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Community-Acquired Pneumonia

In this Issue...

Community-acquired pneumonia (CAP) is the sixth most common cause of death in the US and the major cause of death due to an infectious disease. The majority of patients who die with CAP have major co-morbidities or are elderly; in fact, most are “elderly, elderly” in reference to those over 85 years. Nevertheless, there are few infectious diseases that have spawned such controversy in terms of antibiotic selection and diagnostic testing: new pathogens are frequently detected, resistance in common pathogens continues to evolve, and Centers for Medicare & Medicaid Services (CMS) have made this a target diagnosis so that CAP is now a component of regular audits of all hospitals that receive Medicare funding.

In this issue, we analyze the recently released joint guidelines from the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS), and review some of the practical issues in the clinical management of CAP.

THIS ISSUE

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At the conclusion of this activity, participants should be able to:

- Discuss with colleagues the current recommendations regarding antibiotic selection in the management of pneumonia
- Describe to colleagues the current recommendations regarding diagnostic testing in patients with suspected community-acquired pneumonia
- Discuss with colleagues the rationale for early institution of treatment and the liability of over diagnosis

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COMMENTARY

Despite the controversies surrounding the diagnosis and management of CAP, there does seem to be an evolving consensus in some areas. Regarding therapy, while there have been hundreds of comparative trials, to our knowledge, none have ever shown one antibiotic to be better than another. Now, however, antibiotic selection has been addressed by the joint recommendations of the IDSA/ATS, based on an enormous (over 30,000 patients) database from Medicare. With regard to microbiology, studies over the past 50 years have consistently failed to detect a pathogen in 30-50% of cases even with the best techniques available at the time. In the past few years there have been major advances in diagnostic microbiology, especially with molecular diagnostics. But paradoxically, there is currently a sharp

decrease in the quality of standard microbiology with respiratory secretions, reflecting issues of cost, need, the Clinical Laboratory Improvement Amendments (CLIA) requirements that eliminated ward-based laboratories, the Medicare mandate for rapid evaluation, the low priority often given to microbiology by laboratory directors, and outsourcing. The result is that over 80% of patients with CAP are treated empirically with no microbiology results for guidance.

The papers reviewed herein discuss practical issues in the management of CAP. Perhaps most important are the recent guidelines from the IDSA/ATS, which provide guidance regarding current recommendations for nearly all clinical decisions. There are few surprises here, since the pathogens are largely the same as they have been for the past decade, and the empiric antibiotic recommendations therefore are also quite similar. There are, however, a few observations that address the more contemporary issues.

The major new pathogen, discussed herein in a Centers for Disease Control and Prevention (CDC) report, is the community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) that has received so much notoriety in the past 3-4 years. While this is a rare cause of CAP, it is devastating when it is seen. Most of the patients are young and previously healthy, the course is rapid, many have necrotizing pneumonia with the sepsis syndrome, and the recommendations for antibiotic selection are quite different than the standard recommendations for CAP. Of note is the observation that the clinical features of this infection are sufficiently unique so that the clinician is unlikely to be fooled. In this setting, diagnostic studies are clearly indicated and microbiology nearly always yields the putative agent in blood cultures and/or expectorated sputum. Antibiotic treatments recommended by the IDSA/ATS guidelines for MRSA pneumonia are vancomycin or linezolid.

Antibiotic recommendations for other patients have been largely dictated by multiple studies, and from guidelines and mandates from Medicare and other agencies. However, none of these have adequately addressed the issue of the duration of treatment. Thus, the report from The Netherlands by el Moussaoul et al, suggesting that 3 days duration of treatment is the equivalent of 8 days, is a start at examining that issue. This paper was highlighted, in part because it reflects some of the current trends in the field of infectious disease, which emphasize short duration antibiotics when feasible. This is quite contrary to standard teaching 10-20 years ago, when we always were instructed to complete the course to assure eradication of the pathogen. Now there is increasing emphasis on short duration antibiotics in the effort to reduce resistance, cost, and side effects. While it is premature to say that 3 days should be a "standard course" of antibiotics for patients with CAP, the data shows that the often customary response of treating for 1 week, 10 days, or 2 weeks for patients with mild or moderate CAP is probably too long for most of them.

