Management of pneumonia in intensive care

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Abstract: Pneumonia, an inflammatory infiltrate of the alveolar airspace, is commonly triggered by bacterial infection of the lungs, or less commonly by viral or fungal infection. It remains the commonest infective reason for admission to intensive care as well as being the most common secondary infection acquired whilst in the intensive care unit (ICU). It presents a significant global burden of disease and is especially prevalent in low- and middle-income countries. The major categories of pneumonia encountered by the Intensive Care clinician are community-acquired, ventilator-acquired, non-ventilator hospital-acquired and pneumonia in the immunocompromised patient. An appreciation of the type of pneumonia a patient has developed is critical to its effective treatment. Pneumonia is the commonest precipitant of acute respiratory distress syndrome (ARDS) and clinicians should be mindful that the evidence-base surrounding ARDS will, in large part, apply to severe pneumonia. The causative organisms which lead to pneumonia vary depending on the site of acquisition (community or hospital-acquired), the immune status of the patient and the presence of intercurrent medications including antibiotics. Current standard microbiological testing is seldom able to give a rapid answer as to which microorganisms is present and causing infection. Therefore, empirical therapy guided by knowledge of local microbial flora and resistance patterns is the recommended course of action. This approach risks the over-treatment of pneumonia with unnecessarily broad-spectrum agents which bring with them the problems of antibiotic-associated harm. Novel rapid diagnostic tests aimed at both the pathogen and the host response hold promise in the rationalisation and appropriate targeting of antimicrobial therapy. At present neither scoring systems nor diagnostic tests are able to accurately risk stratify a patient's need for intensive care admission. Beyond antibiotic therapy, a number of adjuvant therapies have been trialled in pneumonia although none have yet made it into widespread clinical use. Corticosteroids are recommended in some cases of community-acquired pneumonia (CAP), but their role in the patient with severe CAP in ICU remains uncertain whilst they are a risk factor for the development of hospital and ventilator-acquired pneumonia. Immuno-stimulation has not yet translated from small scale clinical trials into clinical use. Supportive management includes lung protective ventilation, and those interventions proven to improve outcomes in ARDS. This review will give an overview of the epidemiology of severe pneumonia, the microbiological causes and diagnostic strategies. It will then turn to management, including antimicrobial therapy, role of adjuvant therapies, respiratory support and prevention of complications.

Keywords: Pneumonia; community-acquired; hospital-acquired; ventilator-acquired; antibiotics

Introduction

Pneumonia is an inflammation of the alveolar airspace, most commonly triggered by bacteria but also arising from other classes of pathogen and less frequently by autoimmune processes. The infiltration of the alveolar space by leucocytes and a fibrinous exudate impairs lung function, and in its more severe forms can require invasive ventilation and admission to an intensive care unit (ICU). This review will focus on severe infectious pneumonia and its management in the ICU.

There are limited data on the incidence of severe pneumonia, although reports from the United States suggest nearly 20% of adults hospitalized with pneumonia will be admitted to ICU (1), with a clear seasonal pattern being evident. However the burden of pneumonia is considerably greater in low and middle income countries where the critical care resources are considerably less (2). Pneumonia is not only a precipitating factor leading to admission to ICU, but is also the commonest secondary infection acquired by critically ill patients (3). ICU-acquired pneumonia is largely ventilator-associated and presents specific problems of diagnosis and management (4).

The causative organisms in pneumonia are heavily influenced by where patients acquire the disease and the condition of their immune system (5), with differences in the flora causing community-acquired and hospital-acquired infections (6). Patients with impaired immune function are at risk of opportunistic pathogens such as fungi and otherwise 'low pathogenicity' bacteria (7), in addition to the more classically pathogenic organisms which infect the immunologically intact as well. This review will consider four broad categories of pneumonia, namely community-acquired, ventilator-acquired pneumonia, hospital-acquired and pneumonia in the immunocompromised host. It will also consider the overlap between pneumonia and acute respiratory distress syndrome (ARDS) (8).

The greatest challenges in the Intensive Care management of pneumonia are in the diagnosis and identification of the causative organisms, the selection of appropriate antibiotics and determining the duration of therapy, and in the prevention of secondary pneumonia. This review will cover the epidemiology of severe pneumonia as well as the aetiology and how our understanding of microbial ecology is changing the concept of infection. It will then turn to diagnosis, considering the existing diagnostic strategies and future directions in diagnostic technologies, before turning to management

of both antibiotic and non-antibiotic therapies. Beyond antimicrobial therapy, management focuses on supportive therapy, protective ventilation and the avoidance of complications of ICU admission.

