ORIGINAL ARTICLE

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality, despite effective therapies. Guidelines for CAP management vary widely in their approach. Resistance of S pneumoniae *to penicillins and other antibiotics has prompted evaluation of the new fluoroquinolones.*

An Update on Community-Acquired Pneumonia in Adults

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INTRODUCTION

Community-acquired pneumonia (CAP) is an infection of pulmonary parenchyma associated with signs and symptoms of a lower respiratory tract infection, not related to recent hospitalization or residence in a long-term care facility, and is associated with a radiographic infiltrate unexplained by other causes.[1] The classical approach to treatment of CAP called for using epidemiologic clues and laboratory testing to identify likely pathogens and basing antimicrobial choices on this information. However, age adjusted mortality rates for influenza and CAP began rising in the late 1970's.[2] This fact, along with ongoing controversies regarding treatment led to the development of several consensus statements. The two best known guidelines in the United States (US) are the American Thoracic Society (ATS) guidelines published in 1993, and the Infectious Diseases Society of America (IDSA) guidelines published in 2000.[1,3] The ATS guidelines called for empirical-based antibiotic choices determined by the patient's age, comorbidity, need for hospitalization, and severity of presentation.[3] The IDSA guidelines allows for pathogen-directed therapy under certain conditions, and incorporates newer antimicrobial medications and more recent resistance data in their treatment recommendations.[1]

EPIDEMIOLOGY

CAP is the sixth leading cause of death in the US, and is the most prevalent fatal infectious disease.[1,4] More than four million cases of CAP occur in the US each year, a rate of 15 per 1,000 people. The annual economic cost was recently estimated to be approximately $23 billion per year.[4] A recent meta-

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analysis reported overall mortality to be 13.7%, ranging from less than 5% in ambulatory patients to over 36% in intensive care unit patients.[5] The elderly are at particular risk of death from pneumonia due to comorbid illnesses, decreased host defenses, aspiration, associated airways disease, and medications which might impair respiratory function (sedatives) or which suppress the immune system.[6-8]

CLINICAL SIGNS AND SYMPTOMS

Patients with CAP can present with various symptoms including, cough, shortness of breath, chest pain, malaise, fever, chills, and sweats.[4,9] Sputum production may or may not be present. Tachypnea is an especially disquieting sign.

Traditional teaching dictated that one can base treatment decisions on whether the presentation was suggestive of a typical organism (high fever, cough, purulent sputum, sudden onset) or an atypical organism (gradual onset, non-productive cough, constitutional symptoms). Today, we realize that these presentations cannot reliably direct treatment decisions.[1,9] In other words, typical pathogens may present atypically, and vice versa. Varying pathogenicity of bacterial strains and differing host responses are possible explanations. Non-classical presentation of CAP is common in the elderly.[10] This presentation may include increased forgetfulness, anorexia, and weakness. With a paucity of classic signs evident, diagnosis may be delayed.

Vital sign abnormalities help to quantify the severity of CAP and help with decisions on whether or not to hospitalize. Pulse oximetry should be obtained on all patients with any abnormality of vital signs. The most common abnormality on physical examination is the presence of adventitial lung sounds. Auscultation of the chest will usually find nonmusical, discontinuous sounds known as crackles or rales. These are best heard with the patient sitting upright and breathing at normal lung volumes. Asking normal patients to breath from residual volume to total lung capacity can result in abnormal findings about 50% of the time.[11]

No combination of signs and symptoms allow one to make a diagnosis of CAP with relative certainty.[12] However, if chest auscultatory findings are absent and the patients vital signs are normal, the likelihood of pneumonia is reduced and further diagnostic work-up is probably unwarranted.

DIAGNOSIS

Chest radiographs are still necessary to make an absolute diagnosis of CAP. A radiographic infiltrate in the proper clinical setting and unexplained by other causes, usually leads to the diagnosis of CAP.[1,4,9] The chest radiograph also quantifies the severity of the pneumonia, and identifies pneumonic complications, such as lung abscess or pleural effusion. Bilateral pleural effusions are independent predictors of short-term mortality in CAP, while other radiographic signs such as multi-lobar infiltrates are not.[13] There are no strict guidelines on when to order a chest radiograph.

