Treatment must cover more virulent pathogens

Health care–associated pneumonia: Meeting the clinical challenges

ABSTRACT: The risk factors for health care–associated pneumonia (HCAP) include hospitalization for 2 or more days within the past 90 days, residence in a nursing home or extended-care facility, home infusion therapy, and long-term dialysis within the past 30 days. Distinguishing between community-acquired pneumonia (CAP) and HCAP is important because of the implications for therapy. Compared with CAP, HCAP is more likely to be caused by multidrug-resistant organisms and is associated with a higher mortality rate. The management of HCAP requires antimicrobial coverage of *Pseudomonas aeruginosa*, *Acinetobacter* species, extended-spectrum ß-lactamase–producing Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus*. Empirical narrowing of therapy is probably safe in patients with culture-negative HCAP who have improved with broad-spectrum therapy. (*J Respir Dis*. 2008;29(5): 208-213)

KEY WORDS: Pneumonia, Antibiotic resistance, MRSA

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More than 1 million patients in the United States are hospitalized annually with community-acquired pneumonia (CAP), at an estimated cost of $26 billion.[1] CAP was the sixth most expensive condition in US hospitals in 2004[1] and the eighth leading cause of death.[2]

The rate of hospitalization for elderly patients with CAP has increased by 30% since 1988, in contrast to all-cause hospitalization rates, which have remained stable. Furthermore, a study comparing patients hospitalized with pneumonia with those hospitalized with the other top-10 listed admission diagnoses found that elderly patients with CAP were 50% more likely to die during their stay.[3] Adverse outcomes extend beyond the hospital stay; 1-year mortality rates for elderly patients with CAP exceed those of hospitalized controls by 9%.[4]

The impact of CAP on elderly patients has fueled efforts by important regulatory agencies such as The Joint Commission and payers such as the Centers for Medicare & Medicaid Services to improve the quality of care for these patients. Performance data for processes of care such as blood cultures, oxygenation assessment, smoking cessation counseling, vaccination of eligible patients, timing of antibiotic delivery, and selection of appropriate antibiotics for patients with pneumonia have been tracked and reported publicly since 2002, resulting in significant improvement in hospitals' compliance with these standards of

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care.[5] Recently, the reporting of inpatient and 30-day mortality rates has been added.

The choice of an appropriate initial antibiotic regimen is one of the most important predictors of outcome in patients hospitalized with CAP. Mortensen and associates[6] evaluated the antibiotic regimens administered within 48 hours of admission for 420 inpatients with CAP and classified them as concordant or discordant with existing published guidelines. The risk-adjusted 30-day mortality rate in the group who received guideline-discordant therapy was 21.7%, compared with 6.2% in the guideline-concordant group (odds ratio, 5.7; $P < .001$).[6]

In a subsequent study, the investigators found that the inpatient mortality rate was reduced from 7% to 4% in patients receiving guideline-concordant therapy (relative risk reduction, 63%; $P = .04$).[7] Furthermore, length of stay and duration of intravenous antibiotic therapy were less in the concordant group.

Given the impact of appropriate antibiotic selection on outcomes, it is imperative that clinicians be familiar with published guidelines that define best practices. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) have authored the most widely referenced guidelines for CAP as well as for hospital-acquired pneumonia and ventilator-associated pneumonia.[8-11]

A new category of pneumonia—health care–associated pneumonia (HCAP)—was defined in a jointly authored publication in 2005.[12] This was done in recognition of the fact that many community-dwelling patients regularly have contact with the health care system and are thus at risk for exposure to pathogens that are more virulent than those defined in CAP guidelines. Patients with HCAP are at increased risk for infections caused by multidrug-resistant (MDR) organisms.

Because the mortality rates associated with HCAP are almost double those of CAP,[13,14] the implications for therapy are significant and appropriate classification of patients is critical. Clinicians must become familiar with the risk factors for HCAP, because HCAP includes some cases of pneumonia that would previously have been categorized as CAP.

In this article, I will review the distinctions between the practice guidelines for CAP and those for HCAP and explore some of the limitations of the guidelines as they are applied to actual practice.

