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Medicine & Health RHODE ISLAND

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Pneumonia

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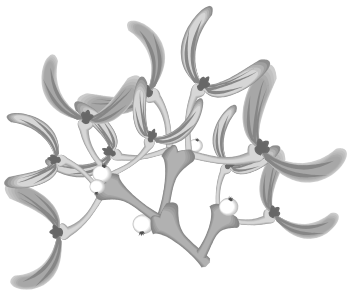
Commentaries



Hanging the Crepe

"Hanging the crepe" is an old phrase, referring to the no-fail ploy of foretelling a bad outcome to patient, family and friends. If the prediction comes true, the doctor was prescient, and if not true, a savior. I recall, many years ago, a resident who was working under my supervision, and with whom I was particularly close, telling me that he couldn't believe that I had just told a patient and family that I was optimistic the patient would make a good recovery from a stroke. I don't recall why I told them that, and while I think the patient did, in fact, recover nicely, I do recall that I worried quite a bit for a few days. The resident may have been correct. I think I'm generally pretty cautious, and usually pessimistic, but I do share my optimism as well but don't routinely hang the crepe. Of course my practice is entirely out-patient now, and what and how we tell our patients with incurable, progressive disorders is a crucial part of our jobs.

Recently I evaluated a patient, a recently retired physician, who was extremely active physically. "I came to see you for a second opinion. Another neurologist told me that I had Parkinson's disease, had to give up skiing now and would be in a wheelchair in ten years." This is hanging the crepe big time.

I was stunned. First of all, I was able to give someone that rare bit of good news that comes out of my office, "No, you don't have Parkinson's disease (PD)," or something worse. This was essential tremor, a condition occasionally misinterpreted as PD. This misdiagnosis is not all that rare and certainly can be forgiven, because the distinction may be quite challenging early on, but the bad prognosis could not be. I tried to put myself in the shoes of my colleague. Why would he say something like that? I asked the doctor if our colleague had really said that, not that he heard something not actually said, but dredged up from his inner fear. "He clearly said that. I asked about the skiing because it is so important to me. And I asked about the wheelchair in ten years. That's really why I'm here. I didn't think I had PD. My athletic abilities are just the same as they've always been. And why should I stop skiing if I'm going to be in a wheelchair in ten years?"

When and how to give a prognosis is a tricky thing and one size certainly does not fit all. I have the unfortunate responsibility, like many doctors, of telling people things they'd rather not hear. How we do so is important, even though what we say, or better still, what we think we say, and what they hear, may be so divergent. This is a running theme through our careers and I wonder how much we change with our increased experience both in life and our professions.

Telling someone with PD not to ski actually makes little sense. Simply having the diagnosis doesn't alter anything. We should be advising people on their capabilities and not their diagnoses, unless those diagnoses have hidden risks. Lifting weights with a dissecting aneurysm in any artery is a bad idea. But simply knowing you have PD, which is certainly associated with impaired balance, doesn't suddenly make your balance worse. If you could ski safely yesterday, you can ski safely today. The issue really is whether the patient can properly assess his skills and the resultant risks, not whether he has PD. This is simply common sense, and the physician hearing the admonition to desist from skiing simply couldn't understand it. Why not ski?

More bothersome to me was the statement, at least as heard by my patient, that he'd be in a wheelchair in 10 years. It is not so much that the statement isn't true, and it isn't, is the fact that almost all neurodegenerative diseases are fairly variable so that while there is data on disease progression in general, it never applies specifically to one individual. As with everything biological, there is a great deal of variability. The progression of neurodegenerative disorders is analogous to aging. We don't know when they begin. When did we become old? Is slowing down due to Parkinson's disease, arthritis or getting old? Sometimes it makes itself known in a flash, with injuries. The processes are usually so insidious that no clear onset can be distinguished, And they progress like aging. Some people age gracefully, and look 10 years younger than they are while some look 10 years older.

I always tell patients that their disorder is progressive but that the progression is measured over months to years, so there will be time to see disabilities developing. Nothing happens overnight. In addition, the progression varies enormously from person to person, so that one person may have minimal disability even after 10 years while another will be in a wheelchair in five years and that only time will tell. In the meanwhile exercise is critical in reducing disability, whichever track the patient is on. Thus, at our first meeting I can give the bad news, but also hold out hope. There must always be some hope.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001-2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.

Senescence By the Numbers

The psalmist declared plaintively: "Cast me not off in the time of old age; forsake me not when my strength faileth." The Roman poet Horace, who barely lived to 57 years, spoke eloquently of a golden age opening before humans as they trespass into the senior years. Somewhere, between the psalmist's despair and Horace's benevolent vision of a senior's years, there must exist a less poetic materiality of what life beyond age 80 is truly like. These are the elders that demographers refer to as "the oldest old."

Most elderly who dare to discuss candidly the quality of their lives, those who have made the weary pilgrimage to a state of varying decrepitude, tend to agree with William B. Yeats (1865 – 1939):

> What shall I do with this absurdity –
> O heart, O troubled heart – this caricature,
> Decrepit age that has been tied to me
> As to a dog's tail?

Most humans are too preoccupied with a multitude of impediments, leaving them with little time to reflect upon the larger social dimensions of aging or to offer any expansive vision of trends in aging. But fortunately the United Nations and its Department of Economic and Social Affairs periodically provides us with global statistics on aging.

