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CLINICAL FEATURE REVIEW

Community-acquired pneumonia: An overview

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Abstract

Community-acquired pneumonia is still a significant cause of morbidity and mortality and is often misdiagnosed and inappropriately treated. Although it can be caused by a wide variety of micro-organisms, the pneumococcus, atypicals, such as *Mycoplasma pneumoniae* and *Chlamydo-phila pneumoniae*, *Staphylococcus aureus* and certain Gram-negative rods are the usual pathogens encountered. The site-of-care decision is critical in determining the site and type of care as well as the extent of diagnostic workup. Antimicrobial therapy should be started as soon as possible particularly in those requiring admission to hospital, but typically the physician does not know with any degree of certainty the identity of the etiologic pathogen. A number of national guidelines have been published to help the physician with this choice. The initial drug(s) can be modified if necessary if the pathogen and its antimicrobial susceptibility pattern becomes known. Adjunctive therapy such as pressors and fluid replacement are of value and macrolides appear to help as well, likely secondary to their immunomodulatory effects. Recent data also suggest a role for steroids.

Keywords:

Community-acquired pneumonia, pneumococcus, site of care, guidelines, adjunctive therapy, vaccines

History

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Pneumonia by definition is an infection of the lung or pulmonary parenchyma. Until recently, it was considered to be either community-acquired pneumonia (CAP) or hospital- (and/or ventilator) acquired pneumonia (HAP/VAP). It was noted that there is a subgroup of outpatients who have had contact with the healthcare system and who present with pneumonias caused by organisms more similar to those causing HAP than CAP [1]. A new category of pneumonia called healthcare-associated pneumonia (HCAP) was defined [2]. However, recent data have raised questions about whether the concerns regarding the types of pathogens and their resistance patterns in HCAP will in fact hold up [3,4]. It is likely that this subgroup will be modified considerably.

CAP itself is a common infection and is often misdiagnosed and inappropriately treated. While it can often present as a relatively mild illness, overall it still remains a cause of considerable morbidity and mortality. It is not a reportable disease, so data are not exact, but it is estimated that each year over 5 million cases occur in the USA with over 1 million hospitalizations and 60,000 deaths from pneumonia and influenza [5]. Typically, about 80% of these cases are treated as outpatients and 20–25% in the hospital setting. The overall mortality rate for outpatient CAP is in the region of 1%, but for those ill enough to require hospitalization 30-day mortality rates up to 23% have been reported. Incidence rates are greatest at the extremes of age with an overall rate in adults

in the USA of 5.16–6.11 cases per 1000 persons per year but being as high as 12–18 per 1000 among children <4 years and 20 per 1000 among those over 60 years [6].

Etiology

Although there are a large number of microbial pathogens that have been associated with CAP, in the immunocompetent patient, the list is relatively short and reasonably stable [7,8]. Newer pathogens have been documented including *Hantavirus* in 1993, human *metapneumovirus* in 2001, the *coronavirus* associated with SARS in 2002 and more recently (2012) the middle east respiratory syndrome. Community-acquired strains of methicillin-resistant *Staphylococcus aureus* (MRSA) have also become CAP pathogens relatively recently [9]. Most cases of CAP, however, are caused by the pathogens mentioned in Table 1.

With the advent of polymerase chain reaction (PCR), the detection of viruses in respiratory samples has increased significantly and in some studies viruses have been found in up to one-third of adult CAP patients [10,11]. The presence of a virus, however, does not prove causality as nasopharyngeal swabs can yield respiratory viruses in 20–30% of healthy adults [12]. Interestingly, mixed infections with both bacterial and viral organisms have been found in about 20% of CAP cases and tend to be associated with more severe infection than those caused by a bacterium only.

Table 1. Most common etiologies of community-acquired pneumonia.

Ambulatory patients	Hospital non-ICU	Severe (ICU)
<i>Streptococcus pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>Mycoplasma pneumoniae</i>	<i>M. pneumoniae</i>	
<i>Haemophilus influenzae</i>	<i>Chlamydomphila pneumoniae</i>	<i>Staphylococcus aureus</i>
<i>C. pneumoniae</i>	<i>H. influenzae</i>	<i>Legionella</i> spp.
Respiratory viruses ^a	<i>Legionella</i> spp.	Gram-negative bacilli
	Aspiration	<i>H. influenzae</i>
	Respiratory viruses ^a	

^aInfluenza A and B, adenovirus, respiratory syncytial virus, parainfluenza.

