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Evaluation and Management of Community and Hospital-Acquired Pneumonia for the Primary Care Providers

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Abstract

Context: The incidence and prevalence of both community and hospital acquired pneumonia has remained relatively constant over the last several years. This paper reviews the current treatment guidelines as well as highlight new antibiotics that have recently become available for use as well.

Evidence Acquisition: We evaluated guidelines provided by the infectious diseases society of America (IDSA) for the management of community-acquired pneumonia (CAP), published in 2007, and hospital-acquired pneumonia (HAP) published in 2005. We also reviewed literature published from January 2005 to December 2015 using PubMed to evaluate how the treatment of these types of pneumonia have evolved.

Results: Through our literature review, it was found that despite the advances made in the diagnosis and management of both CAP and HAP, it remains a significant challenge to diagnose and often treat. Two new IV antibiotics (tigecycline and ceftaroline) introduced for the management of CAP and telavancin was approved for HAP. Moreover, treatment of these two types of pneumonia often involves being creative with antimicrobial therapy due to the increasing multi-drug resistance.

Conclusions: CAP/HAP remains one of the leading causes of morbidity and mortality in the world. Bacterial resistance is increasing and adds to the difficulty in treating these patients. Newer drugs are available but should be used judiciously and in the right setting.

Keywords: Pneumonia, Bacterial Resistance, Antimicrobial Therapy

1. Context

Pneumonia is still one of the leading causes of hospitalizations in the United States with approximately 3 million people infected each year. Along with influenza, pneumonia is considered the eighth leading cause of death and is the most common hospital-acquired infection. The emergence of multidrug-resistant pathogens presents an ongoing challenge for clinicians to choose the most appropriate antibiotic regimen. Although there have been advances in the general understanding, diagnosis, and treatment of pneumonia, it still is a significant clinical issue that requires careful evaluation by the healthcare community. Regarding epidemiology, community-acquired pneumonia (CAP) is one of the most common infectious diseases encountered by health care workers, both in the outpatient as well as inpatient setting. The pathogens that cause community-acquired pneumonia, as well as nosocomial pneumonia, have not changed much over the years, but relative positions of importance differ regionally and have changed. Clinicians need to be aware of the major organisms causing pneumonia so that empiric therapy is started with the most cost-effective and appropriate antibiotic.

In the 1970s, the most common organisms for CAP were *Streptococcus pneumonia*, *Mycoplasma pneumonia*, *Haemophilus influenza*, and *Staphylococcus aureus*. Although *S. pneumonia* is acknowledged as the most common cause of CAP, frequency has declined due to the extensive use of pneumococcal vaccinations. Other organisms such as viruses, fungi, mycobacterium, and Pneumocystis all play a significant role as well. Because a pathogen is usually not identified in up to 50% of CAP cases, the etiology of pneumonia in the community (EPIC) study was conducted by the CDC. They collected specimens from 2010 to 2012 among five different medical institutions to detect a particular source for various cases of CAP. It was discovered that viruses were a source in 27% of patients with CAP and bacteria comprised of 14% of instances. Human rhinovirus (HRV) was the most commonly detected virus followed by Influenza A. Human metapneumovirus, respiratory syncytial virus (RSV), parainfluenza virus, coronavirus, and adenovirus was found all together in 13% of cases. *S. pneumoniae* was the most common bacterium detected and caused approximately fives times more hospitalizations in the older population (> 65 years of age) ver-

sus younger adults. *M. pneumonia*, *Legionella pneumophila*, and *Chlamydophila pneumoniae* is found in 4% of patients (1).

The annual number of CAP cases reported in the United States is between 4 to 5 million per year with approximately 25% of these cases resulting in hospitalizations (2).

