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STATE OF THE ART REVIEW

Advances in the causes and management of community acquired pneumonia in adults

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ABSTRACT

Community acquired pneumonia remains a common cause of morbidity and mortality. Usually, the causal organism is not identified and treatment remains empiric. Recent computed tomography and magnetic resonance imaging studies have challenged the accuracy of the clinical diagnosis of pneumonia, and epidemiologic studies are changing our perspective of what causes community acquired pneumonia, especially the role of viral pathogens and the frequent finding of multiple pathogens. The past decade has seen increasing overuse of empiric coverage of meticillin resistant *Staphylococcus aureus* and antibiotic resistant Gram negative pathogens owing to inappropriate application of guidelines for healthcare associated pneumonia. Optimal treatment remains a matter for debate, especially in very sick patients, including the role of combination antibiotic therapy and corticosteroids. Pneumonia care bundles are being defined to improve outcomes. Increased recognition of both acute and long term cardiac complications is shifting our concept of pneumonia from an acute lung disease to a multisystem problem with adverse chronic health consequences.

Introduction

Community acquired pneumonia (CAP) remains a major health concern worldwide with substantial morbidity and mortality.[1-3] The entire range of physicians, from primary care to intensivists and from generalists to subspecialists, will encounter CAP in one form or another.[4] CAP is in the differential diagnosis of the respiratory tract symptoms that are the most common cause of urgent outpatient primary care and emergency department visits.[5 6] CAP is one of the most common medical causes of admission in most healthcare systems; in the US, it is exceeded only by live births.[7]

Treatment for infections is generally based on an accurate determination of the cause. As microbiologic tests have yet to deliver on rapid, accurate pathogen based diagnosis in most patients, treatment remains empiric and is based on the likely pathogens and clinical scenario. Therefore, newer information on causes, even if determined by diagnostic tests not available in usual practice, can have implications for treatment decisions.

Pneumonia that occurs in patients known to be immunocompromised is not generally considered to be CAP because of the expanded spectrum of pathogens. Despite this, many immunocompromised patients have infections with the same causes as hosts with normal immune systems.[8 9] Also, the range of immunosuppressants used for non-malignant disease is increasing rapidly, and many of these patients are disproportionately prone to usual CAP pathogens.[10] For this review, we will exclude the most severely immunocompromised patients—those with acute leukemias and lymphomas, recent bone marrow or solid organ transplant recipients, those receiving active chemotherapy especially with neutropenia, and those with untreated or poorly treated AIDS or known severe congenital immunodeficiency syndromes. Equally, patients presenting from the community but who have had a recent hospital admission are not treated as having CAP, as they have a spectrum of pathogens more similar to hospital acquired pneumonia.[11 12] Finally, pneumonia that occurs in children also has very different clinical features, and studies and guidelines in adults do not necessarily apply.[13 14] This review will therefore not discuss the management of CAP in children.

Cursory review of current guidelines for treating CAP compared with those from 20 years ago might suggest very little change in the field. In reality, a large shift in the evidence base around optimal treatment of CAP is changing how the diagnosis is made, what pathogens cause disease, and what the optimal bundle of therapies contains. This review will focus in particular on new developments in the field of CAP.

In summary, this review will focus on management of CAP in patients in hospital. The information will be appropriate for primary care practitioners and emergency

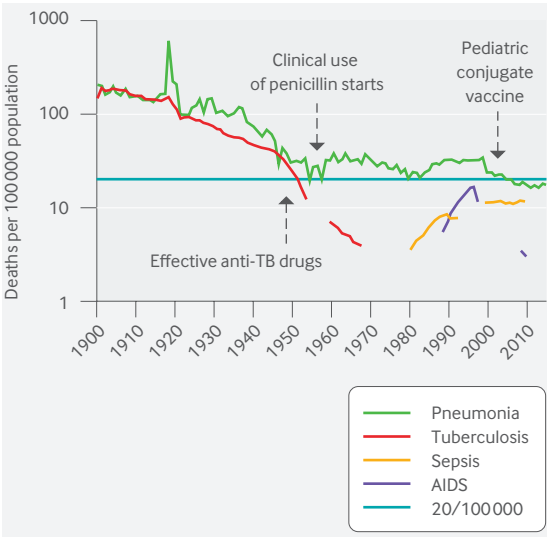

Fig 1 | Temporal trends in US mortality from pneumonia and influenza compared with other important infections since 1900 (source: Centers for Disease Control and Prevention). TB=tuberculosis

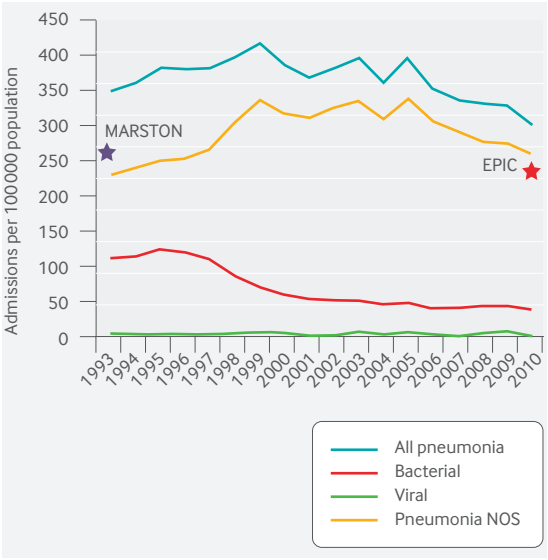

Fig 2 | Trends in discharges coded for pneumonia from the National Inpatient Sample.[20] NOS=not otherwise specified. Stars show two Centers for Disease Control sponsored, population based estimates[19 21]

department physicians who would initially see these patients and start treatment. Subsequent management by hospitalists, internists, and specialists, such as infectious diseases, pulmonary, and critical care physicians, will also be covered.

