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Published in:
Seminars in Respiratory and Critical Care Medicine

DOI:
[10.1055/s-0036-1592125](https://doi.org/10.1055/s-0036-1592125)

Publication date:
2016

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Chalmers, J. D. (2016). The Modern Diagnostic Approach to Community-Acquired Pneumonia in Adults. *Seminars in Respiratory and Critical Care Medicine*, 37(6), 876-885. <https://doi.org/10.1055/s-0036-1592125>

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The Modern Diagnostic Approach to Community-acquired pneumonia in adults

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Keywords: Chest radiograph, community-acquired pneumonia, Epidemiology; Microbiology; Polymerase chain reaction, risk factors, *Streptococcus pneumoniae*

Word count: 4555 words

Respiratory tract infections, the majority of which are community-acquired, are among the leading causes of death worldwide and a leading indication for hospital admission. The burden of disease demonstrates a “U” shaped distribution, primarily affecting young children as the immune system matures, and older adults as the process of immunosenescence and accumulation of co-morbidities leads to increased susceptibility to infection.

Diagnosis of community-acquired pneumonia is traditionally based on demonstration of a new infiltrate on a chest radiograph in a patient presenting with an acute respiratory illness or sepsis. Advances in diagnosis have been slow, and although there are increasing data on the value of computed tomography or lung ultrasound as more sensitive diagnostic methodologies, they are not widely used as initial diagnostic tests. There are a wide range of differential diagnoses and pneumonia “mimics” which should be considered in patients presenting with CAP.

Once the diagnosis of CAP has been made, identifying the causative microorganism is the next stage in the diagnostic process. Traditional culture based approaches are relatively insensitive and achieve a positive diagnosis in only 30-70% of cases, even when rigorously applied. Urinary antigen tests, polymerase chain reaction assays and even next generation sequencing technologies have become available and are increasing the rates of positive diagnosis.

In an era of increasing antimicrobial resistance, the accurate diagnosis of CAP and determining the causative pathogen are ever more important. Getting these both right are the key steps to both reducing morbidity and mortality from CAP and appropriate antimicrobial stewardship which is now an international healthcare priority.

Introduction

Acute respiratory tract infections are the leading cause of death in developing countries, while remaining a leading cause of death in developed nations.(1,2) The Global Burden of Disease study revealed that the number of deaths from acute respiratory tract infections has fallen over the past 2 decades. Nevertheless, respiratory infections will continue to have a profound impact worldwide.(1,2) The exact prevalence of acute respiratory tract infections worldwide is nearly impossible to calculate, but there are an estimated 4 million deaths per year, with up to ¼ of those deaths being in children under the age of 5.

Determining the precise impact of community-acquired pneumonia (CAP) worldwide is made more difficult by the use of a definition that relies on chest radiographic evidence of consolidation.(3-5) It is estimated that up to 80% of episodes of CAP in developed countries are treated without the patient ever receiving a chest x-ray. In developing nations, this proportion will be higher still.(5-7)

Whether in primary care or in the hospital setting, CAP must be quickly recognised and treated, as severe CAP can be life threatening.(8) In the emergency setting, prompt resuscitation and administration of intravenous antibiotics are essential steps in reducing the morbidity and mortality from CAP which stands at 5-15% for hospitalised patients and often >25% for patients requiring admission to an intensive care unit.(8-10) In this context, CAP must be differentiated from other conditions causing acute respiratory failure and septic shock. In the less acute setting, in outpatients or in primary care, the challenge is more to differentiate patients with CAP who may benefit from antibiotic therapy, from that much larger group of patients with acute cough who will not.(5,7,11,12)

Once the diagnosis of CAP has been made, antibiotic treatment is commenced according to the severity of disease and to cover the most likely causative pathogens.(13,14) Testing to determine the possible causative pathogen serves a number of important functions include 1- to de-escalate initial broad-spectrum antibiotic treatment if a pathogen is identified that can be treated with narrower spectrum therapy (15) 2- to identify unusual or drug resistant pathogens that will not be covered by the initial empirical regime(16) 3- to provide local data on the frequency of different causative

pathogens and antibiotic resistant rates that can be used to guide future empirical treatment guidelines.(17)

The goal of this review is to discuss the diagnostic approach in CAP, with a focus on how to make the initial diagnosis and the emerging methods for determining the underlying pathogen.

What is community-acquired pneumonia?