CAP versus HCAP

Current guidelines define CAP as pneumonia in adults who are not institutionalized in a health care facility and who are not immunosuppressed.[11] Antibiotic recommendations for hospitalized patients are based on level of care, with slight differences between patients treated on the wards and those in the ICU. Broad-spectrum therapy is recommended for patients at risk for pseudomonal pneumonia at all levels of care; risk factors include severe bronchopulmonary disease, long-term use of corticosteroids, alcoholism, and frequent antibiotic therapy.

Antibiotic coverage of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suggested when appropriate, but the guidelines state that MRSA remains an uncommon cause of CAP. Risk factors for MRSA infection include end-stage renal disease, injection drug use, prior influenza, and recent antibiotic therapy.[11] As detailed below, several of these comorbidities classify the pneumonia as HCAP. Current recommendations for antibiotic treatment of hospitalized patients who have CAP are outlined in Table 1.

The risk factors for HCAP expand the patient population considered

Table 1 – Recommended initial antibiotics for hospitalized patients with CAP

Inpatients, non-ICU treatment
Respiratory fluoroquinolone
ß-Lactam plus a macrolide
Inpatients, ICU treatment
ß-Lactam plus either azithromycin or a respiratory fluoroquinolone
Penicillin-allergic patients: respiratory fluoroquinolone plus aztreonam
Concern for *Pseudomonas* infection
Antipneumococcal, antipseudomonal ß-lactam plus either ciprofloxacin or levofloxacin
Antipneumococcal, antipseudomonal ß-lactam plus an aminoglycoside and azithromycin
Antipneumococcal, antipseudomonal ß-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone
Penicillin-allergic patients: substitute aztreonam for the antipneumococcal, antipseudomonal ß-lactam
Concern for MRSA infection
Vancomycin (in addition to the above-mentioned agents)
Linezolid (in addition to the above-mentioned agents)

CAP, community-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus.*
Adapted from Mandell LA et al. *Clin Infect Dis.* 2007.[11]

Table 2 – Risk factors for HCAP

Risk factors for HCAP
Hospitalization for ≥ 2 days within the past 90 days
Residence in a nursing home or extended-care facility
Home infusion therapy (including antibiotics) within the past 30 days
Long-term dialysis within the past 30 days
Home wound care within the past 30 days
Family member with a multidrug-resistant infection
Other risk factors for multidrug-resistant infections
Antimicrobial treatment in the past 90 days
Current hospitalization of ≥ 5 days
Immunosuppressive disease and/or therapy
High prevalence of antibiotic resistance in the community or specific hospital unit

HCAP, health care–associated pneumonia.
Adapted from American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2005.[12]

to be at risk for MDR infections, especially patients who otherwise appear clinically well (Table 2). Thus, clinicians who treat hospitalized patients on the basis of CAP guidelines alone risk undertreating a significant number of patients.

The management of HCAP is equivalent to the management of late-onset hospital-acquired pneumonia or ventilator-associated pneumonia; thus, antimicrobial coverage of organisms such as *Pseudomonas aeruginosa, Acinetobacter* species, extended-spectrum ß-lactamase–producing Enterobacteriaceae, and MRSA is recommended. Notably, HCAP guidelines emphasize empirical coverage of both *Pseudomonas* species and MRSA, while CAP guidelines focus on ensuring appropriate pneumococcal coverage. The recommended antibiotic regimens are presented in Table 3.

Challenges in HCAP management

The move toward increasing the number of patients who are receiving broader-spectrum antimicrobial treatment raises concerns about the development of antibiotic resistance. The guidelines suggest a strategy of initial broad-spectrum therapy to ensure that MDR organisms are adequately covered, with narrowing of therapy according to results of sputum cultures and clinical response after 2 to 3 days. These recommendations were based almost entirely on experience with patients with ventilator-associated pneumonia, from whom adequate sputum samples via tracheal aspiration are relatively easy to obtain and in whom the absence of organisms on Gram stain rules out pneumonia with a negative predictive value of 93%.[15]

In contrast, the ability to obtain an adequate sputum sample in nonventilated patients is quite limited. In a cohort of 1669 patients with CAP presenting to the emergency department of a university teaching hospital in Spain, 59% were able to produce a sputum sample, but only 14% provided a good-quality sample that yielded a predominant morphotype.[16] Greater severity of illness did not improve the yield.

