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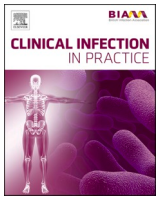

Practical clinical reviews

Management of Non-Ventilated hospital acquired pneumonia

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A B S T R A C T

Non-ventilated hospital acquired pneumonia (NV-HAP) is defined as pneumonia that develops at least 48 h after hospital admission in the non-invasively ventilated patient. Guidance in the management of NV-HAP has historically used extrapolated research from the wider field of HAP, which includes patients with the separate clinical entity of ventilator associated pneumonia (VAP), or the field of community acquired pneumonia (CAP). However, NV-HAP is being increasingly recognised as a subtype of HAP owing to its high incidence, mortality, morbidity and health-economic burden. With a wide range of underlying causative organisms, the management approach focuses on initial broad-spectrum coverage of common bacterial pathogens. If microbiological results are available, targeted treatment can be started. Throughout all phases of treatment, supportive measures must also be considered. This includes the use of physiotherapy, oxygen and ventilatory support, fluid therapy and nutritional support. Research is ongoing into novel treatments, including new antimicrobials, nebulised therapies and monoclonal antibodies. Future research would benefit from a focussed approach that aims to standardise clinical and research definitions and treats NV-HAP as a separate entity to VAP. Collection of specific data would allow for the development of risk-stratification or severity tools which have been fundamental in improving the management of other pneumonia patients, for example, the use of CURB-65 in CAP. Review of commonplace supportive measures in the NV-HAP population would also be beneficial in view of the mostly frail co-morbid population affected.

Introduction

Aim

Hospital acquired pneumonia (HAP) is defined as an acute lower respiratory tract infection which is acquired after at least 48 h of admission to hospital and was not incubating at admission (Nice, 2018). This definition has been widely adopted and has meant that HAP has become a distinct subtype of pneumonia in clinical, research and policy settings. The subcategorising of HAP into non-ventilated HAP (NV-HAP) and ventilator associated pneumonia (VAP) has been driven by the varied causative organisms and management strategies of these discrete phenomena (di Pasquale et al., 2016). Whilst the evidence base for VAP is vast, there is a paucity of understanding surrounding NV-HAP. Subsequently, much of clinical practice is guided by extrapolated data from research into community acquired pneumonia (CAP) and VAP. Although there is clearly a degree of commonality in these pulmonary infections, the extrapolated evidence approach is being increasingly recognised as suboptimal. Each of these conditions has unique causes and differently impacts distinct patient populations with varying treatments and complications (Di Pasquale et al., 2016 Feb 25). This review aims to provide a narrative summary of the available evidence base for the management of NV-HAP to guide clinicians, researchers and commissioners.

Epidemiology

NV-HAP is a common phenomenon and carries a significant mortality. In Europe, point prevalence studies have demonstrated that 1.38 % of hospitalised patients have a HAP or lower respiratory tract infection (Cassini et al., 2016 Oct 18). Similar incidence is reported in the United States (US) where HAP has been reported as occurring in 1 % of all hospitalised patients (Giuliano et al., 2018; Carey et al., 2022;

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Greene, 2020). Furthermore, it has a significant impact on patient morbidity and survival, and is associated with increased lengths of stay, higher healthcare costs and increased 30-day mortality, 1-year mortality, and rates of inpatient sepsis (Cassini et al., 2016 Oct 18; Giuliano et al., 2018; Carey et al., 2022). Longer term outcomes are not known. The healthcare-associated costs are estimated at $40,000 (USD) per patient (Giuliano et al., 2018). Data from the UK National Health Service (NHS) are often combined figures for NV-HAP and VAP. NHS-reported mortality for these combined conditions is between 30 and 70 %, with an increase in hospital length of stay by 7–9 days (NICE, 2019; NICE, 2012). A prospective survey of older adults over a 12 month period in one centre in the UK found the risk of NV-HAP to be 0.3 % per day in hospital, concluding that HAP was over-diagnosed in older age groups (Burton et al., 2016). Healthcare associated infection surveillance reports, which report data from across Europe, demonstrate the scale of the issue – with pneumonia accounting for 21.4 % of health care associated infections (Torres et al., 2017). The epidemiology of NV-HAP specifically within the NHS, and therefore the total cost in financial and patient terms in the United Kingdom (UK), to our knowledge, is not clearly reported.

Available guidelines

There are several guidelines available to clinicians treating NV-HAP, including a National Institute of Clinical Excellence (NICE) guideline (NG139) from 2019 which focuses on antimicrobial prescribing (NICE, 2019). Although these guidelines are useful for clinicians to reference, the stakeholder consultation feedback published alongside NG139 highlights challenges with the production of such recommendations. Most pertinently, the feedback emphasises the imperative to focus on: 1) local resistance patterns and 2) the unique characteristics of the local population when selecting an appropriate antimicrobial. It is exceptionally challenging to provide national or international antibiotic prescribing guidelines for common infectious syndromes with a variety of underlying organisms, and this caveat must be recognised when using guidelines to steer clinical practice.

The European Respiratory Society (ERS) has also produced guidelines on the management of HAP and VAP. This guideline aims to guide the clinical management approach, rather than the particular antimicrobial agent of choice (Torres et al., 2017). In the United States, clinical practice guidance has been produced by the Infectious Diseases Society of America in conjunction with the American Thoracic Society (Kalil et al., 2016 Sep 1). This guidance answers 25 questions in relation to the diagnosis and treatment of VAP and HAP. The relevant recommendations from each of these guidelines are explored in the discussion section of this paper below.

Aetiology

One of the challenges in the management of NV-HAP is the broad range of causative organisms. This review focusses on the management of bacterial causes, but there are also viral and fungal pathogens (Fine, 2020).

The most common bacterial agents in VAP are thought to be the result of aspiration of organisms colonising the upper respiratory tract, and therefore are most commonly gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* spp. (Papazian et al., 2020 May 10). NV-HAP is a different entity and patients with early onset disease (<5 days into hospital admission) usually have a bacterial cause more commonly associated with community acquired pneumonia (CAP), such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *methicillin-susceptible Staphylococcus aureus* (Sopena and Sabrià, 2000). NV-HAP which develops more than 5 days from admission typically has a gram-negative cause, much like VAP (Sopena and Sabrià, 2000). Viral causes, such as influenza or SARS-CoV-2, are largely spread in local outbreaks. Less commonly, NV-HAP is caused by fungal disease such as aspergillosis in vulnerable patient subgroups (Fine, 2020).

Methods

This narrative review provides an overview of the current landscape surrounding the management of NV-HAP and proposes future prospects for treatment. The following search terms, and their synonyms, were used: 'non-ventilated', 'hospital acquired pneumonia' and 'management'. Through a PubMed search undertaken on 11/4/23, 29 results were found between 1995 and 2023 (Appendix 1). 21 of these were excluded after review of abstracts as they were not focused on the management of NV-HAP or did not present novel information; 1 further paper was excluded as it was not available in English (Fig. 1). Subsequently, with such limited direct evidence available, the authors also searched more widely to take learning from the fields of CAP and VAP. Through targeted searches in the areas of interest, utilising the planned subtitles of this paper, a wider pool of publications was able to be drawn upon. The authors also utilised published guidance and manually searched the reference lists of guidelines from the UK, Europe and America for other important publications (Torres et al., 2017; Shen Lim et al., 2015; Kalil et al., 2016).

Discussion

The management of NV-HAP will be discussed through four lenses: 1) disease stratification and initial anti-microbial choice; 2) anti-microbial stewardship; 3) supportive measures and treatment adjuncts and 4) novel therapies.

Current management

International guidelines use variable clinical definitions of NV-HAP, but typically thoracic radiology should be performed where there is clinical suspicion, and a diagnosis made if the patient has new consolidation which is otherwise unexplained within the relevant timeframe already outlined (Nice, 2018).

