Community-Acquired Pneumonia: 2012 History, Mythology, and Science

Gerald R. Donowitz, MD

Abstract

Pneumonia remains one of the major disease entities practicing physicians must manage. It is a leading cause of infection-related morbidity and mortality in all age groups, and a leading cause of death in those older than 65 years of age. Despite its frequency and importance, clinical questions have remained in the therapy of community-acquired pneumonia including when to start antibiotics, when to stop them, who to treat, and what agents to use. Answers to these questions have involved historical practice, mythology, and science—sometimes good science, and sometimes better science. How clinical decisions are made for patients with community-acquired pneumonia serves as an illustrative model for other problem areas of medicine and allows for insight as to how clinical decisions have been made and clinical practice established.

INTRODUCTION

More than 100 years ago, William Osler noted, “Pneumonia remains now, as then, the most serious acute disease with which physicians have to deal…” (1). It is medically humbling to note that the importance of pneumonia has not changed dramatically since Osler's writings. Pneumonia is the leading cause of infection-related mortality for all age groups and the sixth leading cause of death in those greater than 65 years of age (2). The case fatality ratio of pneumonia has not changed dramatically from 1963 to 1998 (3–5). The role of pneumonia-related mortality in the elderly takes on added importance with the estimate that by 2050, 20% of the world's population will be older than the age of 65 years (6).

As a clinical entity, community-acquired pneumonia has become more complex. In 1977, community-acquired pneumonia (as compared to nosocomial pneumonia) consisted of atypical pneumonia, aspiration pneumonia, and “classic” bacterial pneumonia caused by Streptococcus pneumoniae, Haemophilus influenzae, and less frequently Moraxella catarrhalis, Staphylococcus aureus, streptococcal species, and Enterobacteriaceae.

In 2013, community-acquired pneumonia now includes as distinct clinical subcategories pneumonia in the elderly, pneumonia in the immune-suppressed host (including patients with HIV/AIDS, malignancy, solid organ transplant recipients, and immune suppression for other conditions), and nursing home–associated pneumonia.
As the clinical entity of community-acquired pneumonia has evolved, major questions have remained concerning the principles of therapy. These ongoing clinical questions include when to start therapy, when to stop, what agents to use, and who to treat.

The element that is central to these clinical questions is “Why do we do what we do?” With regard to community-acquired pneumonia, the answers fall into several categories including the following: 1) clinical science with flaws leading to outside intervention leading to flawed clinical practice; 2) mythology transformed by good clinical science into sound clinical practice; 3) clinical science leading to more questions, better clinical science, and perhaps a change to more sound clinical practice; and 4) good clinical science leading to sound clinical practice.

It is worth examining examples of each of these because similar categories of answers exist for many other areas of medicine.

**TIMING OF ANTIBIOTICS IN COMMUNITY-ACQUIRED PNEUMONIA: HOW CLINICAL SCIENCE WITH FLAWS LEDING TO OUTSIDE INTERVENTION LEADS TO FLAWED CLINICAL PRACTICE**

In 1997, a study by Meehan et al. retrospectively reviewed more than 14,000 Medicare inpatient stays for pneumonia examining the effect of timing of antibiotic administration on 30-day mortality (7). Measured from arrival to an Emergency Department, 30-day mortality was reported to be decreased if antibiotics were administered within 8 hours (OR, 0.85; 95% CI, 0.75–0.96; \( P < 0.004 \)).

A second study of similar design was published by Houck et al. in 2004 (8). In this study, more than 18,000 Medicare inpatient stays were examined. These authors reported that in-hospital mortality was decreased if antibiotics were given within 4 hours of presentation (6.8% versus 7.4%, AOR, 0.85; 95% CI 0.74–0.98; \( P = 0.03 \)) and that 30-day mortality was decreased (11.6% versus 12.7% AOR 0.85; 95% CI 0.76–0.95; \( P < .005 \)).

Neither study examined pneumonia etiology, which antibiotics were used, or what other support measures were instituted. In 2005, despite these flaws, and the lack of any prospective, randomized studies of any kind, the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations, JCAHO) as well as the Centers for Medicare and Medicaid services established the “4-hour” rule in patients with community-acquired pneumonia as a core quality measure by which hospitals and individuals would be reviewed.