Incidence

CAP is the leading infectious cause and eighth most common overall cause of death in the US.[15] Pneumonia causes an even higher proportion of deaths worldwide, with 3.2 million estimated deaths globally, exceeding all other infections including tuberculosis, HIV infection, and malaria.[1] Lower respiratory tract infections are the most common cause of death in low income countries, whereas pneumonia is the only infection in the top 10 causes of death in high income economies.

Importantly, although some progress in decreasing overall mortality has been made both nationally and worldwide, the fall in deaths from pneumonia is substantially less than has been achieved recently for other infections such as diarrhea, HIV, and malaria.[1] In addition, pneumonia is often the direct cause of death ascribed to other common causes, such as Alzheimer's disease, lung cancer, and chronic obstructive lung disease.[16-18]

Figure 1 illustrates the difficulty in improving mortality due to CAP. Pneumonia and influenza have remained in the top 10 causes of death in the US since 1900. After substantial improvements in the mortality rate as a result of better hygiene and public health throughout the first part of the 20th century (note the log scale on the y axis of figure 1), once penicillin became routinely available the mortality rate from pneumonia and influenza essentially plateaued. Only in the past 10 years has the US mortality rate consistently stayed below 20 deaths per 100 000 population. Two factors likely explain this improvement in mortality—routine vaccination of children with the protein conjugate pneumococcal vaccine and public reporting of CAP process of care, mortality, and readmission rates.

The annual incidence of CAP in the US has recently been estimated at 248 cases per 10 000 adults,[19] with some variation on a year-by-year basis (fig 2). The rate estimated by Jain et al in 2010-11 is very similar to that found in the previous Centers for Disease Control and Prevention (CDC) sponsored epidemiologic study from 1991.[19 21] It also correlates fairly well with data on discharge diagnoses from the National Inpatient Sample.[20] In contrast, rates in other countries with different healthcare systems are very different; for example, 8.1 hospital admissions per 10 000 adults in Vietnam and 31.2 per 10 000 adults in the UK.[22 23] However, admissions for CAP have been increasing over the past 16 years in areas of England.[24] Different rates may partially reflect differences in age as well as healthcare settings. The incidence is clearly higher in older adults. Recent published estimates from others countries include 130.5 per 10 000 adults aged over 65 years in Malaysia,[25] 172.4 cases per 10 000 for adults aged 85 and over in the Netherlands,[26] and 29.6 per 10 000 for all ages and 76.5 for adults aged 65 and over in Germany.[27]

Sources and selection criteria

We searched PubMed from 1 January 2007 to 1 January 2017. We chose this time span as roughly the interval since the last extensive review for the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) consensus guidelines on community acquired pneumonia was completed.[11] We primarily focused on original articles on "community-acquired pneumonia" listed as "clinical trials" in "humans", "19+/adults", and published in English. This strategy yielded 160 articles. Review of the abstracts of these manuscripts resulted in 25 being chosen for further review. Most of the manuscripts not chosen were subgroup analyses of primary studies, small single center studies with limited new information, or negative trials of agents not currently available clinically. Additional modifiers and cross search

terms including "healthcare associated pneumonia", "community-onset pneumonia", "viral pneumonia", "influenza", "*Staphylococcus aureus*", "*Streptococcus pneumoniae*", "mycoplasma", and "atypical pneumonia" did not result in significant additional manuscripts. However, for specific sections, we crossed these primary search phrases with specific terms such as "corticosteroids", "microbiome", "microbiota", "deep sequencing", and "next generation sequencing" for further insights. Only articles published in English were reviewed. The final reference list is based on relevance to the topics covered in the review.

How imaging technology is challenging the clinical diagnosis of pneumonia

CAP has always been a clinical diagnosis combining features of an acute respiratory infection and a new (and consistent) infiltrate on chest radiograph. Although this is seemingly straightforward, the not infrequent disagreement between independent observers regarding presence or absence of pneumonia on re-evaluation of chest radiographs is well known.[28-32] This misdiagnosis rate is perhaps not very surprising given that various common co-pathologies, especially cardiac failure and chronic obstructive pulmonary disease, can also cause infiltrates that may be mistaken for areas of consolidation in patients with acute shortness of breath.

Until recently, no realistic alternative to plain chest radiography existed. Therefore, despite the limitations, diagnosis by the physician (including interpretation of the chest radiograph) was the gold standard for clinical studies of CAP. Two recent studies challenge the validity of this approach and the future of chest radiography in the diagnosis of CAP.

A prospective observational study in 319 patients presenting to hospital with acute respiratory symptoms consistent with CAP assessed the potential effect of chest computed tomography (CT).[33] Clinicians were asked to determine whether the patient had CAP on the basis of the clinical features (history and examination) and their interpretation of the chest radiograph; all patients then had a chest CT scan. Significant discordance between the clinician's diagnosis and the CT determination of pneumonia occurred in nearly 40%. Most importantly, nearly a third of patients diagnosed as having pneumonia did not have any infiltrate visible on the CT scan. These findings are consistent with an observational study in emergency departments where 3423 patients had both chest radiography and a CT scan as part of routine care.[34] Using the CT scan as the gold standard, the sensitivity and specificity of the detection of an opacity by chest radiography were only 43.5% and 93.0% respectively.

In a smaller prospective study in 77 outpatients with CAP, findings on chest radiography were compared with those of CT scans and magnetic resonance imaging (MRI) taken at the time of diagnosis and 30 days later in all patients with positive results.[35] Pneumonia was identified in 32 patients by CT scan, 30 by MRI, and 23 by chest radiography. The false positive chest radiography rate was much smaller in this study with only four false positives (and none with MRI); however, all were reported by a radiologist rather than interpreted by the clinician, and the 30 day follow-up studies were available for comparison.