Hospital-acquired pneumonia (HAP) usually develops within 48 hours of hospital admission. HAP also encompasses patients with postoperative pneumonia, and ventilator-associated pneumonia (VAP), Most hospital-acquired pneumonia are primarily non-bacteremic with the majority related to aspiration. Most appear to reflect organisms, which have colonized the upper respiratory tract. Some sites of respiratory tract usually contain bacteria, while others are sterile. *S. pneumonia*, *H. influenza*, and methicillin-sensitive *S. aureus* are the most commonly identified bacteria for HAP when pneumonia develops within seven days of inpatient admission. During longer periods of hospitalization or intubation, *Pseudomonas* and MRSA and other antibiotic-resistant pathogens become a concern. Hospital-acquired pneumonia has a high mortality of up to 20% in community hospitals and as high as 50% in teaching hospitals although one-third is directly attributable to pneumonia itself. Bacteremia commonly occurs in nosocomial pneumonia in the range of 2% to 6%, which increases the mortality threefold. Mortality is related to the organism causing nosocomial pneumonia, i.e., Gram-negative organisms cause approximately a mortality of 50% and Gram-positive organisms approximately 5% to 24 %. Organisms like *Pseudomonas aeruginosa* have mortalities ranging up to 70% to 80% (2).

2. Evidence Acquisition

Guidelines by the infectious diseases society of America (IDSA) for the management of community-acquired pneumonia (CAP) published in 2007 and the 2005 guidelines for hospital-acquired pneumonia (HAP) were evaluated and summarized for the current standards of management of these disease states. We then used a medical database (PubMed) to review literature published from January 2005 to December 2015 to evaluate how the nature of CAP and HAP have changed regarding increasing multidrug-resistant pathogens, and consequently, how treatment regimens have altered as well.

3. Results

3.1. Microbiology

S. pneumonia is typically the most identified in cases of CAP. Other pathogens, however, also play important roles depending on specific locations and patient populations (Table 1).

It is important to note that up to 50% of patients presenting with CAP do not have a particular pathogen identified.

3.2. Typical Pneumonias

Typical microorganisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, Psittacosis, Q jenei, and *Francisella tularensis*. Atypical types of pneumonia commonly present as community-acquired pneumonia and need to be considered diagnostically and therapeutically. The organisms are most likely to cause atypical pneumonia are mentioned above. Recognition of atypical pneumonia is necessary because of the relative significance in causing community-acquired pneumonia and because the therapeutic approach is adjusted accordingly. With the exception of aspiration pneumonia, the presence of multiple atypical pathogens of mixed typical and atypical.

3.3. Clinical Presentations of Typical and Atypical Pneumonia

A. Typical pneumonia: These patients usually have pneumonia that has an abrupt onset. They have minimal extrapulmonary symptoms. They appear to be toxic with leukocytosis, productive cough, and purulent sputum. The chest exam and chest X-ray are usually well correlated.

B. Atypical pneumonia: These patients often present with a gradual onset of symptoms, which are moderate in intensity. The extrapulmonary symptoms are present; however, the patient is usually not toxic. Leukocytosis is not common. The cough appears to be dry with clear mucoid sputum. Chest X-ray and the chest examination do not correlate.

The occurrence of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, in cases of CAP, is estimated to be at least 20% of instances of different populations studied but with significant variation in frequency of each pathogen depending on the site of care (4).

Recommendation for treatment of "atypical pathogens" with regards to these three pathogens includes using macrolides, fluoroquinolones, or tetracyclines. B-Lactams have little to no activity against these atypical microbes. According to some randomized trials and study reviews, however, there was no compelling evidence to show clinical improvement in patients treated with antibiotics for atypical pneumonia with exception to patients infected by *Legionnaires pneumophila* (5).

Table 1. Risk Factors for Specific Bacteria Causing Community-Acquired Pneumonia (3)

Patient Condition/History	Associated Organisms
Alcoholism	*S. pneumonia*, *M. tuberculosis*, oral anaerobes, *K. pneumonia*
Chronic obstructive lung disease (COPD)	*S. pneumoniae*, *H. influenza*, *M. catarrhalis*, *Legionella* sp.
Exposure to bat/bird droppings, construction sites, caves	*Histoplasma capsulatum*
Exposure to birds	*Chlamydia psttiaci*
Exposure to rabbits	*Francisella tularenis*
HIV infection	*S. pneumoniae*, *M. tuberculosis*, *Pneumocystis jiroveci*, CMV, *Cryptococcus* spp., *Histoplasma* spp., *Coccidiodes* spp.
Travel to desert/southwest US	*Coccidioides* spp., *Hantavirus*
Exposure to farm	*Coxiella burnetii*, *Aspergillus* spp.
IV drug User	*S. aureus*, anaerobes, *M tuberculosis*, *S. pneumoniae*
Neutropenia	*Aspergillus*, *Zygomycetes*

3.4. Laboratory Evaluation

Lab studies are useful, and workup includes:

1. CBC and differential.
2. Liver function tests.
3. Sputum Gram's stain and culture.
4. Blood cultures.
5. Serologies for unusual, atypical pathogens such as Q fever, Psittacosis, *Legionella*, *Mycoplasma pneumoniae*.
6. Specific diagnostic tests, including urine antigen.
7. Immunofluorescent assay.
8. Chest X-ray.
9. Bronchoscopy.