Institutions could be faced with a reduction in Medicare dollars if data were not submitted on timing of antibiotics for this diagnosis. Further, hospitals began to offer incentives to physicians who complied with the 4-hour rule, and suggestions of disincentives for non-compliance. Antibiotics for community-acquired pneumonia given within 4 hours of presentation became the standard of care.
Subsequently, there have been series of untoward effects documented because of the 4-hour rule. In one series, although there was a 60% increase in those admitted with the diagnosis of pneumonia, there was a < 25% increase in pneumonia as a discharge diagnosis (9). Outbreaks of *C. difficile* were documented for which 80% of patients who developed diarrhea were being treated for pneumonia, but 50% of patients so treated may not have had the disease (10). Finally, delays in making the correct diagnosis for patients who had been admitted with an initial diagnosis of pneumonia and received antibiotics within 4 hours were observed after the 4-hour rule had been instituted (11).

Several years after the 4-hour rule had been instituted, critical reviews of studies examining the question could not confirm the original findings (12). Definitions of time to the start of antibiotic therapy were imprecise, severity adjustment was often lacking, and overall mortality varied greatly between studies. The single study reviewed that was prospective and adjusted for severity of disease actually reported an increased mortality in patients receiving antibiotics within 4 hours.

It was not until 5 years after their initial establishment of the 4-hour rule that the Joint Commission reviewed the data and its prior policy and stated that now Immune-competent patients with Community-Acquired Pneumonia who received an initial antibiotic regimen during the first 24 hours that is consistent with current guidelines would be in compliance (13).

In contrast, the Infectious Disease Society of America (IDSA) at the time stated a more common sense approach that antibiotic therapy should be started “as soon as possible after the diagnosis is considered likely” (14).

**HOW LONG TO TREAT PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA: HOW MYTHOLOGY TRANSFORMED BY GOOD CLINICAL SCIENCE LEADS TO GOOD CLINICAL PRACTICE**

Until relatively recently, evidence-based medicine concerning the optimal length of therapy for patients with community-acquired pneumonia has been lacking. The guiding concept was “to treat long enough to eradicate the pathogen, and prevent recurrence, but not long enough to select for resistance” (15). Over the years, this was translated to mean 5 to 7 days, 7 to 10 days, or 10 to 14 days.

The 2007 Maxwell Finland Lecture for IDSA provided a review of the relevant data leading to this practice (16). The pertinent data concerning duration of therapy primarily involved pneumococcal pneumonia. In 1943, Keefer et al. reviewed 500 patients treated with penicillin and noted that the majority of those with pneumococcal disease recovered in 2 to 3 days. Dawson and Hobby in 1944 reviewed 100 patients treated with penicillin and noted that 1 ½ to 2 days of therapy were adequate. In the same year, Tillet et al. showed that 3 to 4 days of therapy was adequate. Finally, in 1945, Meads et al. treated 44 patients until there was clinical stability and a temperature of less than 100°F for 12 hours, and then several days thereafter…for no clear reason. Of note, 2 of 44 patients relapsed, suggesting that longer therapy was needed. This seems to have been
the evidence for 5 to 7, 7 to 10, or 10 to 14 days of treatment for community-acquired pneumonia that became the standard of care for decades.

Important refinements to the concept of proper duration of therapy for patients with community-acquired pneumonia occurred 43 years later. At this time, Halm et al. reviewed 686 patients with community-acquired pneumonia (17). The authors measured the time until clinical stability was achieved defined as a pulse <100 beats/minute, blood pressure >90 mm Hg, respiratory rate <24 breaths/minute, O₂ saturation > 90% on room air, and temperature < 37.8 °C. Stability was reached in 2 to 3 days for each of these parameters. Seventy-five percent of all abnormalities stabilized within 4 days. Once clinical stability was reached, there was less than 1% chance of clinical deterioration. This study represented one of the earliest attempts to add clinical science to the mythology of therapy for pneumonia.