By convention, pneumonia is an acute respiratory illness associated with a new infiltrate on the chest radiograph.(13) In practice, pneumonia is an extremely heterogeneous clinical disorder. While many patients present with classic symptoms of a combination of cough, sputum production, breathlessness, fever and pleuritic chest pain, many patients do not. Particularly in the elderly, fever may be absent, and pneumonia may present with episodes of decreased mobility, delirium, acute cardiac disorders (such as new onset atrial fibrillation) or abdominal pain without obvious respiratory symptoms.(18) Pneumonia is the most common cause of community acquired sepsis along with urinary tract infections and should be considered in all patients presenting with the clinical syndrome of sepsis.

Pneumonia is divided into community and hospital acquired.(17) Arbitrarily, HAP is considered to be present if pneumonia developed >48 hours after admission to a hospital or healthcare environment, with all other cases of pneumonia being considered community-acquired.(19) The causative pathogens in community-acquired pneumonia are typically upper respiratory tract commensals and include Gram-positive organisms (most frequently *Streptococcus pneumoniae*, but also *Staphylococcus aureus*), Gram-negative organisms (most frequently *Haemophilus influenzae*, but also less frequently *Moraxella catarrhalis* and the enterobacteriaceae or *Pseudomonas aeruginosa*) and the atypical pathogens (including *Legionella pneumophila*, *Mycoplasma pneumoniae* and others.(20,21) Viruses are increasingly recognised as the cause of CAP, and may be detected in

patients with an identified bacterial pathogen or in those without an identified bacteria.(22) Fungi are not, thus far, identified as a common cause of CAP in immunocompetent adults.

In contrast, the causative pathogens in HAP are most frequently organisms such as Methicillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, enterobacteriaceae with atypical pathogens being rare.(17,19)

This classical dichotomy hides a much greater degree of complexity. Among patients with CAP, there are patients with few co-morbidities who are at very low risk of antibiotic resistant pathogens and are most likely to have pneumococcal or atypical pneumonia.(16,17) In contrast, among elderly patients and those with co-morbidities atypical pathogens are uncommon, but the incidence of enterobacteriaceae and *Pseudomonas aeruginosa* increases sharply.(23,24) Other groups deserve special mention. Patients with HIV and those with other forms of immunosuppression may be at risk of opportunistic pathogens not typically considered in CAP therapy.(25) This leads many authors to suggest that CAP with immunosuppression should be regarded as a separate clinical entity.(26) Patients with HIV are at significantly increased risk of CAP, but in the era of highly active anti-retroviral therapy the most frequent aetiological agent is *S. pneumoniae*, as with CAP not associated with HIV. *Pneumocystis jirovecii* is the most frequent aetiology in patients with a CD4 count <200 per mm³.(25,27)

Similarly, the lines between community and hospital are increasingly blurred as the population ages and healthcare is delivered increasingly in the community. Nursing home acquired pneumonia (NHAP) has been proposed as a separate entity, but at least in Europe there is little evidence that they require different empirical therapy.(28) A study from Germany compared 518 patients with NHAP and 2569 CAP patients and found only minor differences in aetiology- with more *S. aureus* and less atypical pathogens in the NHAP group. Differences in outcome were due to worse functional status and co-morbidities in NHAP rather than differences in bacteriology.(28,29) Similar results have been reported from Spain and elsewhere.(28,29)

The concept of healthcare associated pneumonia was proposed in 2005 by the IDSA/ATS HAP/VAP guidelines as a means of dealing with this increasing complexity.(17,19) Their proposal to treat patients from nursing homes, those with prior hospitalisation or prior antibiotic treatment and other risk factors as HAP patients led to 20-30% of those previously regarded as CAP being treated with broad-spectrum antibiotic therapy.(19,30,31) Recent data from the United States suggests that approximately 30% of community-acquired pneumonia is now being treated with anti-MRSA directed therapy, despite the prevalence of MRSA being approximately 1% in this group.(19,30,31) There is a consensus that while the HCAP criteria represent risk factors for a different spectrum of pathogens, they did not function as a method of selecting empirical antibiotic treatment, leading to overtreatment.(19,23,26,32) Revision of this guidance is currently underway.