We learn, for example, that currently there are 737 million humans, world-wide, who are 60 years of age or older. And further, that this number will increase to two billion by the year 2050. By that year, 40 years hence, the number of elderly will outnumber the global youth (those 14 years or younger) for the first time in recorded history. The elderly, today, constitute 11% of the global population. By the year 2050, this will increase to 22%.

The oldest old, those 80 years of age or older, now number 103.2 million. The number of centenarians, those living to age 100 years and beyond, now number 454,000; by 2050 they will number 4.1 million souls. Not long ago a person reaching age 100 justified a front-page news story.

By various standards, and certainly by biological realities, males are more fragile than females. Currently, for every 100 living females there are 83 living males. In the year 2050, despite anticipated advances in medicine, there will only be 59 males for every 100 living females. In those nations where selective illiteracy, restrictive standards and poverty combine selectively to depress female health, the ratio of males to females is approximately equal.

And, for those reaching age 60 years, what is their life expectancy? For males world-wide, it is 18 years; for females worldwide, 21 years. But these global averages hide the immense and troublesome disparities between the wealthy and impoverished nations. In Japan, for example, the average 60-year old woman may expect to live an additional 28 years. In some west African nations, a sixty-year old woman may anticipate, on average, only 10 more years.

What else may we distill from this mountain of statistics? Since there is a discrepancy between male and female longevity, more elderly women than elderly men may be expected to live alone. This is borne out by statistics. Globally, about 9% of males older that 60 live alone. More than twice as many women, 19%, over the age of 60 now live alone (in L'Enclos' words: "Old age is woman's hell."). And does it matter in which nation one lives? In the poorer nations, a substantially *smaller* percent of the elderly live alone. Thus in the subSaharan nations the percent of elderly males living alone is about 6% and for elderly females, 11%. This may be interpreted variously as indicating that the poorer nations are more family-oriented, more concerned with their grandparents and therefore less likely to abandon them. Or, alternatively, that the poorer nations are too impoverished to build independent assisted-living facilities for their elderly.

Cicero (106-43 BCE) called old age "the crown of life, our play's last act." But neither the Romans, nor those who followed in the succeeding 19 centuries, lived much beyond age 60. Our knowledge of such burdens as Alzheimer's disease is only one century old. Old age, for many, is no longer that golden interval when one may reflect upon the privileges of seniority while admiring the antics of one's grandchildren. Old age becomes a haven surrounded by peril where identity and cognition may depart prematurely. And when contemplating the fundamentals of old age, back again to Horace: "Grant me sound of body and of mind, to pass an old age lacking neither honor nor lyre." And Seneca, his colleague (8 BCE – 65) declaring: "Old age is an incurable disease."

– Stanley M. Aronson, MD

Stanley M. Aronson, MD is dean of medicine emeritus, Brown University.

Disclosure of Financial Interests

Stanley M. Aronson, MD, and spouse/significant other have no financial interests to disclose.

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Pneumonia: Introduction

Fredric J. Silverblatt, MD

Pneumonia, along with influenza, is the leading cause of death from infectious diseases and overall is the eighth leading cause of death. Newly recognized pathogens, emergence of organisms highly resistant to antibiotics and novel clinical scenarios present ongoing challenges for diagnosis, treatment and prevention of lower respiratory tract infections. In recent years, epidemiologic and microbiologic studies have clearly delineated different paradigms. Recognition of the organisms most likely responsible for community acquired pneumonias and healthcare associated pneumonias have allowed the development of rational choices for empiric therapy for each setting. These have been promulgated in guidelines by national subspecialty organizations and are reviewed in articles by Al-Qadi et al. and by Silverblatt. The recent pandemic of novel H1N1 influenza has served to remind us of the potential devastating consequences of this infection. The history of the great influenza pandemic of 1918 and a review of what we have learned with the current outbreak is covered by Irizarry and Puius. Finally, Penelope Dennehy reviewed pneumonias in the pediatric population. Despite advances in understanding the pathogenesis, etiology and improvement in diagnostic and therapeutic modalities, pneumonia remains a significant clinical problem. Renewed appreciation of this illness should be of interest to clinicians in all medical disciplines.

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Community Acquired Pneumonia

Mazen O. Al-Qadi, MD, Ali Al-Alwan, MD, Steven M. Opal, MD, Brian Cillley, DO, Fredric J. Silverblatt, MD

Pneumonia, along with influenza, is the eighth leading cause of death in the United States.[1] Pneumonia is common within all age ranges and comprises a significant cause of mortality, particularly in elderly individuals.[2,3] Although the introduction of antibiotics substantially reduced the mortality associated with pneumonia, significant mortality persists. This is likely due to host factors such as worsened prognosis and risk of aspiration associated with advancing age, increasing populations of immune-suppressed individuals and to pathogen-related factors such as antibiotic resistance and constantly evolving virulence mechanisms. In recent years clinicians have distinguished **community acquired pneumonia (CAP)** from those acquired in a **health care facility (HCAP)** because the difference in likely pathogens in each setting facilitates rational empiric choice of antibiotics. In this article we discuss the causes, diagnosis and treatment of CAP.

