Guidelines for hospital-acquired pneumonia and health-care-associated pneumonia: a vulnerability, a pitfall, and a fatal flaw

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Lancet Infect Dis 2011; 11: 248–52

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The 2005 American Thoracic Society and Infectious Disease Society of America's guidelines for pneumonia introduced the new category of health-care-associated pneumonia, which increased the number of people to whom the guidelines for multidrug-resistant pathogens applied. Three fundamental issues inherent in the definition of hospital-acquired pneumonia and health-care-associated pneumonia undermined the credibility of these guidelines and the applicability of their recommendations: a vulnerability, a pitfall, and a fatal flaw. The vulnerability is the extreme heterogeneity of the population of patients. The fatal flaw is the failure to accurately diagnose hospital-acquired pneumonia and ventilator-associated pneumonia; inability to distinguish colonisation from infection in respiratory-tract cultures renders the guidelines inherently unstable. The pitfall is spiralling empiricism of antibiotic use for severely ill patients in whom infection might not be present. A vicious circle of antibiotic overuse leading to emergence of resistant microflora can become established, leading to unnecessary use of empirical broad-spectrum combination antibiotics and increased mortality. Controlled studies now show that administration of broad-spectrum combination antibiotic therapy can lead to increased mortality in uninfected patients. Proposed solutions include the use of individualised assessment of patients. Health-care-associated pneumonia should be broken down into several distinct subgroups so narrow-spectrum antibiotic therapy can be used. Emphasis should be placed on defining the microbial cause of the pneumonia rather than reflex administration of empirical combination therapy.

Introduction

In 2005, the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) published guidelines[1] for management of adults with hospital-acquired pneumonia. A new category, defined as health-care-associated pneumonia, was introduced that broadened the scope of the guidelines to include ambulatory patients who were regarded as likely to have multidrug-resistant pathogens.

Unlike guidelines for community-acquired pneumonia,[2] confirmation of the approach and acceptance by clinicians of the 2005 hospital-acquired pneumonia guidelines has been marginal.[3,4] Shigeki Fujitani and I[5] pointed out that the 2005 guidelines were laudable in their intent, although poor in execution. Ewig and colleagues issued a reasoned critique[6] of the 2005 guidelines that was notable for its comprehension and backed by a critical and insightful review of the published work.

In this issue of *The Lancet Infectious Diseases*, in a prospective study of compliance versus non-compliance to the 2005 guidelines,[1] Daniel Kett and colleagues[7] report that 28-day mortality was significantly higher in patients who received antibacterial therapy classified as compliant than in those whose treatments were non-compliant. Compliance was essentially the use of combination broad-spectrum treatment whereas non-compliance was a surrogate for monotherapy. The reason and mechanism for this surprising result is unclear, but this finding was consistent in the overall group and numerous subgroups. Moreover, the higher mortality for the combination group compared with the monotherapy group could not be ascribed to the adverse effects of aminoglycoside therapy, which is often used as a component of combination antibacterial agent therapy.

History of pneumonia guidelines

One of the most successful and influential of all medical guidelines was the consensus piece for community-acquired pneumonia, first initiated 17 years ago by Thomas Marrie and subsequently chaired by Lionel Mandell, Michael Niederman, and John Bartlett. Therefore, formulation of guidelines for hospital-acquired pneumonia was logical and tempting, and, in 1996, the ATS–IDSA did so. New additions to the 2005 guidelines included newer definitions of nosocomial, hospital-acquired, ventilator-associated, and health-care-associated pneumonia. Problems immediately surfaced: the classifications were imprecise,[5] not easily generalisable, and the definitions varied from country to country. Marginal data, cherry-picking, and the small number of studies on which they were based weakened the validity of the 2005 guidelines.[6]