Thus the classification of pneumonia remains into CAP and HAP, but recognises that within CAP there are subgroups of patients that will require additional investigation and consideration of a different spectrum of causative pathogens. (figure 1)

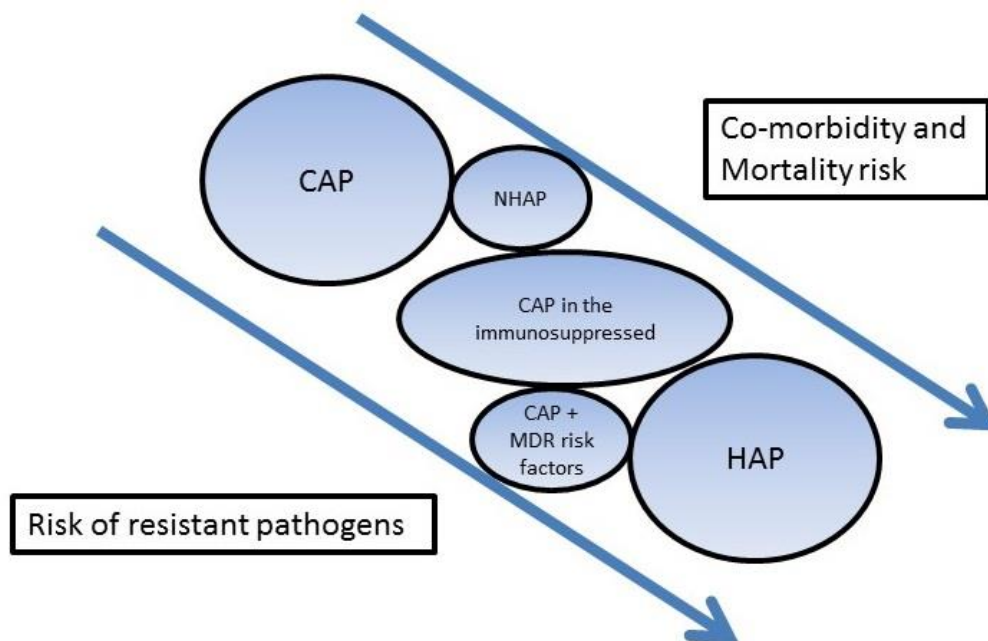


Figure 1. Classification of pneumonia. Abbreviations CAP= community-acquired pneumonia, HAP= hospital acquired pneumonia, MDR= multidrug resistant. NHAP= nursing home acquired pneumonia.

The risk factors for multidrug resistant pathogens are dealt with more extensively in another review in this series but are strongly linked to age, multimorbidity, co-morbidities such as respiratory disease, dementia and renal failure, and antibiotic use.(33-35)

Diagnosis of CAP in the hospital setting

As described above, in practical terms CAP should be diagnosed in patients with acute respiratory symptoms and a new consolidation on the chest radiograph. In practice, diagnosis is challenging and misdiagnosis is common.(3) The gold standard is the detection of microorganisms in lung tissue, which is not practical and not available in the emergency department.

When accuracy of chest radiographs for diagnosis of pneumonia have been evaluated, the agreement between clinicians and radiologists, or between two radiologists is often poor.(36,37) A recent study by Claessens has clarified these difficulties in diagnosis.(38) The French study examined

319 patients with suspected CAP by chest radiograph and chest CT.(38) The results revealed a remarkable level of disagreement between x-ray, CT and clinical evaluation. In summary 1/3 of patients with a “normal” chest x-ray had an infiltrate on CT, and excluded CAP in 30% of patients with an apparent chest x-ray infiltrate.(38) Using CT as the gold standard, the diagnostic decision was changed in nearly 60% of cases.

Unfortunately, routine use of CT for the diagnosis of pneumonia is unlikely to be widely available in the near future. Chest x-ray will remain the standard investigation. Nevertheless, as a result of this and other studies it is important to question the diagnosis of CAP, particularly when x-ray is equivocal, and to re-evaluate the accuracy of the diagnosis if patients do not respond to treatment as expected.(39)

Lung ultrasound has been proposed as an alternative, and is attractive because ultrasound has become a routine skill for respiratory physicians in the management of pleural disease.(40-42)

A systematic review of the use of lung ultrasound for diagnosis of CAP in adults concluded it has a sensitivity of 95%, specificity of 90% and that based on a final discharge diagnosis of CAP, it therefore had a superior sensitivity and similar specificity to chest x-ray.(42). A multicentre study by Reissig et al studied 229 patients with CAP. They found a sensitivity 93% and specificity of 98% but crucially found that approximately 8% of pneumonic lesions were not visible on ultrasound, indicating that lung ultrasound cannot be considered to exclude CAP.(43)

A further recent systematic review and meta-analysis of 1172 patients investigated with ultrasound suggested the procedure took approximately 13 minutes to perform and had a sensitivity of 94%, specificity of 96%, therefore comparing favourably with alternative tests.(44) Studies were performed by highly skilled and trained sonographers, therefore limiting the applicability of this data beyond expert settings.