Of the potential viral pathogens, *influenza* is the most important, although *respiratory syncytial virus*, *adeno*, *parainfluenza* and *corona* viruses may also have roles to play.

Although the influenza virus is certainly capable of causing pneumonia on its own and a severe one at that, it is more often seen as a primary infection that then becomes secondarily infected by a bacterium such as *S. aureus* or *Streptococcus pneumoniae*.

Table 1 is taken from the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) CAP guidelines and although respiratory viruses and influenza are included as a footnote in Table 1, it is believed that it is proper to consider the influenza virus in particular as a potential cause of severe (intensive care unit [ICU]) pneumonia as well.

It simplifies matters somewhat to separate the etiologic agents into “typical” bacterial pathogens and “atypical” pathogens. The former group includes *S. pneumoniae* as the most common of the identified bacteria and other bacteria such as *Haemophilus influenzae* and *S. aureus*, and Gram-negative rods such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and anaerobes. Anaerobic bacteria may be seen in cases of gross aspiration pneumonia in patients with unprotected airways (seizure, substance or alcohol abuse) and/or gingivitis. It is worth noting that *S. pneumoniae* seems to be decreasing in frequency with widespread use of pneumococcal vaccines and the atypical pathogens such as *M. pneumoniae* and *Chlamydomphila pneumoniae* are becoming more important particularly in young adults [13]. Other atypicals such as *Legionella* and a variety of viral pathogens can play a role as well. Generally, fungal and protozoal infections are not usually seen in the normal host with CAP except under specific circumstances such as coccidioidomycosis and cryptococcosis. PCR studies show that viral pathogens may be present in 20% of CAP patients, but whether they are etiologic agents, co-pathogens or simply colonizers cannot always be determined [14]. A discussion of individual pathogens is beyond the scope of this article.

Certain risk factors and epidemiologic circumstances have been identified in CAP patients. Risk factors for CAP itself include alcoholism, asthma, immunosuppression, institutionalization, age over 70 years, crowded living conditions and

close contact with children [15,16]. It is important to realize that pneumonia is certainly not the old man’s friend. It has been shown that for elderly CAP patients requiring hospitalization the overall mortality rate is greater than that of the general hospital population and this enhanced mortality extends out to 1 year [17]. It is thought that this may be at least partially explained by an increase in vascular events including myocardial infarction and stroke possibly as a result of an overall enhancement of the systemic inflammatory response in such patients [18].

Risk factors for pneumococcal pneumonia include dementia, seizures, cerebrovascular disease, heart failure, alcoholism, smoking, chronic obstructive pulmonary disease and HIV infection. Community-associated MRSA is more likely to be seen in patients colonized by this organism and Gram-negative bacilli like *P. aeruginosa* are typically seen in patients with severe structural lung disease such as bronchiectasis or cystic fibrosis.

Pathophysiology

For pneumonia to occur pathogens must reach the alveoli, multiply and incite a host response. Access to the lower airways can occur a number of ways including inhalation, aspiration, direct inoculation and hematogenous or contiguous spread from an adjacent focus. Direct inoculation might occur with a penetrating thoracic injury or spread from a contiguous focus of infection such as mediastinitis may occur but both are very unusual. Hematogenous spread in cases of tricuspid endocarditis might be seen in iv drug abusers. The most likely routes, however, are by small volume aspiration of bacteria in the patient’s oropharynx as can occur during sleep and by inhalation of contaminated droplets. Protection against such occurrences is dependent to a large extent on mechanical mechanisms supplemented by both innate and acquired host defenses [19].

Nasal hairs and turbinates, intact gag and cough reflexes and a branching tracheobronchial tree with an efficient mucociliary clearance mechanism play a large role in keeping pathogens at bay. Just as in the gut, the normal oropharyngeal colonizing microbial flora plays a role in holding off potential pathogens.