The foundation for initial community-acquired pneumonia guidelines[2] was a prospective observational study,[8] based on intensive microbiology for all patients; this study uncovered new microbial causes that were underappreciated at the time, including *Chlamydophila pneumoniae* and *Legionella* spp. A quantitative analysis was also done for the outcome of patients admitted to hospital that suggested that factors could be identified to minimise hospital admissions without adversely affecting outcomes.[9] Numerous confirmatory observational studies from other hospitals

and other countries strengthened the conclusions of the community-acquired pneumonia guidelines.[2,10–13]

With time, adherence to guidelines for community-acquired pneumonia improved outcomes in this group of patients. Most importantly, hospital pharmacies developed clinical pathways and the US Centers for Medicare and Medicaid Services and Joint Commission developed performance measures that mandated doctors' adherence to the guidelines. Other countries and societies issued their own guidelines for community-acquired pneumonia—imitation is the sincerest form of flattery. Of note was that therapy recommendations derived from the guidelines were different from existing practice at the time of its introduction. It was a credit to the pharmaceutical industry that subsequent development included new respiratory-tract macrolides and quinolones that were active against all the common pathogens of community-acquired pneumonia; this advance allowed a feasible and straightforward strategy of empirical antibiotic therapy. Could this success be transferred to guidelines for hospital-acquired pneumonia and health-care-associated pneumonia? Unfortunately, it could not.

Health-care-associated pneumonia

The vulnerability of the 2005 guidelines for health-care-associated pneumonia was the extreme heterogeneity of the population. This heterogeneity resulted from the desire of the guidelines committee to devise a straightforward approach of broad-spectrum empirical antibiotic therapy for the largest possible group of patients. Haemodialysis patients were lumped together with patients in nursing homes. Even within the category of patients in nursing homes, substantial variation existed. For example, the functional status of patients ranged from ambulatory to bedridden,[6] and underlying diseases now ranged from psychiatric problems to immunosuppressive disorders.

The key to selection of appropriate antibiotics depends on accurate identification of pathogens. The fatal flaw of any of the guidelines for nosocomial pneumonia involves the traditionally difficult issue of colonisation versus pathogenicity for microbes isolated from patients' respiratory secretions.

Oropharyngeal colonisation by Gram-negative bacilli is commonplace in patients admitted to hospitals, especially in intensive-care units. For intensive-care unit pneumonia, the pathogens are more diverse because of overgrowth of normal flora by Gram-negative bacilli. Moreover, intense antibiotic use promotes the emergence of resistant organisms. Because it is difficult to distinguish colonising organisms from infecting organisms, the definitive identification of the true pulmonary pathogens has always been problematic in hospital-acquired pneumonia. Colonisation rather than pathogenicity remains a complex issue.[14] The gold standard for definition of hospital-acquired pneumonia and ventilator-associated pneumonia is contentious. The best validated gold standard remains the seminal study by French investigators of patients with pneumonia in 31 intensive-care units.[15] An invasive procedure (bronchoalveolar lavage or protected specimen brush) plus quantitative criteria of cultures was used to distinguish pathogenicity from colonisation. Nevertheless, consensus on this criterion is not universal.[16] The logistics of an invasive procedure and necessity for the procedure before antibiotics can be given were also obstacles to widespread application. So, definitive identification of respiratory pathogens involved in hospital-acquired pneumonia remains elusive, despite the use of invasive diagnostic procedures and the advent of biomarkers of inflammation.

Because of the fatal flaw in making of an accurate diagnosis of intensive-care unit pneumonia and the inherent inability to separate uninfected colonised patients from infected patients, it is probable that a notable number of uninfected patients received unnecessary broad-spectrum combination therapy in Kett and colleagues' study.[7] I suggest that this unnecessary treatment might be the basis for the increased mortality given the widespread incentive to clinicians for overtreatment. At least three prospective controlled comparative studies have shown that giving broad-spectrum antibiotics to uninfected patients leads to significantly increased mortality.[15,17,18]

The presence of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* poses special dilemmas for empirical therapy. These two pathogens cause an imbalance in antibiotic therapy because MRSA requires Gram-positive coverage not routinely given for community-acquired pneumonia. *P aeruginosa* pneumonia is traditionally covered with combination therapy consisting of an antipseudomonal β lactam and an aminoglycoside; the aminoglycoside has little other application and is somewhat toxic.