Although time to stability had a relatively narrow range in this study, it was clear that a variety of factors relating to the host (immune status, co-morbid conditions, underlying lung disease), the clinical presentation of disease (extent of disease, physiologic compromise), and the organism involved (inherent virulence, inoculum, susceptibility to available therapy) would likely influence recovery time. Menendez et al., in a series of observations complementing those of Halm et al., examined these factors (18). The authors reviewed more than 1,400 patients with community-acquired pneumonia and examined the factors associated with patients attaining clinical stability. Although the median time to stability was 4 days (not significantly different from the findings of the study of Halm et al.), a variety of factors including the presence of co-morbidities, Pneumonia Severity Index classification, organism involved, radiologic extent of disease, and presence of complications were shown to decrease the number of patients reaching clinical stability within 4 days.

Both these studies lead to a more rational and evidence-based approach to the duration of therapy for community-acquired pneumonia. Although therapy for each patient needs to be individualized based on the factors involved in history, presentation, and physiologic disruption due to the disease, the previous practice of 10 to 14 days of therapy no matter what, had finally been replaced.

EMPIRIC ANTIBIOTIC THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA: CLINICAL SCIENCE LEADING TO MORE QUESTIONS, TO BETTER CLINICAL SCIENCE, AND PERHAPS A CHANGE TO MORE SOUND CLINICAL PRACTICE

More than a decade ago, a series of clinical observations suggested that azalide/macrolide agents, used in combination with beta-lactam agents, led to improved outcomes in elderly populations with community-acquired pneumonia (19, 20). Decreased mortality rates and decreased hospital stays were noted. The studies, however, were retrospective, no microbiologic etiology was determined in 60% to 90% of cases, and there were variable controls, if any, for confounding variables. Despite
these weaknesses in study design, the use of azithromycin with a beta-lactam became a therapy of choice for pneumonia in the outpatient setting for patients with significant co-morbidities and in patients requiring hospitalization.

Why this combination of agents would work was not clear. Potential explanations included the possibility that etiologic agents involved in atypical pneumonia were being better treated, or perhaps that the more common bacterial agents involved were being treated synergistically. The weakness of the first possible explanation was that atypical pneumonia caused by mycoplasma or chlamydophila species is not commonly documented in the elderly. Further, therapy of community-acquired pneumonia in the elderly with fluoroquinolones or tetracyclines, which would provide excellent coverage for the agents of atypical pneumonia, did not mimic the findings noted in the initial studies.

With regard to the second possible explanation, synergy between the beta-lactams and azalides/macroldes has never been proven for the major organisms involved in community-acquired pneumonia.

The most likely explanation as to why combination therapy worked in the therapy of community-acquired pneumonia in the elderly involves the immune-modulatory effect of macroldes and azalides. It has been shown that these agents can decrease the secretion of IL-8, IL-6, and human oncogene α while increasing the oxidative burst of neutrophils and increasing neutrophil degranulation. This was followed by a decrease in oxidative burst and an increase in apoptosis (21, 22).

These findings occurred at a time when there was a great knowledge burst in the understanding of the inflammatory response associated with community-acquired pneumonia. It is well beyond the scope of this article to review this topic, but a simplified description of the process includes recognition of foreign protein complexes belonging to microbial pathogens by Toll-like receptors and IL-1–receptors, among others, leading to the production of early-response cytokines that stimulate transcription factors to produce pro-inflammatory and then anti-inflammatory cytokines. The explanation of why this system works would be that pro-inflammatory cytokines need to function long enough to destroy invading organisms, but need to be countered by anti-inflammatory cytokines so “collateral damage” to surrounding tissue does not occur.

The proposed effects of azalides and macroldes fit in well with these concepts and stimulated further investigation as to what other modifiers could play a potentially beneficial role in the therapy of pneumonia. Thus far, the agents most commonly studied have been corticosteroids. The type of corticosteroid used, their dosing, and the duration of their administration have varied widely from study to study as have the type of patients studied, as well the controls for severity of disease and co-morbidities. Although interesting in theory, there have been no consistent findings to suggest that corticosteroids should play a role in the therapy of community-acquired pneumonia.

Despite the lack of significant clinical findings thus far, the study of the inflammatory response in community-acquired pneumonia offers the potential of future interventions that may prove beneficial. These studies are clearly in their early phases and much remains unknown about how and when immune modulations may be used.
A recent study by Kellum et al. monitored the cytokine responses of 1,886 patients with community-acquired pneumonia and severe sepsis (23). Levels of tumor necrosis factor (TNF), and IL-6 as pro-inflammatory cytokines, and IL-10 as an anti-inflammatory cytokine were monitored. Their findings suggest that prior views of potential times and sites for immune-modulation may have been oversimplified. They noted that elevation of cytokines was not universal, that both pro- and anti-inflammatory cytokines seemed to have peaked by the first day of presentation, that cytokine elevation lasted longer than symptoms, and that preponderance of either pro- or anti-inflammatory cytokines was neither common nor clearly associated with an increase in morbidity or mortality.