3.5. Update on the Treatment of Community-Acquired Pneumonia and Nosocomial Pneumonia

The rationale for early empiric treatment in community-acquired pneumonia is based on the fact that 50% of all patients have an unknown etiology. Due to this, there is a delayed therapy, which increases the complications and length of stay in the hospital. Also, 3 to 14 hours often passes before the first dose in the hospital. Therefore, the administration of empiric parenteral antibiotics is imperative as soon as possible. Therefore, administration of antibiotics should occur before admission at the site of diagnosis and usually within three hours of assessment.

Choosing an empiric antibiotic for community-acquired requires the following principles:

1. Broad-spectrum coverage of most common community-acquired pathogens.
2. The parenteral route for hospitalized patients.
3. Safety and tolerability.
4. Dosing frequency.
5. Ease of administration.
6. Total cost.

The management of CAP is highly dependent on the evaluation of its severity. Prognostic models such as the pneumonia severity index (PSI) and the CURB-65 Score are useful to determine the site of care. Small PSI is a clinical tool used to predict mortality in adult patients presenting with CAP. CURB-65 Severity Score estimates mortality in patients with CAP to determine whether they should be treated as outpatient or inpatient (Table 2) (6). Patients who fall in the very low to low risk group, for the most part, can be treated as an outpatient with oral antibiotics or parenteral antibiotics followed by oral antibiotics. Those that fall in the moderate to the high-risk group usually, should be addressed as an inpatient with IV antibiotics.

The infectious disease society of America has made new recommendations for the treatment of community-acquired pneumonia that include the following principles.

1. It is increasingly important to distinguish Pneumococcal pneumonia from other pneumonia by Gram's stain and clinical presentation.

2. The sputum Gram's stain and cultures are performed on all patients with suspected Pneumococcal pneumonia.

3. Susceptibility studies are critical for both the treatment and the local epidemiological studies.

4. Judicious use of empiric regimen and attempts to use specific therapy to contain the problem of antibiotic-resistant respiratory infections are important.

Most CAP cases still rely on empirical antibiotic treatment as the initial step in therapy due to the absence of more rapid and accurate identification of a pathogenic source. The IDSA recommendations are provided in Table 3 with regards to particular patient characteristics (4).

Table 2. CURB-65 Severity Scores for CAP

Clinical Factors		Points
Confusion		1
Blood urea nitrogen >20 mg/dL		1
Respiratory rate > 30 breaths/min		1
Systolic blood pressure < 90 mmHg or diastole < 60		1
Age > 65 y		1
Total Points		
CURB-65 score	**Deaths, %[a]**	**Recommendations[b]**
0	0.6	Low risk; consider home treatment
1	2.7	Low risk; consider home treatment
2	6.8	Admit to ward
3	14	Severe: hospitalize and consider ICU
4 or 5	27.8	Severe: hospitalize and consider ICU

[a] Data are weighted averages from validation studies.
[b] Recommendation consistent with British Thoracic Society Guidelines. Clinical judgment may overrule recommendations.

Table 3. Initial Empirical Antibiotic Therapy for Suspected Bacterial CAP

Patient Variable	Treatment Option
Outpatient	
Previously healthy[a]	Macrolide OR doxycycline
Comorbidities[b]	Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin OR B-Lactam (high dose amoxicillin (1 gm TID) or amoxicillin-clavulanate, plus a macrolide. Alternative B-lactams are ceftriaxone, cefpodoxime, cefuroxime
In Regions With a 25% or Higher Rate of Infection With High-Level (MIC > 16 mcg.mL) Macrolide-Resistant *S.pneumoniae*	
Inpatient	
Medical ward	Respiratory fluoroquinolones OR B-Lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem for selected patients) plus a macrolide (doxycycline is an alternative to macrolide)
Intensive care unit (ICU)	B-Lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) + either azithromycin or a respiratory fluoroquinolone, Penicillin allergic: Respiratory fluoroquinolones and aztreonam
Special concerns	
Pseudomonas infection	Antipseudomonal B-lactam (cefepime, imipenem, meropenem, piperacillin-tazobactam) + ciprofloxacin OR levofloxacin or B-lactam + an aminoglycoside and azithromycin OR B-lactam + an anti-pneumococcal fluoroquinolone
CA- MRSA is a consideration	Add linezolid or vancomycin