Therefore in future, the diagnostic pathway for community-acquired pneumonia may include chest CT and/or thoracic ultrasound.

A number of common and uncommon disorders can present initially with suspected community-acquired pneumonia and an awareness of these possible alternative diagnoses is essential. These are summarised in Table 1.

Diagnosis	Radiological features	Clinical features
Common		
Acute bronchitis (47)	No X-ray changes	Acute cough, without evidence of sepsis. May be a viral prodrome or accompanying viral symptoms
Exacerbation of COPD(48)	Hyperinflation and chronic changes but no consolidation	History of COPD, cough, sputum and breathlessness with wheeze on examination.
Exacerbation of asthma(49)	May be hyperinflation, but no consolidation	History of asthma, cough, breathlessness, wheeze. May be accompanied by viral prodrome
Exacerbation of bronchiectasis(50)	Often normal, mucus plugging may lead to opacities suggesting pneumonia	Cough, sputum, breathlessness, chest pain, fever and malaise. Past history of bronchiectasis.
Cardiac failure and pulmonary oedema (51)	Cardiomegaly, pleural effusions, alveolar opacities (classically perihilar) upper lobe venous diversion	Orthopnoea, Paroxysmal nocturnal dyspnoea, ankle oedema, absence of sepsis. Response to diuretics and nitrates. Often a past history of cardiac failure or cardiac disease. Elevated cardiac biomarkers but low inflammatory markers.
Lung cancer/malignancy including lymphoma(52)	Multiple possible imaging features	Lack of inflammatory response, chronic symptoms, associated red flag symptoms (weight loss/haemoptysis)
Non-respiratory sepsis(53)	Severe sepsis from any source e.g UTI, intraabdominal, pancreatitis can be associated with consolidation (often bilateral)	Initial history lacking in respiratory symptoms, clinical indicators of sepsis outside the respiratory tract. Isolation of pathogens not usually associated with CAP.

Pulmonary embolism(54)	Atelectasis, pleural effusion, elevated diaphragm, Westermarks sign, unilateral or bilateral opacities	Difficult to differentiate clinically. Prominent hypoxaemia, pleuritic chest pain, collapse/syncope. Clinical evidence of DVT usually absent.
Uncommon		
Acute interstitial pneumonia(55)	Appearances similar to ARDS.	Short history (often 1-2 weeks) cough, sputum, fever and progressive breathlessness.
Cryptogenic organising pneumonia(56)	Reversed halo sign, “flitting” shadows over time, concave opacities	Relatively chronic course (usually >1 month)
Chronic eosinophilic pneumonia(57)	Bilateral nonsegmental consolidation with peripheral predominance	Subacute or chronic presentation. Peripheral pulmonary infiltrates. Eosinophilia (peripheral or on BAL). More common in females than males.
Acute eosinophilic pneumonia(58)	Diffuse radiographic infiltrates	Often occurs in young adults. Peripheral blood eosinophilia
Lipoid pneumonia(59)	Presence of fat within consolidation on CT.	Non-specific presentation- Dyspnoea and cough
Tuberculosis(60)	Upper lobe changes, cavitation	Chronic course, absence of sepsis, haemoptysis, weight loss, night sweats.

Table 2. Differential diagnoses of community-acquired pneumonia in patients presenting to hospital or the emergency department. The list is no exhaustive but gives examples of differential diagnoses.

The possibility of lung malignancy should be particularly considered in all patients presenting with CAP. Up to 10% of CAP patients admitted to hospital will be ultimately diagnosed with pulmonary malignancy.(52,61,62) In a cohort study in Canada of 3398 patients, lung cancer was diagnosed in 1% of patients at 12 months.(62) Lung cancer was most frequent in patients over the age of 50, men and smokers.(62) In a cohort study of 40,744 patients with CAP, Mortensen and colleagues demonstrated that the most important risk factors were a history of COPD, prior malignancy, white race and tobacco use.(61) The diagnosis should be considered in all patients, but particularly those over the age of 50 and with a history of cigarette smoking.