The issue of pathogen-directed therapy versus empiric treatment (van der Eerden et al, reviewed herein) is of interest in view of the ongoing debate regarding the merits of microbiology in CAP. Both sides were winners in this report: while efficacy was virtually identical in both arms, there was a difference in the high rate of adverse reactions with standard empiric regimens. It might be noted that most of the adverse reactions here were GI intolerance due to erythromycin, and this effect would be unlikely with the macrolides used most frequently in the US. Nevertheless, despite the adequacy of outcome with empiric drugs found in this report, there may be some important benefits for microbiology in terms of detecting epidemics, identifying shifting resistance patterns, and the detection of pathogens of substantial importance such as *Legionella*, MRSA, SARS, Avian influenza, agents of bioterrorism, etc.

Another controversial issue to address is the Medicare audits that now include CAP, with the expected (later in 2008) implementation of public reporting and pay-for-performance as mandated by Congress. The most controversial component of the auditing done to date has been the requirement to give antibiotics within 4 hours of registration. It is worth emphasizing the fact that rapid institution of antibiotics may be as important as the selection of specific agents in terms of outcome. However, the need to treat rapidly has also resulted in antibiotic abuse with additional cost, toxicity, and resistance. Studies to define these "unintended consequences" have resulted in two important 11th hour changes: the first is a new category called "diagnostic uncertainty" of the CAP diagnosis, which eliminates this 4 hour

requirement from the audit because it indicates that there may be congestive failure, pulmonary embolism, or some other diagnosis that would result in antibiotic abuse. The second "correction factor" has been to eliminate this measure as a criterion in the "pay-for-performance" decision.

ANALYSIS OF THE IDSA/ATS CONSENSUS GUIDELINES

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD et al. **Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults.** *Clin Infect Dis.* 2007;44 Suppl 2:S27-72.

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The 2007 Guidelines for the Management of CAP from the IDSA/ATS discuss nearly all facets of community-acquired pneumonia. Among the key questions answered:

- **What conditions are covered in these guidelines?** The document deals with CAP but excludes aspiration pneumonia, pneumonia caused by viruses including influenza, pneumonia in the immunocompromised host, and the recently recognized healthcare-associated pneumonia which applies to patients in nursing homes and those engaged in the healthcare system through dialysis, outpatient infusion therapy, etc.

- **What tests should be done?** Routine diagnostic testing should include a history, physical exam, imaging (generally chest x-ray), pulse oximetry, and highly selective use of the microbiology laboratory. The chest x-ray is necessary to show pneumonia and distinguish it from bronchitis. High resolution CT scan will show more pulmonary infiltrates, compared to plain chest x-rays, but the clinical significance of these false-negative x-rays is unclear.[1] Previously, routine blood cultures were performed prior to antibiotics for all patients who are hospitalized with pneumonia; this routine blood culture is now recognized as “optional” except in patients who are sufficiently ill to require hospitalization in the intensive care unit (ICU). The reason is that positive blood cultures usually yield *S. pneumoniae*, which is covered with the standard empiric antibiotics. Further, many patients have blood cultures contaminated with coagulase-negative *Staphylococcus*, which has often prompted treatment with vancomycin for suspected *S. aureus* before the gram-positive cocci (GPC) are identified. With regard to sputum cultures and gram stains, these are now regarded as “optional” for hospitalized patients and recommended primarily for those patients who have a suspected pathogen that is not treatable with the empiric antibiotics that are listed in the table below.