Diagnostic work-up may include Gram stain and culture of sputum, blood culture, thoracentesis, and serologic testing. The role of the Gram stain is disputed.[1,3] Material should be obtained from the lower respiratory tract and screened to ensure that there are less than 10 squamous epithelial and greater than 25 polymorphonuclear cells per low power field. The material should be examined by qualified laboratory personnel in a timely fashion. Only about 25% of sputum samples submitted for analysis are of good quality.[14] Even when a sample of good quality is obtained, there is not always concordance with blood culture results. Anaerobic organisms and atypical pathogens may also be missed by a Gram stain.

Sputum culture may reflect colonizing organisms rather then true pathogens. In addition, a negative result does not rule out the presence of a bacterial pathogen. Sputum cultures may be useful when antimicrobial therapy fails and antimicrobial susceptibility of a particular pathogen is required.

Blood cultures are still usually obtained from all hospitalized patients with CAP and are reportedly useful in 11% of patients.[15] The cost-effectiveness of blood cultures has been questioned since they rarely alter the antibiotic regimen.

Delayed reporting and poor specificity adversely affect the useful of many conventional serologic tests. This testing should be considered for those with severe disease, not responding to treatment, or for epidemiologic reasons. In areas of high endemicity, appropriate fungal serologies may need to be considered (e.g., coccidioidomycoses in the Southwest; histoplasmosis in the Mississippi and Ohio valley areas). Newer diagnostic techniques such as polyermase chain reaction (PCR) and other amplification techniques are exciting but their role remains to be determined.

Various severity scales have been proposed to stratify patients by illness severity and to help make decisions on whether hospitalization is warranted.[1] A good scale ideally should take into account the patient's age, comorbidities, vital signs, and laboratory abnormalities.

MICROBIOLOGY

The pathogens associated with CAP can be divided into different categories. Most clinicians categorize them based upon a combination of microbiological identification schemes (i.e., Gram- positive or negative; aerobic or anaerobic), and/or clinical presentation (i.e., "atypical").

Gram-Positive Aerobes. The CAP pathogen that falls under this category is *Streptococcus pneumoniae*. For years, this bacterium has been identified as the most common pathogen involved in CAP.[1,3,4,16,17] In more recent years, concern has risen regarding the susceptibility of *S pneumoniae* to penicillin. Epidemiology and susceptibility studies published in the last few years have indicated a growing number of penicillin-resistant strains of *S pneumoniae*.[18-20] *S pneumoniae* strains are now identified by their penicillin minimum inhibitory concentrations (MICs). A Kirby-Bauer oxacillin disk is usually dropped onto an agar plate containing confluent growth of *S pneumoniae* and if resistance is found, further susceptibility testing by broth dilution is performed.[21] If the oxacillin MIC is ≤ 0.06 µg/mL, the *S pneumoniae* isolate is considered penicillin susceptible; if the MIC is 0.125–1.0 µg/mL, then it is considered to be penicillin-intermediately susceptible (or resistant); an MIC of ≥ 2.0 µg/mL is considered to be penicillin-resistant. These penicillin susceptibility guidelines were set by the National Committee of Clinical Laboratory Standards, and were originally designed to reflect *S pneumoniae* isolates from patients with meningitis, rather than pneumonia.[22] Amoxicillin's susceptibility breakpoints have been changed to the following: susceptible ≤ 2.0 µg/mL; intermediately susceptible 4.0 µg/mL; and resistant ≥ 8.0 µg/mL.

The mechanism of resistance for these *S pneumoniae* strains is not enzyme degradation, (e.g., β-lactamase), but rather an alteration in the target site in the organism's cell wall to which β-lactam antibiotics normally bind, coupled with efflux of the antibiotic molecules.[22] Therefore, penicillin and cephalosporin antibiotics are both affected to varying degrees by this mutation. Other antibiotic classes are also affected by greater resistance to actions, even though they do not work through alternate mechanisms.