[a] No recent antibiotic therapy within previous three months, and no risk for drug-resistant *S. pneumonia*.
[b] COPD, diabetes, chronic heart, liver lung, or renal disease, malignancy, alcoholism, asplenic patients and immunocompromised patients and or use of antimicrobials within last 3 months.

3.6. Antibiotic Resistance

Due to the emergence of antibiotic resistance among commonly used antibiotics for CAP, it is important for physicians to tailor their therapy with local hospital antibiograms in mind. Drug-resistant *S. pneumoniae* (DSRP) has been identified in cases with increasing resistance to macrolides (7). DSRP in association with CAP, however, has not been well documented. B-lactam resistance has been documented but can still successfully be used to treat cases associated DSRP when the appropriate B-lactam and dose is used.

3.7. New Antibiotics for Treatment of CAP

Two intravenous antibiotics were approved by the food and drug administration (FDA) for the treatment of CAP since the IDSA/ATS guidelines was published in 2007. These antibiotics include tigecycline and ceftaroline fosamil.

Tigecycline, a glycylcycline antibiotic, was introduced in 2009 with indications for CAP caused by *S. pneumoniae* (penicillin-susceptible) including cases with concurrent bacteremia, *H influenza* (beta-lactamase-negative isolates), and *Legionella pneumophila*. One study concluded that tigecycline was as similar in cure rates compared to levofloxacin in hospitalized patients being treated for CAP (8). Tigecycline does, however, carry a U.S. boxed warning for an increase in all-cause mortality compared with comparator antibiotics in a meta-analysis of Phase 3 and four clinical trials. Deaths were usually a result of worsening infection, comorbidities or underlying complication of infections (9) adverse events such as gastrointestinal side effects have also been noted with use of tigecycline (10).

Ceftaroline fosamil is a fifth generation cephalosporin that was approved in 2010 by the FDA for treating adult patients with CAP caused by *S. pneumoniae* including cases with concurrent bacteremia, *S. aureus* (methicillin-susceptible isolates only), *K. pneumonia*, *K. oxytoca* and *H. influenza*. Although ceftaroline does have in-vitro activity against MRSA, there is no clinical evidence to support its use for MRSA pneumonia (10).

Also, vaccinations for certain groups is of vital importance to reduce the incidence of community-acquired pneumonia. Such groups would include the elderly, resident of long-term nursing homes, chronic underlying heart or lung disease, immunosuppressive transplant recipients, AIDS patients, diabetics, and chronic renal dysfunction patients. Groups that should be considered for vaccinations also include health care workers, employees of chronic care facilities, and household contacts of persons in high-risk groups. Table 4 present immunization recommendations by the IDSA for prevention of CAP.

3.8. Nosocomial Pneumonia

The workup for nosocomial pneumonia includes the following:

1. Obtain cultures for diagnosis, including sputum, blood, urine, and fluids that may be present.

-It is recommended by current guidelines that Gram stains of bronchoalveolar lavage (BAL) or endotracheal aspirates be used to guide initial antibiotic treatment (11).

2. Evaluate unique risk factors, including prior antibiotic exposures in the patient, including oral regimens, previous infections, known colonization in the patient, immunocompromised state versus immunocompetent state, devitalized tissue such as mediastinitis and empyema.

3. Antibiotics as per IDSA/ATS guidelines is summarized in Tables 5 and 6 (11):

IDSA/ATS guidelines currently do not recommend combination therapy for HAP or VAP associated with *P. aeruginosa*. This is based on a study, which compared imipenem monotherapy to imipenem in combination with netilmicin for nosocomial pneumonia, sepsis and severe peritonitis (2, 11). Guidelines instead recommend a maximum five days of treatment with an aminoglycoside. Combination therapy can be used if organism sensitivity is unknown until it is identified (11).