Epidemiology of severe pneumonia

Severe pneumonia lacks a unifying definition, however for community-acquired infection the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) definition being pneumonia which requires admission to an ICU (9,10) is widely used. Although this definition concerns community-acquired pneumonia (CAP), it can also be extended to hospital-acquired pneumonia and pneumonia in the immunocompromised host. Ventilator-associated pneumonia (VAP), with its attributable mortality of 8–10% (11) and its restriction to critically ill patients, can be similarly considered 'severe'.

ARDS, being defined as respiratory compromise with bilateral radiographic infiltrates not fully explained by cardiac failure (12), clearly has considerable overlap with the diagnosis of severe pneumonia. It is therefore unsurprising that pneumonia constitutes around 60% of patients in studies of ARDS (8). The evidence which underpins practice in ARDS applies to those patients with severe pneumonia who meet the criteria for ARDS, and has been reviewed recently elsewhere (13) and will be summarised below.

Amongst patients hospitalized with CAP, up to 20% may require admission to ICU (1), although this proportion may vary widely by country (14) and by availability of ICU beds (15), and shows marked seasonal variability (16). Pneumonia is the commonest cause of death in low income countries, whilst in upper-middle income and higher income countries it is the 6th commonest cause of death and the leading infectious cause of death (17). Estimates of the mortality rates from European countries show a wide range of reported values from <1% to 48% although differences in reporting may be responsible for some of this variation. From the perspective of an ICU clinician, in England at least, pneumonia remains the commonest infectious cause of admission, and carries a mortality rate of 35% (18) and in international surveys is the commonest infection found in ICU patients (19).

Pneumonia is also a frequent complication of hospital stay, with hospital-acquired pneumonias (HAP) developing in between 1% and 5% of all hospitalized patients (20,21). HAP is defined as pneumonia developing at least 48 hours after hospital admission, and is generally considered to be

'non-ventilator associated' as VAP is its own diagnostic entity (22). Giuliano and colleagues recently assessed the mortality associated with HAP in a large US database (21), the crude mortality of 13.1% exceeded that of a population matched for illness severity without pneumonia (mortality 11.2%) and those admitted with CAP (mortality 3.5%), with only patients with VAP having a higher mortality (17.5%). There is limited data on the rates of admission to ICU for HAP. However what data there is suggests that, despite the reported mortality, ICU admission may occur in only 3–5% of patients developing HAP (23). One of the significant difficulties in determining the epidemiology of HAP is the frequency with which it is over-diagnosed (20,23), an issue we will return to when considering VAP.

To further complicate matters, the entity of 'healthcare associated pneumonia' or HCAP had been proposed by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) (22), as a an infection developing in someone with close healthcare contact such as recent hospital admission, nursing home residence or in receipt of intravenous antibiotics within the past 30 days (22). It was felt that such a definition was required as patients with HCAP are thought to be at increased risk of infections with multi-drug resistant (MDR) organisms. However more recent studies examining the differences in MDR rates between CAP and HCAP have indicated that MDR organisms are not restricted to HCAP patients and can be predicted by individual patient characteristics rather than needing to be considered as a separate entity (5,24) and HCAP was removed from the most recent IDSA/ATS guidelines (25).

Patients with immunocompromise, be that through immunosuppressive drugs, infection with HIV, haematological malignancy or primary and secondary immune deficiency disorders are at risk of infections in general and pneumonia specifically. Whilst specific rates of infection will vary depending on the cause and severity of the immune deficiency, this group are worth highlighting because of their susceptibility to opportunistic infections such as fungi and parasites, alongside the more conventional pneumonia pathogens. This will be discussed further in the next section.

The final category of pneumonia which will be considered in this review is VAP, which by its very definition is solely confined to the ICU. VAP remains the commonest secondary infection to occur in ventilated ICU patients (26), despite considerable efforts to reduce and control this disease (27,28). VAP affects around 16% of ICU patients (29),

although as incidence is significantly altered as a function of exposure (30) it is usually expressed as incident density (cases per 1,000 ventilator days) (31), with quoted rates of 13.6 cases per 1,000 ventilator days globally (29). The mortality associated with VAP is difficult to disentangle from the severity of the underlying illness, however the most rigorous estimates indicate that VAP incurs an additional mortality burden of 6–10% (30,32).

Microbiology of severe pneumonia

The microbial pathogens which cause pneumonia are influenced by the environmental exposure of the patient prior to them developing infection, as well as their underlying immune state. The generally accepted pathogenesis of bacterial pneumonia involves colonisation of the upper respiratory tract by the organism, followed by migration to the lower respiratory tract and proliferation leading to infection. It remains unclear why some people become colonized with pathogenic organisms but do not progress to pneumonia, whilst others do, although being resistant to colonisation with a specific organism does appear to protect against infection from that same organism (33). The acquisition of viral pneumonia is likely to differ from that of bacterial, in that exposure leads to viral infection and proliferation, although again there is a wide range of responses to viral infection ranging from resistance, through asymptomatic shedding to severe pneumonitis (34).