If pathogens gain access to the alveoli, then resident alveolar macrophages and surfactant proteins (SPs) A and D enter the fray. Surfactants generally act to lower surface tension between two liquids or a liquid–solid interface. SP A and D are collagenous glycoproteins that play a number of roles in the lung. They are felt to take part in innate immunity, they can clear apoptotic cells and can bind non-self structures such as bacteria and fungi [20,21]. If these defenses are also unsuccessful and the infection challenge persists then the inflammatory response of the patient comes into play and accounts ultimately for most of the signs and symptoms of pneumonia. If the pro-inflammatory cytokine response is excessive then the process may progress to sepsis, organ failure and possibly shock and even death. In cases of severe infection, various inflammatory mediators including IL-1, TNF, IL-8 and granulocyte-colony stimulating factor result in fever and the release of neutrophils and their attraction to the

lung. An alveolar-capillary leak may develop resulting in filling of the alveoli and subsequent hypoxemia and findings of pneumonia on auscultation and on chest x-ray. If this process is severe, the secondary changes in lung volume and compliance may eventually result in the patient's demise [22,23].

During the pneumonic process a number of phases occur at the tissue level. Initially, there is edema caused by the presence of a proteinaceous exudate in the alveoli followed by a phase of red hepatization. This is caused by the presence of many red cells and is followed by the gray hepatization phase in which the red cells are lysed or degraded and neutrophils and fibrin deposition begin to dominate. Next is the resolution phase in which the macrophages take over, debris is cleared and the inflammatory response has subsided.

Clinical manifestations

The inflammatory response to infection is primarily responsible for the various clinical findings in CAP. Depending on the host and to some extent the pathogen, the disease can vary in its presentation from reasonably benign to fulminant and from mild to fatal in severity. The various signs and symptoms encountered involve not only the lung, but may be constitutional as well.

The typical patient has an elevated temperature and heart rate and may have noted some chills as well as myalgias and arthralgias. There may be some cough and shortness of breath and the former may vary from non-productive to productive of purulent and possibly blood-tinged sputum. Chest pain may occur secondary to coughing or to pleuritic involvement. Interestingly up to 20% of CAP patients may experience gastrointestinal symptoms in the form of nausea, vomiting or diarrhea.

On examination, the findings will depend on the extent of local involvement of the pulmonary parenchyma and the presence or absence of an effusion as well as the extent of systemic response to the release of cytokines. On inspection, the patient may be flushed and/or cyanotic and may be using accessory muscles of respiration. On palpation, tactile fremitus may be noted and a dull or a flat percussion note may indicate consolidation or pleural effusion, respectively. On listening to the chest, one may hear rales, rhonchi, bronchial breath sounds and possibly a pleural friction rub.

The physical examination can be misleading and is neither particularly sensitive nor specific for pneumonia [24]. In the elderly especially, both the clinical presentation and the findings on examination may be misleading and some elderly patients may simply present with confusion [25].

Diagnosis

As with any medical illness, the diagnosis is usually based on information obtained by a careful history, a physical examination and appropriate laboratory tests or procedures. In the case of CAP, a similar approach is used, modified as necessary based on severity of the initial presentation of the patient. With a possible CAP patient the physician must basically ask two questions: Is this pneumonia and if so what is the likeliest pathogen? The former question is typically answered through the use of clinical and radiographic

methods while the latter requires the use of laboratory tests and/or certain procedures.

Clinical diagnosis

The physician must try to determine if the patient has infection or if a non-infectious illness is accounting for the signs and symptoms. Entities which may be mistaken for CAP include acute bronchitis, acute exacerbation of chronic bronchitis, radiation pneumonitis, congestive heart failure and pulmonary emboli to name just a few.

Usually, the diagnosis of CAP is based upon findings suggestive of infection such as fever, chills or increased white count plus signs and/or symptoms localized to the respiratory system. These include cough, shortness of breath, increased sputum production, abnormal physical examination and a new or changed infiltrate on chest radiograph [26,27]. Occasionally, radiographic findings may suggest a particular pathogen, for example, upper lobe cavities with tuberculosis, pneumotoceles with *S. aureus*. The sensitivity and specificity of the physical examination, however, is not good with values of 56 and 67%, respectively.