At present, a majority of adult populations studied still have penicillin-susceptible *S pneumoniae* strains isolated as pathogens,[23] though the percentage of penicillin-resistant isolates will likely increase. Elderly populations in long-term care facilities are at greater risk of penicillin-intermediate and penicillin-resistant *S pneumoniae* strains as pathogens and colonizers.[24,25]

Gram-Positive Anaerobes. These bacteria are rarely isolated from patients with CAP. Peptostreptococci, *Prevotella* species, and other oral anaerobes are more common in adults who have experienced aspiration pneumonia.[8,26,27]

Gram-Negative Aerobes. Gram-negative aerobes normally associated with CAP in adults are *Haemophilus influenzae* and *Moraxella catarrhalis* (formerly *Neisseria catarrhalis* and *Branhamella catarrhalis*).

Haemophilus influenzae. This coccobacillus is more commonly found as a pathogen in elderly adults (age ≥ 75 years old), primarily those with underlying lung disease, as opposed to young adults.[10,28-30] The incidence of *H influenzae* as the pathogen in adult CAP patients ranges from 2%–15%.[4,9,17,28,29] Resistance to ampicillin and amoxicillin by *H influenzae* due to narrow-spectrum β-lactamases has prompted the use of other antibiotics. At present, nationwide the US has reported an average of 30%–40% of *H influenzae* isolates that are resistant to ampicillin/amoxicillin.[31]

Moraxella catarrhalis. This Gram-negative coccus is an uncommon pathogen in adult CAP, but is associated with other respiratory tract infections such as otitis media, bronchitis, and sinusitis.[32] Nevertheless, *M catarrhalis* may be the causative pathogen in the adult CAP in 5% or less of cases, but is more common in patients with pre-existing lung disease, similar to *H influenzae*.[33-35] β-Lactamase production is more common with *M catarrhalis* than with *H influenzae*; current monitoring studies report approximately ≥ 90% of isolates are β-lactamase positive.[36,37]

Atypical Organisms. These pathogens were originally described as "atypical" because their uncharacteristic clinical presentation in patients who acquired these pathogens as infections.[38]

An interesting finding of patients with infections caused by *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Legionella pneumophila* is that coexisting infection with other bacterial species (e.g., *S pneumoniae*) may often exist.[38,39]

Chlamydia pneumoniae. This pathogen has been reported to be one of the top four causative pathogens of CAP, depending upon the study and the time of year.[1,8,38-41] *C pneumoniae* is an intracellular pathogen and does not have a cell wall. Therefore, antibiotics whose mechanism involves inhibition of cell wall synthesis (e.g., β-lactams, vancomycin) are not effective in killing *Chlamydia* species. Identification can be difficult, requiring fluorescent-antibody staining or some other special staining (e.g., Giemsa, iodine) since *Chlamydia* do not grow on regular media.

Mycoplasma pneumoniae. This is another fastidious pathogen that occurs more commonly in outbreaks, usually during certain seasons of the year, and in areas where people live and work in crowded environments (e.g., university dormitories, military barracks, etc.).[38,42] *Mycoplasma* is another intracellular pathogen, does not have a cell wall, and is difficult to culture. Identification is usually obtained by serologic testing for *Mycoplasma* antigen titers using cold agglutinins.[38,42] Reported incidence of this pathogen in CAP varies, ranging from 2%–30%.[1,43,44]

Legionella pneumophila. *L pneumophila* is an infrequent cause of CAP. It is more often associated with outbreaks, usually contaminating air coolant systems because *Legionella* are hydrophilic.[45] *L pneumophila* also is an intracellular pathogen, without a cell wall and requires PCR antigen testing of urine or some other body fluid for early detection.[45] A special yeast and charcoal growth media is necessary for isolation and growth in the laboratory. Incidence rates of *Legionella* pneumonia have generally been reported in the 1%–5% range,[45,46] although one retrospective study reported a rate of 16%.[47]

PREVENTATIVE THERAPY

Preventative therapy for disease states has come to the forefront of US medicine. In the case of infectious diseases and respiratory pathogens, vaccines that have been available for decades and newly developed vaccines are receiving more acceptance and use as cost-effective therapies to reduce morbidity and mortality.[28,48-50]