Disease stratification and initial anti-microbial choice

Antibiotic treatment should be initiated as soon as possible and always within 4 h of identifying the diagnosis; the patient must also be assessed for sepsis early and have received antibiotic treatment within one hour of a suspected sepsis diagnosis (NICE, 2019). The ERS guidelines advise the use of organ dysfunction scores such as Organ Dysfunction and Infection System (ODIN), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiological Score II (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II) in

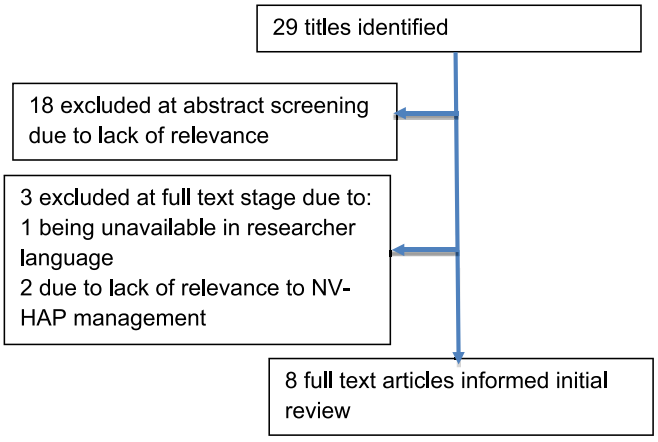

Fig. 1. Consort style diagram of initial search strategy.

the HAP setting (Torres et al., 2017). As NV- HAP is a leading cause of nosocomial sepsis, the prompt initiation of treatment is imperative to reduce its associated morbidity and mortality (Ranes et al., 2010).

Guidance suggests that the choice of antibiotic should be determined by disease severity and host risk factors for a resistant causative organism (NICE, 2019). The challenge with a severity-based approach to treatment is that there are no well-known validated scoring systems to guide clinicians on disease severity (NICE, 2019). Although a range of disease severity scores have been applied in clinical trials, for example the clinical pulmonary infection score (CPIS) and the acute physiology and chronic health evaluation score (APACHE), these are yet to be commonplace in clinical settings. This appears to be due to heterogeneity in the study populations to which they have been applied and a lack of reliability in their ability to predict NV-HAP severity (Napolitano, 2010). Researchers have looked to apply CAP severity scores, such as CURB-65, to NV-HAP to address this (Carrabba et al., 2012). However, the stark difference in performance of these scores in immunosuppressed versus immunocompetent patients in hospital has meant that they generally perform poorly for the cohort of hospitalised patients as a whole (Carrabba et al., 2012).

Due to the importance of prompt initiation of treatment, a broad approach to early antimicrobial cover has been applied to date. Researchers have reviewed the benefit of invasive initial investigation (using protective brush sampling of specimens) to allow for targeted initial treatment; however, there is a trend towards higher mortality when using this approach, and therefore it is not recommended (Herer et al., 2009). In the UK, national guidance advocates following local microbiology resistance data when making an antibiotic choice. NICE have recommended the use of broad-spectrum intravenous (IV) penicillins, cephalosporins or carbapenems as first line options for those with severe symptoms/signs or those at higher risk of resistance (NICE, 2019). In mild or moderate disease and those not at higher risk of resistance, NICE have recommended oral co-amoxiclav as a first line option (NICE, 2019). NICE have advised that patients should be considered at higher risk of resistance if: their symptoms or signs have started more than 5 days after hospital admission; they have a comorbidity which would put them at increased risk e.g. severe lung disease or immunosuppression, they have recently received a broad-spectrum antibiotic; they have known colonisation with multidrug-resistant bacteria; or a recent contact with a health or social care setting before their current admission (NICE, 2019). This recommendation is based on expert opinion, and there is little original research to support this. The recently published severe CAP guidance from the ERS advises integrating risk factors based on known local epidemiology and previous colonisation to guide decision making on drug resistance (Martin-Loeches et al., 0000). They also discuss the use of scores to assess resistance risk, and acknowledge that there are several validated scores available, but these are most valuable in identifying low risk patients who do not require empirical treatment for drug resistant pathogens (Martin-Loeches et al., 0000). The risk profile in NV-HAP is likely to be different to that of severe CAP, so NV-HAP specific scores are needed.

Guidelines suggest that empirical treatment of drug-resistant organisms should be considered in certain cases, for example, those with suspected or confirmed *methicillin resistant Staphylococcus aureus* (MRSA) infection/colonisation. Due to the limited choice of oral antibiotics with adequate MRSA coverage, this is typically with IV vancomycin or teicoplanin (NICE, 2019). ERS guidelines, which pertain to both NV-HAP and VAP, suggest that empirical MRSA therapy should be given to those with over 15 % risk of mortality who are being treated in an environment where more than 25 % of the *Staphylococcus aureus* isolates are methicillin resistant (Torres et al., 2017). The systematic review and *meta*-analysis on which this recommendation is based does not use a specific scoring system to assess mortality risk at a patient level and therefore the guidelines have not suggested how clinicians can assess this (Torres et al., 2017; Kumar et al., 2010 Aug). Unfortunately, this makes this recommendation challenging for clinicians to implement.

The European guidance, utilising extrapolated data from VAP studies, also discusses the benefits and harms of monotherapy versus combination therapy in the context of multi-drug resistant pathogens. Evidence underpinning this guidance suggests that monotherapy is effective in patients with mild or moderate disease where there is a monotherapy effective against $>$ 90 % of gram-negative bacteria locally. However, in severe illness or septic shock, this recommendation cannot be safely applied as these patients were outside of the populations studied (Torres et al., 2017; Heyland et al., 2008; Aarts et al., 2008).

In order to be able to move patients into the second phase of treatment (targeted therapy), adequate microbiological samples need to have been acquired. In most patients, this will at least be sputum microscopy and culture, nasopharyngeal swabs, including viral polymerase chain reaction, and blood cultures (NICE, 2019). However, the rate of sampling is thought to be low. A retrospective study examining the yield of microbiological samples in NV-HAP found that only 29.4 % of the 1,172 patients in the study had a sputum sample sent (Naidus et al., 2018 Jan 1). Moreover, only 13.2 % of the samples resulted in a positive culture (Naidus et al., 2018 Jan 1). This highlights the need not only for improved sampling frequency, but also quality and perhaps focus on improving methods of microbiological testing. Urinary antigen testing for legionella species in NV-HAP is often only considered in areas with high local prevalence or hospital-based outbreaks. Legionella is less commonly associated with NV-HAP than CAP, but research does suggest that nosocomial legionella infection carries a higher mortality than disease acquired in the community (Dagan et al., 2021; Sreenath et al., 2020). It has been hypothesised that this is due to delayed diagnosis and initiation of appropriate treatment (Dagan et al., 2021).

Antimicrobial stewardship

Point of care diagnostics. Antimicrobial stewardship is of significant concern in the management of all bacterial infections and needs to be of high priority for clinicians treating NV-HAP. The cornerstone of stewardship is reviewing the choice of antimicrobial therapy as soon as microbiological results are available. This approach is hindered by waiting for culture results, which take at least 48–72 h and lack sensitivity, and the low rate of microbiological sampling (Wagner et al., 2020). The INHALE study, published in 2022, aimed to evaluate the use of rapid molecular diagnostics to guide antibiotic choices in HAP/VAP in the intensive care unit (ICU), looking at two systems – BioFire® (Biomerieux) film array pneumonia panel and Unyvero (OpGen) pneumonia panel (Enne et al., 2022 Dec). Rapid point of care diagnostic interventions such as that evaluated by INHALE have the potential to eliminate the need for initial broad-spectrum cover whilst awaiting culture results (High et al., 2021). The study found that these syndromic PCR-based diagnostic tests offer improved sensitivity for the microbiological diagnosis of HAP and VAP compared with standard of care routine culture (Enne et al., 2022 Dec). The study does include patients with NV-HAP but only in the ICU setting – further research is needed to evaluate the use of rapid point of care diagnostics in the non-ICU ward-based environment. The real-world application of such interventions is not known, with their impact on hospital length of stay, mortality, morbidity, or patient experience not yet explored.