Risk Factors

Microorganisms gain entry into the lower respiratory tract through two common routes, micro aspiration of nasopharyngeal contents and direct inhalation of airborne microbial pathogens. Hematogenous spread of the organism to the lung is another less common source of acquiring CAP. In order to cause pneumonia, these organisms have to overcome numerous host defense mechanisms that protect the lung from infection. Impaired mucociliary function due to viral infections or tobacco smoking can cause damage to the ciliated respiratory epithelium. Impaired clearance of the organisms with excessive production of secretions accumulate in the alveoli, serving as an excellent media for bacterial growth. Influenza infection is one of the important predisposing factors to bacterial pneumonia, especially infection with *S. pneumoniae* and *S. aureus.* Disorders of mucociliary dysfunction (e.g. Kartagener's syndrome) or conditions associated with highly viscous and difficult to clear sputum (e.g. cystic fibrosis) predispose patients to recurrent pneumonia because of ineffective clearance of these secretions and increased colonization with resistant organisms, predominantly gram-negative bacteria and *S. aureus*.[4] In addition, impaired cough reflex and epiglottal function because of swallowing difficulties (e.g. stroke) or altered level of consciousness due to seizure or alcohol intoxication will predispose patients to aspiration. Pneumonia following aspiration of nasopharyngeal contents is associated with an increase in the incidence of anaerobic infection. Patients with AIDS, hypocomplementemia, asplenia, hematologic malignancy (especially multiple myeloma), organ-transplant receiving immunosuppressant therapy, diabetes mellitus, and chronic kidney disease all have altered immune system and are at greater risk of developing pneumonia.[5] Those individuals with immunodeficiency disorders are at risk of developing pneumonia from common respiratory pathogens and opportunistic pathogens.

Etiology

Despite the wide variation in etiology, *Streptococcus pneumoniae* remains the principal, causative pathogen of CAP worldwide. Although the organism responsible for CAP can be identified in only 40-50% of cases, several pathogens were recognized to cause CAP (Table 1)[6]

Table 1. The most common pathogens causing CAP

Organism	% of Cases
Streptococcus pneumoniae	20–60
Haemophilus influenzae	3–10
Gram-negative bacilli	3–10
Legionella spp.	2–8
Chlamydophila pneumoniae	4–6
Mycoplasma spp.	1–6
Staphylococcus aureus	3–5
Viral	2-15
Other (mixed anaerobes, *Moroxella* spp., Fungi, mycobacteria, etc.)	6-10

Streptococcus pneumoniae

S. pneumonia has 91 recognized serotypes based on the polysaccharide capsular structure. However, most CAP cases are caused by few serotypes (1, 2, 3, 4, 7, 8, and 12), with serotypes 2 and 3 being considered the most virulent. The thick capsule of *S. pneumoniae* resists phagocytosis mediated by immunoglobulins and complement factors (C3b). Patients with hypogammaglobulinemia, multiple myeloma, sickle cell disease, and early complement deficiencies (C1, C2, C3, and C4) are rendered at great risk for developing severe and recurrent pneumococcal infections. Another virulence factor of *S. pneumoniae* is the exotoxin pneumolysin expressed by almost all pathogenic strains of *S. pneumoniae*. This potent cytotoxin causes lysis to host cells, impairment of epithelial ciliary function, and induces inflammation[7]. CAP caused by *S. pneumoniae* usually begins with a sudden, single rigor and might be associated with the characteristic rusty sputum. In addition, pneumococcal infection commonly involves the pleura causing pleurisy and parapneumonic effusion. Bacteremia, empyema and metastatic infections (e.g meningitis) are potential complications and should be considered if fever persists despite adequate treatment. (Figure 1)

H. influenzae

Both strains (Group B and nontypable) *H. influenzae* can cause CAP. The incidence of *H. influenzae* B infection has significantly decreased because of the vaccination in children with the HiB conjugate. Risk factors of *H. influenzae* infection include advance age, COPD, pregnancy, splenectomy, and HIV infection. Appropriate treatment of *H. influenzae* consists of a respiratory flouroquinolone, a macrolide, or a β-lactam–β-lactamase inhibitor combination (e.g. ampicillin-sulbactam) as *H. influenzae* is resistant to ampicillin in up to 40% of the cases.

Legionella pneumophila

The most common source of *Legionella* infection is inhalation of water droplets contaminated with this pathogen. Individuals at risk are elderly and immunocompromised patients. Clinically, it is usually associated with high fever, dyspnea, and variable extra pulmonary manifestations. These include myalgias, confusion, headache, diarrhea, and relative bradycardia.[8] Classic laboratory findings include hyponatremia, hypophosphatemia, marked leukocytosis, and elevated transaminases. When suspected, the highly sensitive and specific urinary antigen should be used to confirm the diagnosis. Treatment usually consists of a macrolide, fluoroquinolone, or doxycycline.

Mycoplasma pneumoniae

Mycoplasma is a common cause of CAP, especially in young healthy people. It is usually acute in onset, starts with headache and fever, and dry cough develops later. Physical examination is usually out of proportion to the radiographic findings. Extra pulmonary manifestations are common (e.g. bullous myringitis, Guillain-Barr• syndrome, aseptic meningitis, and hemolytic anemia).[9] Specific complement fixation test is recommended to make the diagnosis, as cold agglutinins are nonspecific. As in other atypical CAP, macrolides, or fluoroquinolones are usually appropriate therapies.