The 23-valent pneumococcal vaccine has received a great deal of praise and mention in medical literature as an effective method of preventing *S pneumoniae* infection.[1,28,48,51] Those populations who should receive pneumococcal vaccine include immunocompromised individuals (e.g., spleenectomized, HIV-positive organ transplant recipients, severe cardiovascular and/or pulmonary disease, etc.) and people ≥ 65 years of age.[51] Repeat vaccination for immunocompromised individuals and the elderly is recommended at 5 years.[52] Elderly patients' abilities to mount sufficient pneumococcal antibodies from the 23-valent vaccine is still unclear, with one study finding a sufficient reaction to the vaccine,[53] while another reported an insufficient antibody response.[54] A survey in 1997 of the elderly (age ≥ 65 years) in the US found that only 45% of persons in this age group had received a pneumococcal vaccination.[55] Although the efficacy of repeat pneumococcal vaccination for the elderly has not been studied, recommendations generally call for a similar time-frame as for other individuals requiring repeat vaccination.

Influenza vaccination is also important and may help to prevent severe infectious illness in an elderly population.[1,28,51] Newer therapy modalities may also prove useful by making immunization easier to perform. The influenza neuraminidase-inhibitor, zanamivir nasal spray, which has activity against influenza A and B, and may be used for treatment as well as prophylaxis.[56,57]

A supplement on immunization against pneumococcal disease and influenza in the *American Journal of Health-system Pharmacy,* may prove valuable reading to health-care professionals.[58]

ANTIMICROBIAL THERAPY

Treatment of infectious diseases involves the triad of the patient, the medication, and the microorganisms. These factors must all be considered when choosing when and what antimicrobial therapy should be utilized. In addition, issues like pharmacoeconomics and pathogenic resistance need also to be considered.

If the decision is to prescribe an antimicrobial, then the following factors should be considered to determine which medication(s) is/are most beneficial:

1. Inherent activity against the known or presumed pathogen(s)
2. Slow emergence of resistance
3. Optimal pharmacokinetic and pharmacodynamic characteristics
4. Good penetration to the site of infection and rapid killing
5. Well tolerated (low incidence and severity of adverse effects)
6. History of good clinical response rates

Empirically knowing the susceptibility patterns of microbial pathogens in a clinician's area/region, which antimicrobial cover the particular organism(s), and facts about the patient, such as site of the infection, age, drug allergies, kidney and liver function, help to increase the chances of a successful clinical outcome.

The β-Lactams. This class includes the penicillins, cephalosporins, and carbapenems. These antibiotics kill bacteria by binding to certain proteins within the bacteria's cell wall that will eventually lead to poor structure and lysis of the cell.[59]

Penicillins. The most common medications in this group used in treating CAP are listed in Table 1. They are classified based upon their activity against certain bacteria.

In addition, β-lactamase inhibitors that have similar chemical structures to the β-lactams are com-

TABLE 1

Penicillin G/Penicillin V*

- Losing activity against *S pneumoniae* but still effective against most clinical isolates
- Not effective against the "atypical" pathogens
- *H influenzae* and *M catarrhalis* are often resistant
- Not effective against most Gram-negative bacteria (e.g., *Klebsiella pneumoniae*)
- Majority of anaerobic Gram-positives are still susceptible

Advantages

— Less expensive than many other antimicrobials for CAP

— Still effective for most *S pneumoniae* isolates depending on geographic location

— Available in intravenous or oral formulations

Disadvantages

— Ineffective for most *M catarrhalis* and *H influenzae* isolates

— Many respiratory pathogens are resistant (e.g., *M pneumoniae*, *C pneumoniae*)

— Dosing frequency decreases compliance

— Adverse effects (diarrhea) and allergies

— Oral medications tend to have poor activity against *Enterobacteriaceae* and *M catarrhalis*

*Adapted from Wright AJ. The penicillins. *Mayo Clin Proc.* 1999;74:290-307.

bined with some of the penicillins to serve as "suicide-inhibitors" against certain β-lactamases and restore some of the parent penicillin's spectrum. The currently licensed β-lactamase inhibitors include clavulanic acid, sulbactam, and tazobactam. Interestingly, these β-lactamase inhibitors can also increase the production of the β-lactamase enzyme by the bacteria to variable degrees.[60-62]