Across all types of pneumonia, culture-negative infection remains the commonest reported state, occurring in around 65% of CAP patients (35), and up to 70% of patients with suspected VAP (36) with similar rates reported for patients with HAP (37). Whilst some culture-negative results may reflect misdiagnosis, especially in the case of VAP where so many conditions may mimic it (38), a significant proportion are likely to be due to the imperfect nature of conventional microbiology (39). The limitations of current diagnostics will be discussed below, but any appreciation of the microbial ecology of pneumonia needs to be considered in this light.

When an organism is detected in CAP, the dominant organism remains *Streptococcus pneumoniae*, with gram negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* as well as the atypical or intracellular organisms (*Legionella pneumophilia*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Chlamydia psittaci*). Although there is considerable anxiety about community-acquired staphylococcal pneumonia, and particularly methicillin

Table 1 Proportions of infections arising from different organisms in community-acquired and ventilator-acquired pneumonia

Organism	Hospital-acquired	Community-acquired
Gram-positive	32%	49%
Staphylococcus aureus	20% (Methecillin resistant 11%)	7%
Coagulase negative Staphylococcus	1%	0.2%
Streptococcus pneumoniae	4%	39%
Other Streptococcus spp.	8%	3%
Gram-negative	65%	36.9%
Enterobacteriaceae	14%	9%
Pseudomonas aeruginosa	24%	4.5%
Haemophilus spp.	10%	19%
Acinetobacter spp.	8%	0.2%
Neisseria spp.	3%	0.2%
Stenotrophomonas maltophilia	2%	0%
Other Gram–negative	4%	4%
'Atypical' bacteria	0%	8%
Anaerobes	1%	0.2%
Fungi	1%	0%
Respiratory viruses	0%*	36%

Data drawn from 24 studies of VAP reviewed in Chastre and Fagon (43), and pooled data from 5 studies of community-acquired pneumonia (39,44-47). Totals do not sum to 100% as some patients have more than one infecting organism. *, the advent of widespread molecular testing since the publication of Chastre and Fagon's review has revealed more viral involvement in HAP although the true extent of these agents as causes of HAP remains unclear.

resistant *Staph. aureus* (MRSA), surveillance reports suggest that it is rare (40,41).

With the advent of routine use of viral polymerase chain reaction (PCR) testing of respiratory samples, viral coinfection is increasingly recognised and may comprise up to a third of cases presenting to hospital (39). It is also now more widely accepted that several respiratory viruses, and not just influenza, can cause a widespread pneumonitis (42).

The microbiological aetiology of ventilator and hospital-acquired pneumonia differs somewhat from that seen in CAP, with gram-negative organisms being far more prevalent alongside *Staphylococcus aureus* which forms the predominant gram-positive organism. *Table 1* below illustrates the difference.

The microbial aetiology of HAP is similar to VAP (48,49), although there is a growing recognition of nosocomial viral infections (49), which have mostly been reported in HAP

rather than VAP (43).

Fungal pneumonia is often considered in patients with immunocompromise, such as those taking immunosuppressive drugs for autoimmune disease or solid organ transplantation (50,51), haematology-oncology patients (52) and those with HIV (53), although broad-spectrum antibiotic use, mechanical ventilation and major surgery are also recognised risk factors (50,51). Critically ill patients frequently develop immunoparesis during the course of their illness (26,54), and fungal pneumonia is reported although remains rare in the absence of additional causes of immunosuppression such as neutropaenia or use of immunosuppressant drugs (43,55).

The reasons for the different microbial aetiology of community and hospital-acquired pneumonias may reflect different environmental exposure, as the hospital environment is much more likely to contain the multi-resistant gram-negative organisms which typify

HAP/VAP (56). In addition, HAP/VAP tends to occur after patients have been exposed to antibiotics, which will exert selective pressure on microorganisms and lead to a predominantly resistant flora emerging (57). However it is also apparent that severe illness itself can induce a change in the pulmonary microbiota, with a shift towards enteric-type gram negative organisms and a reduction in diversity (58) which may be independent of inter-current antibiotic therapy (59). Changes in bacterial ingress, elimination and growth during acute illness alter the balance of lung microbiota (60), and it has been suggested that VAP (and possibly HAP) represent more 'overgrowth' of pathogenic bacteria rather than *de-novo* acquisition and infection (61). A high prevalence of oral commensals such as *Mycoplasma salivarium* has been reported in VAP, and these organisms may also drive immune suppression and facilitate further infection (62).