Chlamydophila pneumoniae

C. pneumoniae is responsible for 10% of all CAP cases. The clinical and radiographic manifestations are usually indistinguishable from CAP due to *Mycoplasma spp*. Patients usually present with dry cough associated with sore throat and fever. Upper and lower airways are involved, with hoarseness of voice and wheezing. *C. pneumoniae* is thought to play a role in the pathogenesis of coronary artery disease. Chest x-ray usually shows unilateral patchy infiltrate. Specific testing is usually not recommended, and treatment is usually empirical.

Community Acquired-MRSA

The incidence of CA-MRSA pneumonia is increasing. The virulence of these resistant strains of MRSA is related to the Panton-Valentine leukocidin protein and other virulence properties. CA-MRSA can cause severe necrotizing and hemorrhagic pneumonia. CA-MRSA should be anticipated in patients with cavitary CAP, severe CAP complicated by shock or respiratory failure, and in CAP preceded by

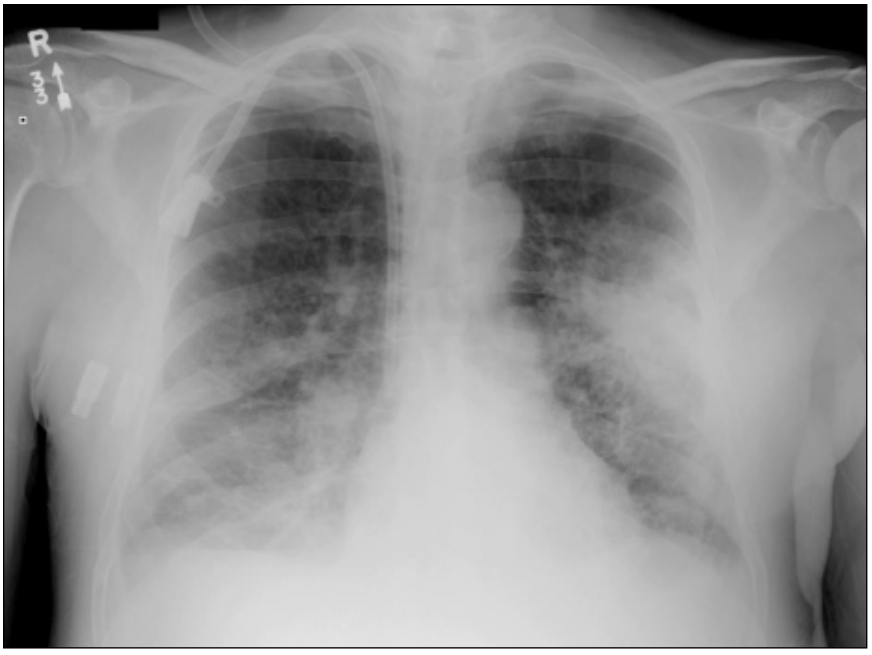

Figure 1. Anterior-Posterior view of a chest radiograph from a patient with severe pneumococcal pneumonia with bilateral infiltrates and a dense consolidation at the left mid lung field.

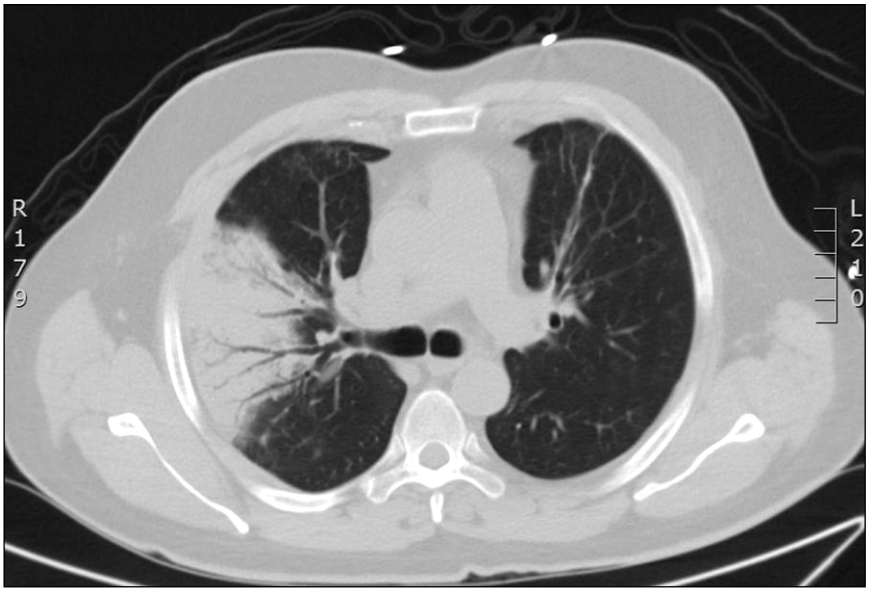

Figure 2. Computerized tomography of the lung showing a dense right sided infiltrate secondary to CAP from *S. aureus.*

influenza[10]. When CA- MRSA is suspected, vancomycin or linezolid should be included in the antibiotic regimen used for treatment. CA-MRSA is usually resistant to all β-lactams. Unlike nosocomial strains, CA-MRSA can be susceptible to clindamycin. (Figure 2)

Influenza and other Respiratory viruses

Viruses account for about 6% of CAP. This past year saw a pandemic of a novel H1N1 strain. Influenza and other respiratory viruses are considered in greater detail in accompanying articles in this issue.