Recent data suggest that *P aeruginosa* might be overestimated as a pneumonia pathogen in intensive-care units.[14,19,20] A frequent coloniser of patients with chronic obstructive pulmonary disease, *P aeruginosa* might be regarded as a pathogen when isolated from respiratory secretions of patients presenting with pulmonary infiltrates, even if these infiltrates are secondary to congestive heart failure. The bitter irony is that antibiotic overprescription has led to the emergence of MRSA and multidrug-resistant *P aeruginosa*.

The 2005 guidelines[1] and proceedings of the Health-Care-Associated Pneumonia Summit[21] recommend initiation of empirical antibiotic selection by the explicit reporting of "health-care-associated pneumonia, ventilator-associated pneumonia, or health-care-associated pneumonia, suspected" (figure). Administration of empirical antibiotics on the basis of "suspicion of hospital-acquired pneumonia" is a pitfall that can readily lead to antibiotic misuse. The authors did recognise that such a strategy might lead to a situation in which antibiotics could be given for a non-infectious process and they encouraged de-escalation on the basis of serial clinical assessments

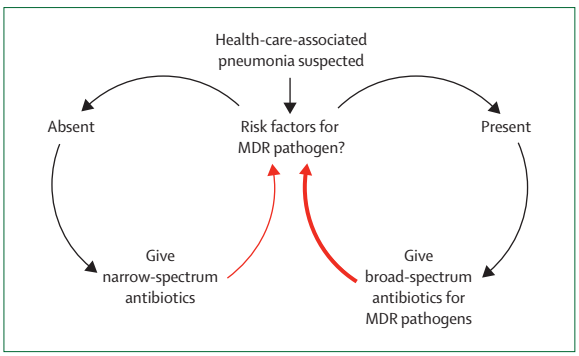

Figure: **The vicious circle within the hospital-acquired pneumonia and health-care-associated pneumonia guidelines[1]**
The key decision point is that of risk factors for multidrug-resistant pathogens, but the most important risk factor is previous administration of antibiotics (red arrows; thickness denotes relative risk). This classification can lead to widespread overuse of broad-spectrum antibiotics. MDR=multidrug-resistant.

and cultures. For example, the Clinical Pulmonary Infection Score criteria as applied by Singh and colleagues[17] identified patients who needed only 3 days of therapy (presumably because most did not really have pneumonia).

Advocates of empiricism emphasise that severe illness is an indicator of multidrug-resistant pathogens;[22] however, I suggest that severity of illness does not directly indicate microbial cause. When faced with patients who might die, many doctors feel the urge to cover every scenario no matter how unlikely. So, the notion that doctors are unwilling to miss anything has become a greater driving force for spiralling empiricism than has the likelihood that the pneumonia pathogen is *P aeruginosa* or MRSA. Because of the high mortality attributed to patients with hospital-acquired pneumonia who received inappropriate therapy, clinicians who cared for a population with high mortality needed to assure themselves that everything that could be done for critically ill patients would be done.

When I was an intern, antibiotics had become antipyretic agents—to be provided for fever of any unknown cause. This strategy was formalised for the neutropenic host and the floodgates opened. Any patient with an underlying comorbidity with a fever would be given an antibiotic. When I was a faculty member, antibiotics had become antihypotensive agents for the intensivist, and patients were given antibiotics if they "looked septic".