Length of treatment. This second phase of targeted treatment is made even more challenging by the decision of when to switch from IV to oral therapy, and when to cease treatment altogether. Guidance suggests that an IV to oral switch should be considered at 48 h after treatment initiation, but this recommendation is based on expert opinion rather than clinical trial data in NV-HAP. Treatment is widely expected to be needed for at least 5 days to be effective, which is similarly based on expert opinion (NICE, 2019). Several studies in CAP and HAP have demonstrated that short antibiotic courses – typically less than 7 days – are effective at increasing antibiotic-free days whilst not impacting

mortality rates, and also reduce the recurrence of pneumonia due to resistant organisms (Shebl et al., 2019; Li et al., 2007; Pugh et al., 2015). There is little evidence from randomised controlled trials (RCTs) comparing durations of therapy specifically in NV-HAP, but a Cochrane review did conclude that on the basis of a single study from 1998, short-course (three-day) therapy for HAP does not appear to be associated with worsened clinical outcomes (Pugh et al., 2015). It must be noted that this study only included patient populations where there was a low probability of pneumonia according to the CPIS, and therefore the applicability of this result in a patient with high clinical probability of NV-HAP is debatable (Pugh et al., 2015). The same study also caveated their conclusions that in patients with VAP caused by non-fermenting gram-negative bacilli, short course therapy was associated with a higher risk of recurrence, although no increase in mortality was seen (Pugh et al., 2015).

Clinical biomarkers. Although there is limited direct evidence in NV-HAP, most clinicians and guidelines would advocate the use of clinical biomarkers, such as C-Reactive Protein (CRP) and procalcitonin (PCT), alongside microbiological results and the clinical signs and symptoms of the patient to guide treatment duration (Kalil et al., 2016; Zilahi et al., 2016; Iankova et al., 2018; Lim et al., 2009). Evidence in CAP has shown CRP to be a sensitive marker of clinical progress. Failure of the CRP to fall by 50 % by day 4 of illness has been linked with increased rates of complications (higher 30-day mortality, need for ICU level interventions and development of empyema) (Lim et al., 2009; Chalmers et al., 2008 Mar). The evidence supporting the use of PCT to guide therapy has been mixed. A large systematic review and *meta*-analysis published in 2018 analysed data from 6708 patients receiving PCT guided antibiotic therapy for acute respiratory infections (Schuetz et al., 2018 Jan). PCT guided therapy significantly reduced 30-day mortality, antibiotic exposure and antibiotic related side effects. However, the studies included in this *meta*-analysis were highly heterogenous, using PCT across a variety of settings and respiratory infections. A more recent, large randomised controlled trial failed to replicate these findings, with no significant difference found between the antibiotic usage in PCT guided therapy or standard care in suspected lower respiratory tract infections presenting to the emergency department (Huang et al., 2018 Jul 19). Studies investigating the applicability of using PCT in NV-HAP are lacking and therefore the utility in this setting remains unknown.

Complications. Due to the lack of NV-HAP specific guidance, there is a requirement for clinicians to be vigilant for complications in all patients with NV-HAP. This can include monitoring for complications such as those in Fig. 2. From data available on CAP, it is known that para-pneumonic effusions are common, developing in up to 57 % of those with bacterial pneumonia (Shen Lim et al., 2015). Lung abscess (Fig. 3) are rarer, but should be considered in those with risk factors e.g. alcohol dependence or following aspiration (Shen Lim et al., 2015). Patients who are not improving as expected should have further imaging including plain chest radiographs or computed tomography to assess the pulmonary vasculature or lung parenchyma, and will also require thoracic ultrasound to identify the presence of pleural effusions with subsequent sampling and intervention. All patients who are not improving as expected with first line treatment, or who have any resistant pathogens, should be discussed with microbiology specialists (NICE, 2019). If microbiological samples have also not identified a target for treatment, clinicians may also consider an induced sputum or broncho-alveolar lavage. A study on 200 critically unwell NV-HAP patients found that invasive sampling methods increased the yield of microbiological results to 56 % when compared with non-invasive sampling which had a yield of 39 % ($p = 0.018$) (Ranzani et al., 2019 Feb 18).

Supportive measures and treatment adjuncts

Supportive measures need to be considered and implemented throughout all stages of treatment. Although there is little original research supporting the use of these therapies in NV-HAP specifically, the evidence from the wider field of pneumonia management is typically applied cautiously given the heterogeneous clinical course of this distinct diagnosis and syndrome.

Guidelines advocate for use of targeted oxygen therapy with oxygen

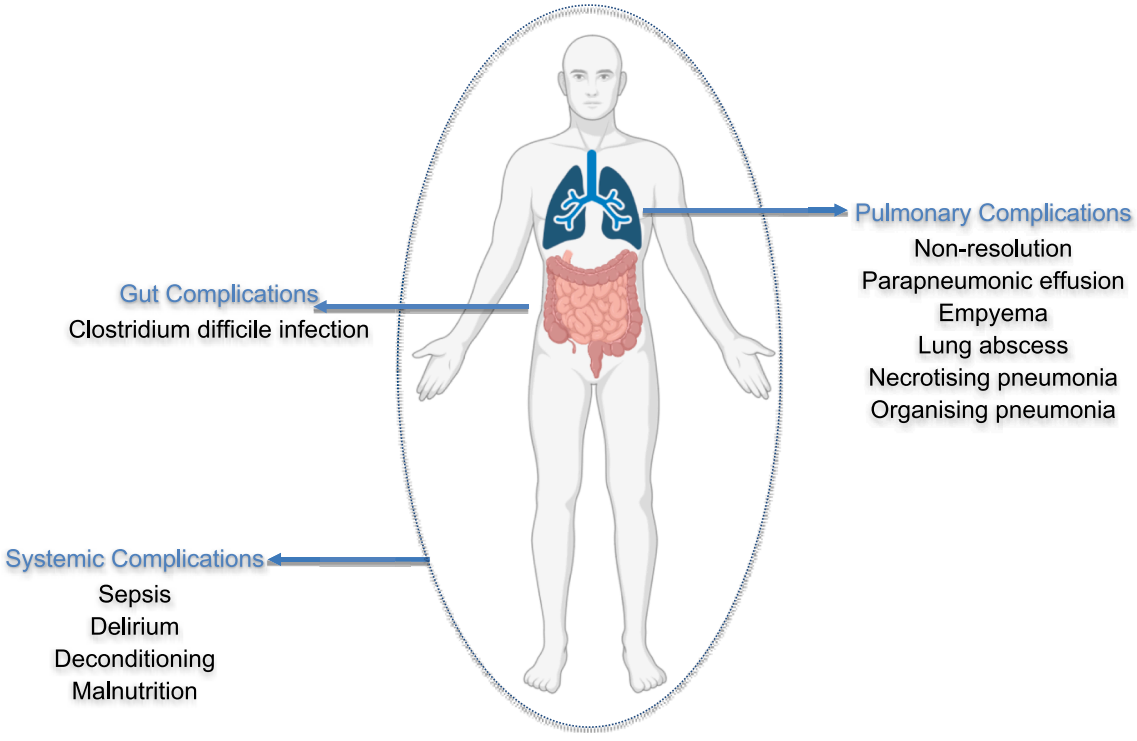

Fig. 2. Complications of NV-HAP or its treatment. Created with BioRender.com.