Diagnosis

Laboratory Workup

In young healthy individuals with mild CAP, few laboratory tests are usually required. **White blood count (WBC), blood urea nitrogen (BUN)** and serum creatinine are helpful for the initial evaluation and to assess for the severity and hydration status of the patients. Blood culture is not required as part of the workup in mild CAP as would be seen in the outpatient setting. Only 10% of all hospitalized patients with CAP have positive blood cultures.[11] However, blood culture becomes essential in patients with severe CAP who require ICU admission and when antibiotic resistance is a concern. Pulse oximetry or ABG should also be done to evaluate for adequate oxygenation. Specific workup to identify the specific pathogen should not be done routinely. (Table 2) However, in the presence of epidemiologic clues or if the clinical presentation is suggestive of an unusual organism, further testing is required.[12] Furthermore, testing for specific pathogen is crucial in patients with severe CAP as pathogen-directed therapy was associated with higher survival rate in ICU patients. In those patients, studies should include sputum (or endotracheal aspirate if intubated patient) culture, blood culture, and urinary antigen for *Legionella spp.* and *S. pneumoniae*[13]. Although the diagnostic yield of sputum Gram stain and culture is not high, negative results are usually sufficient to withhold broad-spectrum antimicrobial coverage (e.g. empiric coverage for MRSA and *P. aeruginosa).*

Sputum Gram stain and culture are also recommended for hospitalized patients who failed outpatient therapy, have structural lung disease or cavitary infiltrate on chest x-ray, positive urine antigen test for pneumococcus or *Legionella spp.* and patients with pleural effusion.[13]

Radiography

The clinical diagnosis of CAP based on symptoms (chest pain, cough, and dyspnea) and signs (fever, tachycardia, and abnormal breath sounds) was unreliable compared to the combination of chest x-ray and clinical features.[18] Chest radiographs are considered the cornerstone in the diagnosis of CAP. However, chest radiographs can be falsely-negative in patients with early (first 24 to 48 h) pneumonia, neutropenia, or dehydration. In addition, chronic radiographic changes (as in lung cancer, or congestive heart failure) may obscure of pneumonia infiltrates. Although the pattern of infiltrate on chest radiography is not a reliable predictor, it serves as a rough guide to possible microorganism causing CAP. (Table 3)[19] The presence of a homogenous density that involves a distinct lobe of the lung (lobar pneumonia) and does not cross the fissures is suggestive of bacterial pneumonia. A bilateral patchy infiltrate usually indicates a bronchopneumonia where the infection extends along bronchi to adjacent areas and is not confined by the pulmonary fissures. Patients with immunodeficiency conditions (e.g. AIDS) are prone to unusual organisms which tend to primarily involve the interstitium, causing interstitial pneumonia and result in a diffuse granular infiltrate. Fungal infections usually result in diffuse reticulonodular opacities which may cavitate, and are associated with hilar and mediastinal lymphadenopathy. Septic emboli to the lung from right-sided endocarditis can also present with multiple nodular le-

Table 2: Diagnostic tests for CAP14,15,16, 17

Diagnostic study	*Sensitivity (%)*	*Specificity (%)*
Pneumococcal urinary Antigen	50-80%	> 90%
Legionella Urinary antigen	70-90%	99%
Influenza antigen	50-70%	100%
Blood culture	5%–14%	–
Sputum culture	Yield 20-79%	Yield 20-79%
Sputum Gram stain Pneumococci	15-100%	11-100%
Chlamydophila spp. Rapid PCR (sputum, BAL)	30-95%	>95%
Serology	10-100%	
Other (*Mycoplasma, Chlamydophila, Legionella* spp., Viral or fungal pathogens.		

Table 3: Radiographic findings and possiblecausative pathogens

Radiographic Pattern	*Possible Pathogens*
Lobar pneumonia	*S. pneumoniae*, *H. influenzae*, *Legionella spp.*
Bronchopneumonia	Viral, *Mycoplasma, Chlamydophila spp., S. aureus.*
Interstitial pneumonia	Influenza, CMV, *Pneumocystis jirovecii,* miliary TB.
Nodular lesions	Histoplasmosis, Coccidioidomycosis, Cryptococcosis, septic emboli
Cavitary lesions	Anaerobes (aspiration), *S. aureus,* Tuberculosis, Fungal, Nocardia.
"Bulging fissure" sign	*Klebsiella pneumoniae*
Wide mediastinum	Anthrax

sions which mimic pulmonary metastases. Cavitary lung lesions are commonly seen in patients with tuberculosis and alcoholics with aspiration pneumonia. Cavities result from tissue necrosis and are usually filled with necrotic material. (Figure 1)

High resolution computed tomography (HRCT) can be used to detect infiltrates in patients with structural lung disease (e.g. patients with malignancy). In addition, HRCT is superior to chest radiographs in patients with cavitary lesions or hilar lymphadenopathy.[20, 21]

