time since onset of symptoms. *Am J Respir Crit Care Med* 2018;198:370-8. doi: 10.1164/rccm.201709-1908OC
226 Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006;174:84-93. doi: 10.1164/rccm.200512-1922OC
227 Schuetz P, Christ-Crain M, Thomann R, et al, ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009;302:1059-66. doi: 10.1001/jama.2009.1297
228 Akagi T, Nagata N, Wakamatsu K, et al. Procalcitonin-guided antibiotic discontinuation might shorten the duration of antibiotic treatment without increasing pneumonia recurrence. *Am J Med Sci* 2019;358:33-44. doi: 10.1016/j.amjms.2019.04.005

229 Ito A, Ishida T, Tokumasu H, et al. Impact of procalcitonin‐guided therapy for hospitalized community‐acquired pneumonia on reducing antibiotic consumption and costs in Japan. *J Infect Chemother* 2017;23:142‐7. doi: 10.1016/j.jiac.2016.11.006
230 Chalmers JD, Singanayagam A, Hill AT. C‐reactive protein is an independent predictor of severity in community‐acquired pneumonia. *Am J Med* 2008;121:219‐25. doi: 10.1016/j.amjmed.2007.10.033
231 Menéndez R, Cavalcanti M, Reyes S, et al. Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax* 2008;63:447‐52 doi: 10.1136/thx.2007.086785.
232 McCluskey SM, Schuetz P, Abers MS, et al. Serial Procalcitonin as a Predictor of Bacteremia and Need for Intensive Care Unit Care in Adults With Pneumonia, Including Those With Highest Severity: A Prospective Cohort Study. *Open Forum Infect Dis* 2017;4:ofw238. doi: 10.1093/ofid/ofw238
233 Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin‐guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta‐analysis. *Lancet Infect Dis* 2018;18:95‐107. doi: 10.1016/S1473‐3099(17)30592‐3
234 Shi SJ, Li H, Liu M, et al. Mortality prediction to hospitalized patients with influenza pneumonia: PO_2 /FiO_2 combined lymphocyte count is the answer. *Clin Respir J* 2017;11:352‐60. doi: 10.1111/crj.12346
235 Ceccato A, Panagiotarakou M, Ranzani OT, et al. Lymphocytopenia as a predictor of mortality in patients with ICU‐acquired pneumonia. *J Clin Med* 2019;8:843. doi: 10.3390/jcm8060843
236 Torres A, Serra‐Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992;116:540‐3. doi: 10.7326/0003‐4819‐116‐7‐540
237 Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999;354:1851‐8. doi: 10.1016/S0140‐6736(98)12251‐1
238 Wang L, Li X, Yang Z, et al. Semi‐recumbent position versus supine position for the prevention of ventilator‐associated pneumonia in adults requiring mechanical ventilation. *Cochrane Database Syst Rev* 2016;(1):CD009946. doi: 10.1002/14651858.CD009946.pub2
239 Klompas M, Li L, Kleinman K, Szumita PM, Massaro AF. Associations between ventilator bundle components and outcomes. *JAMA Intern Med* 2016;176:1277‐83. doi: 10.1001/jamainternmed.2016.2427
240 Li Bassi G, Panigada M, Ranzani OT, et al, GravitasVAP Network. Randomized, multicenter trial of lateral Trendelenburg versus semirecumbent body position for the prevention of ventilator‐associated pneumonia. *Intensive Care Med* 2017;43:1572‐84. doi: 10.1007/s00134‐017‐4858‐1
241 Krein SL, Greene MT, Apisarnthanarak A, et al. Infection prevention practices in Japan, Thailand, and the United States: results from national surveys. *Clin Infect Dis* 2017;64(suppl_2):S105‐11. doi: 10.1093/cid/cix073
242 Saint S, Greene MT, Fowler KE, et al. What US hospitals are currently doing to prevent common device‐associated infections: results from a national survey. *BMJ Qual Saf* 2019;28:741‐9. doi: 10.1136/bmjqs‐2018‐009111
243 Blot S, Koulenti D, Dimopoulos G, et al, EUVAP Study Investigators. Prevalence, risk factors, and mortality for ventilator‐associated pneumonia in middle‐aged, old, and very old critically ill patients*. *Crit Care Med* 2014;42:601‐9. doi: 10.1097/01.ccm.0000435665.07446.50
244 Liu Y, Di Y, Fu S. Risk factors for ventilator‐associated pneumonia among patients undergoing major oncological surgery for head and neck cancer. *Front Med* 2017;11:239‐46. doi: 10.1007/s11684‐017‐0509‐8
245 Ding C, Zhang Y, Yang Z, et al. Incidence, temporal trend and factors associated with ventilator‐associated pneumonia in mainland China: a systematic review and meta‐analysis. *BMC Infect Dis* 2017;17:468. doi: 10.1186/s12879‐017‐2566‐7
246 Frat JP, Thille AW, Mercat A, et al, FLORALI Study Group, REVA Network. High‐flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185‐96. doi: 10.1056/NEJMoa1503326
247 Monro‐Somerville T, Sim M, Ruddy J, Vilas M, Gillies MA. The effect of high‐flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure: a systematic review and meta‐analysis. *Crit Care Med* 2017;45:e449‐56. doi: 10.1097/CCM.0000000000002091
248 Burns KEA, Meade MO, Premji A, Adhikari NKJ. Noninvasive positive‐pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2013;(12):CD004127. doi: 10.1002/14651858.CD004127.pub3