Penicillin G/Penicillin V. These penicillins are gradually losing their activity against *S pneumoniae* but remain effective against most clinical isolates. Higher doses of penicillins may be just as effective at eradicating the intermediately susceptible strains of *S pneumoniae* (MIC of 0.125–1.0 μg/mL). They are not effective against the "atypical" pathogens like *Chlamydia* or *Mycoplasma*. Also, *H influenzae* and *M catarrhalis* are typically resistant. However, the majority of anaerobic Gram-positive bacteria (e.g., peptostreptococci) are still susceptible. See Table 1 for the advantages and disadvantages of these antibiotics.

Ampicillin/Amoxicillin. These medications are also losing their activity against the newer penicillin highly-resistant *S pneumoniae* strains, but may be just as effective against the intermediately-susceptible strains of *S pneumoniae* if higher doses can be used. Atypical pathogens are still resistant to these and other β-lactams. Also, many strains of *H influenzae* and *M catarrhalis* are resistant due to narrow-spectrum β-lactamases. The addition of β-lactamase inhibitors (clavulanic acid with amoxicillin; sulbactam with ampicillin) has returned some of the spectrum that was lost by some β-lactamase producing strains of these bacteria. Most oral anaerobes like peptostreptococci still tend to be susceptible to ampicillin and amoxicillin. Tables 2 and 3 contain a list of advantages and disadvantages for these antibiotics.

Cephalosporins. This section will focus on the oral cephalosporins. These β-lactams are also not effective against the "atypical" pathogens *Mycoplasma, Chlamydia, Legionella*. These antibiotics can be divided into two categories: the first generation, and the extended-spectrum group. The first generation includes cephalexin, cephradine, and cefadroxil. This group typically has activity against most *S pneumoniae* strains, but their activity against *H influenzae* and *M catarrhalis* is unreliable (i.e., higher MICs) as the extended-spectrum cephalosporins.[63-65]

The oral extended-spectrum cephalosporins include cefaclor, loracarbef, cefuroxime axetil, cefixime, cefprozil, cefpodoxime proxetil, ceftibuten, and cefdinir. These medications are dosed less frequently than their first generation counterparts, and their activity against *H influenzae* and *M catarrhalis* is also more reliable.[63-66]

The extended-spectrum group has variable activity against *S pneumoniae* depending on the strain's susceptibility to penicillin. Cefpodoxime, cefuroxime, and cefprozil seem to have better activity against the penicillin-intermediately susceptible strains than the other other oral cephalosporins, but this can vary from location to location.[23,67] See Table 4 for a list of the oral cephalosporins currently approved in the US and their general advantages and disadvantages.

The parenteral cephalosporins, cefotaxime and ceftriaxone, have been advocated as being reliable against penicillin-intermediate *S pneumoniae* infections, including CAP.[68] Cefepime may also retain its activity against the penicillin-intermediate strains of *S pneumoniae*,[28] but ceftizoxime apparently has a significant loss of activity against these strains.[68]

TABLE 2

Advantages and Disadvantages of Ampicillin/Amoxicillin in treating CAP*

Advantages

- Less expensive
- Still effective for most *S pneumoniae* and possibly *H influenzae*
- Available in intravenous or oral formulations (ampicillin)

Disadvantages

- Many respiratory pathogens are resistant
- Dosing frequency decreases compliance
- Adverse effects (diarrhea) and allergies

*Adapted from Wright AJ. The penicillins. *Mayo Clin Proc.* 1999;74:290-307.

TABLE 3

Advantages and Disadvantages of Amoxicillin/Clavulanate in treating CAP*

Advantages

- Improved activity against *H influenzae* and *M catarrhalis*
  - Still not effective against the "atypical" pathogens
- New dosage strength helps improve compliance

Disadvantages

- Incidence of diarrhea is increased due to clavulanate component
- May induce greater amount of β-lactamases to be produced by some bacteria
- Not currently available intravenous (use ampicillin/sulbactam instead?)