Prognosis and Clinical Decision-Making

Mortality rates in patients with severe pneumonia have been reported as high as 28%. Approximately 10% of patients with CAP will develop severe disease, as defined by admission to an intensive care unit due to shock or respiratory failure. Approximately one third of patients who develop severe pneumonia have no prior history of significant comorbidities. Determining the severity of illness at presentation is important for prognosis and clinical decision making; assessing whether patients need to be hospitalized or can be managed at home, whether they can be assigned to a general medical bed or require close physiological monitoring in the setting of an ICU. Two tools for assessing severity of illness have proven useful: the CURB-65 and **pneumonia severity index (PSI).** In addition to pre-existing risk factors (listed above), these tools have identified confusion, uremia, respiratory rate greater than thirty per minute, hypotension (SBP < 90 or DBP < 60), hypothermia (< 35 C) or hyperpyrexia (>40 C) as poor prognostic indicators. Both of these indices have been validated and recommended by the IDSA/ATS community-acquired pneumonia guidelines. The relative disadvantages of these indices include risk factors not included in the CURB-65 criteria, the time-occupying and cumbersome nature of the PSI, and the fact that they may be either redundant or inferior to the clinical judgment of the physician.

Two tools for assessing severity of illness have proven useful: the CURB-65 and pneumonia severity index (PSI).

Treatment of CAP

Multiple studies have demonstrated that a limited number of micro-organisms are responsible for the majority of CAP. From what is known of the likely antibiotic sensitivities of these pathogens, recommendations have been formulated for antibiotic choices before the results of culture and sensitivity studies are known. The most widely used guidelines are those issued by the joint committee of the Infectious Diseases Society of America and the American Thoracic Society[13]. They recommend that empiric treatment of pneumonia in the outpatient setting in a patient who is overall healthy and has no risk factors for antibiotic-resistant pathogens can be treated with either:

Macrolide

- Azithromycin 500 mg orally once, then 250 mg orally daily for the following 4 days
- Clarithromycin 500 mg orally twice daily
- Erythromycin 500 mg orally three times daily; or
- Doxycycline
- 100 mg orally twice daily

For patients with risk factors such as chronic, liver, heart, lung, or kidney disease, diabetes, alcohol usage, asplenia, immunosuppression, any antibiotics in the preceding 3 months, or other risk factors for drug-resistant *S. pneumoniae* (DRSP) including a community-wide prevalence above 25%,

- Beta-lactam plus a macrolide (or doxycycline)
- Amoxicillin 1 gram orally three times daily
- Cefpodoxime 400 mg orally twice daily
- Cefuroxime axetil 500 mg orally twice daily

The outpatient with pneumonia should be encouraged to contact the treating physician or an emergency room if severe dyspnea or worsening clinical status develops. Reassessment of clinical status either by the patient or a health care provider should occur at 48-72 hours to assess for an appropriate response to antibiotics.

For patients warranting admission to the hospital, monotherapy with azithromycin or doxycycline is **not** recommended due to varying prevalence of antibiotic resistance. Non-ICU patients can be treated with either:

- A fluoroquinolone alone for 7-10 days, such as
  Levofloxacin 750mg, IV/PO q 24h
  Moxifloxacin 400mg IV/PO q 24h
- **Or** Beta-lactam, such as
  Ceftriaxone, 1 g IV q 24h
  Cefotaxime, 1g IV q 8h
- **Plus**, either Azithromycin, Clarithromycin, or Doxycycline

Development of a worsening clinical exam should prompt repeat radiographic examination. An assessment for an adequate response should occur at 48-72 hours of antibiotic administration. Persistent fever should prompt investigation for bacteremic pneumonia including repeating blood cultures.

Most patients with CAP who necessitate admission to an **intensive care unit** (**ICU**) either have a tenuous or failing respiratory status. The logic behind expanding coverage in patients with similar risk factors to more stable patients reflects the severity of the consequences of leaving the pathogen inadequately covered by the antibiotics chosen. Combination therapy is indicated for these patients. The following are recommended in the guidelines:

- Beta-lactam plus a macrolide or a flouroquinolone
  e.g. Ampicillin/Sulbactam, Ceftriaxone, Cefotaxime, Ertapenem
- PLUS Azithromycin, Levofloxacin, or Ciprofloxacin
- For penicillin-allergic patients, Aztreonam plus Levofloxacin or Moxifloxacin is recommended.
- Coverage of MRSA with either Vancomycin or Linezolid should be considered
- If Pseudomonas is a suspected pathogen, Piperacillin/tazobactam, Imipenem, Meropenem, or Doripenem should be the beta-lactams used and these should be combined with either Levofloxacin or Ciprofloxacin (400mg IV q8h.)
- Aminoglycoside usage can be considered

Risk factors for MRSA infection should be considered, such as prior colonization, current colonization, home wound care, hemodialysis, and close contacts with an individual with MRSA. Linezolid or vancomycin should be empirically added to the above regimens when suspected. MRSA pneumonias more commonly cause necrotizing infections and empyemas than other pneumonic pathogens.

De-Escalation and Duration of Antibiotic Treatment

Concern for the rising costs of treatment and the rise of antibiotic resistant strains has focused optimizing the duration of intravenous antibiotic use. Conversion from intravenous to oral antibiotics should occur in patients with stable hemodynamics (Temperature 38C or less, pulse ox >92% and respiratory rate 24 or less) who are able swallow and absorb oral medications.

Duration of therapy is usually 5-7 days. A full two weeks rarely needs to be given for community-acquired pneumonia, except for CAP due to atypical organisms such as *Mycoplasma, Chlamydophila* and *Legionella* species. When a patient shows no or little sign of clinical instability and a clear trend toward improvement, a consideration for stopping antibiotics should occur.