249 Vaschetto R, Longhini F, Persona P, et al. Early extubation followed by immediate noninvasive ventilation vs. standard extubation in hypoxemic patients: a randomized clinical trial. *Intensive Care Med* 2019;45:627‐1. doi: 10.1007/s00134‐018‐5478‐0
250 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342:1471‐7. doi: 10.1056/NEJM200005183422002
251 Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126‐34. doi: 10.1016/S0140‐6736(08)60105‐1
252 Klompas M. Potential strategies to prevent ventilator‐associated events. *Am J Respir Crit Care Med* 2015;192:1420‐30. doi: 10.1164/rccm.201506‐1161CI
253 Philippart F, Gaudry S, Quinquis L, et al, TOP‐Cuff Study Group. Randomized intubation with polyurethane or conical cuffs to prevent pneumonia in ventilated patients. *Am J Respir Crit Care Med* 2015;191:637‐45. doi: 10.1164/rccm.201408‐1398OC
254 Saito M, Maruyama K, Mihara T, Hoshijima H, Hirabayashi G, Andoh T. Comparison of polyurethane tracheal tube cuffs and conventional polyvinyl chloride tube cuff for prevention of ventilator‐associated pneumonia: A systematic review with meta‐analysis. *Medicine (Baltimore)* 2021;100:e24906. doi: 10.1097/MD.0000000000024906
255 Jaillette E, Girault C, Brunin G, et al, BestCuff Study Group and the BoRéal Network. Impact of tapered‐cuff tracheal tube on microaspiration of gastric contents in intubated critically ill patients: a multicenter cluster‐randomized cross‐over controlled trial. *Intensive Care Med* 2017;43:1562‐71. doi: 10.1007/s00134‐017‐4736‐x
256 Maertens B, Blot K, Blot S. Prevention of ventilator‐associated and early postoperative pneumonia through tapered endotracheal tube cuffs: a systematic review and meta‐analysis of randomized controlled trials. *Crit Care Med* 2018;46:316‐23. doi: 10.1097/CCM.0000000000002889
257 Caroff DA, Li L, Muscedere J, Klompas M. Subglottic secretion drainage and objective outcomes: a systematic review and meta‐analysis. *Crit Care Med* 2016;44:830‐40. doi: 10.1097/CCM.0000000000001414
258 Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator‐associated pneumonia: a systematic review and meta‐analysis. *Crit Care Med* 2011;39:1985‐91. doi: 10.1097/CCM.0b013e318218a4d9
259 Bouza E, Pérez MJ, Muñoz P, Rincón C, Barrio JM, Hortal J. Continuous aspiration of subglottic secretions in the prevention of ventilator‐associated pneumonia in the postoperative period of major heart surgery. *Chest* 2008;134:938‐46. doi: 10.1378/chest.08‐0103
260 Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator‐associated pneumonia: a meta‐analysis. *Am J Med* 2005;118:11‐8. doi: 10.1016/j.amjmed.2004.07.051
261 Frost SA, Azeem A, Alexandrou E, et al. Subglottic secretion drainage for preventing ventilator associated pneumonia: a meta‐analysis. *Aust Crit Care* 2013;26:180‐3. doi: 10.1016/j.aucc.2013.03.003
262 Mao Z, Gao L, Wang G, et al. Subglottic secretion suction for preventing ventilator‐associated pneumonia: an updated meta‐analysis and trial sequential analysis. *Crit Care* 2016;20:353. doi: 10.1186/s13054‐016‐1527‐7
263 Pozuelo‐Carrascosa DP, Herráiz‐Adillo Á, Alvarez‐Bueno C, Añón JM, Martínez‐Vizcaíno V, Cavero‐Redondo I. Subglottic secretion drainage for preventing ventilator‐associated pneumonia: an overview of systematic reviews and an updated meta‐analysis. *Eur Respir Rev* 2020;29:190107. doi: 10.1183/16000617.0107‐2019
264 Huang XA, Du YP, Fu BB, Li LX. Influence of subglottic secretion drainage on the microorganisms of ventilator associated pneumonia: A meta‐analysis for subglottic secretion drainage. *Medicine (Baltimore)* 2018;97:e11223. doi: 10.1097/MD.0000000000011223
265 de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003;362:1011‐6. doi: 10.1016/S0140‐6736(03)14409‐1
266 de Smet AMGA, Kluytmans JAJW, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009;360:20‐31. doi: 10.1056/NEJMoa0800394
267 Plantinga NL, de Smet AMGA, Oostdijk EAN, et al. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta‐analysis. *Clin Microbiol Infect* 2018;24:505‐13. doi: 10.1016/j.cmi.2017.08.019
268 Bhalodi AA, van Engelen TSR, Virk HS, Wiersinga WJ. Impact of antimicrobial therapy on the gut microbiome. *J Antimicrob Chemother* 2019;74(Suppl 1):i6‐15. doi: 10.1093/jac/dky530
269 Buelow E, Bello González TDJ, Fuentes S, et al. Comparative gut microbiota and resistome profiling of intensive care patients receiving selective digestive tract decontamination and healthy subjects. *Microbiome* 2017;5:88. doi: 10.1186/s40168‐017‐0309‐z

270 Wittekamp BH, Plantinga NL, Cooper BS, et al. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a randomized clinical trial. *JAMA* 2018;320:2087-98. doi: 10.1001/jama.2018.13765
271 Zhao T, Wu X, Zhang Q, Li C, Worthington HV, Hua F. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2020;12:CD008367.