*Adapted from Wright AJ. The penicillins. *Mayo Clin Proc.* 1999;74:290-307; Weber DA, Sanders CC. Diverse potential of β-lactamase inhibitors to induce class I enzymes. *Antimicrob Agents Chemother.* 1990;34:156-158; and Sanders CC, Sanders WE Jr. Type I β-lactamases of gram-negative bacteria: interactions with β-lactam antibiotics. *J Infect Dis.* 1986;154:792-800.

Macrolides. These antimicrobials are considered to be bacteriostatic and act by binding to the 50s ribosomal subunit, crippling bacterial replication.[69] Erythromycin, dirithromycin, azithromycin, and clarithromycin fall into this antibiotic group.

Macrolide antibiotics are also losing their activity against the penicillin-intermediate and resistant strains of *S pneumoniae*.[70] However, macrolides are normally active against the "atypical" pathogens. *H influenzae* is not typically susceptible to erythromycin, but may be more susceptible to azithromycin and in some cases to the hydroxy-metabolite of clarithromycin.[69] Since it is clarithromycin's hydroxy-metabolite that has activity against *H influenzae*, clarithromycin's degree of anti-*H influenzae* activity in vivo is dependent upon the

TABLE 4

Oral Cephalosporins*

1st Generation

- Cephalexin, cephradine, and cefadroxil

Extended spectrum

- Cefaclor, loracarbef, cefuroxime axetil, cefixime, cefprozil, cefpodoxime proxetil, ceftibuten, and cefdinir

General Properties

- Losing activity against *S pneumoniae* but still effective against most clinical isolates
  - Most are effective against penicillin-intermediate *S pneumoniae*, but still not effective against highly resistant isolates
  - Ceftriaxone and cefotaxime are still very effective against penicillin-intermediate *S pneumoniae*
- Not effective against the "atypical" pathogens
- *H influenzae* and *M catarrhalis* are usually susceptible
- Effective against most Gram-negative bacteria (e.g., *Klebsiella*)

Cephalosporin Advantages

- Older antimicrobials are less expensive
- Still effective for most *S pneumoniae*, *H influenzae*, and *M catarrhalis*
- Available in parenteral and oral dosage forms, including suspensions
- Newer medications have daily or twice-daily dosing

Cephalosporin Disadvantages

- Atypical pathogens are still resistant
- Older antimicrobials dosing frequency decreases compliance
- Allergies to β-lactams
- Newer medications tend to be relatively expensive

*Adapted from references 63-68.

TABLE 5

Macrolides/Azalides*

General Properties

- Losing activity against *S pneumoniae* but still effective against most clinical isolates
- Effective against the "atypical" pathogens
- *H influenzae* and *M catarrhalis* are not usually sensitive based upon achievable plasma concentrations, but patients do tend to respond clinically to clarithromycin or azithromycin
- Not effective against Gram-negative CAP bacteria or anaerobes

Advantages

- Erythromycin is less expensive than many newer antibiotics
- Still effective for most *S pneumoniae* and possibly *H influenzae*
- Available in parenteral or oral forms (erythromycin & azithromycin)
- New medications are dosed daily or twice-daily

Disadvantages

- More respiratory pathogens (*S pneumoniae*, *H influenzae*) are becoming resistant
- Adverse effects (GI upset) and drug interactions (p450) with clarithromycin and erythromycin
- New antimicrobials are more expensive

GI, gastrointestinal.

*Adapted from references 69-71.

amount of hydroxy-clarithromycin formed from hepatic oxidative metabolism. In general, in vitro activity of azithromycin and clarithromycin on *H influenzae*, is decreasing.[70] Macrolides are also not active against anaerobes. Table 5 lists this class's general advantages and disadvantages.

Ketides are a new antimicrobial class, closely related to the macrolides and azalides. Telithromycin is one example of this new class and is expected to be approved within the next one or two years in the US.

Tetracyclines. Tetracyclines act by binding to the 30s ribosomal subunit, interfering with bacterial replication.[71] They are also losing their activity against the penicillin-resistant *S pneumoniae* strains, and their activity against *H influenzae* and *M catarrhalis* is also variable. However, doxycycline and minocycline tend to be more active than the parent compound, tetracycline.[72,73] These antimicrobials are also active against "atypical" pathogens, but have no activity against anaerobes.[72,73] Their advantages and disadvantages are displayed in Table 6.