30–70% of patients with pulmonary infiltrates who receive antibiotics for suspected hospital-acquired pneumonia or ventilator-associated pneumonia do not have pneumonia.[18,23,24] Furthermore, this contagious behaviour of overprescription has infected doctors in emergency departments. The US Centers for Medicare and Medicaid Services mandate penalises emergency departments if antibacterial drugs for community-acquired pneumonia are not given within 6 h of admission.[25] As many as 50% of patients in some emergency rooms who receive empirical antibiotics for such infection will not have pneumonia.[26]

Proposed solutions

The heterogeneity of the population for which the 2005 guidelines[1] were intended and the elusiveness of a gold standard for establishment of microbial cause render them inherently unstable. The main objective of these guidelines was to ensure empirical antibiotic therapy would cover multidrug-resistant pathogens. Notably, the precipitating factor for emergence of multidrug-resistant pathogens including MRSA is prior antibiotic therapy, which propagates and aggravates the situation with unnecessary broad-spectrum antibiotic therapy. Two studies[15,17] that showed improved outcomes from pneumonia in intensive-care units reported that restriction of the common practice of broad-spectrum antibiotic was more important to improving outcomes than was use of the broader coverage sought by the guidelines committee. Monotherapy was effective in many patients with health-care-associated pneumonia who were ambulatory and not severely ill.[5,6] Therefore, the results in the study[7] by Kett and colleagues should perhaps not be surprising.

In an attempt to rectify the shortcomings of the guidelines, revisionists proposed to use the concept of risk factors for multidrug-resistant pathogens. Combination broad-spectrum therapy would be given to those patients with health-care-associated pneumonia and risk factors for multidrug-resistance and monotherapy would be given to the remaining patients with health-care-associated pneumonia.[21,22] This solution is exemplified by the vicious circle engendered by the 2005 guidelines (figure). Keep in mind that prior antibiotic therapy is the most important risk factor leading to multidrug-resistant pathogens.[2] Although the figure might seem to be an ironic exaggeration, it is not. It is figure 2 in the 2005 guidelines,[1] figure 6 in the proceedings[21] of the Health-Care-Associated Pneumonia Summit, and a variant of figure 1 in a review article on health-care-associated pneumonia.[22]

I believe the solution is straightforward—individualisation. If individualisation is applied to antibiotic selection, the regional differences in antibiotic use, unique characteristics of the population, and special situations can be taken into consideration. Every patient can be assessed with respect to their individual risk factors. The vulnerability of heterogeneity can be resolved by explicitly accepting that certain subgroups of patients have their own distinctive epidemiology and risk factors. For example, if a patient on haemodialysis is a known MRSA nasal carrier with a past history of MRSA infection or if *Legionella* spp are present in the drinking water of the hospital, such knowledge can improve antibiotic selection. Individualisation is useful when the patient's history is sufficiently complex that a one-size-fits-all approach is no longer feasible; this generalisation is the Achilles' heel of the health-care-associated pneumonia guidelines.[1] The guidelines expanded the population, so overprescription with broad-spectrum

antibiotic combination therapy was an imminent consequence. For example, provision of empirical MRSA coverage to a select population of drug addicts in Los Angeles, CA, USA who have a high prevalence of community-acquired MRSA would be rational, but blanket MRSA coverage might not be in Scandinavia, which has a low prevalence of such infections.

For an individualised approach, doctors require reasoning and a fund of knowledge. Administration of a single quinolone for community-acquired pneumonia was so much simpler; this widespread approach became the ultimate one-size-fits-all strategy. It was inexpensive and required neither contemplation nor cognition. Even microbiology tests for diagnosis became unnecessary.

I recommend guidelines be tailored to those specific settings that provide clues to the most likely pathogens: extended-care facilities and nursing homes (stratified by functional status), immunosuppressed hosts (stratified by patients with neutropenia, HIV status, or transplanted organ), and pneumonia in intensive-care units (stratified by ventilator-associated pneumonia and postoperative pneumonia). Patients receiving home intravenous therapy should not be included in the guidelines but their immunosuppressed status is pertinent.