3.9. New Antibiotics for Treatment of HAP

Telavancin is a lipoglycopeptide that received approval in 2013 by the FDA for the treatment of Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by *S. aureus*. Telavancin was evaluated and compared with vancomycin in two clinical trials where it was concluded that mortality rates were comparable between each antibiotic among patients presumed to have HAPB/VAPB caused by *S. aureus*. Patients with pre-existing renal problems, however, had higher mortality rates when receiving telavancin versus vancomycin (12).

3.10. De-Escalation of Therapy

If clinical improvement occurs through chest X-ray findings and white blood cell count, total treatment duration in responders can be completed by seven days. This short duration of treatment recommendation is based on studies that found shorter treatment courses to be as efficient as extended therapies (13). Patients with *P aeruginosa* VAP require a longer length of treatment per guidelines (11, 14).

Preventions of nosocomial pneumonia include several infectious control measures, including:

1. Environmental control such as hand washing, equipment care, and decontamination.

2. Minimal use of antibiotics, especially broad-spectrum antibiotics.

3. Evaluate recommendations, i.e., changing the tube on the ventilator every 24 hours.

4. There is some data that is present regarding endotracheal antibiotics, which help to decrease pneumonia, but emerging resistance has been associated with this route of antibiotic therapy.

5. Selective digestive decontamination, which is the application of topical non-absorbable antibiotics through the gastrointestinal tract, has been shown to reduce incidents of pneumonia in severely ill patients.

6. Immunoprophylaxis: This modality of treatment which will include vaccinations for organisms such as Pseudomonas, etc.

4. Conclusions

Current IDSA treatment guidelines for both CAP and HAP remain helpful in guiding clinicians on how to treat

Table 4. Vaccine Recommendations for Prevention of CAP (4)

	Pneumococcal Polysaccharide Vaccine	Inactivated Influenza Vaccine	Live Attenuated Influenza Vaccine
Route of administration	IM injection	IM injection	Intranasal
Recommended group	> 65 years of age; high risk 2 - 64 years of age; Current smokers	> 50 years of age; high risk six months - 49 years if age; healthcare, providers; 6 to 23 months of age	Healthy 5 - 49 years of age including health care providers and household contacts of high-risk contacts
Specific high-risk indications for vaccination	Chronic cardiovascular, pulmonary, renal, or liver disease; diabetes mellitus; alcoholism; Asplenia; cerebrospinal fluid leaks; immunocompromising onditions/medications -; Native Americans/Alaska natives; long-term care, residents	Chronic cardiovascular/pulmonary disease (asthma); chronic metabolic disease (diabetes mellitus); renal dysfunction; hemoglobinopathies; immunocompromising conditions/medications -; pregnancy; long-term care, residents; aspirin therapy < 18 years of age	Avoid in high riskpatients

Table 5. Initial Empiric Antibiotic Treatment for Early Onset HAP/VAP With No Risk Factors for Multidrug-Resistant (MDR) Pathogens

Pathogen	Antibiotic Choice
S. pneumoniae	Ceftriaxone OR
H. influenza	Levofloxacin, moxifloxacin, ciprofloxacin OR
MSSA	Ampicillin/sulbactam OR
Antibiotic sensitive Gram-negative bacilli	Ertapenem

Table 6. Initial Empiric Antibiotic Treatment for HAP/VAP and Healthcare-Associated Pneumonia for Late-Onset or Risk Factors for MDR Pathogen

Pathogen	Combination Antibiotic Therapy
MDR bacteria	
1) *Pseudomonas aeruginosa*; 2) *Klebsiella pneumoniae* (ESBL)[a]; 3) *Acinetobacter* species[a]	1) Antipseudomonal cephalosporin (cefepime, ceftazidime); OR 2) antipseudomonal carbapenem (imipenem or meropenem); OR 3) piperacillin-tazobactam PLUS antipseudomonal fluoroquinolone (Ciprofloxacin or Levofloxacin); OR 4) aminoglycoside (amikacin, gentamicin, tobramycin) PLUS
MRSA	Vancomycin or linezolid

[a] Carbapenem is antibiotic of choice for ESBL strain or Acinetobacter species suspected.

patients whether it be for outpatient or inpatient status. Without seeing any steady decline in the occurrence of this infectious disease, however, and a rise in drug-resistant pathogens, novel antibiotics that have approved offer a new advantage for physicians to help treat their patients.

Footnote

Authors' Contribution: Both authors had equal parts in the writing of this paper.

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