Although the fact that pneumonia may be missed by chest radiography has been known for some time, overdiagnosis of pneumonia by clinicians in these studies raises the fundamental question of how many patients without pneumonia were enrolled into the clinical trials on which treatment, quality of care, and remuneration benchmarks are based. If much of what is called pneumonia is not pneumonia, potential light is also shed on discrepancies between findings of CAP studies.

A CT scan for the routine diagnostic investigation of a patient with CAP is not practical in many settings. However, the increasing availability of CT scanners in emergency departments and the ability of a modern generation of CT scanners to image as fast as and with equivalent radiation to convention chest radiography suggests this may be the future of care.[36 37] The alternative is point-of-care ultrasonography, which can also confirm the presence of infiltrates and distinguish between parenchymal and pleural abnormalities.[38]

Further research on the radiographic evidence for pneumonia is clearly needed. In addition to comparison of CT and ultrasonography confirmation of radiographic diagnosis, determination of whether chest radiograph negative, CT or ultrasound positive cases have the same or different pathogens, outcomes, and therefore treatment recommendations as confirmed chest radiograph positive disease is needed. In addition, the traditional approach of independent review of the actual chest radiographs by two or more clinicians is probably no longer adequate confirmation of radiographic criteria for CAP in clinical trials.

How understanding of the pathogens causing CAP is evolving

Standard pathogens

The standard list of pathogens causing CAP in any textbook starts with *Streptococcus pneumoniae* and then in varying order lists *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, group A streptococci, *Legionella* species, *Chlamydophila*, and *Moraxella catarrhalis*. Viral causes are usually listed somewhere in the top half a dozen pathogens, with a long list including influenza A and B, respiratory syncytial virus, adenovirus, and a variety of coronaviruses.

Data on the causes of CAP predominantly come from studies using conventional culture techniques, with or without serologic tests, all of which have substantial limitations. Considerable improvements in the sensitivity, availability, and affordability of molecular pathogen testing in the past decade now influence our understanding of the causes of CAP. At the same time, the conjugate pneumococcal vaccines have affected pneumococcal disease in adults,[39] even when given only to children.[40] This decline in pneumococcal disease has been accompanied by a decline in total hospital admissions for pneumonia, at least in the US.[41]

A 2015 study of CAP in the US by the CDC found that *S pneumoniae* was only the third most common cause detected, after rhinovirus and influenza (fig 3).[19] A

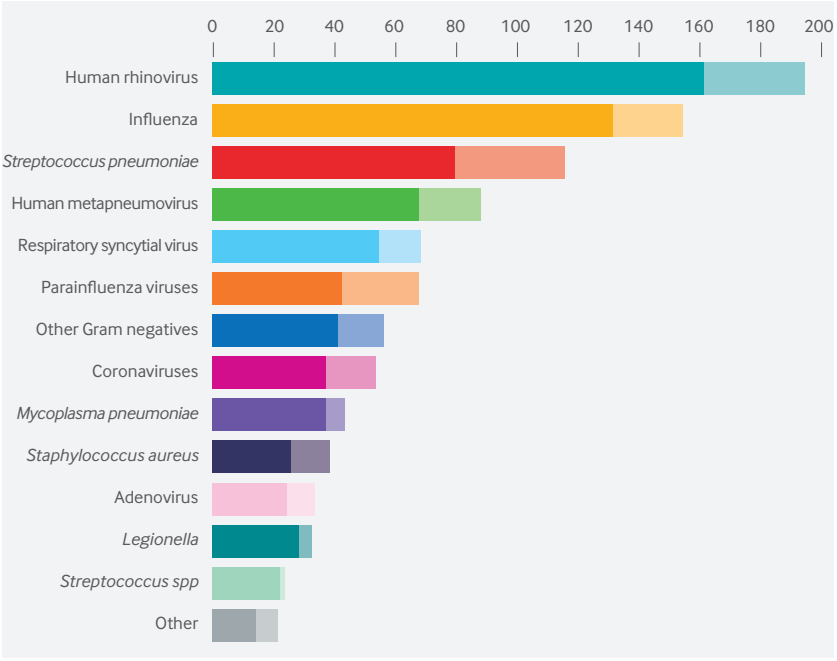

Fig 3| Pathogens detected in patients with radiographic community acquired pneumonia from the Centers for Disease Control EPIC study. Lighter bars indicate co-detections of more than one pathogen. From Jain et al[19]

Norwegian study that also used a wide array of diagnostic techniques found that *S pneumoniae* remained the most common cause identified, but the proportion due to other pathogens, especially viruses, was much higher than traditionally reported.[42] The most important observation in both of these recent studies was that two or more pathogens were identified in more than one third of cases, typically a virus/bacteria combination.[19 42]

A key unresolved question is whether the detection of a virus in the upper airways reflects the pneumonia pathogen(s), particularly in the setting of multiple detections. Some viruses persist for weeks after acute infection, raising the question of whether the viruses detected were the residual of a resolving, initial upper respiratory tract infection that set the scene for secondary bacterial pneumonia. Data suggest that higher counts of virus in the upper airways is more likely to correlate with viral pneumonia, at least in children,[43] and future studies using serial quantitative assays may help to answer this important clinical question.

Newer pathogens

New pathogens continue to emerge as causes of CAP. Metapneumovirus, first reported in 2001,[44] is now often identified as one of the top half dozen pathogens causing CAP. Although it is typically associated with milder disease, fatal cases of metapneumovirus pneumonia have been reported. Coronaviruses have also emerged as major epidemic threats, first with severe acute respiratory syndrome and more recently with Middle East respiratory syndrome. Influenza also continues to be a threat, with concerns about the potential for several strains of avian influenza, particularly H5N1 and H7N9, to mutate enough to allow sustained human-to-human transmission with resultant pandemics.