It would therefore seem that the observations of the effect of the azalides/macrolides on community-acquired pneumonia may have only touched, in a very superficial way, an area in which better understanding may influence the outcome of this disease process although how and why remain areas for future study.

**BIOMARKERS IN THE DIAGNOSIS OF COMMUNITY-ACQUIRED PNEUMONIA: GOOD CLINICAL SCIENCE LEADING TO IMPROVED CLINICAL PRACTICE**

The recognition that overuse of antibiotics may lead to antibiotic resistance as well as an increasing incidence of *C. difficile* colitis has stimulated studies seeking more efficient means of diagnosing community-acquired pneumonia and monitoring clinical stability to determine duration of antibiotic therapy. The role of biomarkers has been a central theme in these investigations (24).

A variety of biomarkers have been associated with the presence of pneumonia including C-reactive protein, procalcitonin, s(TREM)-1, copeptin, CD 64, and various components of atrial natriuretic peptide. Much of the recent emphasis has involved procalcitonin.

Procalcitonin is a precursor of calcitonin and is part of a peptide superfamily of gene-related products. It is viewed as a homokine that can function as a hormone or a cytokine. Release of procalcitonin may be directly stimulated by microbial products or indirectly by inflammatory mediators such as TNFα, IL-1β, and IL-6. Interestingly, and pertinent for its use as an indicator of community-acquired pneumonia, induction of procalcitonin can be blocked by mediators of viral infection such as interferon. Procalcitonin has been shown to increase within 6 to 12 hours of infection with an increase proportional to severity of infection. Values may decrease by 50% per day when infection is being treated successfully.

Because of these characteristics, procalcitonin has been studied in emergency departments, outpatient clinics, and intensive care units to determine who should be treated, and when antibiotics should be stopped (25, 26).

The most recent investigation of procalcitonin as an indicator for making the diagnosis of pneumonia and indicating that antibiotics are necessary was performed by Albrich et al. involving centers in three countries (27). Procalcitonin levels <0.1ng/L discouraged
antibiotic use unless the patient was admitted to an ICU, had significant co-morbidities, complications such as empyema, hard to treat organisms such as Legionella, elevated pneumonia severity index, or decreased oxygenation. Antibiotics were recommended for procalcitonin levels >0.26ng/L. If antibiotics were started, a significant decrease in procalcitonin levels (>80% to 90% of peak levels) led to recommendation for antibiotic discontinuation without untoward consequences.

Shorter durations of antibiotic therapy (5.9 days versus 7.4 days; P<0.001) were noted without increased mortality or complications rates. This is one of a number of important studies defining how diagnosis and therapy of community-acquired pneumonia can be improved. Interestingly, only 35% of US centers were compliant with the study algorithm. As summarized in an invited commentary to the study, “it is all about confidence” in what appears to be a major advancement of clinical practice (28).

CONCLUSION

What I have tried to show in this commentary is that the current practice of medicine in general, and the therapy of community-acquired pneumonia specifically, is based on a combination of mythology, good science, and better science. The term mythology is not pejorative, but a recognition of clinical decisions made with minimal scientific evidence available. As long as the question “Why do we do what we do?” is asked, by our students, our residents, and ourselves, that progression from mythology to good science to better science to improved clinical practice will occur even with outside intervention by non-medical agencies.

Footnotes

Potential Conflicts of Interest: None disclosed.

DISCUSSION

Wolf, Boston: Gerry, how are you treating your patients with community-acquired pneumonia?

Donowitz, Charlottesville: That's a good question. We actually use the Port Score. When we get ER admissions, we have our house staff review the patient's history and physical exam and the Port Score and we ask the question, “Are you sure they have pneumonia?” It's amazing how many get admitted without an x-ray. House staff are also asked to evaluate what the risk factors are for resistant organisms. If there are none, then we are going to start to use the standard of care, ceftriaxone and the azithromycin. I'm not sure that azithro is really needed, but it may, in fact, be a real effect. We also ask house staff, “How long do you want to treat?” By the time physiologic abnormalities are normalized, we stop therapy and that's around 5 or 6 days, but the majority of the patients we admit have multiple co-morbidities.