Microbial etiology

The use of the clinical syndrome approach does not allow one to determine the pathogen reliably and usually once having determined that the patient has CAP, the antibiotic treatment must be started on an empiric basis since the physician does not know with any degree of certainty what the pathogen is [8]. For those patients who will be managed in the community, it is not cost-effective to do any testing or investigations other than the history, physical examination and chest x-ray. For those patients admitted to the hospital and particularly to the ICU, additional testing should be done. Identifying an unexpected pathogen allows specific antimicrobial treatment to be given which decreases antibiotic selection pressure and results in treatment of an organism that might otherwise have been missed [28]. Public health issues are addressed by documenting organisms such as *Mycobacterium tuberculosis* or influenza. Another important reason for trying to identify the pathogen is that without having susceptibility data trends in antimicrobial resistance cannot be documented and followed accurately.

The following are the available tests/procedure to help identify CAP pathogens. Depending upon the circumstances and severity of illness, appropriate test samples should be obtained as quickly as possible and then treatment started.

Gram stain and culture of sputum/respiratory secretions

Testing of expectorated sputum has limitation since in some series up to 40% of patients may be unable to produce an appropriate sample (>25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low power field). In other cases, patients might already have started on antibiotics on their own using a family member's drug. A data base of 33,000 hospitalized CAP patients revealed that in only 7.6%

of cases was a pathogen found [29]. For cases admitted to the ICU and intubated, a deep suction aspirate or BAL sample can be a relatively high-yield procedure [8]. Depending upon the circumstances, other stains, for example, for tuberculosis and fungi may be done as well.

Blood cultures

The yield from blood cultures is surprisingly poor and overall only about 7% to 16% of blood cultures from hospitalized patients are positive, although the yield tends to be higher in cases of *S. aureus* pneumonia [30,31]. Because of the relatively low yield and overall low impact on treatment outcomes, blood cultures are not recommended for all hospitalized CAP patients. For certain higher risk patients such as those with asplenia, chronic liver disease and complement deficiency, decreased white count secondary to pneumonia and severe CAP blood cultures should be done [8].

Urine antigen tests

Antigens from pneumococcus and *Legionella pneumophila* serogroup 1 can be detected in urine with sensitivity and specificity values of 80% and 90% and 90% and 99%, respectively [32,33]. An advantage is that both tests are able to detect antigen even after antibiotic treatment has been started.

Polymerase chain reaction

These tests amplify the nucleic acid of a pathogen allowing rapid and accurate identification. There are now commercially available PCR kits for identifying certain respiratory viruses including influenza as well as *M. pneumoniae* and *C. pneumoniae* [34,35]. Despite its rapidity, sensitivity and specificity, one of the major problems with PCR is that it does not distinguish between colonizers and actual pathogens. Clinical judgment would have to be exercised whenever PCR is used.

Serology

Serologic tests generally depend upon a rise (usually four-fold) in IgM antibody between acute and convalescent phase serum samples. Generally, they are less frequently used especially for *M. pneumoniae* because of accuracy issues and the time required for a convalescent sample to be obtained.

Biomarkers

A number of biomarkers have been identified, although the two most frequently used in cases of pneumonia are procalcitonin (PCT) and C-reactive protein. These, like other biomarkers are considered to be indicative of inflammation and as such are considered helpful in certain circumstances for diagnosis of infection and for initiating or stopping antimicrobial therapy. PCT is produced as part of the host response to bacterial but not viral infection. Individual trials and the Cochrane meta-analysis have shown that use of PCT in the management of CAP can result in less antibiotic use without any increase in mortality [36,37].

A review of 14 randomized controlled trials ($n = 4467$ patients) assessing the use of PCT algorithms for antibiotic decisions showed that appropriate use of this biomarker can reduce the amount of antibiotic used without increasing mortality [38].