A new development might assist with the solution. Molecular-based diagnostic tests are being introduced to the clinical setting at the point of care.[27–29] The emphasis on empirical therapy can be reduced if the microbial pathogens of pneumonia can be identified before antibiotic initiation. So, I suggest that a worthy effort of pneumonia investigators would be to apply, assess, and validate these new innovative diagnostic tests, including those for inflammatory biomarkers (especially procalcitonin).[30–32] A solution, if one exists, must focus on accurate identification of the pathogens of health-care-associated pneumonia.

The reflex pronouncement for more studies as a way of improving the 2005 guidelines is a safe recommendation, but not an easy solution. The 1996 and 2005 hospital-acquired pneumonia and health-care-associated pneumonia guidelines were formulated with the awareness that the basis for definitive pathogen identification for both infections was soft. It was thought that a consensus committee could somehow resolve this complex issue by a thorough review of the literature. This proved not to be the case. As Ewig and colleagues showed,[6] review of studies of health-care-associated pneumonia showed inconsistent and non-credible results, largely because of varying case definitions and inadequate bacteriology. Retrospective databases are unreliable for formulation of guidelines for antibiotic therapy. As an example, MRSA was the most common cause of community-acquired pneumonia (25%) and health-care-associated pneumonia followed by *S pneumoniae* (20·3%) in one such retrospective study[33]—a surprising finding that is unlikely to be replicated elsewhere.

Thus, the current literature cannot be used as an evidence-based foundation for guidelines on hospital-acquired pneumonia or health-care-associated pneumonia. One critique of the 2005 guidelines was aptly subtitled "eminence- rather than evidence-based".[34] For maximum effectiveness, new, large-scale, prospective studies on these infections need to be commissioned. Strict study design with objective endpoints is necessary. Standardised microbiological methods should be used, which must be applied to all patients. This flaw in previous studies was underscored by a study by Maruyama and colleagues,[35] which was the only recent study that detected atypical pathogens in health-care-associated pneumonia;[22,35] it was also the only study to test for such atypical pathogens. The net effect of selective testing of a pathogen rather than universal testing is underestimation for that particular pathogen in the population because the diagnostic test is not ordered, or overestimation of the virulence of the pathogen when tests are targeted for patients not responding to therapy or those who are severely ill. Such studies would also provide the opportunity to also assess molecular diagnostic tests and biomarkers.

A series of smaller studies with a well-defined population with health-care-associated pneumonia (eg, patients in a nursing home) is preferable to one large study with a heterogeneous study population. Because study populations in the numerous studies previously reviewed have been heterogeneous, the confidence intervals of the variables studied were inherently wide.

Obtaining appropriate evidence on which to base future guidelines is no small task, and federal funding sources will probably be needed. The investigators must be experienced; the CAPO[36] and CAPNETZ[30] study groups are candidates for leading such investigations. Much fruit would be borne if such studies could be done. And, if multiple studies were done, the foundation for evidence-based guidelines would be strengthened.

Conclusions

The 2005 ATS–IDSA guidelines lead to potential overtreatment. Because of the results of the study by Kett and colleagues,[7] doctors caring for patients in intensive-care should exercise restraint in antibiotic use. If point-of-care microbiological tests are not revealing, then monotherapy should be used for only 3 days in non-severely ill patients in intensive-care units as described in an algorithm published elsewhere[37] and then antibiotic therapy should be stopped when culture evidence suggests absence of infection. Because of the irremediable weakness of present data, the fundamental principles of infectious diseases need to be applied for hospital-acquired pneumonia and health-care-associated pneumonia until newer, more rigorous studies are done. Determine microbial aetiology and use empirical therapy only if necessary. A rational solution for effective management of pneumonia will ultimately rely on these principles.

Conflicts of interest

I declare that I have no conflicts of interest

Acknowledgments

I thank Calvin M Kunin, Gordon A Wong, Daniel M Musher, Julio Ramirez, and Nina Singh for their helpful discussion of concepts elucidated in this Personal View. Thomas J Marrie, Thomas File, Naomi O'Grady, and Jean Chastre provided critical reviews.

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