Diagnosis of pneumonia in ICU

Pneumonia is defined as inflammation of the airspaces (63), and as such the gold standard for diagnosis is histopathological examination. However, in the vast majority of cases, lung biopsy is neither practical nor desirable in a severely ill patient, whilst post-mortem examination is clearly too late to alter management. Clinicians are, therefore, required to rely on surrogate markers of alveolar inflammation and infection which present a degree of uncertainty.

Clinical criteria

The clinical criteria for pneumonia comprise evidence of systemic inflammation, such as pyrexia, tachycardia and leukocytosis/neutrophilia, combined with localizing chest signs such as rales, crepitations and bronchial breathing (64,65). These will frequently be accompanied by productive cough and breathlessness. However, clinical examination has limited sensitivity and specificity in the relatively uncomplicated primary care setting (66). It loses further diagnostic performance in Intensive Care where examination is restricted, mechanical ventilation induces auscultatory artifact (67) and where many disease processes may mimic the non-specific findings in pneumonia (38).

Given the poor performance of clinical criteria alone, these are often combined with radiographic techniques, including plain chest X-rays, ultrasound and computed tomography.

Radiographic criteria

Radiological investigations in suspected pneumonia aim to demonstrate the presence of alveolar inflammation, either in the form of lobar/sub-lobar consolidation or diffuse alveolitis. The gold standard for radiological examination of the lungs is computed tomography (CT), given its ability to localize and characterise pulmonary lesions to a much greater resolution than plain radiographs (67). However CT of the chest requires the patient to be moved off the ICU, which increases the risk of adverse events in both ventilated and non-ventilated patients (68) and is therefore not a routine investigation for ICU patients with suspected pneumonia.

Plain chest radiography (CXR) can be performed at the bedside, and is the recommended modality for imaging in CAP (9,64). Interestingly, neither the most recent European (69) nor American (25) guidelines on Hospital- and Ventilator-acquired pneumonia make recommendations on radiological investigation of pneumonia, despite the fact that nearly all clinical studies of HAP/VAP require presence of radiographic infiltrates as an inclusion criteria and both European Centre for Disease Control (70) and US Centres for Disease Control (71) definitions require radiographic demonstration of infiltrates. Amongst ICU clinicians, in the UK at least, up to 1/3rd do not think radiographic evidence is required to diagnose pneumonia (72).

Bedside ultrasound may outperform plain radiography (67,73) in the detection of consolidation, although lesions must be relatively superficial within the lung to be detected. To date no guidelines have adopted chest ultrasound as a recommended diagnostic modality, and no study has demonstrated its use changing outcomes for patients.

Microbiological culture

As noted at the start of this article, pneumonia requires the presence of an infectious organism and therefore detection of the responsible organism should guide treatment. Microbiological cultures are an imperfect method of detection, and frequently give rise of false negative results (39). In CAP the ATS/IDSA (9) and British Thoracic Society (BTS) guidelines (64) recommend routine microbiological sampling of sputum and blood in severe pneumonia, which will cover all cases admitted to Intensive Care, alongside specific antigen testing for *Legionella pneumophilia* and *Streptococcus pneumoniae*. The use of invasive sampling, by bronchoscopy or fine needle aspiration

are discussed but not specifically recommended, in part due to a lack of systematic examination of the role of invasive sampling in CAP, and the generally good performance of sputum relative to bronchoalveolar lavage (BAL) when theses samples have been compared head to head (74). For the intubated patient, endotracheal aspirate (ETA) is a form of sputum sample which is less prone to contamination from the oropharynx and is the sample most likely to be available in ventilated ICU patients. Where BAL may have a role is in patients who do not have productive sputum or where there is a failure to respond to conventional treatment (74). The pre-test probability of pneumonia is higher in patients presenting with apparent CAP than VAP, and therefore culture or detection of a pathogenic organism is generally considered diagnostic without the need for quantitative cultures.

In VAP the need for deep respiratory cultures is equally strong, and both US and European guidelines recommend obtaining samples by ETA and undertaking quantitative or semi-quantitative cultures. Debate continues within the critical care and infectious disease community regarding the role of BAL and protected specimen brush (PSB), being more invasive than ETA, in the diagnosis of pneumonia. The issues revolve around the rapid and near universal colonisation of the trachea and upper bronchial tree within a few days of mechanical ventilation (75), and whether the benefits of targeting antimicrobial therapy outweigh the risks of invasive sampling. Given the high prevalence of upper bronchial colonisation and the lack of specificity of clinical features of pneumonia (38), ETA culture is likely to significantly overestimate the rate of true pneumonia (76), whilst applying high quantitative cut-offs may lead to false negative results (76). BAL and quantitative culture has therefore become the standard in biological research in VAP, where a well-defined clinical phenotype is required (77,78). What remains less certain is the benefit in clinical practice of invasive sampling, although intuitively directing antibiotics only at those patients with proven pneumonia seems to be rational approach.