Recommendations based on PCT were made according to whether patients had a moderate or a high-acuity pulmonary infection (high risk, sepsis) in the ICU. Cutoffs were: moderate-acuity group: <0.10 UG/L, <0.25 , >0.25 and >0.50 . For the high-acuity group, they were <0.25 , <0.50 , >0.50 and >1 . The recommendation for antibiotic use for each of these cutoffs was: strongly discouraged, discouraged, encouraged and strongly encouraged.

For the moderate-acuity group, testing is recommended every other day and antibiotics can be stopped when levels drop below 0.25 or by at least 80–90% of peak value in patients showing clinical improvement. For the high-acuity group, no specific frequency of testing was given, only a recommendation for ‘periodic monitoring’. Antibiotics could be discontinued when the level was <0.5 or had dropped by 80–90% from baseline in patients exhibiting a positive clinical response.

There are fewer data available regarding the utility of C-reactive protein and pneumonia and at present it seems not to be as sensitive as PCT in the diagnosis of bacterial pneumonia [39].

Such tests must be interpreted in conjunction with the clinical presentation and other information available regarding the patient with CAP.

There are no hard and fast rules on the use of these various tests, although generally virtually none would be used in outpatients with CAP. For those admitted to hospital and to our center in particular, we try to get an appropriate respiratory secretion sample for stain and culture by expectoration or deep suction or bronchoscopy if the patient is intubated. We do not however delay treatment if the sample is unobtainable for whatever reason. We do tend to do blood cultures on most patients admitted to hospital and certainly on all patients admitted to the ICU. As a general rule, we do not do urine antigen testing routinely on hospitalized patients, but in some centers this is quite routine. We do not use serologic testing routinely, nor do we rely on biomarkers, although in some centers particularly in Europe, biomarkers are followed more closely. Use of PCR testing varies quite a bit from center to center and has not become standard at this point in most Canadian centers.

Treatment

Site of care

Once a diagnosis of CAP has been made, the extent and type of investigation as well as the type of treatment will depend upon the site of care, that is, as an outpatient or in the hospital setting (ward or ICU). Rather than using a subjective assessment as was done in the past, the physician now has a number of prediction tools available to help with this decision. The two best known are the Pneumonia Severity Index (PSI) and CURB-65 [40,41]. PSI was initially developed to

identify CAP patients well enough to be treated in the community and the CURB-65 is a true severity of illness score. Both assign points to patients based on various criteria, but there the similarity ends. The PSI uses 20 variables and relegates patients to 1 of 5 categories, while CURB-65 uses only 5 variables and puts patients into 1 of 3 categories. Both have their pros and cons; although the CURB-65 is easier to use and both perform quite well for most patients, neither is particularly good for determining the need for ICU care. Whichever tool one chooses, other factors must also be considered that are relevant to a particular patient such as ability to comply with an oral antibiotic regimen and resources available to the patient in the community setting.

The problem with both the PSI and CURB-65 is that they provide only a “snapshot” of what is happening to the patient at the time the assessment is carried out. Combining the CURB-65 with measurement of a biomarker may improve the discriminatory power of the CURB-65. Proadrenomedullin is a member of the calcitonin family and can act either as a hormone or as a cytokine depending upon the circumstances surrounding its production. A Swiss study which combined CURB-65 scores with levels of proadrenomedullin showed better risk prediction in relation to adverse events and mortality in CAP [42].

For admission to the ICU, there are major and minor criteria proposed by the IDSA/ATS guidelines [8]. These include one of two major criteria such as septic shock or the need for mechanical ventilation or the presence of three of nine minor criteria [8]. Whenever assessing CAP patients regarding site of care, it should be kept in mind that the situation may change and the patient's condition may suddenly deteriorate. Patients admitted initially to the floor setting who subsequently worsen have lower survival rates than equally ill patients who were cared for in an ICU setting.

Antibiotic issues

Resistance

Antimicrobial resistance is certainly not a new issue. If anything it continues to threaten the utility of drugs available to us and the need to minimize resistance is one of the best arguments for effective antibiotic stewardship programs. The resistance problem should be considered from the point of view of both the pathogen and the drugs. In CAP, the organisms of interest are primarily *S. pneumoniae*, atypicals such as *M. pneumoniae*, and also *S. aureus* and certain Gram-negative rods. The usual drug classes used for CAP include the β -lactams, macrolides, fluoroquinolones and tetracycline [8,43]. Organisms resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered to be multi-drug resistant.