Table 1: Empiric Selection of Antibiotics

Outpatient

1. Previously healthy:
   - Doxycycline or
   - Macrolide: clarithromycin or azithromycin
2. Co-morbidity, healthcare associated or antibiotics within 90 days:
   - Respiratory fluoroquinolone
   - ß-lactam + macrolide

Hospitalized patients – general admission

- ß-lactam* + macrolide** or
- Respiratory fluoroquinolone***

Hospitalized patients – ICU

- ß-lactam* + macrolide**
- ß-lactam* + respiratory fluoroquinolone***
- Penicillin allergy: aztreonan + fluoroquinolone***

Pathogen-specific

P. aeruginosa:

- ß-lactam (piperacillin/tazobactam, cefepime, imipenem or meropenem) + ciprofloxacin or levofloxacin (750 mg)
- ß-lactam + an aminoglycoside + azithromycin
- ß-lactam + an aminoglycoside + antipneumococcal fluoroquinolone

CA-MRSA:

- ß-lactam + vancomycin + linezolid

*ß-lactam: ceftriaxone, cefotaxime or ampicillin/sulbactam
**Macrolide: azithromycin or clarithromycin
***Respiratory fluoroquinolone: levofloxacin (750 mg/d) or moxifloxacin

- **What antibiotics should be given?** Antibiotic selection is largely empiric and based on site of care and severity of illness. The table above summarizes the current antibiotic recommendations for outpatients, patients hospitalized in the general medical service, and patient hospitalized in the intensive care unit. In general, the recommendations provide optimal coverage for the major categories of pathogens, including *S. pneumoniae*, *Haemophilus influenzae* and the atypical agents such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella*. For patients hospitalized in the intensive care unit, the major target of the empiric selection is *S. pneumoniae* and *Legionella*, both of which are the most common and the most likely to cause devastating infection. Recommendations are also provided for pathogen-specific treatment for infections involving methicillin-resistant-*S. aureus* (USA 300 strains) using vancomycin or linezolid, and for *Pseudomonas aeruginosa* with regimens that will also cover *S. pneumoniae* and *Legionella*, since these are much more common.

  The rationale for this selection of drugs is largely based on in vitro activity against the major pulmonary pathogens and excellent performance in clinical trials. An analysis of a very large database from Medicare, with over 30,000 patients, that stratified them according to severity of illness, antibiotic regimen, time to start therapy, length-of-stay (LOS), and outcome supported the same conclusions. These data showed that the regimens advocated are superior to others in terms of mortality.[2,3] The initial analysis, in 1999, compared a β-lactam to over 30 other regimens and noted that the combination of a β-lactam plus macrolide reduced mortality by 26%, and the use of a fluoroquinolone, alone, reduced mortality by 36%.

- **What accounts for the failure to improve?** The list includes: a resistant pathogen (rare), undrained pus (empyema or metastatic infection), erroneous diagnosis (pulmonary embolism, aspiration, adult respiratory distress syndrome (ARDS), congestive heart failure, bronchiolitis obliterans organizing pneumonia (BOOP), etc), severity of illness, complication of treatment (drug fever, *Clostridium difficile* infection, line sepsis), or pulmonary superinfection. In practice, the most common cause is simply persistent infection with severe illness, nosocomial infection, or a non-infectious disease cause of the pulmonary infiltrate.[4] A resistant or neglected pathogen is uncommon, although the physician must be alert to the possibility of tuberculosis or *Pneumocystis* pneumonia as well as other resistant pathogens.

- **How can we prevent pneumonia?** Among the most important findings are smoking cessation, appropriate use of influenza vaccine, and the use of the protein-conjugated pneumococcal vaccine for children.[5] Pneumococcal vaccine polyvalent is advocated for patients at risk for pneumococcal infections, but actually shows a relatively modest effect on the frequency of pneumonia or pneumococcal pneumonia; its major effect appears to be a 40-50% reduction in the frequency of pneumococcal bacteremia.[6,7] The most impressive result has been with the pediatric vaccine given to children under two years of age, which has resulted in an 80% reduction in the frequency of invasive pneumococcal infections in elderly[5]; the implication is that young children are the major vectors of pneumococcal infections.