Antibiotic resistance

Penicillin resistance in *S pneumoniae* has been a concern. However, apart from occasional case reports, little evidence exists to justify modification of guideline concordant empiric antibiotic regimens in any region. Macrolide resistance in pneumococci and *Mycoplasma* is greater than β lactam resistance in most areas, but the clinical importance remains unclear. In pneumococci, macrolide resistance seems to have little effect on the outcome of patients admitted to hospital,[45] in part because macrolide monotherapy is not recommended in this setting. Macrolide resistance in *M pneumoniae* is reported to be associated with prolonged symptoms and slower resolution of fever.[46] Therefore, in confirmed *M pneumoniae* infections with a slow clinical response, switching to an alternate agent such as a tetracycline or fluoroquinolone would be appropriate.

Meticillin resistant *S aureus*

The rise of meticillin resistant *S aureus* (MRSA) has predominantly been a feature of hospital acquired infections. However, true community acquired MRSA infections have recently been detected and are becoming increasingly common, especially in the US. Many MRSA strains, as well as related meticillin sensitive strains, secrete specific exotoxins that can lead to severe necrotizing pneumonia,[47] although the exotoxin repertoire may vary geographically. To date, community acquired MRSA has not been sufficiently widespread to require empiric coverage,[48 49] but clinicians need to know their local epidemiology, especially in very sick (that is, intensive care) patients. The USA300 clone that causes the most dramatic and lethal CAPs in North America has a fairly characteristic clinical presentation (box 1).[50 51] Suspicion of this pathogen warrants adjunctive or definitive treatment with antibiotics that suppress toxin production, such as linezolid or clindamycin, even for meticillin susceptible strains.[52 53] Cultures are always positive, but the emergence of rapid molecular diagnostic tests allows even earlier discontinuation of anti-MRSA treatment.[54 55]

The lung microbiome

Discovery of a normal lung microbiome that includes many of the bacteria commonly causing CAP, such as *S pneumoniae* and *Mycoplasma* spp, threatens the primary concept of pneumonia pathogenesis.[56 57] Aspiration or inhalation of "pathogenic" bacteria into sterile alveoli is thought to be the primary step in development of pneumonia. Rather than occurring in a sterile environment, CAP may result from a dysbiosis of the normal flora,[58]

Box 1 | Clinical features suggestive of community acquired MRSA

- Rapid progression of pulmonary infiltrates or pleural effusions
- Evidence of lung necrosis at presentation or early in course
- "Dirty dishwasher" appearance of pleural fluid
- Gross hemoptysis
- Young previously healthy patient
- History of MRSA skin lesions
- Erythematous rash—toxic shock, scalded skin syndromes

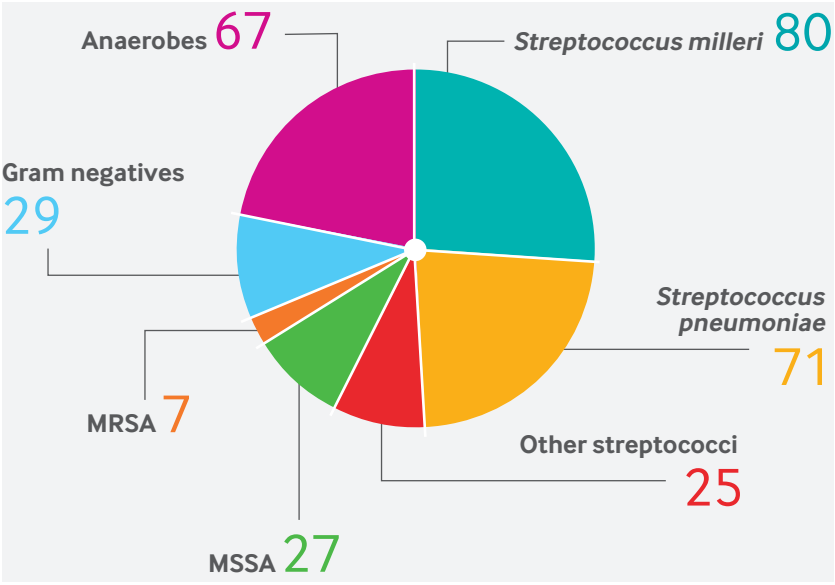

Fig 4| Etiology of community acquired empyema determined by 16S rRNA sequencing. MRSA=meticillin resistant *Staphylococcus aureus*; MSSA=meticillin sensitive *Staph aureus*. From Maskell et al[59]

allowing overgrowth of one or more of the resident flora. This concept may partially explain the high proportion of cases that are culture negative despite aggressive diagnosis.[19] A hint that "normal" flora may be the cause of CAP comes from molecular diagnosis of community acquired empyema: "normal flora" *Streptococcus* spp cause a larger proportion than *S pneumoniae* (fig 4).[59]

The most likely cause of this dysbiosis is antecedent or concomitant viral respiratory tract infection. The enigmatic but frequent association of human rhinovirus infection with clinical CAP may be explained by this phenomenon. Whether antibiotics help or hinder a return to the normal lung microbiome pattern in these cases is unclear. Possibly, ultrashort courses of antibiotic, such as a single dose of ceftriaxone, may be sufficient for clinical cure. Daptomycin, an antibiotic that was subsequently shown to be inactivated by surfactant, was compared with ceftriaxone in a registration trial for a CAP indication.[60] Patients admitted to hospital with CAP were allowed to have up to 24 hours of therapy before randomization, which was usually a single dose of ceftriaxone. The clinical cure rate in the subgroup of 97 patients who received a single dose of a long acting antibiotic such as ceftriaxone was 91% compared with 88% in patients who received a seven day course of ceftriaxone (95% confidence interval for the difference between cure rates −6.1% to 11.5%). In 272 patients randomized to daptomycin without previous antibiotic treatment (essentially placebo treatment), the clinical cure rate was still 75%, although this was significantly lower than in the equivalent number who received a seven day course of ceftriaxone (95% confidence interval for difference −18.8% to −6.0%). These findings are consistent with findings of procalcitonin directed treatment in which 15% or more of patients with CAP were safely managed without antibiotics.[61 62]

The advent of newer molecular diagnostic techniques may revolutionize the diagnosis of CAP. Nucleic acid amplification can dramatically increase the diagnostic yield of good quality sputum.[42 63] The biggest limitation of any new molecular diagnostic technique is the lack of a gold standard for comparison. However, the potential for deep sequencing of appropriate respiratory samples raises the possibility of determining the entire lung microbiome to validate other molecular techniques as well as to discover new bacterial or viral causes of CAP.