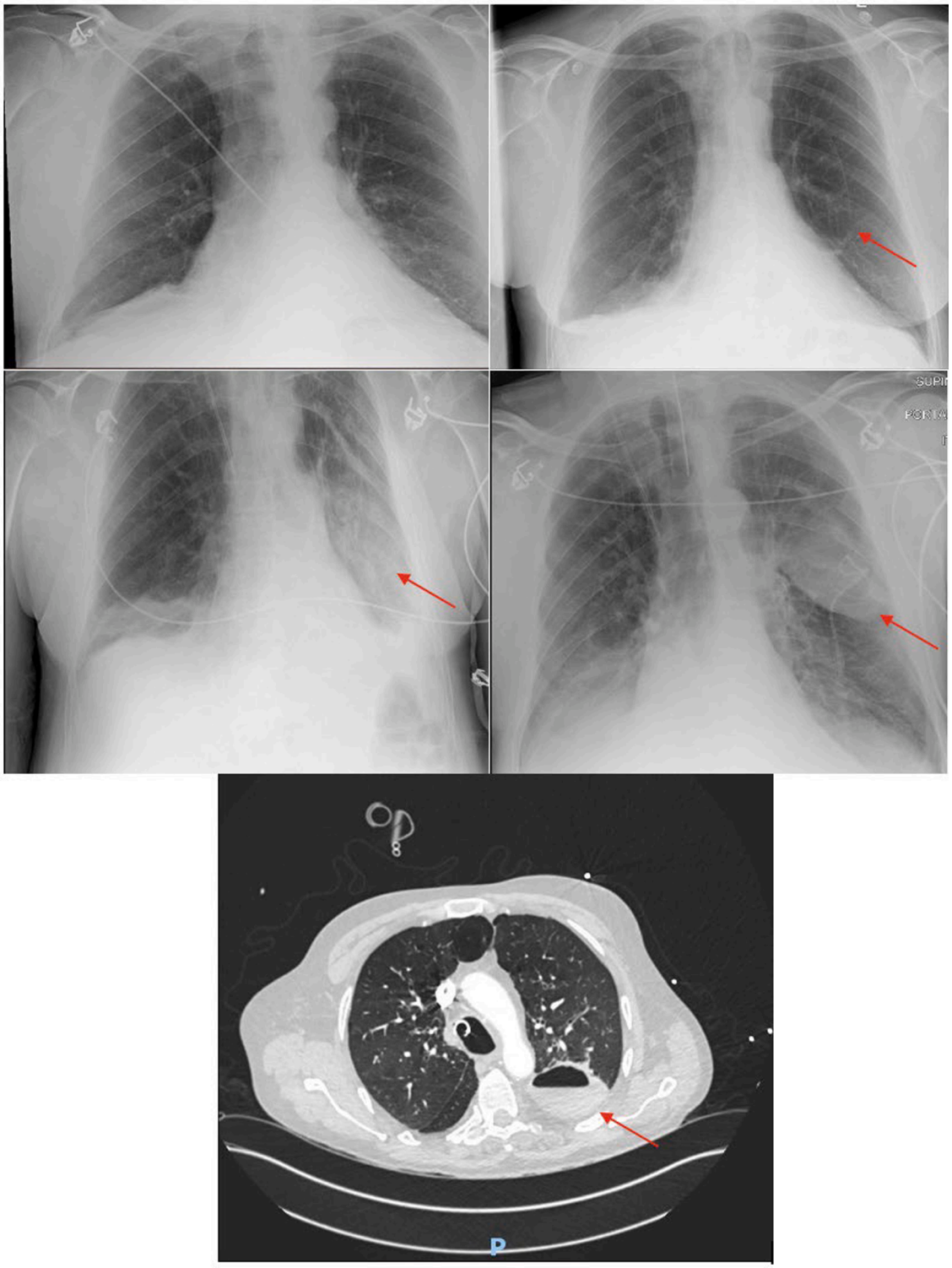

Fig. 3. These chest radiographs and a section of a computed tomography scan demonstrate the evolution of a lung abscess in a patient with pseudomonas associated HAP. The top left image was taken on admission, the top right 5 days after admission, the middle left 10 days after admission and the middle right 20 days after admission with the insertion of an interventional radiology assisted drain into the abscess. The bottom image is a slice of a CT scan demonstrating the abscess taken 11 days after admission.

saturations appropriately set for the individual patient based on their risk of hypercapnic respiratory failure, fluid therapy guided by clinical hydration status and VTE prophylaxis for all patients who are not fully mobile or at increased thrombotic risk (Shen Lim et al., 2015; Lim et al., 2009). This recommendation is supported by robust *meta*-analysis data which demonstrates a 56 % and 58 % reduction in DVT and PE respectively when using heparins for venous thromboembolism prophylaxis when compared with control in medical inpatients (Mismetti et al., 2000 Jan).

Increased nutritional support, which can be via enteral (including

nasogastric tube) or parental routes, is also commonly recommended in guidelines to enhance recovery in those with severe pneumonia requiring prolonged admission (Shen Lim et al., 2015). Research data has demonstrated an increased risk of pneumonia in the malnourished and an increased mortality risk from pneumonia in those with markers of poor nutritional status such as low BMI, albumin and arm circumference (LaCroix et al., 1989; Riquelme et al., 1997 Dec 1). A randomised controlled trial of hospitalised adults with risk factors for malnutrition and confirmed lower respiratory tract infection (not exclusively NV-HAP) in the non-ICU setting, has also found that individualized nutritional support to reach protein and energy goals confers a mortality benefit with a 25 % reduction in 30-day mortality risk (control 12.2 % vs. intervention 9.1 % with an OR 0.47 (95 % CI 0.12 to 1.27)), although the results for the NV-HAP subgroup analysis did not reach statistical significance (Baumgartner et al., 2021 Apr).

Similarly to the evidence base for nutritional support, the evidence for fluid therapy in NV-HAP is rooted in the treatment of sepsis and pneumonia in general. Guidelines suggest assessment of fluid status to guide fluid replacement (Shen Lim et al., 2015). The CLASSIC trial enrolled 1554 patients with septic shock in the ICU setting in an unblinded randomised controlled trial to restrictive or standard IV fluid therapies (Meyhoff et al., 2022 Jun 30). Approximately 25 % of participants had a pulmonary source of infection and the authors analysed this as a subgroup. They concluded that there was no mortality difference between either group and this was true at pneumonia subgroup level as well (Meyhoff et al., 2022 Jun 30). More research in NV-HAP is needed on the best approaches to IV fluid therapy and whether a restrictive approach would also be successful in this patient group, particularly given the difference in frailty, age and co-morbid status of NV-HAP patients in comparison to those treated in ICU which can compound challenges of fluid therapy.

Currently, due to a highly heterogeneous evidence base, guidelines recommend against the use of non-invasive ventilation (NIV, both continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)) to support patients with respiratory failure secondary to CAP; in practice this same approach has been applied to patients with NV-HAP (Shen Lim et al., 2015). There is, however, growing early evidence that NIV and high flow nasal oxygen (HFNO) can be safe and effective in sub-groups of patients with pneumonia, and particularly so in a closely monitored environment (Yang et al., 2013; Waseem et al., 2021; Ibrahim and Mohamed, 2018; Kunieda et al., 2016). In the setting of viral pneumonia, the RECOVERY-RS trial examined the use of respiratory support in patients with COVID-19 and acute respiratory failure, including patients with nosocomial COVID-19. They concluded that patients who received CPAP were less likely to require invasive ventilation than those who received standard therapy, and that HFNO has no benefit over standard oxygen therapy (Perkins et al., 2022 Feb 8). Guidance does not indicate when escalation of care to an ICU may be best sought in the NV-HAP setting (Melgaard et al., 2018).