Prevention

Prevention of CAP in adults includes vaccinating appropriate groups annually for Influenza and the polysaccharide pneumococcal vaccine. Asplenic patients should be given pneumococcal and the *Haemophilus influenzae* type B vaccines, which may prevent bacteremic pneumonias in this group. Patients admitted to a hospital should be assessed for vaccination status at admission and vaccinated at time of discharge. Encouraging reduction and cessation of smoking in the general and high-risk populations likely will reduce incidence and severities of pneumonia.

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Managing Health Care Facility Associated Pneumonias: Diagnosis, Treatment and Prevention

Fredric J. Silverblatt, MD

Pneumonias acquired in a healthcare facility have different epidemiology, risk factors, responsible pathogens, treatments and outcomes than those acquired in the community. Patients with such infections generally have greater mortality and incur greater medical costs. Initially, hospitals were regarded as the major site for this paradigm; more recently, long term care facilities, rehabilitation institutions, dialysis centers and outpatient infusion facilities have also been recognized as posing similar risks. Pneumonias that occur in the ICU carry particularly serious implications. In 2005, a joint committee of the Infectious Diseases Society of America and the American Thoracic Society issued guidelines to help diagnose and manage these infections.[1] Additional research has shown that these infections are not inevitable and that focused, coordinated efforts can reduce their risk and the subsequent serious consequences.

Definitions

The 2005 IDSA/ATS guidelines provided the following definitions:

- A **Hospital-acquired pneumonia (HAP)** is one that presents clinically at 48 or more hours of admission in the absence of evolving, pre-existing infection.
- A **Healthcare-associated pneumonia (HCAP)** is one that occurs in a non-hospitalized patient with one or more of the following risks:
  – Hospitalization in an acute care facility for 2 or more days during the preceding 90 days.
  – Residence in a long term care or rehabilitation facility.
  – Receipt of IV antibiotics, chemotheraphy or wound care within the prior 30 days or attended a hospital or outpatient dialysis center.
- **Ventilator-associated pneumonia (VAP)** refers to a pneumonia that occurs 48-72 h after endotracheal intubation. This is a subset of HAP.

Epidemiology

Pneumonias are the second most common nosocomial infection after urinary tract infections. They carry a high morbidity and mortality rate and account for considerable increase in length of stay and contribute substantially to the rise in hospital expenses.[2] Most cases of HAP occur among patients who are not in the ICU; however, the highest expenses and mortality are found in those admitted to ICUs. This is particularly true for patients who develop VAP. Warren, Shulka et al. compared outcomes and costs of VAP in their ICU. The rate of pneumonia was 127/879 (15.5%) of patients requiring intubation. Infected patients had an increase in length of stay (26 v 4 days), increase in mortality (50 v 34%) and an increase in attributable costs ($118,097).[3] The **Centers for Medicare and Medicaid Services (CMS)** report there were an estimated 30,867 episodes of VAP in American hospitals in 2007 with an average cost of $135,795 per hospital stay.[4] In 2008 the CMS proposed adding VAP to its list of non-reimbursable expenses.

Pathogenesis

For the most part, both nosocomial pneumonias (HAP/VAP and HCAP) and **pneumonias acquired in the community (CAP)**, result from aspiration of oropharyngeal secretions contaminated by potential pathogens. Whereas with CAP those pathogens tend to be *Streptococcus pneumoniae* and other respiratory pathogens with a low rate of antibiotic resistance, in the case of HAP, aspirated material is more likely to be contaminated with organisms resistant to multiple antibiotic. Within a few days of hospitalization, patients undergo replacement of their community flora with "hospital flora" that are more adapted to the hospital environment, i.e., able survive exposure to multiple antibiotics. A similar replacement occurs in non-hospitalized individuals with chronic medical conditions in long term or rehab facilities. Micro aspiration occurs commonly, even among healthy ambulatory individuals, but the virulent hospital organisms are more likely to overwhelm local host in the lower respiratory tract and cause disease. While endotracheal tubes would be expected to protect against aspiration, contaminated secretions can pass into the lower respiratory tract between the outside of the tube and the surface of the trachea.

Other factors that contribute to the risk of HAP are medications and treatments that increase the risk of aspiration or impair the ability of the host to clear aspirated material. Sedatives and many medications for pain blunt the epiglottal reflex. Other medications impair the muco-cilliary elevator mechanism, reducing clearance of aspirated material from the lower respiratory tract. Patients recovering from upper abdominal or thoracic surgery cannot cough without pain and are at greater risk of post-operative pneumonia. Patients on mechanical ventilation are at risk from pooled oral secretions or contaminated solutions from the surfaces of tubing and other components of the ventilator. The normal acidity of gastric fluid inhibits the growth of many potential pathogens and the routine use of H2 blockers and proton pump inhibitors has been linked to the risk of HAP/VAP. The common practice of maintaining intubated patients in a prone position, especially during enteral feeding, facilitates aspiration.[5] Patients can become colonized and then infected from exposure to contaminated environmental surfaces such as the hands and clothing of health care workers, instruments used in patient care and from nearby infected patients.