Optimal antibiotic management

As the causative pathogen of CAP is almost never known initially in either inpatients or outpatients, treatment is virtually always empiric. As delay in starting antibiotics is associated with worse outcomes for patients, treatment should be started as soon as possible after a diagnosis is made, preferably within three to four hours of presentation.[11]

First line treatment for CAP varies from region to region but is generally a β lactam/macrolide combination or a respiratory fluoroquinolone for patients in hospital.[11] In the outpatient setting, monotherapy with a β lactam, macrolide, or tetracycline is generally recommended unless risk factors for antibiotic resistant pathogens are present, mainly recent use of the same antibiotic or a high prevalence of resistant isolates in the community. Respiratory fluoroquinolones are also widely used for outpatients in some countries, including the US, but from an antibiotic stewardship perspective, narrower coverage is clearly preferable.[64]

The optimal treatment of severe CAP is severely limited by lack of prospective clinical trials. More than a dozen retrospective studies suggest that combination antibiotics, particularly a β lactam and a macrolide, improve survival for patients admitted to hospital with pneumococcal pneumonia, as well as all cause CAP, compared with monotherapy with a β lactam.[65] Whether a β lactam/macrolide combination is superior to fluoroquinolone monotherapy is less clear, with conflicting findings and insufficient data in patients with severe disease.[66] As introduction of macrolide combination therapy was associated with a substantial drop in mortality in CAP patients in the intensive care unit (ICU),[67] administrative databases consistently show lower mortality with macrolide combination therapy,[68-70] and meta-analysis shows a beneficial mortality risk ratio of 0.75 (95% confidence interval 0.58 to 0.96; P=0.02) for macrolide combination therapy in critically ill patients,[71] until high quality data from randomized controlled trials (RCTs) are available, this should be the standard of care in severe CAP.[11]

Non-intensive care patients

Treatment of patients admitted to hospital but not to ICU is the most contentious area of management. Two recent prospective trials have attempted to resolve the debate about combination antibiotic therapy for non-ICU patients. A Swiss RCT in patients admitted to hospital with CAP compared β lactam monotherapy with the identical β lactam combined with a macrolide and aimed to show that monotherapy was not inferior to combination therapy.[72] The primary endpoint was time to clinical stability,[73] probably the most clinically relevant endpoint as inpatient mortality in non-ICU patients should be very

low. The trial failed to show that monotherapy was non-inferior in terms of time to clinical stability; only 34% (97/289) of monotherapy patients had reached clinical stability at day seven of therapy compared with 41% (120/291) for combination therapy, with the upper limit of the one sided 95% confidence interval (13%) exceeding the pre-specified boundary of 8%. Although the event rates were low, additional safety problems (deaths, ICU transfer, readmissions) also favored combination therapy. By this criterion, if monotherapy was being introduced as a new therapy for CAP in hospital, it would not be approved by regulatory authorities.[74]

The second RCT conducted in the Netherlands used a more public health based approach. Seven hospitals were cluster randomized and crossed over between three treatment regimens as the "standard" for a four month period. This large (656-888 patients in each group) study found no significant difference in 90 day mortality between patients given β lactam or fluoroquinolone monotherapy or β lactam/macrolide combination.[75] Described as a "pragmatic randomised controlled trial," this trial design had several major flaws. About 25% of patients did not have radiologic evidence of pneumonia. Monotherapy and no antibiotics are standard care for acute exacerbations of obstructive lung disease and heart failure, respectively, the most common causes of suspected CAP with a negative chest radiograph. The pragmatic design allowed clinicians to deviate from the "standard" therapy: 39% of the β lactam "monotherapy" patients actually also received atypical coverage, and 12% of patients in the combination therapy group did not get a macrolide. The choice of antibiotics within class also varied: 24% of patients in the combination therapy arm received penicillin as their β lactam, whereas only 2% received this in the β lactam monotherapy arm. Penicillin was strongly discouraged in the β lactam monotherapy arm because of resistance problems: the addition of a macrolide would not necessarily overcome the penicillin resistance. Clearly, a gradient of efficacy and spectrum of activity exists between β lactams and possibly even between members of the same class such as cephalosporins.[76] Erythromycin was also given to 35% of patients in the combination therapy arm, rather than other macrolides. Given the stronger association with acute cardiac events for erythromycin than for other macrolides,[77 78] this may bias results in a study with a 90 day mortality endpoint. In addition, the four month randomization blocks may lead to a differential in recruitment in the "non-respiratory season" from May to early October in the northern hemisphere. During this time, atypical pathogens cause a higher proportion of documented causes of CAP. In the Netherlands, other studies suggest that 40% of documented causes of CAP during this time are atypical bacterial pathogens, with an even higher proportion in younger patients.[79] However, the greatest problem with the study is the choice of 90 day mortality as the primary endpoint. For patients who are not admitted to the ICU, mortality from uncontrolled infection is unlikely,[80-82] so the ability of this endpoint to discriminate antibiotic treatment effects is unclear. Most patients with CAP either die of acute cardiovascular events while in hospital or after discharge or die of their chronic comorbidities.[77-84] Therefore, although important from a public health standpoint, this RCT does not clearly inform the decision of which antibiotic treatment is "best" for non-ICU patients in hospital.