Diagnosis of CAP in primary care

In the community, diagnosis is even more challenging where the majority of acute respiratory infections are not investigated by chest x-ray.(63) Even where chest x-rays are performed, diagnosis may be missed. In a study of 12 European countries, 3% of 1885 patients with LRTI not thought to be pneumonia had CXR evidence of pneumonia on independent radiology review.(5)

Biomarkers can assist in the diagnostic pathway. In a study in 12 European countries of 2820 patients with lower respiratory tract infections, where x-rays were performed, 140 (5%) had pneumonia. Clinical features had a moderate ability to identify pneumonia, where pneumonia was more frequent with the absence of a runny nose, the presence of breathlessness, crackles, diminished breath sounds on auscultation, tachycardia and fever. Addition of CRP>30mg/L to this model greatly improved the diagnostic accuracy (from area under the curve 0.70 to 0.77).(64) Procalcitonin did not help diagnosis in this model.(64)

Patients with radiologically proven pneumonia appear to derive benefit from antibiotic treatment. In a 12 country randomized controlled trial of amoxicillin for LRTI in primary care (n=1038 amoxicillin, n=1023 placebo) there was no impact of antibiotics on duration of symptoms or symptom severity with the antibiotic treatment.(65) Nevertheless, in a post-hoc analysis of patients subsequently found to have radiological pneumonia, patients with x-ray changes treated with antibiotics had a more rapid resolution of symptoms and lower severity of symptoms.(5)

Since x-ray is impractical in terms of detecting pneumonia in primary care on a routine basis, alternatives are needed. Current guidance recommends the use of point of care C-reactive protein (CRP) testing as an alternative.(66) Randomized controlled trials show that use of CRP can reduce antibiotic use for LRTI without adverse effects.(67,68) A cluster randomized controlled trial in the Netherlands showed that CRP could halve the rate of antibiotic prescription. Recommended cut-offs vary but studies suggest a cut-off of 30mg/L is most accurate to predict pneumonia.(67-70)

Thus in primary care a combination of clinical history, markers of severity such as the CRB65 scoring system(71,72), and the use of point of care CRP testing where available is most effective in identifying those patients requiring antibiotic treatment.

CAP pathogens and diagnostic tests

Once a diagnosis of CAP is made and empirical therapy is being considered or has been administered, the diagnostic process moves towards determining the underlying causative pathogen. Routine use of microbiological investigations in primary care is generally not recommended due to the low rate of true pneumonia among such patients. Nevertheless, it is known that the spectrum of pathogens in outpatients is very similar to those in inpatients.(72-74)

There is some variation globally in the proportions of different pathogens reported as the causes of community-acquired pneumonia, but in general the list of pathogens is remarkably consistent.(16,75-78) In figure 2 we select representative cohort studies from North America, South America, Northern Europe, Southern Europe, Asia and Australasia, and demonstrate that the predominant pathogens are broadly similar.(75-78) *Streptococcus pneumoniae* remains the most frequently isolated bacterial pathogen in community-acquired pneumonia across the world which is why it is a focus of vaccination efforts.(79,80) Approximately 1/3 of patients with pneumococcal pneumonia will have bacteraemia.(81) It is controversial whether bacteraemia is associated with worse outcomes, and recent data suggests that bacteraemic infection may have different clinical characteristics but similar outcomes.(81,82)