- **What is the most contentious issue?** Unquestionably, the most controversial issue is the “4-Hour Rule”. Medicare audited charts in selected categories to determine the quality of care. For CAP, they require compliance with the antibiotic recommendations previously discussed for hospitalized patients, and, further, also require that antibiotics be given within 4 hours of the time of registration in a hospital or emergency room. This latter requirement is based on audits which show further delays in the initiation of antibiotics are associated with significant increases in mortality.[2,3] The plan was to use hospital audits for compliance with the "4-Hour Rule" for public reporting and pay-for-performance when these mandates are implemented later in 2008. The concern about this measure is that it has forced antibiotic decisions leading to antibiotic abuse. In one report there were actually several deaths due to *C. difficile* infections that resulted from fluoroquinolones given for CAP that, on review, was never established based on chest x-ray review.[8] The result is that Medicare has now recognized this “unintended consequence” of the “4-Hour Rule” and has consequently implemented a new category designated “diagnostic uncertainty”[9] that eliminates the case from audit; more recently they have eliminated the “4-Hour Rule” completely from the pay-for-performance category.

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MRSA CAP

Centers for Disease Control and Prevention (CDC). **Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza — Louisiana and Georgia, December 2006-January 2007.** CDC:*MMWR Morb Mortal Wkly Rep.* 2007;56:325-329.

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This 2007 CDC paper reports on CAP associated with influenza and MRSA superinfection in 10 cases reported from Louisiana and Georgia. The patients were previously healthy and generally young (median age 18 years). They presented with severe pneumonia that was associated with pulmonary necrosis, severe pulmonary symptoms, and a mortality rate of 60%. The median duration of symptoms from onset to death was only 3.5 days. The infective agent is the relatively recently recognized “community-acquired-MRSA” that is generally designated as the “USA 300 strain”. A widely quoted report from the CDC has called attention to the two distinct forms of MRSA[1], noting that the USA 300 strains have recently become far more prevalent in the community than the USA 100 strains that have been predominant in hospital-acquired infections over the past 3 decades.

The relevance of these observations to CAP is the recognition of MRSA as a rare but very important cause. It is usually a complication of influenza, the host is often young and previously healthy, the course is rapid, progressive and often lethal, and the common presentation is rapidly progressive sepsis with pulmonary necrosis and/or empyema. The virulence factors responsible for this devastating complication are not clear. Some have opined that the critical virulence factor for pulmonary necrosis has been the Panton-Valentine leukocidin toxin[2], but more recent studies suggest that virulence is defined by high concentrations of cytolytic peptides that recruit, activate, and then lyse neutrophils.[3] With regard to treatment, the current ISDA/ATS recommendation is for vancomycin or linezolid.

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DISCONTINUING ANTIBIOTIC TREATMENT AFTER 3 DAYS VERSUS 8 DAYS

el Moussaoui R, de Borgie CA, van den Broek P, Hustinx WN, Bresser P, et al. **Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community-acquired pneumonia: randomized, double blind study.** *BMJ.* 2006;332(7554):1355.

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The duration of antibiotic treatment for CAP is not supported by scientific evidence and there is increasing concern that prolonged antibiotic abuse is contributing to resistance, cost, and toxicity. This report by el Moussaoui et al from The Netherlands directly addresses this issue.

Patients judged to have mild or moderate-severe CAP were randomized to receive intravenous amoxicillin and evaluated for response at 3 days. Those who were judged to have substantial improvement at 3 days were randomized for either oral amoxicillin or placebo for 5 days. The primary outcome measure was the clinical evaluation at day 10, with secondary outcome measured at day 28. Results were evaluated by follow-up cultures, x-rays, and description of clinical symptoms at 10 and 28 days.

The results, summarized below, showed no difference with treatment for 3 versus 8 days in terms of clinical cure, bacteriologic cure, and radiologic cure at the evaluation at 10 days as well as the evaluation at 28 days.

Table 2: Outcome in Patients Treated for CAP with Antibiotics for 3 Days vs. 8 Days

	3 days n=56	8 days n=63
Day 10 analysis		
Clinical Cure	50/56 (89%)	58/63 (89%)
Bacteriological Cure	22/25 (88%)	19/20 (95%)
Radiologic Cure	48/56 (86%)	52/63 (83%)
Day 28 analysis		
Clinical Cure	47/56 (84%)	49/63 (78%)
Radiologic Cure	48/56 (86%)	50/63 (79%)

The authors conclude that discontinuing amoxicillin treatment after 3 days is comparable to continued amoxicillin in patients with mild to moderately severe CAP if there is clinical improvement at day 3.