For the pneumococcus the change in break points to penicillin for non-meningeal isolates to ≤ 2 , 2–4 and ≥ 8 $\mu\text{g/ml}$ for susceptible, intermediate and resistant respectively, dramatically etc., increased the proportion of pneumococcal isolates considered sensitive [44,45]. Pneumococcal resistance to β -lactams is the result of low affinity to penicillin-binding proteins.

Resistance to macrolides can be mediated by a change in the target site or the presence of an efflux mechanism [46,47]. Target site modification is encoded by the *ermB* gene and results in ribosomal methylation in the 23S rRNA and high level ($\text{MIC} \geq 64$ $\mu\text{g/ml}$) resistance. The *mef* gene is responsible for efflux of antibiotics and low-level resistance ($\text{MIC} \leq 32$ $\mu\text{g/ml}$). Pneumococcal macrolide resistance is increasing worldwide, although in North America it tends to be more often of the M phenotype or low-level resistant variety. Elsewhere, it is more commonly the high-level variety.

Mycoplasma resistant to macrolides is now well documented as well and is due to mutations in binding positions in domain V of 23S rRNA [48,49]. *S. aureus* has developed resistance to virtually all β -lactams except ceftaroline through the *mecA* gene and is referred to as MRSA. Methicillin was one of the original penicillinase-resistant semi-synthetic penicillins. There are both hospital- and community-acquired MRSA strains, and the community-acquired strains are generally less resistant than the hospital-acquired ones and are often susceptible to clindamycin, trimethoprim-sulfamethoxazole, tetracycline and the cephalosporin ceftaroline as well as to linezolid and vancomycin [50–53]. They are also usually sensitive to daptomycin, but this drug is inactivated by surfactant and should not be used for the treatment of pneumonia.

Gram-negative bacilli including *P. aeruginosa* causing CAP may be treated with a variety of drugs including third-generation cephalosporins and anti-pseudomonal penicillins, carbapenems and fluoroquinolones. Fluoroquinolones work by binding to DNA gyrase and topoisomerase iv and ultimately interfering with bacterial replication [54]. Mutations in either of these can lead to resistance.

Antibiotic treatment

As already mentioned, the physician usually does not know with any certainty what the etiologic pathogen is when treatment is initiated. In effect it is an “educated guess” situation and national guidelines have been prepared in a number of countries to help physicians with this decision. In Canada and the USA, initial coverage always includes the pneumococcus and atypicals such as *Mycoplasma*, *Chlamydia* and *Legionella* [8,55]. Guidelines from certain European countries, for example, Sweden and the UK do not call for such coverage routinely, but this difference is generally based on local epidemiologic data [7,56].

The North American approach is supported by retrospective data from administrative databases including thousands of patients and several individual studies which support this as well [57,58]. In a recent paper on CAP in the *New England Journal of Medicine*, referring to the IDSA/ATS CAP guidelines, the authors state “little has changed regarding antibiotic treatment of CAP and the recommendations in this article are generally consistent with these guidelines” [13].

In the last few months however, there has been increased interest in the treatment of CAP patient requiring hospitalization, but not ICU care. In particular, the question of β -lactam-macrolide combination therapy versus β -lactam monotherapy

Table 2. Recommended empirical antibiotics for initial treatment of CAP.

Treatment type	Details
Outpatient treatment	<p>Previously healthy and no use of antimicrobials within the previous 3 months:</p> <p>A macrolide</p> <p>Doxycycline</p> <p>Presence of comorbidities or use of antimicrobials within the previous 3 months (in which case, an alternative from a different class should be selected):</p> <p>Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin [750 mg])</p> <p>β-Lactam PLUS a macrolide</p> <p>In regions with a high rate of “high-level” macrolide-resistant <i>S. pneumoniae</i>, consider use of alternative agents listed above in patients with comorbidities</p>
Inpatients, non-ICU treatment	Respiratory fluoroquinolone
Inpatients, ICU treatment	β-Lactam PLUS a macrolide
	A β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam) PLUS either azithromycin OR a respiratory fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)
Special concerns	<p>If <i>Pseudomonas</i> is a consideration:</p> <p>An antipneumococcal, antipseudomonal, β-lactam (piperacillin/tazobactam, cefepime, imipenem, meropenem) plus either ciprofloxacin or levofloxacin (750 mg dosage)</p> <p>OR</p> <p>The above β-lactam plus an aminoglycoside and azithromycin</p> <p>OR</p> <p>The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam)</p> <p>If CA-MRSA is a consideration: add linezolid or vancomycin</p>