Quesenberry, Providence: Great talk. It was interesting that one of the most nebulous discussions on many, many patients was, “How long do we keep the antibiotics going?”— and that was for urinary tract infection, pneumonia and it didn't matter whether we have ID consults or not, usually, nobody knew.
**Donowitz, Charlottesville:** I think the problem is that, as always, no matter whether it's ID or hem/onc or some other subspecialty, there is always a part of mythology in what we do. The important part of that is asking, “Where does that data come from?” It was mentioned this morning that the use of guidelines and protocols sort of take that question away, but I think the concept is knowing it's a guideline and only a guideline and so asking that question, “Where does the data come from?”, and going back to the original literature if you can find it, is really critical.

**Quesenberry, Providence:** I must admit, it usually came down to 7 to 10 days.

**Donowitz, Charlottesville:** That's a good multiple. ID people are not imaginative.

**Baum, New York:** Very nice talk, and having written an Op-Ed, I guess in CID (Clinical Infectious Diseases) about guideline tyranny, I think for this group, it really extends beyond my articles on community-acquired pneumonia but I think in terms of all guidelines, I think this society and other specialty societies have to be very active in making sure that guidelines don't become tyrannical and don't mandate things that turn out either not to be true or even if true have consequences that are really very important.

**Donowitz, Charlottesville:** I think the concept of guideline is it's merely a guide that shouldn't be written in stone and it's a help but again, the individual patient is what's going to make that the reason to do whatever you do.

**Benz, Boston:** Maybe I'll throw a comment in at this based on some recent things that if you use the InterMountain Health Group, which has been a real pioneer in the use of guidelines, they have configured the way they use guidelines with committees that constantly evaluate the guidelines and have tried to turn the paradigm from the guidelines being a way of evaluating a physician's practice to a physician's practice being a way to evaluate the guidelines, and I think that's the ballgame that's going to be out there as reform comes into play. Not that the guidelines drive the care, but the care drives the evolution of better and better guidelines otherwise new technology and new knowledge, the kinds of things you talked about, will never get into practice.

**Donowitz, Charlottesville:** Brett James would say that getting the users to sit in a room, to look at the question that is being asked, and let them come up with the answer.

**LeBlond, Iowa City:** A couple things. When we talk about what antibiotic we are going to start and how long, those are sort of statements that seem very concrete, and what we really should be thinking about, I think, is hypotheses. This is how clinical medicine goes; so rather than say the patient has pneumonia, as a conclusion, we have to say we think this patient has pneumonia. Our prediction if they have pneumonia is if we do these things, over what period of time, what's the time course of the response, what should we see and then how do we reevaluate it rather than thinking in these absolutes so we can detect trajectories of illness. Illness is a vector. It's got a direction and it's got a magnitude so we can detect the people who aren't progressing in the right way. I think that's a much better way to think about how we design our interventions.

**Donowitz, Charlottesville:** For the sake of time, I didn't really go over the use of procalcitonin but that's exactly what it does. If you think someone has pneumonia you'll start antibiotics. Usually the procalcitonin would be over and above the index that is
used. Within 2 to 3 days, either the patient is getting better or they're not. If the procalcitonin level drops by 50% in that 2- to 3-day period, you should say, “You know, I think the patient is better. I'm going to stop.” If it remains elevated or goes up, hopefully you will be saying to yourself clinically, “I don't think the patient is getting better. There is some other complication that is going on.” But again, the procalcitonin would be a guide for that.

Le Blond, Iowa City: So I instruct my residents that the diagnosis is what you put on the discharge summary. Up front you have hypotheses and problems and you conclude what the diagnosis was at discharge.

Donowitz, Charlottesville: Fair enough.

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Gerald R. Donowitz, MD
Gerald R. Donowitz, Charlottesville, Virginia;
Correspondence and reprint requests: Gerald R. Donowitz, MD, PO Box 800466, Charlottesville, VA 22908-0466, Phone: 434-924-1918, Fax: 434-243-0399, ; Email: GRD/at/VIRGINIA.EDU.
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REFERENCES