These studies show that β lactam monotherapy can safely be given to many patients admitted to hospital but not to ICU. Macrolide monotherapy can also likely be effective for some patients, such as young patients during the non-respiratory season. However, for purposes of a standard default treatment regimen, a β lactam/macrolide combination or fluoroquinolone monotherapy gives the most reliable results. Focusing on avoiding macrolide combination or fluoroquinolone treatment of documented CAP for antibiotic stewardship reasons is likely to have a minimal effect compared with avoiding antibiotic treatment for febrile upper respiratory tract or urinary tract infections.[64]

Healthcare associated pneumonia

A subgroup of CAP termed "healthcare associated pneumonia" (HCAP) was introduced in the 2005 ATS/IDSA pneumonia guidelines.[85] Two US based studies reported a subgroup of patients with a high prevalence of pathogens more in keeping with hospital acquired pneumonia than with CAP, in particular a high rate of identification of MRSA and *Pseudomonas aeruginosa*.[86] The major risk factors for HCAP were identified as nursing home residence, recent hospital admission, dialysis, and chronic wound care,[87] and the guidelines suggested consideration of empiric coverage of MRSA and *P aeruginosa* if these risk factors were present.[85]

Since publication of the guidelines, widespread adoption of the HCAP concept without consideration of local epidemiology has led to a vast overuse of inappropriately broad spectrum antibiotics (particularly vancomycin and β lactam/β lactamase combinations) despite little evidence that these are needed outside of major urban centers in the US.[88-91] The CDC EPIC study, which included some patients with risk factors for HCAP in two major urban centers, found less than 3% of cases with MRSA or *Pseudomonas*.[19]

In addition, retrospective analyses have shown that empiric treatment for patients with the original HCAP risk factors is associated with no better or even worse mortality than treatment with usual CAP therapy.[92-94] A Japanese study with excellent microbiologic diagnosis showed that only 27% had pathogens resistant to the usual CAP drugs.[95]Box 2 lists risk factors for these pathogens. Importantly, two or three risk factors were needed before the frequency of resistant pathogens warranted treatment outside the usual CAP drugs. In patients in the lowest risk category (0-1 risk factors), use of broad spectrum antibiotics, theoretically given to prevent inappropriate initial therapy, was actually associated with higher mortality than when inappropriate therapy was actually delivered (fig 5). Also, the undue attention to multidrug resistant pathogens often results in dropping the macrolide from the combination, with the attendant excess mortality.

Consequently, many publications call for abandonment of the HCAP classification on the grounds that it has done more harm than good.[88-96] Clinicians must be aware of their local ecology and whether studies identifying risk

Box 2 | Independent risk factors for pneumonia[95]

CAP drug resistant pathogens
- Hospital admission in previous 90 days
- Antibiotics in previous 90 days
- Gastric acid suppression
- Immunosuppression
- Enteral tube feedings
- Non-ambulatory status

MRSA only*
- Hospital admission in previous 90 days
- Antibiotics in previous 90 days
- Gastric acid suppression
- Chronic hemodialysis
- Previous MRSA colonization
- Congestive heart failure

*Should include at least one MRSA specific risk (bottom three bullet points). CAP=community acquired pneumonia; MRSA=meticillin resistant *Staphylococcus aureus*

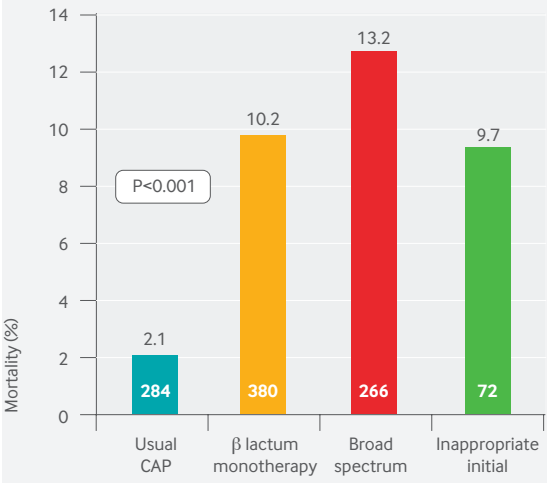

Fig 5 | Mortality in patients at low risk for resistant pathogens on basis of initial empiric antibiotic therapy. Numbers in bars represent patients. CAP=community acquired pneumonia. From Shindo et al[95]

factors for pathogens not covered by standard empiric therapy for CAP are applicable to their own setting. Published evidence suggests that the number of hospitals where the prevalence of MRSA or *Pseudomonas* is high enough to justify empirically covering these organisms is low.[19 49]

Corticosteroids

Recent meta-analyses sparked debate about the potential benefit of corticosteroids in the setting of severe CAP.[97-99] Despite the strong perception that meta-analyses represent the highest level of evidence, they are highly dependent on the quality of the primary studies. In the case of corticosteroids for CAP, the findings of meta-analyses are seriously undermined by the primary studies. Only two primary studies showed significant improvement in a meaningful clinical outcome. One RCT of 23 patients with severe CAP who received a 200 mg bolus of hydrocortisone, then an infusion of 10 mg/h for seven days, were compared with 23 patients taking placebo.[100] No deaths occurred in the hydrocortisone group and only 26% needed mechanical ventilation, compared with 38% mortality and 65% ventilation with placebo (P<0.001 for both). An Egyptian single blind study of 80 patients found that mortality was significantly reduced in patients taking a similar solumedrol regimen versus placebo (four deaths versus six for placebo; P<0.05).[101] As no other study, including larger studies using the same dosing regimen, has shown even remotely comparable benefits, these results are not considered generalizable.