TABLE 6

Tetracyclines*

General Properties

- Losing activity against *S pneumoniae* but still effective against most clinical isolates
- Effective against the "atypical" pathogens
- Not effective against most Gram-negative bacteria or anaerobes
- *H influenzae* and *M catarrhalis* are variably sensitive
  - Better for doxycycline and minocycline

Advantages

- Relatively inexpensive compared to newer antibiotics for CAP
- Still effective for most *S pneumoniae* and possibly *H influenzae* and *M catarrhalis*
- Available in parenteral and oral dosage forms (doxycycline and minocycline)
- Doxycycline and minocycline are dosed daily or twice-daily

Disadvantages

- More respiratory pathogens are becoming resistant
- Contraindications (children, pregnancy) and interactions (polyvalent cations, e.g., calcium, magnesium, iron, etc.)

*Adapted from references 71-73.

Fluoroquinolones. Fluoroquinolones are bactericidal antimicrobials and inhibit enzymes involved in the supercoiling of susceptible bacterias' DNA.[74] The latest fluoroquinolones include levofloxacin, sparfloxacin, gatifloxacin, and moxifloxacin. In June 1999, shortly after strong warnings and restrictions in the European market, the US Food and Drug Administration (FDA) sent letters to physicians and pharmacists that warned of possible hepatotoxicity with trovafloxacin. The FDA restricted the use of trovafloxacin to inpatient (hospital or long-term care facility) use only for nosocomial pneumonia, community-acquired pneumonia, complicated intraabdominal infections, gynecologic and pelvic infection, or complicated skin and skin structure infections (including diabetic foot infections). Also in 1999, the makers of grepafloxacin voluntarily removed this antimicrobial from the market due to reports of cardiotoxicity.

Most of these newer fluoroquinolones have better activity against Gram-positive bacteria compared to their older counterparts. Another advantage to the fluoroquinolones is they are unaffected by the current mechanisms of resistance that are found in penicillin-resistant strains of *S pneumoniae*.[75] Their activity against atypical pathogens varies depending upon the individual fluoroquinolone. *H influenzae* and *M catarrhalis* strains display very low MICs to all of the fluoroquinolones that are currently marketed or in development.[76] Their activity against oral anaerobic pathogens is often poor, but newer fluoroquinolones like moxifloxacin may have appreciable activity against these bacteria.[78]

Moxifloxacin, gatifloxacin, and the soon-to-be-marketed gemifloxacin have good-to-excellent in vitro activity against all of the major community bacterial and atypical pathogens normally encountered in CAP, and can be dosed once daily.[76,78-80] See Table 7 for a summary of the fluoroquinolones that may be used in treating CAP.

CAP TREATMENT GUIDELINES

The British Thoracic Society (BTS), the ATS, the IDSA, the Canadian Infectious Diseases Society, and the Canadian Thoracic Society have all published guidelines regarding the management of CAP in the last seven years, and will likely update these guidelines in the months or years to come.[1,3,81,82] These guidelines all differ in their management recommendations. This is not surprising, since data supporting decisions in infectious diseases are often unreliable due to confounding factors during clinical studies (age, comorbidity, antimicrobial dosing, immune status, and function, etc.) and patient populations which are too small to detect an appreciable difference between treatment groups. Indeed, infectious diseases are often short, self-limiting disease-states in which the outcome is nominal: cure or death. This fact also complicates CAP healthcare economic studies, unlike long-term illnesses such as diabetes mellitus or hypertension. Publication of various CAP management guidelines has also increased commentary about their merits and detriments.[83-86] A visual example comparing how the three major guidelines differ in terms of treatment can be seen in Table 8.