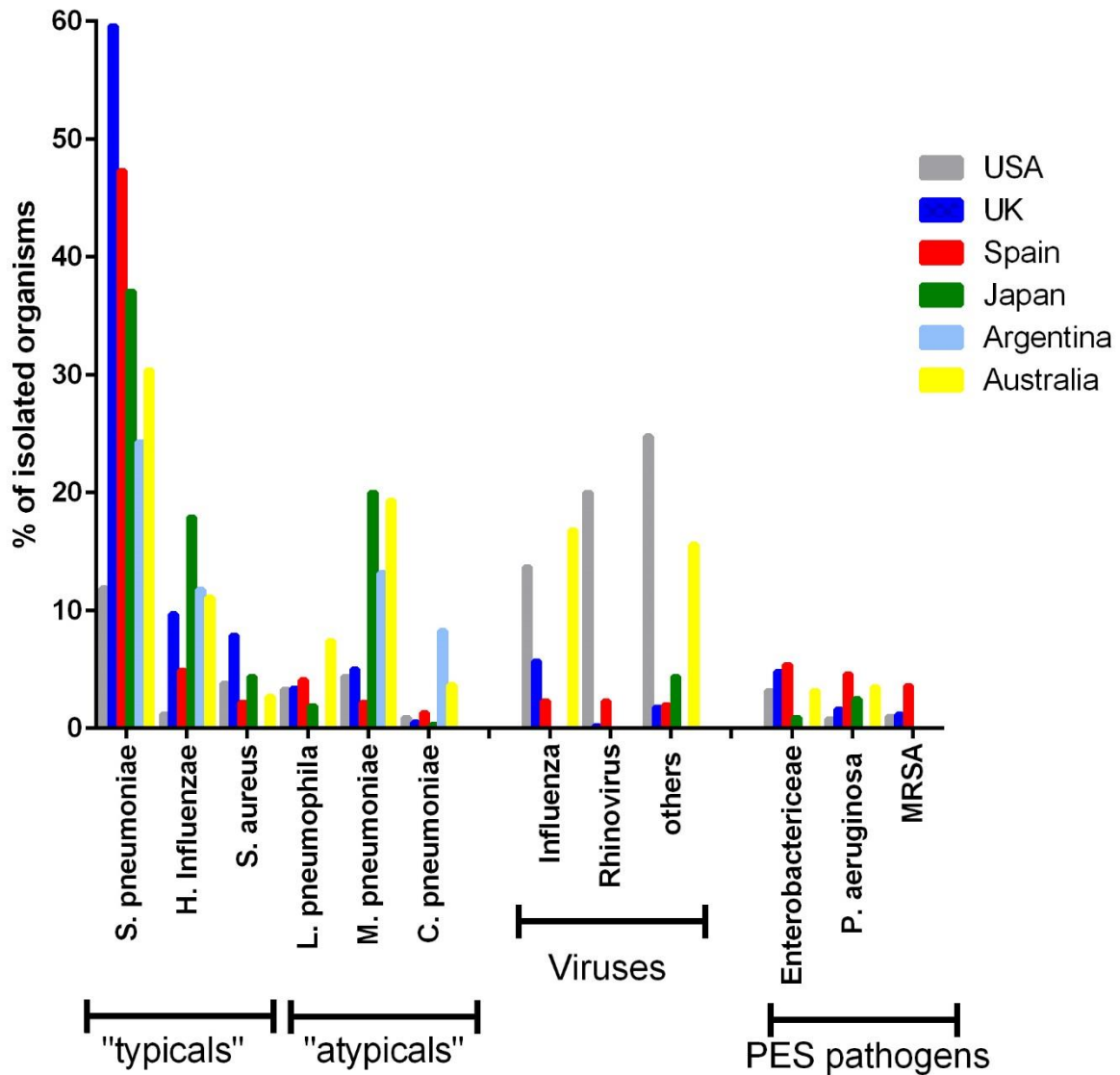


Figure 2. Representative frequency of pathogens across Global CAP cohorts. Data from refs 12,75-78. Cohort were selected as being prospectively enrolled with standardised testing for organisms.

The recent EPIC study supported by the Centre for Disease Control and Prevention in the United States has provided a clearer view of the aetiology of CAP in North America.(75) The study was conducted at 5 hospitals in Nashville and Chicago, USA.(75) 2488 patients were enrolled of which 2320 had radiographic pneumonia. The study enrolled predominantly milder CAP patients, with an average age of 57 and 65% of patients being in PSI risk class 1-3, where patients would normally be treated as outpatients.(83) Extensive aetiological testing revealed a pathogen in 38%, with viruses being more frequent than bacteria. Rhinovirus was most frequently detected in 9% of patients,

influenza in 6% and *S. pneumoniae* in 5%.(75) Other pathogens were infrequent (figure 2). This data suggests that viral infections may be more frequent than bacteria in mild CAP in the United States.(75)

Co-infection is common across a number of studies.(84) The presence of a viral infection does not imply the absence of bacterial infection in patients with CAP.

Most empirical regimes cover both typical and atypical pathogens and this is appropriate because studies suggest that atypical organisms are common throughout the world.(17,66) A study by Arnold et al identified rates of atypical pathogens to be 22% in North America, 28% in Europe, 21% in Latin America and 20% in Africa, justifying the universal use of atypical coverage.(85) Even in outpatients or patients in primary care it is common to identify atypical organisms and particularly *Mycoplasma pneumoniae*.(86) Consistent observational data suggests that the addition of macrolide to beta-lactam therapy provides benefits in terms of reduced time to clinical stability and reduced mortality compared to beta-lactam alone.(87,88) This data is the basis of international guidelines recommendations to use atypical coverage in all inpatients, and particularly in patients with severe pneumonia.(17,66)