Despite being commonplace in the management of NV-HAP, chest physiotherapy has an inconclusive evidence base and traditional airway clearance is not recommended for uncomplicated pneumonia (Shen Lim et al., 2015; Lim et al., 2009; Yang et al., 2013). Although there has been demonstrable benefit to clinical parameters such as oxygen saturations and respiratory rate in certain subtypes of pneumonia, such as aspiration and VAP, there is little evidence of overall outcome improvement (Waseem et al., 2021; Ibrahim and Mohamed, 2018). The topic has been assessed through a Cochrane review, which included patients with CAP, NV-HAP and VAP (Yang et al., 2013). The authors did not perform subgroup analysis by pneumonia type. Across the spectrum of pneumonia included there is evidence that very specific techniques in adults, such as osteopathic manipulative treatment and positive expiratory pressure can cause a modest benefit in a variety of important outcomes such as lengths of stay, duration of IV antibiotics and duration of fever, but again there is no clear mortality benefit (Yang et al., 2013). Physiotherapy which looks to improve early mobilisation has been shown to be particularly effective at reducing length of stay (Kunieda et al., 2016; Mundy et al., 2003; Melgaard et al., 2018; Larsen et al., 2019). Given this, current guidance supports early mobilisation with mobility increased on each subsequent day of admission (Shen Lim et al., 2015).

During the SARS-CoV-2 pandemic, the positive effect seen within the dexamethasone arm of the RECOVERY trial reignited the debate surrounding the benefit of corticosteroids for the treatment of pneumonia (RECOVERY Collaborative Group et al., 2021 Feb 25). Research in the field of bacterial pneumonia suggests a benefit in severe disease where there is a requirement for invasive mechanical ventilation or evidence of septic shock (Stern et al., 2017; Ceccato et al., 2021). However, there has been increased mortality observed in a smaller study investigating systemic steroid use in intensive care unit acquired pneumonia, particularly in those with NV-HAP or lower disease severity (Ranzani et al., 2012). Recent ERS guidelines in severe CAP advise the use of corticosteroids in the presence of shock and that further research into the role of steroids in bacterial pneumonia is needed to draw firm conclusions on their efficacy and safety (Martin-Loeches et al., 0000).

Novel therapies

Novel therapies for NV-HAP are needed in the face of progressive antimicrobial resistance and high levels of mortality and morbidity with current therapeutic options. These include the development of new antimicrobials, new routes of administration and the innovative use of monoclonal antibodies.

New antimicrobials

Recent years have seen the development of new antibiotics to treat multi-drug resistant (MDR) pathogens, and many of these have been trialled and approved in HAP. The major advantage of these newer antibiotics is their activity against MDR gram negative bacteria in particular – a sample of these are explored in further detail below.

Ceftobiprole, a fifth-generation cephalosporin, was approved for use in CAP and NV-HAP in Europe in 2015 (Liapikou et al., 2015). It is a particularly useful addition to the armoury of available agents because of its activity against MRSA (Bassetti et al., 2022; el Solh, 2009; Barberán, 2019; Martínez Pérez-Crespo and López Cortés, 2021 Sep). It has demonstrated non-inferiority in a Phase 3 study comparing it to ceftazidime with linezolid in HAP, with clinically evaluable cure rates of 77.8 % versus 76.2 % respectively (Awad et al., 2014). Treatment-related adverse events were also similar between the two groups, demonstrating ceftobiprole to be a safe and effective option for NV-HAP (Awad et al., 2014). Another cephalosporin with promise for the treatment of HAP is cefiderocol, a siderophore which inhibits gram-negative bacterial cell wall synthesis through binding to penicillin-binding proteins. It received marketing authorisation in the UK in 2020 and has been recommended by NICE for treating severe, drug-resistant gram-negative bacterial infections in guidance published in 2022 (NICE, 2022). It's been evaluated in several Phase 3 randomized, double-blind clinical trials, and has demonstrated non-inferiority to meropenem for NV-HAP/VAP (Wunderink et al., 2021). In patients with carbapenem-resistant infections, it has also been shown to be comparable to best available therapy (Bassetti et al., 2021). However, the cefiderocol group in this study did have a higher all-cause mortality, particularly those patients infected with *Acinetobacter baumannii* (Bassetti et al., 2021). Subsequently, a warning of increased all-cause mortality for patients with carbapenem-resistant *A. baumannii* infections treated with cefiderocol monotherapy has been released (Shionogi. Fetroja., 2022).

Telavancin is a lipoglycopeptide antibiotic with a dual mechanism of action: inhibition of cell-wall synthesis and disruption of the bacterial membrane barrier function (Rubinstein et al., 2014 May). In a post-hoc analysis of a double-blind phase 3 randomised controlled trial, telavancin was found to be non-inferior to vancomycin in patients with NV-HAP, and to have fewer incidences of renal side effects (Rubinstein et al., 2014 May). This makes telavancin an attractive option in NV-HAP

particularly where there is a strain of *S. aureus* with reduced activity against vancomycin (Rubinstein et al., 2014 May). The growing frequency of MRSA has also led to increased interest in antimicrobials which can treat the serious infections it causes (Gould et al., 2012 Feb). Linezolid is a good example of another antimicrobial with growing favour thanks to proven anti-MRSA activity. It has been evaluated in a large RCT and found to have a significantly higher clinical cure rate (although similar 60-day mortality) in MRSA nosocomial pneumonia to vancomycin; it should be noted that approximately two thirds of the patients in this study were mechanically ventilated (Wunderink et al., 2012 Mar 1).

The following new combinations of Beta-lactamase inhibitors with another antibiotic are also being explored for NV-HAP. Ceftolozane-tazobactam has shown enhanced activity against *Pseudomonas aeruginosa* with particular efficacy against drug resistant strains (Pfaller et al., 2021). It has been proven to be non-inferior to meropenem in treating VAP and has a licence for both NV-HAP and VAP in the UK (Kollef et al., 2019). Meropenem-vaborbactam has exhibited superior efficacy in carbapenem-resistant Enterobacteriaceae (CRE) infections (including a number of patients with respiratory infections), decreasing mortality and reducing nephrotoxicity when compared with best available treatment in a Phase 3 open label RCT (Wunderink et al., 2018). The composite end points of clinical failure or nephrotoxicity demonstrated a superior risk–benefit for meropenem-vaborbactam over best available treatment at 31.3 % vs 80 % with a $p < 0.001$ (Wunderink et al., 2018). Imipenem-cilastatin-relebactam has also been proven to be efficacious in gram-negative NV-HAP/VAP, even in those who are critically unwell, in a double-blind Phase 3 RCT; it has a licence in Europe for those with limited treatment options under specialist advice (Titov et al., 2021). Evaluation of aztreonam-avibactam in a Phase 3 RCT has recently completed (NCT03329092). This study has included 421 participants with either HAP, VAP or intra-abdominal infection and has taken place worldwide; the expected date of result read out has not been published (Clinicaltrials.gov. A Study to Determine the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem (MER) ± Colistin (COL) for the Treatment of Serious Infections Due to Gram Negative Bacteria. (REVISIT)., 2023).

Nebulised antimicrobials

Nebulised antibiotics have long been used in the care of patients with respiratory conditions – namely in the treatment of cystic fibrosis (CF) and non-CF bronchiectasis (Maselli et al., 2017; Conway, 1999). The use of nebulised therapy in pneumonia is thought to be particularly promising, with the potential for increased, more targeted concentration to the pulmonary tissue and subsequently more infrequent systemic side effects. Currently they are primarily used as salvage therapy, as an addition to systemic treatments in patients with MDR gram-negative bacteria (Niederman, 2019). Colistin and aminoglycosides have been the most commonly used treatments in pneumonia but large-scale trials, particularly in those with NV-HAP are lacking (Boisson et al., 2022).