PATHOGEN DIRECTED vs EMPIRIC ANTIBIOTIC TREATMENT

van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Bronsveld W. **Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomized study.** *Thorax.* 2005;60:672-678.

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The authors address the value of microbiology studies in patients with CAP in one of the rare clinical trials comparing pathogen-directed treatment versus empiric treatment using standard CAP guidelines for empiric treatment.

Participants were hospitalized patients with CAP, and were randomized for treatment based on microbiology results or empiric treatment. The former group underwent extensive diagnostic testing including sputum gram stain and culture of sputum or bronchoscopic aspirates with serology for viruses (influenza, parainfluenza virus, respiratory syncytial virus (RSV) adenovirus and atypicals), and urinary antigen assay for *S. pneumoniae* and *Legionella* serology for atypicals. This arm received penicillin for pneumococcal pneumonia, erythromycin for atypical pathogens, and amoxicillin-clavulanate for most other bacteria. Those given empiric treatment received a β-lactam/β-lactamase inhibitor plus erythromycin; for ICU admissions, the empiric treatment was ceftazidime plus erythromycin.

The evaluation included 134 patients in the pathogen-directed group and 128 in the empiric treatment group. The clinical outcome was essentially the same in the two groups in terms of mortality, rate of clinical failure, length of stay, duration of antibiotics, and time to defervescence (results detailed in the table below). However, there was a very significant difference in terms of adverse events: 17% in the pathogen-directed group compared to 60% in those receiving empiric treatment. The main difference was in the frequency of GI intolerance, and less commonly, phlebitis and reversible hearing loss.

Table 3: Outcome of CAP with Pathogen Directed or Empiric Therapy

	Path Directed Antibiotics n=134	Empiric Antibiotics n=128
Mortality	8%	15%
Clinical Failure	21%	23%
LOS (mean, days)	14.3%	13.2%
Duration Abx (mean)	10.8%	9.9%
Time to defervesence (mean, days)	2.9%	2.5%
Adverse events*	17%	60%

*Most common: GI intolerance (9 vs. 42%), phlebitis (8 vs. 38%), reversible hearing loss (5 vs. 14%).

The authors conclude that empiric treatment with broad spectrum antibiotics for the management of hospitalized patients with CAP shows efficacy that is comparable to pathogen-directed treatment, although the rate of side effects is much greater with empiric treatment.

REDUCTION IN MORTALITY ASSOCIATED WITH INFLUENZA TREATMENT IN HOSPITALIZED ADULTS

McGeer A, Green K, Plevneshi A, et al. for the Toronto Invasive Bacterial Diseases Network. **Antiviral therapy and outcome of influenza requiring hospitalization in Ontario, Canada.** *Clin Infect Dis.* 2007;45(12):1568-1575.

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Influenza remains a common cause of morbidity and mortality among older adults. Influenza can be a primary cause of pneumonia or can place an individual at risk for post-influenza bacterial pneumonia. While early therapy with neuraminidase inhibitors has been shown to reduce the risk of complications associated with influenza, the trials demonstrating this effect involved relatively young, healthy adult outpatients treated within 48 hours after the onset of symptoms. The investigators performed a prospective, cohort study of elderly patients with confirmed influenza infection randomized to receive oseltamivir or no antiviral treatment. The median age was 77 years, 75% had chronic associated conditions, and 71% had been vaccinated against influenza. Of 327 patients enrolled, 16% required intensive care unit admission. The overall mortality rate was 8.3% within 15 days of onset of symptoms. Some of the patients received amantadine, but this was inactive against influenza during the study period of 2005 and 2006, so these patients were considered in the non-treatment group.

The overall result showed that patients given oseltamivir had a 80% reduction in mortality rate compared to those that did not receive an effective antiviral (odds ratio 0.21, p=0.03), thus suggesting the benefit of neuraminidase inhibitor antiviral therapy in reducing influenza-associated CAP in elderly patients.

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- Describe to colleagues the current recommendations regarding diagnostic testing in patients with suspected community-acquired pneumonia
- Discuss with colleagues the rationale for early institution of treatment and the liability of over diagnosis

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- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil, Cadence Pharmaceuticals, and Theravance/Astellas.

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