In some geographical regions, the distinction between typical bacterial pneumonia and *Mycobacterium tuberculosis* (MTb) infection can be difficult, leading to MTb being listed as a cause of CAP. The United States Centre for Disease Control has listed 22 risk factors that can identify patients at high risk of MTb infection, and in patients with suspected CAP the five strongest risk factors were night sweats, weight loss, haemoptysis, prior exposure to MTb and upper lobe infiltrates, these all being classical of TB infection.(89)

Diagnostic testing for the underlying cause is directed therefore against a range of pathogens most likely to be identified, or less common pathogens that would nevertheless change treatment such as the atypical organisms or multidrug resistant organisms.(90,91)

Standard cultures and urinary antigen testing

Conventional culture based microbiology is still the mainstay of microbiological diagnosis. Most international CAP guidelines recommend blood cultures for patients on admission to hospital, ideally prior to antibiotic treatment.(17,66) Sputum culture is recommended in expectorating patients. Some guidelines such as the British Thoracic Society guidelines in the UK and subsequent NICE update recommend omitting microbiological investigations in patients with mild pneumonia.(66) This has potential advantages in terms of reducing costs, but has limitations in terms of identifying local microbiology patterns and also initial assessment of severity of disease is often unreliable. Most guidelines internationally suggest blood and sputum cultures in those patients to be treated as inpatients and this is the authors practice as well.

Sputum cultures are most likely to be positive in patients with chronic respiratory diseases such as COPD, bronchiectasis and asthma.(92,93) Studies based largely on sputum cultures will report high frequencies of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* for this reason, while studies based on alternative diagnostic tests will report these organisms less frequently as they are less commonly identified in the blood.(92-95)

Urinary antigen testing for *S. pneumoniae* and *Legionella pneumophila* have become standard care in many hospitals in the United States, Europe and internationally. (17,66)

Urinary antigen testing for *L. pneumophila* are well established and have a sensitivity of 75-80% and a specificity approaching 100%. The limitation is that existing tests only identify *L. pneumophila* serogroup 1.(96)

Detection of viruses and atypical organisms

Atypical pathogens have characteristic clinical features, for example hyponatraemia, abnormal liver function tests, diarrhoea and very high levels of C-reactive protein in *L. pneumophila* infection.(97,98) None of the clinical prediction tools or individual clinical characteristics are sufficiently sensitive or specific to be used to guide antibiotic treatment. Therefore all patients should be considered for testing for atypical pathogens. Detection of rising IgM antibody titres to *M. pneumoniae*, *L. pneumophila* and other atypical pathogens has been long recommended in guidelines, but reported sensitivity is only 30-60% and can only be determined retrospectively.(97,98) It is therefore not useful to guide treatment. PCR is now the treatment of choice for detection of all atypical pathogens in throat or lower respiratory tract samples.(99,100)

Viral diagnostics are increasingly used. Their value is in identifying patients who may benefit from anti-viral treatment such as neuraminidase inhibitors (while recognising the current controversy over the effectiveness or otherwise of these drugs) and for isolation of potential infectious patients.(101-103) Diagnostic immunoassays are available for use in throat swabs, sputum and bronchoalveolar lavage. Reported sensitivity ranges from 40-70% indicating that a negative assay cannot rule out the presence of influenza. PCR is the test of choice with a higher sensitivity and specificity and multiplex assays are available covering the majority of clinically important respiratory viruses. Differential influenza virokinetics across the respiratory tract means that samples can be negative in nasopharyngeal or throat swabs but may be subsequently positive on sputum or BAL samples. As a result, lower respiratory tract samples should be preferred. (104-106)

PCR for Streptococcus pneumoniae, including assessment of bacterial load

Studies have shown a higher sensitivity of PCR for detection of *S. pneumoniae* in sputum compared to conventional culture.(107) Studies have generally used primers directed at the specific pneumolysin or *LytA* genes.(107-110) Reasons for improved sensitivity likely relate to the poor

survival of *S. pneumoniae* in sputum samples and the fact that PCR can detect non-viable *S. pneumoniae* and other bacteria and so is not affected by prior antibiotic treatment.(107-111)

Rello et al evaluated DNA load, based on quantitative PCR, in blood from patients with pneumococcal pneumonia and demonstrated a clear relationship between DNA load and septic shock, a finding that has been confirmed in two other studies where DNA load correlated with severity markers in pneumonia.(109)

Therefore PCR assays targeting *S. pneumoniae* are more sensitive than culture, are not limited by the requirement for organisms to be viable and therefore for samples to be taken prior to antibiotic treatment, and preliminary evidence suggests quantification could provide valuable prognostic information. This has not yet entered clinical practice but holds some promise.