Monoclonal antibodies

The innovative use of monoclonal antibodies heralds an exciting development in the treatment of NV-HAP. Biologic treatments do not have the same toxicity as many antibiotics, are generally felt to have less potential to develop resistance, and usually target one pathogen specifically which helps to avoid disruption of the hosts microbiome (Zurawski and v., McLendon MK., 2020; Kollef and Betthauser, 2021). Biologic treatments may be pathogen-directed or host-directed. Host-directed monoclonals exhibit their beneficial effects by interfering with the host cellular processes needed for pathogen replication or survival or targeting the host immune response to infection (Wallis et al., 2023 Feb). As demonstrated in the examples discussed below, trials in monoclonals have trended towards being focussed on patients with VAP. There is a clear need to also focus on patients with NV-HAP in order to develop viable options in the face of growing anti-microbial resistance.

Although promising, the widespread production and use of monoclonals in bacterial infection has been slow to progress. As a group of drugs, they are expensive to produce and their progression to routine clinical use can be unpredictable. For example, KB001-A, an engineered human antibody Fab fragment that binds with high affinity to the *Pseudomonas aeruginosa* PcrV protein, demonstrated potent in vitro neutralisation and successfully protected mouse models against lethal pulmonary challenges of the bacteria (Baer et al., 2009 Mar). Initial human studies of mechanically ventilated patients demonstrated safety and an early suggestion of efficacy, although in a very small number of patients (François et al., 2012 Aug 31). However, the product has failed to progress to phase 3 studies, with little communication from the company about the reasons for this (Zurawski and v., McLendon MK., 2020).

There are no monoclonal antibodies currently in routine use for NV-HAP, however, there are several monoclonals in development which could be beneficial for this patient group. The main focus has been against *Staphylococcus aureus* and *Pseudomonas aeruginosa* as common causes of nosocomial infection, and therefore highly commercially viable targets (Zurawski and v., McLendon MK., 2020). AR301, which targets *Staphylococcus aureus* (including MRSA) and its secreted alpha toxin, has demonstrated improved eradication rates when given in combination with antibiotics when compared with antibiotics alone. It has subsequently been granted orphan drug status for treatment of *S. aureus* pneumonia by the European Medicines Agency and fast track designation United States Federation for Drug Administration (FDA) (Zurawski and v., McLendon MK., 2020). Phase 3 trials are underway in VAP patients and the top line read out from the first of these planned trials revealed positive results, however these did not reach statistical significance though this may be a consequence of the small sample size (Pharmaceuticals, 2023 Jan 25).

Other products, such as MEDI3902, have shown anti-pseudomonal activity (Zurawski and v., McLendon MK., 2020). MEDI3902 targets the same protein as KB001-A, as well as having additional activity by targeting a surface polysaccharide and affecting *P. aeruginosa*'s ability to form biofilms. However, in a phase 2 trial in VAP patients, despite reaching serum concentrations associated with benefit in animal models and being safe, there was no reduction in development of *P. aeruginosa* pneumonia in the treatment group (Chastre et al., 2022).

Future research

Although the development of novel therapies is interesting, the care of patients with NV-HAP is unlikely to see significant improvements without a focus on several other key research areas. Firstly, the research and clinical community need to agree a unified definition and NV-HAP needs to be recognised as its own entity separate to VAP in research. Secondly, NV-HAP specific data collection is required which will allow for the development of risk stratification and severity scores. Finally, the optimisation of widely available treatments for example fluid therapy, physiotherapy, oxygen, ventilatory therapy, and nutritional support in the context of NV-HAPs mostly frail co-morbid population is required. Without focussing on these areas first, the research community could miss the opportunity to create a cohesive approach which allows for streamlined translation of research results into clinical practice.

Conclusion

In conclusion, NV-HAP is becoming increasingly recognised as a distinct phenomenon with high mortality, morbidity and health-economic impact. In order to manage NV-HAP effectively clinicians must focus on early identification followed by prompt broad-spectrum treatment which moves into targeted therapy when results are available; throughout all stages of treatment supportive therapies must be considered and implemented. New antibiotics, novel delivery mechanisms and innovative biologics will likely be required in the face of

progressive antimicrobial resistance. Future research priorities should focus on the collection of NV-HAP specific data, the development of severity scoring to enable clinicians to best risk stratify patients, as well as the development of novel therapies.

CRediT authorship contribution statement

Harriet Pittaway: Writing – original draft. **Frances Grudzinska:** Writing – review & editing. **Alana Livesey:** Writing – review & editing. **Samuel Quarton:** Writing – review & editing. **Aditya Adiga:** Writing – review & editing. **Davinder Dosanjh:** Supervision. **Dhruv Parekh:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Aarts, M.A.W., Hancock, J.N., Heyland, D., McLeod, R.S., Marshall, J.C., 2008. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials. Crit Care Med. 36 (1).

Awad, S.S., Rodriguez, A.H., Chuang, Y.C., Marjanek, Z., Pareigis, A.J., Reis, G., et al., 2014. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clinical Infectious Diseases. 59 (1).

Baer, M., Sawa, T., Flynn, P., Luehrsen, K., Martinez, D., Wiener-Kronish, J.P., et al., 2009 Mar. An engineered human antibody fab fragment specific for Pseudomonas aeruginosa PcrV antigen has potent antibacterial activity. Infect Immun. 77 (3), 1083–1090.

Barberán J. Possible clinical indications of ceftobiprole. Vol. 32, Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia. 2019.

Bassetti, M., Echols, R., Matsunaga, Y., Ariyasu, M., Doi, Y., Ferrer, R., et al., 2021. 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. 21 (2).

Bassetti, M., Mularoni, A., Giacobbe, D.R., Castaldo, N., Vena, A., 2022. New Antibiotics for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia. Semin Respir Crit Care Med. 43 (2).

Baumgartner, A., Hasenboehler, F., Cantone, J., Hersberger, L., Bargetzi, A., Bargetzi, L., et al., 2021 Apr. Effect of nutritional support in patients with lower respiratory tract infection: Secondary analysis of a randomized clinical trial. Available from Clinical Nutrition [Internet]. 40 (4), 1843–1850. https://linkinghub.elsevier.com/retrieve/pii/S0261561420305379.

Boisson, M., Bouglé, A., Sole-Lleonart, C., Dhanani, J., Arvaniti, K., Rello, J., et al., 2022. Nebulized Antibiotics for Healthcare- and Ventilator-Associated Pneumonia. Semin Respir Crit Care Med. 43 (2).

Burton LA, Price R, Barr KE, Mcauley SM, Allen JB, Clinton AM, et al. Hospital-acquired pneumonia incidence and diagnosis in older patients. Age Ageing [Internet]. 2016 Jan 1 [cited 2023 Apr 10];45(1):171–4. Available from: https://pubmed.ncbi.nlm.nih.gov/26683049/.

Carey, E., Blankenhorn, R., Chen, P., Munro, S., 2022. Non-ventilator associated hospital acquired pneumonia incidence and health outcomes among U.S. veterans from 2016–2020. Am J Infect Control. 50 (1).

Carrabba, M., Zarantonello, M., Bonara, P., Hu, C., Minonzio, F., Cortinovis, I., et al., 2012. Severity assessment of healthcare-associated pneumonia and pneumonia in immunosuppression. European Respiratory Journal. 40 (5).

Cassini, A., Plachouras, D., Eckmanns, T., Abu Sin, M., Blank, H.P., Ducomble, T., et al., 2016 Oct 18. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 13 (10), e1002150.

Ceccato, A., Russo, A., Barbeta, E., Oscanoa, P., Tiseo, G., Gabarrus, A., et al., 2021. Real-world corticosteroid use in severe pneumonia: a propensity-score-matched study. Crit Care. 25 (1).

Chalmers, J.D., Singanayagam, A., Hill, A.T., 2008 Mar. C-Reactive Protein Is an Independent Predictor of Severity in Community-acquired Pneumonia. Am J Med. 121 (3), 219–225.