There have been three randomised trials (79-81) investigating the role of invasive sampling on outcomes in patients with suspected pneumonia, with divergent results. Whilst Solé Violán and colleagues (79), and the Canadian Critical Care Trials Group (81) did not show any change in mortality, Fagon and colleagues (80) demonstrated a significant reduction in mortality. Whilst there may be many reasons for these discrepancies, it is notable that only Fagon and colleagues demonstrated a significant difference

in antibiotic use, with the invasive strategy driving a substantial increase in antibiotic free days. Observational studies do suggest that implementation of invasive strategies in ICU can drive reduction in the use of antibiotics (76,82), and that stopping antibiotics in culture negative patients leads to fewer MDR infections without an increase in mortality (83).

In hospital-acquired pneumonia optimal diagnostic strategy remains uncertain, but obtaining good-quality respiratory secretions for culture by sputum, ETA or BAL is recommended (25). Specific recommendations for immunocompromised patients are lacking.

Molecular diagnostics

PCR

Although culture-free microbiological techniques, such as antigen testing, have existed for a long time, they are limited to single organisms and indeed often specific strains or types of those organisms. By contrast there have been significant recent developments in the field of PCR based diagnostics, which rely on the amplification and detection of specific genetic sequences. Selecting species or genus specific genetic sequences can allow the rapid and sensitive detection of relatively low numbers of gene-copy numbers (84), indicating the presence of an organism's genetic material. The use of real-time (RT) PCR allows for quantitation of gene-copies, which provides an indication of the number of organisms present. However, the existence of multiple copies of a gene within some organisms means that there may not be a direct correlation between the PCR quantitation and organism number (85). Although clinical PCR for respiratory infections was pioneered in the diagnostics of viral infections, there are an increasing number of bacterial PCR-based diagnostics on the market and this number is likely to grow rapidly over the next years.

Multiple single PCR reactions are time consuming and expensive, and therefore groups have looked to combine them into multiplex reactions (86), although the optimisation required for these can be considerable and they may be increasingly susceptible to sample-based inhibitors and internal control failure (87).

The advantage of molecular techniques is that they do not rely on the organism being alive, or capable of division and growth. They are therefore less susceptible to the risks of false negative results arising from inter-current antibiotic

use and have a much higher yield than culture-based techniques (39). However, their increased sensitivity runs the risk of detecting irrelevant or colonising organisms, and DNA from infecting pathogens may persist long after active infection has ended, thus these tests may increase rather than decrease the burden of antibiotics. Conversely the selectivity of these tests may also be a disadvantage, as organisms which are not covered by the included sequences will not be detected. To date, no study has been reported using bacterial or fungal PCR to guide clinical management of severe pneumonia.

Sequencing

An alternative molecular approach to detection of micro-organisms is to sequence the nucleic acids present and then match these against known sequences from databases of microbial DNA. The ubiquity of the 16s ribosomal RNA gene in every bacteria, with pan-bacterial conserved sequences and genus/species specific sequences (88) has been exploited to develop unbiased tests for bacteria. To date the diagnostic performance of these approaches has been disappointing (89), although total burden of 16s DNA may act as a useful marker of bacterial load in VAP (90) and blood culture (91). Until recently the alternative approach of sequencing all base-pairs present in a sample, so called metagenomics, has been prohibitively expensive and too slow to be of use clinically although it forms the basis of many studies of the lung microbiome (58). However the development of devices such as the Nanopore device (92) may bring this approach to clinical utility soon. As with targeted PCR, these highly sensitive approaches risk the detection of clinically irrelevant organisms, and their use requires careful evaluation in well conducted trials before they can be recommended for routine clinical use.

Novel optical techniques

Several novel techniques have been developed for the detection of bacteria, including the use of fluorescent probes for in-vivo imaging via devices such as the alveolar fibroscope developed by Dhaliwal et al. (93). These probes may be combined with those for activated neutrophils (93) so allowing combined confirmation of alveolar bacterial presence and inflammation, the hallmark of pneumonia. These devices remain experimental, and they are currently someway from clinical use.

Ex-vivo automated microscopy of samples, allowing detection of growth of bacteria at much lower numbers than required for conventional microbial culture also holds promise, allowing for the rapid detection of viable bacteria. This approach may provide rapid, sensitive testing whilst reducing the risks of detecting irrelevant organisms (94).

Host markers

The second component of pneumonia is the inflammatory host response, and this has been the focus of considerable research interest over the past couple of decades. Biomarkers can be measured in both pulmonary secretions, ETA or lavage, or blood.