Emerging technologies

Although microbiome sequencing has been successfully applied to chronic respiratory diseases using sputum and bronchoalveolar lavage, there are limited data in CAP patients.(112-114) This technology that sequences all of the bacterial species present in a sample has potential, but is unlikely to reach routine clinical practice due to the bioinformatics challenges associated with analysis of the huge datasets.

Biomarkers to guide diagnosis and antibiotic treatment

Biomarkers have a limited role in the diagnosis of CAP as none are specific for pneumonia, as they are raised in other causes of systemic bacterial infection.(115) Nevertheless, C-reactive protein is raised in the majority of patients with CAP.(45) White blood cell count is unhelpful, as although it is often raised it is non-specific.

PCT has been the most intensively studied as a marker that is rapidly upregulated in the presence of bacterial infection or inflammatory cytokines including interleukin 1 beta, IL-6 and TNF alpha.(115) Viral infections do not generate a strong PCT response leading to the suggestion that PCT can be used to identify infections likely to respond to antibacterial treatment. A number of trials have been conducted comparing biomarker guided treatment with standard care. In the largest of these, the ProHOSP study conducted in Switzerland, an algorithm comparing PCT with standard care (N=1381) resulted in a reduction in antibiotic use of 35% while being non-inferior in terms of clinical outcomes.(116) The study included patients with a range of respiratory tract infections. The impact in the subgroup with community-acquired pneumonia (N=460 randomized to PCT and 465 randomized to standard care) was that 10% of CAP patients could be managed without antibiotics, with a reduction in duration of therapy in total of 3.5 days.(116)

Limitations include that the duration of antibiotic treatment reported in the control arm was long (10 days on average) and might have been reduced with a simple antibiotic stewardship programme rather than a biomarker intervention, and secondly that the greatest value of PCT was in early stopped of antibiotics rather than the initial diagnostic decision.(117,118)

A real life intervention based on PCT also in Switzerland and also France and the United States recruited 1759 patients, demonstrated that implementation of PCT reduced antibiotic treatment by 1.5 days with no increase in adverse events.(119)

A large number of other biomarkers have been evaluated to aid the diagnostic and prognostic decision making process in CAP. The most frequently evaluated have been CRP, PCT, Proadenomedullin (ProADM) and Copeptin.(115)

C-reactive protein has little value in initial diagnosis in secondary care as levels as low as <10mg/L can be detected in patients with CAP.(45) There is only a weak relationship between CRP and severity of disease, but little added value of CRP over and above severity scoring systems.(45)

Nevertheless, CRP is highly effective as a means of assessing treatment response. Mortality is <1% in patients where CRP has fallen by 50% or more at day 3 or day 4.(120,121)

Similarly, Proadrenomedullin has been extensively studied.(122) In a German study of 728 patients, it was the most accurate in evaluating prognosis (patients with the highest levels had a 3.7x increased risk of death) with an area under the curve of 0.81 which was better than the CRB65 score.(122) Independent studies have confirmed the prognostic accuracy of this biomarker. A study by Albrich found that adding ProADM to CURB65 enhanced outcome prediction but there are no studies to date showing that implementation of ProADM improve outcome in clinical practice.(123)

Clinical utility of diagnostic testing: improving outcomes and antimicrobial stewardship

An accurate diagnosis of CAP is important to reduce inappropriate antibiotic use in the context of both primary care and in secondary care. Inaccurate diagnosis of pneumonia and therefore inappropriate antibiotic treatment contributes to antibiotic resistance and to hospital acquired infections such as *Clostridium difficile*, a major problem in Western countries.(124,125) Once the diagnosis is made, identification of the causative pathogen allows de-escalation of treatment.(15) Van der Eerden demonstrated that pathogen directed therapy, using a combination of Gram-stain and clinical features, allowed de-escalation of treatment without compromising clinical outcomes.(126)

Summary

Despite its limitations, Chest x-ray remains the essential diagnostic test to identify CAP in secondary care. In primary care, the diagnosis remains clinical, but CRP measurement at point of care can be valuable to identify those patients requiring antibiotic treatment. Patients in secondary care should have a full battery of available microbiological tests including sputum and blood cultures, PCR for atypical organisms, viruses and urinary antigen testing.

Developments in PCR technology in particular promises to improve diagnostic and prognostic assessment in CAP in the future.

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