Abbreviations: CA-MRSA = Community-associated methicillin-resistant *Staphylococcus aureus*; CAP = Community-acquired pneumonia. Adapted with permission from [8].

has been raised. Several studies have supported combination treatment especially with a macrolide as part of the regimen [59-62]. A meta-analysis of 16 studies involving almost 43,000 patients reported that a β-lactam-macrolide combination reduced mortality significantly and a benefit was seen in both non-ICU and ICU patients [63].

Garin et al. recently reported results of a randomized controlled trial in *JAMA* comparing β-lactam-macrolide versus β-lactam alone for treatment of moderately severe CAP [64]. The study failed to find non-inferiority of the monotherapy regimen with a primary outcome measure being the proportion of patients not reaching clinical stability by day 7. A recent study in the *New England Journal of Medicine* addressed the same question using a different experimental design and a different primary outcome. The design was a cluster-randomized crossover trial with strategies rotated in 4-month periods [65]. The primary outcome was 90-day mortality. In this study, β-lactam monotherapy was non-inferior to either a β-lactam-macrolide combination or a fluoroquinolone alone. In this study however, atypicals were found in only 2.1% of patients and overall severity was not

particularly high with mean CURB-65 and PSI scores of 1 and 85, respectively.

Treatment should be started as soon as possible and for those patients being admitted to the hospital the initial dose should be given in the emergency room to avoid delay (refer to Table 2 for the treatment of CAP). The recommendations given in Table 2 are from the IDSA/ATS guidelines [8]. If and when a pathogen is identified and susceptibility data become available, consideration should be given to de-escalation or streamlining of antimicrobial therapy to a more targeted regimen. In all cases however, this must be tempered by concern about possible co-pathogens and obviously will also depend on the clinical response of the patient.

If MRSA is a possibility then either vancomycin or linezolid may be used, although there are some suggestions that linezolid may be more effective and it certainly is easier to use as it can be given either iv or po and the dose does not need to be adjusted based on renal function. Another option could be vancomycin plus clindamycin with the latter drug added to suppress *Staphylococcus* toxin formation [13,52].

If *P. aeruginosa* is a possibility then in the hopes of maximizing antibiotic susceptibility and possibly providing an additive or synergistic effect as well, dual coverage is recommended initially [8]. If the *Pseudomonas* is documented and the patient is responding to treatment, then the regimen can be narrowed to appropriate monotherapy based upon susceptibility results and the patient’s clinical course.

Length of treatment for otherwise uncomplicated cases is typically 5–7 days [8,66]. In cases of documented bacteremia particularly with pathogens such as *S. aureus* or *P. aeruginosa*, treatment should be given for up to 4 or 2 weeks, respectively [67].

If influenza is suspected either as a pathogen or co-pathogen then antiviral treatment should be given to patients who meet any of the following criteria: require hospitalization, have severe complicated illness, age ≥ 65 years, pregnant women and up to 2 weeks postpartum and patients from long-term care facilities and with a variety of medical conditions. The reader is referred to the recommendations of the Advisory Committee on Immunization Practices for a more detailed discussion of this issue [68]. Treatment with a neuraminidase inhibitor such as zanamivir or oseltamivir should be started as soon as possible and given for 5 days.

Adjunctive therapy

Despite having antimicrobial drugs that are generally quite effective in eradicating micorganisms, CAP continues to be a significant cause of morbidity and mortality. As discussed in the section on pathophysiology, much of this is due to the host response which either overreacts and can result in a cytokine storm or enters a period of quiescence and immunoparalysis which too can lead to problems. Adjunctive therapy measures have been developed to help sustain the patient, for example, vasopressors, fluid replacement and attempts to modulate the host inflammatory response.