Although the list of lavage based biomarkers of ventilator-acquired pneumonia which have been advanced is considerable (95), only one test (based on alveolar concentrations of IL-1 and IL-8) has been successfully validated (77,78). This test is undergoing evaluation as a measure to improve antibiotic stewardship, with the trial having been completed and results expected to be published soon (96) (NCT01972425).

There has been much less work on pulmonary biomarkers in community-acquired and non-VAP hospital-acquired pneumonia, and whilst it is likely that the intense pulmonary inflammation which accompanies VAP (97) is mirrored in these diseases, this remains to be conclusively demonstrated.

Circulating host biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are in routine use as monitors for infection in many ICUs, however evidence of their diagnostic utility in hospital-acquired pneumonia is limited (98,99) and their use for this purpose is not recommended in guidelines (25,69). By contrast, there is some evidence of utility of CRP in community acquired pneumonia (100) and BTS guidelines suggest it can be used to discriminate between pneumonia and non-pneumonic processes (64), whilst the IDSA/ATS guidelines remain silent on the issue (9). This divergence between HAP/VAP and CAP will likely reflect the differing pre-test probability of pneumonia seen in patients presenting with a de-novo infection and those developing secondary complications in hospital. Where PCT may have a role is in the guidance of de-escalation and early discontinuation of antibiotics, with this being studied in critically ill patients with pneumonia being the predominant diagnosis (101). However, patients in the standard management arms of PCT studies tend to have prolonged courses of antibiotics, in the PRORATA study median duration of antibiotic therapy was 13 days whilst

in the PCT group it was 10 days (102), both of which may be longer than is required to treat most pneumonias (see below). By contrast in De Jong's recent study, median antibiotic duration was reduced from 7 to 5 days, with a significant and persistent mortality benefit in the PCT group (101).

Severity scoring and determining which patients require admission to ICU

There are a number of pneumonia severity scores, which use a range of clinical, demographic and laboratory parameters to score patients and assign a severity band to them. This work has come almost entirely from the CAP literature, which is unsurprising as these patients will present to a range of settings from primary care to emergency departments and there is a need to identify those requiring hospital admissions. Patients with CAP who are ventilated immediately have a mortality of 24%, but those who deteriorate at a later time point have a mortality of 49% (14). Although it is unclear to what extent this mortality difference was due to delays in care and to what extent it was due to different disease trajectories, early admission to ICU for patients with markers of severe pneumonia appears prudent.

The two most commonly used pneumonia severity scores, the Pneumonia Severity Index (PSI) (103) and CURB-65 scores (104) are both well validated predictors of mortality at 30 days. However their ability to predict ICU admission or requirement for mechanical ventilation is moderate at best (105), as are the severe pneumonia criteria set out by in the ATS/IDSA guidelines (9). A significant proportion of patients with pneumonia die without being admitted to ICU, due to treatment limitation decisions and comorbidities, and therefore it is perhaps unsurprising that predictors of 30 day mortality may not correspond well with need for ICU admission (10). Kolditz and colleagues identified a number of readily determinable factors which predicted ICU admission, including focal chest signs at presentation, multilobar involvement on CXR, comorbid conditions especially home oxygen requirement and physiological instability (14). However, these criteria have not yet been validated in an external cohort, and neither has a specific score nor criteria been developed.

Management of pneumonia in ICU—antimicrobials

The corner stone of pneumonia management is the

administration of appropriate antibiotics in a timely fashion. Delay, and especially administration of antibiotics which do not cover the infecting organism are associated with adverse outcomes including increased mortality and prolonged length of stay (106). However, given the problems outlined in the microbiological diagnosis of pneumonia above, the infecting organism is almost never known at the time of illness onset and clinicians must use empiric therapy targeted at likely organisms. This approach leads to early use of broad-spectrum antibiotics, especially in patients who are high risk of MDR infection such as those with VAP, HAP, and immunocompromised patients. Once the results of microbiological cultures are known, antibiotics should be adjusted and where appropriate deescalated (9,25,64,69), however this occurs variably in practice (107).

Antibiotic selection should be informed by the local antibiogram, combining data on the prevalent organisms and their likely resistance patterns. Updating the local antibiogram is an important wider societal reason for obtaining microbiological cultures in patients with pneumonia. Given the empiric nature of therapy, it is important to recognise the differences in organism and resistance patterns depending on location of acquisition and risk factors for MDR bacteria (see epidemiology section above). In CAP, empiric therapy is mostly aimed at gram-positive organisms, specifically *Streptococcus pneumoniae*, and generally low-resistance gram-negative organisms such as *Haemophilus influenzae* alongside 'atypical' bacteria. Although specific recommended antibiotics will vary by national availability and local antibiogram, a beta-lactam antibiotic with beta-lactamase resistance or combined with a beta-lactamase inhibitor such as co-amoxiclav or a 2nd generation cephalosporin are advised (6,64). The addition of a macrolide to empiric therapy for CAP is strongly recommended (9,64) and is associated with a reduction in mortality (108). It is unclear if this benefit is solely due to coverage of hard-to-detect atypical organisms, or if the immunomodulatory effects of macrolides are also important (109).