Chastre J, François B, Bourgeois M, Komnos A, Ferrer R, Rahav G, et al. Safety, efficacy, and pharmacokinetics of gremubamab (MEDI3902), an anti-Pseudomonas aeruginosa bispecific human monoclonal antibody, in P. aeruginosa-colonised, mechanically ventilated intensive care unit patients: a randomised controlled trial. Crit Care. 2022 Nov 15;26(1):355.

Clinicaltrials.gov. A Study to Determine the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem (MER) ± Colistin (COL) for the Treatment of Serious Infections Due to Gram Negative Bacteria. (REVISIT). 2023.

Conway, S.P., 1999. Evidence for using nebulised antibiotics in cystic fibrosis. Archives of Disease in Childhood Vol. 80.

Dagan, A., Epstein, D., Mahagneh, A., Nashashibi, J., Geffen, Y., Neuberger, A., et al., 2021. Community-acquired versus nosocomial Legionella pneumonia: factors associated with Legionella-related mortality. European Journal of Clinical Microbiology and Infectious Diseases. 40 (7).

di Pasquale, M., Aliberti, S., Mantero, M., Bianchini, S., Blasi, F., 2016. Non-intensive care unit acquired pneumonia: A new clinical entity? International Journal of Molecular Sciences Vol. 17.

Di Pasquale, M., Aliberti, S., Mantero, M., Bianchini, S., Blasi, F., 2016 Feb 25. Non-Intensive Care Unit Acquired Pneumonia: A New Clinical Entity? Int J Mol Sci. 17 (3), 287.

el Solh, A.A., 2009. Ceftobiprole: A new broad spectrum cephalosporin. Expert Opinion on Pharmacotherapy Vol. 10.

Enne, V.I., Aydin, A., Baldan, R., Owen, D.R., Richardson, H., Ricciardi, F., et al., 2022 Dec. Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. Thorax. 77 (12), 1220–1228.

Fine, L.S., 2020. Non-ventilator health care-associated pneumonia (NV-HAP): Pathogenesis and microbiology of NV-HAP. Am J Infect Control. 48 (5).

François, B., Luyt, C.E., Dugard, A., Wolff, M., Diehl, J.L., Jaber, S., et al., 2012 Aug 31. Safety and pharmacokinetics of an anti-PcrV PEGylated monoclonal antibody fragment in mechanically ventilated patients colonized with Pseudomonas aeruginosa: a randomized, double-blind, placebo-controlled trial. Crit Care Med. 40 (8), 2320–2326.

Giuliano, K.K., Baker, D., Quinn, B., 2018. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. Am J Infect Control. 46 (3).

Gould, I.M., David, M.Z., Esposito, S., Garau, J., Lina, G., Mazzei, T., et al., 2012 Feb. New insights into meticillin-resistant Staphylococcus aureus (MRSA) pathogenesis, treatment and resistance. Int J Antimicrob Agents. 39 (2), 96–104.

Greene, L.R., 2020. Non-ventilator health care-associated pneumonia (NV-HAP): Putting it all together. Am J Infect Control. 48 (5).

Herer, B., Fuhrman, C., Gazevic, Z., Cabrit, R., Chouaïd, C., 2009. Management of nosocomial pneumonia on a medical ward: A comparative study of outcomes and costs of invasive procedures. Clinical Microbiology and Infection. 15 (2).

Heyland, D.K., Dodek, P., Muscedere, J., Day, A., Cook, D., 2008. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 36 (3).

High, J., Enne, V.I., Barber, J.A., Brealey, D., Turner, D.A., Horne, R., et al., 2021. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care—study protocol for a multicentre randomised controlled trial. Trials. 22 (1).

Huang, D.T., Yealy, D.M., Filbin, M.R., Brown, A.M., Chang, C.C.H., Doi, Y., et al., 2018 Jul 19. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. New England Journal of Medicine. 379 (3), 236–249.

Iankova, I., Thompson-Leduc, P., Kirson, N.Y., Rice, B., Hey, J., Krause, A., et al., 2018. Efficacy and safety of procalcitonin guidance in patients with suspected or confirmed sepsis: A systematic review and meta-analysis. Critical Care Medicine Vol. 46.

Ibrahim, A.A., Mohamed, A.R., 2018. Effect of adding different physiotherapy modalities to standard chest physiotherapy for critical ill patients. Res J Pharm Biol Chem Sci. 9 (3).

Kalil, A.C., Metersky, M.L., Klompas, M., Muscedere, J., Sweeney, D.A., Palmer, L.B., et al., 2016. 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. Clinical Infectious Diseases Vol. 63.

Kalil, A.C., Metersky, M.L., Klompas, M., Muscedere, J., Sweeney, D.A., Palmer, L.B., et al., 2016 Sep 1. 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. Clinical Infectious Diseases. 63 (5), e61–e.

Kollef, M.H., Betthauser, K.D., 2021. Monoclonal antibodies as antibacterial therapies: thinking outside of the box. The Lancet Infectious Diseases Vol. 21.

Kollef, M.H., Nováček, M., Kivistik, Ü., Réa-Neto, Á., Shime, N., Martin-Loeches, I., et al., 2019. Ceftolozane–tazobactam versus meropenem for treatment of nosocomial

pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 19 (12).
Kumar, A., Safdar, N., Kethireddy, S., Chateau, D., 2010 Aug. 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. 38 (8), 1651–1664.
Kunieda, Y., Amimoto, K., Miki, H., Yamazaki, R., Adachi, T., Hoshino, H., 2016. Early mobilization prevents pneumonia complications in acute stroke patients. Cerebrovascular Diseases. 41.
LaCroix, A.Z., Lipson, S., Miles, T.P., White, L., 1989. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. Public Health Rep. 104 (4), 350–360.
Larsen, T., Lee, A., Brooks, D., Michieli, S., Robson, M., Veens, J., et al., 2019. Effect of early mobility as a physiotherapy treatment for pneumonia: A systematic review and meta-analysis. Physiotherapy Canada Vol. 71.
Li, J.Z., Winston, L.G., Moore, D.H., Bent, S., 2007. Efficacy of Short-Course Antibiotic Regimens for Community-Acquired Pneumonia: A Meta-analysis. American Journal of Medicine. 120 (9).
Liapikou, A., Cillóniz, C., Torres, A., 2015. Ceftobiprole for the treatment of pneumonia: a European perspective. Drug Des Devel Ther. 9, 4565–4572.
Lim, W.S., Baudouin, S., George, R., Hill, A., Jamieson, C., le Jeune, I., et al., 2009. British Thoracic Society guidelines for the management of community acquired pneumonia in adults: Update 2009. Thorax Vol. 64.
Martínez Pérez-Crespo, P.M., López Cortés, L.E., 2021 Sep. Ceftobiprole: a clinical view. Rev Esp Quimioter. 34 Suppl 1(Suppl1), 32–34.
Martin-Loeches I, Torres A, Nagavci B, Aliberti S, Antonelli M, Bassetti M, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Available from: https://doi.org/10.1007/s00134-023-07033-8.
Maselli, D.J., Keyt, H., Restrepo, M.I., 2017. Inhaled antibiotic therapy in chronic respiratory diseases. International Journal of Molecular Sciences Vol. 18.
Melgaard, D., Baandrup, U., Bøgsted, M., Bendtsen, M.D., Kristensen, M.T., 2018. Early mobilisation of patients with community-acquired pneumonia reduce length of hospitalisation—a pilot study. J Phys Ther Sci. 30 (7).
Meyhoff, T.S., Hjortrup, P.B., Wetterslev, J., Sivapalan, P., Laake, J.H., Cronhjort, M., et al., 2022 Jun 30. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. New England Journal of Medicine. 386 (26), 2459–2470.
Mismetti, P., Laporte-Simitsidis, S., Tardy, B., Cucherat, M., Buchmüller, A., Juillard-Delsart, D., et al., 2000 Jan. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost. 83 (1), 14–19.
Mundy, L.M., Leet, T.L., Darst, K., Schnitzler, M.A., Dunagan, W.C., 2003. Early mobilization of patients hospitalized with community-acquired pneumonia. Chest. 124 (3).
Naidus, E.L., Lasalvia, M.T., Marcantonio, E.R., Herzig, S.J., 2018 Jan 1. The Diagnostic Yield of Noninvasive Microbiologic Sputum Sampling in a Cohort of Patients with Clinically Diagnosed Hospital-Acquired Pneumonia. J Hosp Med. 13 (1), 34–37.
Napolitano LM. Use of severity scoring and stratification factors in clinical trials of Hospital-acquired and ventilator-associated pneumonia. In: Clinical Infectious Diseases. 2010.
Nice, 2018;. Pneumonia in adults: diagnosis and management. Nice. December 2014.
NICE. NICE clinical guideline: Pneumonia scope. 2012.
NICE. National Institute for Health and Care Excellence Guideline. 2019. Pneumonia (hospital-acquired): Antimicrobial prescribing. NICE Guideline [NG139].
NICE. Antimicrobial health technology evaluation guidance. 2022. Cefiderocol for treating severe drug-resistant gram-negative bacterial infections.
Niederman, M.S., 2019. Adjunctive Nebulized Antibiotics: What Is Their Place in ICU Infections? Vol. 6 Frontiers in Medicine.
Papazian, L., Klompas, M., Luyt, C.E., 2020 May 10. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med. 46 (5), 888–906.
Perkins, G.D., Ji, C., Connolly, B.A., Couper, K., Lall, R., Baillie, J.K., et al., 2022 Feb 8. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19. JAMA. 327 (6), 546.
Pfaller, M.A., Shortridge, D., Harris, K.A., Garrison, M.W., DeRyke, C.A., DePestel, D.D., et al., 2021. Ceftolozane-tazobactam activity against clinical isolates of Pseudomonas aeruginosa from ICU patients with pneumonia: United States, 2015–2018. International Journal of Infectious Diseases. 112.
Pharmaceuticals, A., 2023 Jan 25. Aridis Reports Top-Line Results of the Phase 3 Double-Blinded, Superiority Trial of AR-301 For the Treatment of Staphylococcus aureus Ventilator Associated Pneumonia (VAP). GlobalNewswire.
Pugh, R., Grant, C., Cooke, R.P.D., Dempsey, G., 2015. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database of Systematic Reviews Vol. 2015.
Ranes JL, Gordon S, Arroliga AC. Hospital-Acquired, Health Care-Associated, and Ventilator-Associated Pneumonia. In: Current Clinical Medicine: Expert Consult Premium Edition - Enhanced Online Features and Print. 2010.
Ranzani, O.T., Ferrer, M., Esperatti, M., Giunta, V., Bassi, G.L., Carvalho, C.R.R., et al., 2012. Association between systemic corticosteroids and outcomes of intensive care unit-acquired pneumonia. Crit Care Med. 40 (9).
Ranzani, O.T., Senussi, T., Idone, F., Ceccato, A., Li Bassi, G., Ferrer, M., et al., 2019 Feb 18. Invasive and non-invasive diagnostic approaches for microbiological diagnosis of hospital-acquired pneumonia. Crit Care. 23 (1), 51.
RECOVERY Collaborative Group, Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., et al., 2021 Feb 25. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 384 (8), 693–704.
Riquelme, R., Torres, A., El-Ebiary, M., Mensa, J., Estruch, R., Ruiz, M., et al., 1997 Dec 1. Community-acquired Pneumonia in the Elderly. Am J Respir Crit Care Med. 156 (6), 1908–1914.
Rubinstein, E., Stryjewski, M.E., Barriere, S.L., 2014 May. Clinical utility of telavancin for treatment of hospital-acquired pneumonia: focus on non-ventilator-associated pneumonia. Infect Drug Resist. 129.
Schuetz, P., Wirz, Y., Sager, R., Christ-Crain, M., Stolz, D., Tamm, M., et al., 2018 Jan. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis. 18 (1), 95–107.
Shebl E, Said AM, El-Korashi LA, Ibraheem HA. The outcome of hospital-acquired pneumonia in patients admitted for long-term care according to the antibiotic duration. EGYPTIAN JOURNAL OF CHEST DISEASES AND TUBERCULOSIS. 2019;68 (3).
Shen Lim W, Smith D, Wise M, Welham S. 2015 - Annotated BTS Guideline for the management of CAP in adults (2009). British Thoracic Society. 2015.
Shionogi. Fetroja. 2022.
Sopena N, Sabrià M, Neunos 2000 Study Group. Multicenter study of hospital-acquired pneumonia in non-ICU patients. Chest. 2005 Jan;127(1):213–9.
Sreenath K, Dey AB, Kabra SK, Thakur B, Guleria R, Chaudhry R. Legionella pneumophila in Patients with Pneumonia at a Referral Hospital, New Delhi, India, 2015-2020. Am J Trop Med Hyg. 2020;104(3).
Stern, A., Skalsky, K., Avni, T., Carrara, E., Leibovici, L., Paul, M., 2017. Corticosteroids for pneumonia. Cochrane Database of Systematic Reviews Vol. 2017.
Titov, I., Wunderink, R.G., Roquilly, A., Gonzalez, D.R., David-Wang, A., Boucher, H.W., et al., 2021. 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). Clinical Infectious Diseases. 73 (11).
Torres, A., Niederman, M.S., Chastre, J., Ewig, S., Fernandez-Vandellos, P., Hanberger, H., et al., 2017. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. European Respiratory Journal Vol. 50.
Wagner, A.P., Enne, V.I., Livermore, D.M., Craig, J., v., Turner DA., 2020. Review of health economic models exploring and evaluating treatment and management of hospital-acquired pneumonia and ventilator-associated pneumonia. Journal of Hospital Infection. 106.
Wallis, R.S., O'Garra, A., Sher, A., Wack, A., 2023 Feb. Host-directed immunotherapy of viral and bacterial infections: past, present and future. Nat Rev Immunol. 23 (2), 121–133.
Waseem, M.H., Farooq Lasi, F., Valecha, J., Samejo, B., Sangrasi, S.A., Murtaza, A.S., 2021. Effectiveness of chest physiotherapy in cerebrovascular accident patients with aspiration pneumonia. Journal of Modern. Rehabilitation. 15 (1).
Wunderink, R.G., Niederman, M.S., Kollef, M.H., Shorr, A.F., Kunkel, M.J., Baruch, A., et al., 2012 Mar 1. Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized. Controlled Study. Clinical Infectious Diseases. 54 (5), 621–629.
Wunderink, R.G., Giamarellos-Bourboulis, E.J., Rahav, G., Mathers, A.J., Bassetti, M., Vazquez, J., et al., 2018. 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. 7 (4).
Wunderink, R.G., Matsunaga, Y., Ariyasu, M., Clevenbergh, P., Echols, R., Kaye, K.S., et al., 2021. 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. 21 (2).
Yang, M., Yan, Y., Yin, X., Wang, B.Y., Wu, T., Liu, G.J., et al., 2013. Chest physiotherapy for pneumonia in adults. Cochrane Database of Systematic Reviews Vol. 2013.
Zilahi, G., McMahon, M.A., Povoa, P., Martin-Loeches, I., 2016. Duration of antibiotic therapy in the intensive care unit. Journal of Thoracic Disease. 8.
Zurawski D v., McLendon MK. Monoclonal antibodies as an antibacterial approach against bacterial pathogens. Vol. 9, Antibiotics. 2020.