Rosón and associates[17] studied 533 patients hospitalized with CAP and found that a good-quality sputum specimen was obtainable in only 39%. In a smaller study of 74 patients with nonsevere CAP from whom valid sputum specimens were available, a pathogen was identified in only 5%.[18]

Blood cultures did not increase the diagnostic yield, nor have they been shown to significantly affect antibiotic use in other studies of CAP.[19-21] Hence, narrowing coverage in nonventilated patients with HCAP who have achieved clinical stability after several days of treatment will frequently be based on clinical judgment, rather than on microbiological data as suggested by the guidelines.

A sampling of patients with culture-positive pneumonia from a large multi-institutional database revealed that the magnitude of resistant organisms is significant; among 988 patients with HCAP, 25% of the sputum specimens grew *Pseudomonas* species and 26.5% grew *S aureus*.[13] The startlingly high frequency of MDR organisms in this study would make a careful clinician pause before applying clinical judgment to narrow therapy in the absence of culture data. In a patient who has improved with broad-spectrum therapy, how can one distinguish improvement *as a result of* antibiotics from improvement *despite* antibiotics?

In the absence of a known pathogen, it might be tempting to continue prolonged broad-spectrum therapy in patients who have culture-negative HCAP. However, this clearly contradicts the principles of narrowing therapy espoused by the guidelines. The benefits of a shorter duration of antibiotic therapy have been described in multiple studies,[22-26] and the strategy of "hit hard and stop early," as described by File,[27] is becoming the new standard of care.

Even the most severely ill patients have not been shown to

benefit from prolonged antibiotic therapy. Chastre and colleagues[26] randomized 411 patients with ventilator-associated pneumonia to 8- or 15-day antibiotic regimens and found no difference in overall mortality, days on mechanical ventilation, or ICU days. Recurrent infections were more common in the subgroup of patients with *P aeruginosa* pneumonia who received short-course therapy, but other outcomes remained the same.

In addition, the remarkably high frequency of MDR organisms isolated in the above-mentioned study by Kollef and associates[13] is tempered by the study's retrospective design. With such a large database (more than 4500 patients), it was difficult for the investigators to distinguish colonization from infection in individual cases. The fact that the incidence of *S aureus* was 25% and the incidence of *P aeruginosa* was 17% in the subgroup of patients with CAP suggests that not all organisms were pathogens.

A subsequent smaller study that used more stringent criteria for defining causal pathogens demonstrated a significantly lower incidence of *S aureus* and *P aeruginosa* (2.4% and 1.6%, respectively), although the mortality difference between CAP and HCAP remained significant.[14] Clearly, it is impossible to gauge whether the organism burden in patients with HCAP who are unable to provide sputum specimens would be similar to that in the culture-positive patients included in the above-described studies.

So how can we justify narrowing antibiotic therapy in patients with culture-negative HCAP who are clinically improving? First, studies of the impact of antibiotic selection in CAP have consistently shown benefit only in patients with the most severe illness. In the original study of this topic, Gleason and associates[28] evaluated almost 13,000 medicare patients who were hospitalized with CAP. Severity of illness was measured using the Pneumonia Severity Index (PSI), a validated and well-recognized risk stratification tool that uses clinical factors to stratify patients into 5 classes with increasing mortality rates.[29] The investigators found that appropriate empirical antibiotic selection was associated with a reduction in 30-day mortality in the overall study cohort. However, mortality rates among patients with low-risk PSI scores were low (3.3% compared with 34% in the highest-risk group; $P < .001$).

Subsequent smaller studies have shown similar findings.[6,30,31] Thus, patients who are clinically stable when hospitalized with pneumonia may not be affected as much by antibiotic choice.

In addition, studies have shown that adverse outcomes in patients with CAP are rare once clinical stability is achieved. Halm and colleagues[32] studied 688 inpatients with CAP and noted that once clinical stability was achieved, deterioration occurred in (at most) 1%. When more conservative definitions of stability were used, adverse events occurred even less often.[32]

On the basis of this information, investigators in the Netherlands studied the effects of discontinuing antibiotics altogether in patients with CAP who were clinically stable on hospital day 3.[24] Clinical success rates, symptom scores, and radiographic improvement in patients receiving 3 days of antibiotics were equivalent to those in patients receiving a full 8 days of therapy.[24]