In patients who are at greater risk of MDR bacteria empiric therapy needs to cover these organisms, often including *Pseudomonas* and methicillin resistant *Staphylococcus aureus* (MRSA). These two organisms in particular pose a problem as they are frequently resistant to most front-line antibiotics, and their treatment can involve antibiotics such as aminoglycosides and glycopeptides, which have an unfavourable toxicity profile (110). Empiric therapy runs the risk of over-treatment and thus increases the risk of toxic side effects. Therefore, patients need to be assessed for

their risk of harbouring these particularly difficult to treat organisms prior to initiating treatment. Risk factors for *Pseudomonas* and MRSA include prior intravenous antibiotic use, previous culture of these organisms from a colonising or infecting site and recent hospitalisation of >5 days. The problem is that these risk factors describe many of the patients who develop VAP and HAP. The use of dual antibiotic therapy vs monotherapy in HAP and VAP has been examined in several trials (111-113) and a meta-analysis (114). These suggest that, in populations with a moderate rate of pseudomonas infection (14%), no benefit to dual therapy (114). Observational studies, which examine patients with high disease severity, who are often excluded from clinical trials, suggest that patients with septic shock may benefit from dual therapy (115). As a result the European guidelines for HAP and VAP advocate dual therapy for patients with high disease severity (69) whilst IDSA/ATS guidelines advocate dual therapy for those with risk factors for resistant *Pseudomonas* or MRSA (25). However, the findings of Kett and colleagues sound a note of caution over this advice, they observed that patients with HAP treated with IDSA/ATS compliant dual antibiotic therapy had a higher mortality than those treated with monotherapy (116). For patients with, or at risk of, extended spectrum beta-lactamase secreting organisms, carbapenems appear to be superior to piperacillin-tazobactam (117). Although this data comes from blood stream infections mostly arising from urinary and intraabdominal sources, it seems reasonable to apply it to pneumonias at present. In both CAP and HAP/VAP it is likely that the development and widespread adoption of rapid diagnostics will lead to more targeted therapy and will allow more precise trialling of antibiotic strategies.

Nebulised antibiotics are used in the management of MDR bacteria in several contexts, and is supported by the American guidelines on HAP and VAP (25), however this is based on weak evidence and many units do not use nebulised antibiotics at all (118). Where they are used, practice is variable and seldom in accordance with the advised best practice (118). Before this approach achieves widespread adoption, well conducted trials are needed.

The optimal duration of antibiotic therapy in pneumonia remains uncertain. There have been several trials which have examined fixed duration treatments (119-121), which have been analysed in systematic reviews (122). These trials compared 'short' (7–8 days) with long (10–15 days) of therapy, and in meta-analysis there was no benefit to prolonged treatment in terms of mortality, cure rate or

recurrence, whilst prolonged therapy was associated with increased risk of subsequent MDR infection. As these studies excluded patients with lung abscesses and collections, empyema, necrotising pneumonia and bronchiectasis/cystic fibrosis, this approach cannot be extrapolated to these patients. Concern about possible recurrence of Pseudomonal, and other non-fermenting gram-negative organism, infection with short course antibiotics (119) has led to a recommendation that patients with these infections should have 14 days of therapy (25,69). Fixed duration antibiotic therapy applies fairly arbitrary time-scales to patients and fails to account for individual variation. There is now reasonable evidence that 'low risk' patients, as determined by falling CPIS scores or falling PCT levels can have their antibiotics stopped at shorter time points, without harm and with some evidence of benefit (101,123), so allowing more individualised therapy. Conversely, if a patient is failing to improve a reassessment of needs to occur, looking for incorrect diagnosis (for instance missing a non-infective inflammatory process), resistant organisms, inappropriate therapy, super-infection or the development of collections, empyema and lung abscesses.

Management of pneumonia

Adjunctive therapy

Beyond antibiotic therapy, a number of adjuvant therapies have been trialled in pneumonia although none have a proven role in critically ill patients in ICU (124).