DISCUSSION

Despite our best efforts, CAP is still a leading cause of morbidity and mortality in the world. Imperfections of clinical studies and the ambiguity of treatment regimens has led to confusion on how to diagnose and most effectively treat CAP. Often times, the "better treatment" rests in the perspective of who truly benefits, i.e., the patient, the health-care provider(s), the health system, or the ultimate payor. Coupled with therapeutic options are the routine pressures that physicians face, particularly from health-care system managers and the patients, themselves.[87]

Another product of the current US health-care system is the use of treatment pathways for common disease states/problems. Pneumonia pathways are prevalent in many institutional and outpatient

TABLE 7

Fluoroquinolones*

Older	Newer	Investigational
Ciprofloxacin	Levofloxacin	Sitafloxacin
Ofloxacin	Sparfloxacin	Gemifloxacin
	Trovafloxacin	
	Moxifloxacin	
	Gatifloxacin	

General Properties

- Activity against *S pneumoniae* is fair to excellent
- Variably effective against the "atypical" pathogens but generally susceptible
- *H influenzae* and *M catarrhalis* are sensitive
- Effective against most Gram-negative bacteria
- Most fluoroquinolones are not effective against anaerobes
- Some are available in parenteral and oral dosage forms

Fluoroquinolone Advantages

- Improved bioavailability with newer medications compared to older quinolones
- Reduced drug interaction profile with newer antimicrobials
- Improved microbiologic activity, even against penicillin-resistant *S pneumoniae*
- Improved pharmacokinetics, allowing for once-daily dosing with newer medications
- Potent oral dosage forms for older and newer antimicrobials

Fluoroquinolone Disadvantages

- Increased acquisition cost compared to some other antimicrobials used for CAP
- New and different adverse effects for each medications

*Adapted from references 74-80.

TABLE 8

Community-Acquired Pneumonia Guidelines Empiric Antibiotic Therapy for Outpatients: A Comparison*

British Thoracic Society	Amoxicillin or Penicillin Alternative: Erythromycin
American Thoracic Society	
• < 60 years old, no comorbidities	Macrolide or Tetracycline
• > 60 years old or comorbidity	Cephalosporin, or Sulfamethoxazole/ trimethoprim, or β-lactam/β-lactamase inhibitor ± a macrolide
Infectious Diseases Society of America	Macrolide, or Fluoroquinolone, or Doxycycline
Canadian Infectious Diseases Society/ Canadian Thoracic Society	
• outpatient, no comorbidities	Macrolide or Doxycycline
• chronic obstructive lung disease, no antibiotics or steroids	Newer macrolide or Doxycycline
• chronic obstructive lung disease + other risk factors	New Fluoroquinolone, or extended spectrum Cephalosporin + Macrolide, or β-lactam/β-lactamase inhibitor ± macrolide

*Information compiled from references 1, 81-86.

health-systems due to the diagnosis being common and placing a large economic drain on health-care the economy. While other disease states have well-designed, multicentered studies with large patient populations to determine significant treatment effectiveness, studies involving infectious diseases suffer from problems already mentioned: different treatments, different patient populations, inability to capture the human immune response, and low patient population numbers. National guidelines like those offered by the ATS or IDSA also suffer from poor microbiologic epidemiology data at the local level. One consequence of these pathways is the continued use of a few core antimicrobials, which could cause severe environmental pressure to allow greater bacterial resistance to evolve.[87]

An equal problem to over prescribing and overuse of antibiotics is under dosing them to the point that only the very susceptible subpopulations of bacteria are eradicated, leaving behind the heartier, more resistant strains. Therefore, under dosing a patient may lead to an even greater problem (i.e., bacterial resistant subpopulation regrowth) than overdosing.

CONCLUSION

Management of CAP patients continues to provide new challenges as time, healthcare costs, and increasing pathogen resistance force new guidelines to be developed, and old guidelines to be revised. To keep CAP morbidity and mortality outcomes low, requires continued revisitation of the subject and updating of every clinician's personal knowledge base of the effectiveness of various management strategies. Withholding antibiotics from patients without confirmed respiratory tract infections is difficult, but should be done to preserve our antimicrobial armamentarium for patients who truly need them. Proper diagnosis is key in decision-making of when to treat a patient for CAP, as well as which therapy to use. Empiric therapy should be based on local susceptibility data, in addition to factors such as possible adverse effects, drug interactions, and comorbidity. Increased resistance of *S pneumoniae* will require better use of preventive measures and newer antimicrobial medications like the fluoroquinolones to better ensure clinical success and decrease the chance for regrowth of more resistant pathogens. **CT**

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