Although neither of these studies analyzed pa-

Table 3 – Recommended initial antibiotics for patients with HCAP or other risk factors for multidrug-resistant infections

Antibiotic	Regimen
Antipseudomonal cephalosporin	
Cefepime	1 - 2 g q8 - 12h
Ceftazidime	2 g q8h
Or	
Antipseudomonal carbapenem	
Imipenem	500 mg q6h or 1 g q8h
Meropenem	1 g q8h
Or	
ß-Lactam/ß-lactamase inhibitor	
Piperacillin/tazobactam	4.5 g q6h
Plus	
Antipseudomonal fluoroquinolone	
Levofloxacin	750 mg/d
Ciprofloxacin	400 mg q8h
Or	
Aminoglycoside	
Gentamicin	7 mg/kg/d
Tobramycin	7 mg/kg/d
Amikacin	20 mg/kg/d
Consider	
Anti-MRSA agent	
Vancomycin	15 mg/kg q12h
Linezolid	600 mg q12h

HCAP, health care–associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*.

Adapted from American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2005.[12]

tients with HCAP separately, their findings may inform our current practice while we await more definitive answers. If clinical stability and severity of illness are used as benchmarks, empirical narrowing of therapy is likely safe in patients with culture-negative HCAP who have improved with broad-spectrum therapy.

HCAP outside of the hospital

Many patients with pneumonia that fits the definition of HCAP are currently managed outside the hospital, the largest subgroup being residents of chronic-care facilities. The requirement for broad-spectrum intravenous antibiotics adds significant burden and cost to the care of these complex and frail patients. Adequate sputum samples are difficult to obtain, and a lack of controlled trials has fueled controversy about the new recommendations. Some authors have claimed that the prevalence of MDR organisms reported in the guidelines is overrepresented because studies were limited to nursing home patients on ventilators.[33]

There may be some lessons to apply to our practice from a study by Yakovlev and associates[34] of patients with HCAP. The investigators performed a blinded randomized controlled trial of ertapenem versus cefepime in patients in whom pneumonia developed after 48 hours in a hospital or skilled nursing facility. Of note, cefepime is active against *P aeruginosa,* while ertapenem is not. Also important in the study design was that patients' medication was switched to oral antibiotics once clinical stability was achieved. Although antibiotic choice was at the clinician's discretion, ciprofloxacin was used in 96.5% of the patients.

Microbiological data from sputum samples were available in only 53.5% of the patients; the rest were treated empirically. Enterobacteriaceae were the most common isolates (19.5%), and *Pseudomonas* isolates were infrequent (3.6%). In this group of 303 patients with nonsevere HCAP, clinical and microbiological cure rates were similar despite a difference in pseudomonal coverage between groups.[34] Furthermore, transition to empirical oral therapy was successful after clinical stability was achieved.

Unfortunately, the results of this study are not generalizable to all patients with HCAP, because patients who were immunosuppressed or required hemodialysis were excluded. Nonetheless, the study shows that there may be a subset of patients for whom less aggressive therapy is appropriate, and it confirms the safety of narrowing therapy (empirically) when patients improve.

Finally, there is no clear information on how to approach ambulatory patients with pneumonia who have risk factors for HCAP, such as patients receiving outpatient hemodialysis. On the basis of the synopsis above, the mortality risk is low in a patient who appears clinically stable enough for outpatient management, although perhaps more aggressive oral therapy might be considered. Further study in this patient population is warranted.

Therapeutic agents mentioned in this article

Amikacin
Azithromycin
Aztreonam
Cefepime
Ceftazidime
Ciprofloxacin
Ertapenem
Gentamicin
Imipenem
Levofloxacin
Linezolid
Meropenem
Penicillin
Piperacillin/tazobactam
Tobramycin
Vancomycin

Conclusion

The ATS/IDSA guidelines for the treatment of HCAP have expanded the indications for broad-spectrum antibiotic coverage for patients who have pneumonia. While the link between undertreatment and increased mortality is clear, the quandary of narrowing therapy in less severely ill patients who are unable to provide sputum specimens for culture-guided management remains difficult.

Further research is needed to define best practices in this subgroup of patients and to confirm that outcomes in patients with HCAP improve with appropriate antibiotic selection. In the meantime, careful application of clinical judgment based on the clinical criteria described above should help clinicians provide the best care for patients with HCAP.

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