There is some evidence that corticosteroids may enhance recovery in CAP and reduce mortality (125,126), however these trials enrolled very few patients who were in ICU or required mechanical ventilation. Concerns have been raised about the use of steroids to treat severe CAP in ICU (127), with the few observational studies which focus on this group suggesting steroids are associated with a prolonged length of stay (128) and increased mortality (129). In patients with A/H1N1 pandemic influenza, use of steroids was associated with increased mortality and an increase rate of subsequent HAP (130). Hopefully the forthcoming CAPE-COD study of corticosteroids in critically ill patients with CAP will shed more light on this area (NCT02517489). With the exception of those developing vasopressor resistant septic shock (131), there appears to be no place for the use of steroids in the management of HAP and VAP. In patients with HIV who develop *Pneumocystis jirovecii* pneumonia steroids have been demonstrated to improve outcomes (132),

however this is not proven in patients with PCP without HIV and their use in other immunocompromised patients without proven PCP is controversial (133).

Other investigators have adopted an alternative approach of immuno-stimulation in pneumonia, acknowledging the evidence of immune cell failure in both early and late sepsis (26,134). To date immuno-stimulation has been attempted without determining patients' functional immune status, the failure to appropriately target therapy may explain the negative results from trials of G-CSF in pneumonia (135). Alternative strategies such as GM-CSF (136) and interferon gamma (137) are under investigation but no large randomised trials have yet been published (124). Augmented passive immunity is another strategy which shows promise is early work, although here human trials are awaited (138).

Ventilation

The need for respiratory support is the commonest reason for patients with pneumonia to be admitted to ICU (14). There are a growing range of respiratory support options, from simple oxygen therapy, through high flow humidified oxygen (HFO), non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) via various interface devices to full invasive ventilation. HFO has gained considerable popularity in recent years and has in certain circumstances demonstrable benefits relative to NIV/CPAP. Frat and colleagues demonstrated a reduction in intubation rates in patients with more severe respiratory failure and a decreased 90-day mortality compared to simple oxygen therapy and NIV (139), the majority of patients in this study presented with pneumonia. More recently however, in patients with immunocompromise and respiratory failure, HFO did not reduce intubation rates or mortality relative to simple oxygen therapy (140). Whilst NIV has a proven role in the management of exacerbations of chronic obstructive pulmonary disease (COPD) (141), its role in pneumonia including pneumonic exacerbations of COPD is largely restricted to rescue therapy pending mechanical ventilation (64) and intubation should not be delayed by the use of NIV (142).

In patients requiring invasive ventilation, the optimal mode of ventilation remains to be determined. As noted above, pneumonia is the commonest cause of ARDS (8), and as ARDS is frequently missed (8,13), care should be taken to look for this syndrome in patients admitted with or developing severe pneumonia. Patients who meet the criteria for moderate to severe ARDS should be managed with low volume (6 mL/kg predicted body weight) tidal ventilation and limited plateau pressures (143). Adjunctive therapy such as muscle relaxation (144) and early proning (145) are also indicated for those meeting severe ARDS criteria. Care should be taken to avoid fluid overload in patients with severe pneumonia (146), and consideration given to de-resuscitation and trying to minimise extra-vascular lung water (147). For patients who don't meet moderate to severe ARDS criteria the evidence is less clear, a recent trial from Schultz and colleagues demonstrated no benefit of low tidal volumes relative to moderate (8–10 mL/kg PBW) in patients without ARDS (148), however, this study included less than 20% patients with pneumonia. It remains unclear whether patients who are at higher risk of developing ARDS will benefit from low rather than moderate tidal ventilation (149).

Management—prevention of secondary complications

Patients with severe pneumonia in ICU are at risk of the complications of critical care, including deep venous thrombosis (150), stress ulceration (151), decubitus ulcers (152), delirium (153) and secondary infections (19). Careful attention to the risk factor management, appropriate prophylactic therapies and alertness to the development of these complications is key to good clinical management. Patients who present with a primary pneumonia, whether it is community or hospital-acquired, are at high risk of subsequent nosocomial infections, especially if ventilated (30). The various preventative measures for VAP have been reviewed extensively elsewhere (154), their implementation can lead to a reduction in VAP incidence, reduction in antibiotic use and mortality in longer staying patients (27). The reduction in antibiotic use is likely to drive a virtuous circle, reducing colonisation with MDR bacteria and subsequent infections with these hard to treat organisms.

Conclusions

Pneumonia remains both a common reason for intensive care admission and the commonest secondary infection acquired within intensive care. Its effective management relies on the selection of appropriate antimicrobial therapy, which at present is reliant on good epidemiological surveillance to inform empirical antibiotic choice. Identifying patients with risk factors for MDR organisms is critical to ensuring early, appropriate therapy. Diagnostic

uncertainty, especially with regards to VAP, likely leads to over-use of antibiotics and brings with it the risk of antibiotic-associated harm. The advent of rapid diagnostic strategies brings the promise of targeted, appropriate therapy and reduction in unnecessary drugs. For this promise to be realised we will need to change our culture of prescribing and understanding of microbiological tests results in a clinical context.

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Footnote

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