A good example of success is the role played by macrolides. They have a number of immunomodulatory effects including alteration of cytokine expression, leukocyte

function and apoptosis [69,70]. The benefit of these drugs was first documented in the treatment of panbronchiolitis [71].

An increased risk of cardiac events associated with CAP has been attributed to a heightened inflammatory state. Since the statins have some anti-inflammatory activity it was hoped that their use might have a mitigating effect on poor outcomes. The data have been conflicting and somewhat confusing, but generally statins are not felt to play an important role at least from a proactive treatment point of view. One paper which provides a meta-analysis of the role of statins in the prevention and treatment of CAP “reveals a beneficial role” for both the risk of development and mortality with CAP, but by the authors own admission “the results constitute very low qualitative evidence as per the GRADE framework” [72].

Recently, two multi-center double-blind randomized placebo-controlled trials have shown a benefit for steroids in the management of CAP [73,74]. The *Lancet* study randomized hospitalized CAP patients to prednisone 50 mg once daily or placebo for 1 week. The *JAMA* study of severe CAP employed iv methylprednisolone 0.5 mg/kg/12 h for 5 days versus placebo. The primary outcome measures were time to clinical stability and treatment failure, respectively. Steroids showed a statistically significant benefit in each setting in the two studies.

Unfortunately, the story has not been as positive with other agents that have been tried. These include non-steroidal anti-inflammatories, drotrecogin alfa activated and tifacogin (recombinant tissue factor pathway inhibitor) [75].

Prognosis

A number of factors determine the prognosis of CAP including the patient's age and general state of health and whether treatment is given in an outpatient or inpatient setting. The extremes vary from young healthy patients well enough to be treated at home to elderly patients with co-morbid conditions requiring admission to an ICU. Overall, the mortality rate for outpatients is <1%, while for inpatients it can range from 10 to 40% with an overall rate of approximately 14% [76].

Prevention

Fortunately, two vaccines (influenza and pneumococcus) are available to help with the problem of CAP. The influenza vaccine is typically given yearly as the inactivated virus and is quite effective in preventing or attenuating influenza. The pneumococcal vaccine is available as the pneumococcal polysaccharide vaccine 23 and/or as the protein conjugate vaccine (PCV 13). The polysaccharide vaccine contains capsular material from 23 pneumococcal serotypes while the conjugate vaccine has capsular polysaccharide from 13 of the most frequent strains encountered in children and it is linked to an immunogenic protein resulting in production of T-cell-dependent antigens and long-term immunologic memory [77]. Extensive use of this particular vaccine in infants and children has resulted in herd immunity and a reduction in rates of pneumococcal pneumonia [78].

Since the PCV stimulates mucosal immunity thereby preventing colonization and carriage of vaccine pneumococcal serotypes, there is an “opening” created for non-vaccine pneumococcal serotypes to colonize the patient and to potentially cause disease. Use of the PCV7 resulted in a significant reduction in the burden of pneumococcal disease but there was concern that these benefits might be at the cost of an increase in disease caused by non-vaccine serotypes such as 19A [79].

Overall, pneumococcal conjugate vaccines have had a positive effect mediated in part by herd immunity and has resulted in a “greater than 90% decline in pneumococcal disease due to vaccine serotypes” in older children and adults [80,81].

Recommendations of the Advisory Committee on Immunization Practices should be followed for both the influenza and the pneumococcal vaccines [82,83].

Conclusions

Although our understanding of the etiology and pathophysiology of CAP has improved, this infection still remains a significant cause of morbidity and mortality. We need better diagnostic tools to allow rapid identification of etiologic pathogens and potential markers of resistance and we must redouble our efforts to use antimicrobials as expeditiously and judiciously as possible. Further research into adjunctive measures in the management of CAP is necessary as well.

Declaration of interest

LA Mandell has received consulting fees from Bayer, Cempira and Nabriva Therapeutics, and lecture fees from Daiichi Sankyo. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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