Although corticosteroids regimens in studies in CAP are typically called "low dose," in reality at least moderate doses—equivalent to 40 mg per day of prednisolone—are used. Not surprisingly, hyperglycemia is more common in patients receiving steroids. Concern has been raised that steroids may be associated with excess mortality in patients with pneumonia due to influenza pneumonia.[102 103] A recent post hoc analysis of one of the steroid trials also suggested that the benefit "reduced time to clinical stability" was not seen in the group with proven pneumococcal disease,[104] raising further questions about the subgroup of patients who do benefit.

Corticosteroid therapy should not be used routinely in patients with CAP unless another indication is present (to treat a comorbid disease).[105] In patients with septic shock or who need mechanical ventilation and have high inflammatory markers, the risk-benefit balance may be in favor of steroids,[106] but further confirmatory studies are needed. Completion of a large Veterans Affairs Medical Center study of steroids for CAP will add additional information (ClinicalTrials.gov NCT01283009).

The role of biomarkers

A substantial amount of clinical judgment is needed in managing CAP patients, including selection of appropriate antibiotics, assignment of the appropriate location of care, and duration of treatment. An objective test result to reduce clinical uncertainty is appealing. A focus on biomarkers as an aid to clinical decision making has resulted, with procalcitonin being the best studied to date. Multiple studies have assessed the sensitivity and specificity of procalcitonin for the presence of bacterial infection in a variety of lower respiratory tract infections. However, we have focused only on data in patients admitted to hospital with CAP.

Various of cut-off values for procalcitonin have been assessed in the setting of CAP. At a threshold of 1.0 ng/mL, procalcitonin has a reasonably high predictive value for typical bacterial infection.[107 108] However, in the context of withholding antibiotic therapy on the presumption of a viral infection, procalcitonin has several limitations. Firstly, procalcitonin is often not elevated in the setting of *Legionella* and *Mycoplasma* infections.[109-111] Several studies also raise concern that procalcitonin has a poor sensitivity in the presence of mixed bacterial and viral infection.[110-114]

Only one interventional trial in the setting of CAP in adults attempted to withhold antibiotics on the basis of a low procalcitonin result.[61] In this study, 22 of 43 patients with procalcitonin concentrations below 0.25 ng/mL had antibiotics withheld, although five subsequently had antibiotics started owing to a higher reading at six hours. No

adverse effects of withholding antibiotics were observed. On a risk-benefit basis, the data for using a procalcitonin result to withhold antibiotic therapy in patients with CAP remains insufficient.

Another suggested role of procalcitonin is to reduce the duration of antibiotic therapy. Several studies using a serial procalcitonin measurement protocol to determine duration of antibiotic treatment have shown a reduced length of therapy, but in all cases the standard therapy arm had durations well beyond seven days,[61-115] much longer than recommended in current guidelines. Therefore, procalcitonin is likely to be useful only in guiding duration of antibiotic therapy in settings where clinicians routinely exceed the recommended duration.

A potential role for procalcitonin in predicting which patients with CAP are at risk of adverse outcomes has been proposed.[116-119] The benefit of procalcitonin, or any other biomarker, over existing validated clinical scoring systems such as the pneumonia severity index, ATS major and minor criteria, or CURB-65 remains unclear.[120 121]

CAP and acute cardiac disease

Several studies in patients admitted with CAP show an increased risk of acute myocardial infarction,[77-126] cardiac arrhythmia,[77-127] and new onset heart failure.[128] Up to 20% of patients with bacteremic pneumococcal pneumonia can experience these cardiovascular complications.[124] This risk is not just acute but extends outwards for several months to years afterwards.[128-130]

Mechanisms by which CAP provokes cardiovascular events are not clear; however, several possibilities exist.[131] Infection induces a procoagulant state, including increases in clotting factors, platelet numbers, and platelet activation. The degree of platelet activation has been associated with the risk of acute myocardial infarction in the setting of pneumonia.[132] Increases in heart rate and myocardial oxygen consumption may provoke arrhythmia in damaged or vulnerable myocardium. Endothelial dysfunction and inflammatory cytokines may also precipitate acute plaque rupture.[133]

Treatment with antiplatelet agents may be associated with better outcomes in patients with pneumonia in both prospective interventional and retrospective observational studies.[125-135] A dose higher than 100 mg of aspirin seems to be needed, as this dose failed to reduce mortality or myocardial infarction rates in pneumonia and did not lower platelet activation markers.[132] Retrospective data suggest that clopidogrel may be more effective than aspirin at reducing myocardial events in the setting of pneumonia,[136] and ticagrelor even more so.[137] Further studies are needed to determine which patients benefit and the optimal agent, dose, and duration of therapy.

Longer term outcomes

Many studies have documented that patients who survive CAP have a significantly greater mortality rate of up to 30% over the next two to five years,[83-143] even in those without comorbid diseases.[138] In the first 90 days after discharge from hospital, mortality is highest in patients with the highest markers of inflammation[144]: higher levels of pro-adrenomedullin and pro-atrial natriuretic peptide also seem to predict increased long term mortality risk.[142 143] The cause of the excess mortality is multifactorial, but increased cardiac disease including myocardial infarction and heart failure is a prominent reason.[128-130]

Although knowledge of how to reduce the burden of mortality and morbidity in CAP survivors is limited, measures to reduce acute cardiac injury at the time of pneumonia are logical. Given the increasing awareness that pneumonia clearly has long term health implications, this represents a critical area for research and a major paradigm shift for physicians treating patients with CAP.