272 Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis* 2011;11:845-54. doi: 10.1016/S1473-3099(11)70127-X
273 Klompas M. Oropharyngeal decontamination with antiseptics to prevent ventilator-associated pneumonia: rethinking the benefits of chlorhexidine. *Semin Respir Crit Care Med* 2017;38:381-90. doi: 10.1055/s-0037-1602584
274 Hua F, Xie H, Worthington HV, Furness S, Zhang Q, Li C. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2016;10:CD008367. doi: 10.1002/14651858.CD008367.pub3
275 Zand F, Zahed L, Mansouri P, Dehghanrad F, Bahrani M, Ghorbani M. The effects of oral rinse with 0.2% and 2% chlorhexidine on oropharyngeal colonization and ventilator associated pneumonia in adultsí intensive care units. *J Crit Care* 2017;40:318-22. doi: 10.1016/j.jcrc.2017.02.029
276 Deschepper M, Waegeman W, Eeckloo K, Vogelaers D, Blot S. Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. *Intensive Care Med* 2018;44:1017-26. doi: 10.1007/s00134-018-5171-3
277 Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med* 2014;174:751-61. doi: 10.1001/jamainternmed.2014.359
278 Price R, MacLennan G, Glen J, SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ* 2014;348:g2197. doi: 10.1136/bmj.g2197
279 Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. *Vet Hum Toxicol* 2002;44:89-91.
280 Plantinga NL, Wittekamp BHJ, Leleu K, et al. Oral mucosal adverse events with chlorhexidine 2% mouthwash in ICU. *Intensive Care Med* 2016;42:620-1. doi: 10.1007/s00134-016-4217-7
281 Chiewchalermsri C, Sompornrattanaphan M, Wongsa C, Thongngarm T. Chlorhexidine allergy: current challenges and future prospects. *J Asthma Allergy* 2020;13:127-33. doi: 10.2147/JAA.S207980
282 Odedra KM, Farooque S. Chlorhexidine: an unrecognised cause of anaphylaxis. *Postgrad Med J* 2014;90:709-14. doi: 10.1136/postgradmedj-2013-132291
283 La Combe B, Bleibtreu A, Messika J, et al. Decreased susceptibility to chlorhexidine affects a quarter of Escherichia coli isolates responsible for pneumonia in ICU patients. *Intensive Care Med* 2018;44:531-3. doi: 10.1007/s00134-018-5061-8
284 Righy C, do Brasil PEA, Vall-s J, Bozza FA, Martin-Loeches I. Systemic antibiotics for preventing ventilator-associated pneumonia in comatose patients: a systematic review and meta-analysis. *Ann Intensive Care* 2017;7:67. doi: 10.1186/s13613-017-0291-4
285 Leone M, Bouadma L, Bouhemad B, et al. Hospital-acquired pneumonia in ICU. *Anaesth Crit Care Pain Med* 2018;37:83-98. doi: 10.1016/j.accpm.2017.11.006
286 Chiu CY, Miller SA. Clinical metagenomics. *Nat Rev Genet* 2019;20:341-55. doi: 10.1038/s41576-019-0113-7
287 Xie F, Duan Z, Zeng W, et al. Clinical metagenomics assessments improve diagnosis and outcomes in community-acquired pneumonia. *BMC Infect Dis* 2021;21:352. doi: 10.1186/s12879-021-06039-1
288 Chen J, Zhao Y, Shang Y, et al. The clinical significance of simultaneous detection of pathogens from bronchoalveolar lavage fluid and blood samples by metagenomic next-generation sequencing in patients with severe pneumonia. *J Med Microbiol* 2021;70:001259. doi: 10.1099/jmm.0.001259
289 Gonzalo-Calvo D, de , Ben-tez ID, Pinilla L, et al, Circulating microRNA profiles predict the severity of COVID-19 in hospitalized patients. *Transl Res* 2021;236:147-59 doi: 10.1016/j.trsl.2021.05.004.
290 Bonneau E, Neveu B, Kostantin E, Tsongalis GJ, De Guire V. How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. *EJIFCC* 2019;30:114-27.
291 Kyriazopoulou E, Karageorgos A, Liaskou-Antoniou L, et al. BioFire-FilmArray- pneumonia panel for severe lower respiratory tract infections: subgroup analysis of a randomized clinical trial. *Infect Dis Ther* 2021;10:1437-49. doi: 10.1007/s40121-021-00459-x