CAP "bundle of care"

Sepsis now has a well defined bundle of care associated with optimizing patient outcomes.[145] Bundles are more than just a group of interventions; they are a process designed so that each patient receives the optimal care every time, and the interventions are designed on the basis of the best available evidence. A pilot program in Britain showed a reduction in 30 day inpatient mortality from 13.6% to 8.8% with the use of a CAP care bundle of timely antibiotic administration and guideline concordant therapy.[146]

On the basis of the available data, the following interventions should be considered in a CAP care bundle:

- Use of a validated CAP severity score to aid in clinical evaluation and determination of site of care.[147 148]
- Rapid empiric antibiotic administration with a β lactam and macrolide (ideally within three hours of presentation).[67-150]
- Rapid resuscitation, including adequate fluid resuscitation, correcting electrolyte disturbances and hyperglycemia, thromboembolic prophylaxis, and managing hypoxia appropriately.[145]
- Encouraging early ambulation.[150-152]
- Tackling cardiovascular risk factors, including consideration of starting or continuing aspirin at a dose shown to be effective.

Guidelines

Many countries and professional societies publish their own CAP guidelines. In addition to the frequently cited ATS/IDSA guidelines,[11] other widely used guidelines include the British, Canadian,[153] Spanish,[154] Dutch,[155] Chinese,[156] and Japanese guidelines.[157]

Guidelines are appropriately written to reflect local healthcare systems and to meet different needs. Guidelines from professional societies were initially developed to reflect expert opinion for use by clinicians who were less experienced.[11 158] Some, such as the ATS/IDSA guidelines, have evolved into prescriptive rules for third party payers and public reporting measures,[159 160] which in turn forces changes in methods and priorities.

The major differences observed between guidelines primarily reflect these different purposes and different healthcare systems and relate to those areas with an uncertain evidence base discussed above. For example, a large proportion of patients admitted to hospital with CAP have very low acuity and could equally well be managed as outpatients. National Institute for Health and Care Excellence guidelines emphasize that these patients are

equivalent to outpatients as regards etiology and therefore should be treated with monotherapy.[158] The average length of hospital admission for CAP in non-ICU patients in the Netherlands is six days,[75] compared with only three in the US.[19] This allows a longer observation period for β lactam monotherapy with the ability to add atypical coverage for poor responders in the Netherlands,[75] whereas the need for subsequent return to the hospital for failure of monotherapy in the US would have financial and public reporting consequences.

Emerging treatments

Search of ClinicalTrials.gov (PNEUMONIA and COMMUNITY and ACQUIRED) finds 266 studies with 58 open protocols. Emerging treatments include three main categories. The first and most likely area to have an early clinical impact is new diagnostic platforms. The benefit of a greater proportion of and earlier switch to specific therapy rather than the current overwhelming use of empiric antibiotic therapy, even for viral pneumonia, will need to studied. CAP is an easier indication than hospital acquired pneumonia/ventilator associated pneumonia (HAP/VAP) for new diagnostics, given a more limited bacterial spectrum and fewer problems with resistance.

The second area is additional antimicrobials. The most exciting is the spectrum of antivirals other than neuraminidase inhibitors and for pathogens other than influenza that are entering phase II and III clinical trials. The new antibiotics being studied are likely to have a more limited clinical impact. Most seek to replace quinolones or macrolides, for antibiotic stewardship reasons for the first and for emerging but still extremely variable resistance problems for the second. Given the very high success rates for the current standard, mostly generic antibiotic treatment of outpatients and inpatients outside ICU with CAP, the few new classes of antibiotics have a greater future for HAP/VAP if the spectrum allows.

The third area is severe CAP, for which a more rapid diagnosis of its causes or newer antibiotics have lower potential benefit and adjunctive therapy is likely to affect mortality and morbidity to a greater extent. In addition to steroids, novel therapeutic agents being studied include compounds that neutralize toxins, including pneumolysin,[161] monoclonal or polyclonal antibodies to specific pathogens,[162 163] and immunoglobulin therapy.[164] Most deaths directly attributable to CAP involve either septic shock or severe hypoxemic respiratory failure in patients with either viruses or antibiotic susceptible bacteria; improvement in ICU support technologies are therefore a different but very valid strategy to improve outcomes of CAP. Gas exchange support while avoiding injurious ventilator strategies via extracorporeal carbon dioxide removal and a new generation of extracorporeal membrane oxygenators are being studied.[165] In addition, new strategies for vasopressor support can buy time for antibiotic therapy to work.[166]

Conclusions

CAP remains a highly prevalent and serious disease with acute and long term adverse health outcomes. Imaging technology is changing our understanding of CAP, and better diagnostic tools are changing our understanding of the pathogens causing CAP. A clearer picture is emerging of the optimal bundle of care for patients with CAP, with an increasing body of evidence supporting multiple interventions. Optimal treatment remains controversial, and well designed trials are still needed, particularly in severe disease; however, evidence favors a macrolide/β lactam combination for severe disease. Corticosteroids may have a net positive effect in some patients with severe disease, but the evidence base remains weak and further studies are needed to define the subset of patients who benefit. Despite much research, procalcitonin has no clear role in CAP unless physicians are routinely using more than seven days of antibiotic therapy. The most substantial change in focus in CAP is awareness of the significant increase in acute cardiovascular events and the long term adverse health outcomes in survivors, and research is urgently needed to determine the optimal approach to these complications. Combining all available research, the group of interventions likely to produce the best possible outcomes for patients is becoming clearer and should be considered as a therapeutic bundle to optimize care of patients with CAP.

RESEARCH QUESTIONS

- Is thoracic ultrasonography equivalent to computed tomography for diagnostic imaging of pneumonia?
- Can molecular techniques accurately determine the cause in culture negative cases of community acquired pneumonia (CAP)?
- Is short course antibiotic therapy (<24 hours) safe in patients with documented viral pneumonia? Can procalcitonin correctly identify those patients?
- Can primary prevention of atherosclerotic plaque rupture (eg, statin, low dose aspirin) decrease mortality after admission for CAP?
- What, if any, adjunctive therapy can decrease the mortality of severe CAP in previously healthy people.

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