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Microbiology

Microbial species that are believed to cause nosocomial pneumonias are adapted to the healthcare environment. These include Gram-negative species such as enterobacteraceae (e.g., E. coli, Klebsiella spp, enterobacter spp.), and non-enterobacteraceae Gram negative

species (e.g., *Pseudomonas aeruginosa* and Acinetobacter spp.). Gram-positive organisms include streptococcal spp. and *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA). Many infections are polymicrobial or yield no identifiable pathogen on culture. Anaerobes are often isolated in cases of aspiration pneumonia. Fungi are identified primarily in pneumonias that develop in immunocompromised patients and the recovery of candida or aspergillus species from non- immunocompromised patients is most likely due to colonization of the trachea rather than true infection. Respiratory viruses, e.g. influenza, parainfluenza, adenovirus or respiratory syncitial virus only rarely are the cause pneumonia in hospitalized patients, usually in the setting of an outbreak on the ward or in the community.

Clinical Presentation

HAP should be suspected when patients develop a new infiltrate on chest x-ray plus one or more of these following signs and symptoms -cough, production of purulent sputum, dyspnea, tachypnea, leukocytosis and fever. On physical exam patients may have signs of pulmonary infection such as rales, dullness to percussion and a change from voiced "E" to "A" on auscultation. Hospitalized and/or patients with chronic diseases are often elderly or frail and may present without fever. Because of the greater virulence of nosocomial respiratory pathogens, pulmonary necrosis and extension of the infection to the pleural surface is more common. Involvement of the lower lobes may present with predominantly upper abdominal symptoms. It is nonetheless difficult sometimes to distinguish pneumonia from non-infectious clinical conditions that present in a similar fashion, e.g., pulmonary embolism or adult respiratory distress syndrome.

Diagnostic Studies

Given the high mortality of HAP and the high prevalence of antibiotic-resistant organisms, vigorous efforts should be undertaken to obtain lower respiratory secretions to permit identification of the responsible pathogen(s) and antibiotic sensivities. Positive identification of a pathogen also helps distinguish pneumonia from noninfectious conditions with similar clinical presentation. Optimally, recovery of lower respiratory secretions involves the use of bronchoscopy. The usual technique employs either bronchoalveolar lavage or the use of a protected brush. For intubated patients, a catheter can be inserted into the endotracheal tube and the lower respiratory tree washed with saline. Because small amounts of contaminants usually cannot be avoided with of these techniques, the number of organisms recovered should be quantitated. "Significant" growth is usually defined as 10^4 or greater. Gram stains and, where appropriate, acid-fast and fungal stains should be ordered. Expectorated sputum, or material obtained non-bronchoscopically by deep tracheal suction are much less reliable sources of true, uncontaminated alveolar secretions. In practice, however, bronchoscopy is seldom used for this purpose and the diagnosis of HAP is usually made on clinical and radiological grounds. Blood cultures should be obtained in all cases. While the yield is usually not more than 25%, isolation of a respiratory pathogen from the blood is usually is a reliable indicator of causation.

The increasing use of powerful antibiotics has led to an ever increasing cycle of resistant organisms.

Treatment

Once the decision has been made to use antibiotics, the choice of empiric therapy is based on the presence of risk factors **for multi-drug resistant organisms (MDR);** e.g., a high prevalence of resistant organisms in the clinical setting (consult the institutional "antibiogram"), the use, if any, of prior antibiotic therapy (within 90 days), and the time of onset of disease. Pneumonias that develop early (less than 5 days) are less likely to be caused by MDRs than those which develop later in the admission. and sensitivity data of microbial cultures should be interpreted with the caveats mentioned above. The following recommendations were taken from the IDSA/ATS 2005 guidelines for the management of adults with HAP, VAP and HCAP.

Early onset pneumonias and those who do not have other risk factors for MDS are usually due to antibiotic-sensitive organisms. These include *Streptococcal pneumoniae*, *Haemophilus influenzae*, Methicillin-sensitive *Staphylococcus aureus* and antibiotic-sensitive enteric Gram negative bacilli (E. coli, Klebsiella spp. etc).

- Recommended antibiotic for low risk HAP/VAP/HCAP:
  – Ceftriaxone, 2g, IV q24h Or a respiratory fluoroquinolone (e.g, Levofloxacin 750mg or moxifloxicin 400mg IV/PO q24h

Or

  – Ampicillin/sulbactam (3g IV q 6h)

Or

  – Ertapenem 1g IV q 24h.

For late onset pneumonia or in patients with known risk factors for MDR pathogens the responsible pathogens include, in addition to those listed above for early onset pneumonia, Pseudomonas aeruginosa, Extended beta-lactamase producing strains of E.coli and Klebsiella pneumonia (ESBL) and Acinetobacter spp.

- Recommended initial empiric therapy for MDR pathogens:
  – Antipseudomonal cephalosporin (Cefepime, 1-2g IV q 8-12 h, or Ceftazidime, 2g q 8h)

Or

  – Antipseudomonal carbopenem (imipenem or meropenem, 1 g IV q 8h)

Or

  – Beta-lactam/beta-lactamase inhibitor combination (Piperacillin-tazobactam, 4.5g q6h)

Plus

  – Antipseudomonal fluoroquinolone (ciprofloxacin, 400mg IV q 12h or levofloxacin 750mg IV q 24h)

Or

  – Aminoglycoside (gentamicin or tobramycin, 7mg/kg q24h, or Amikacin 20mg/kg q 24h)

Plus

  – Anti –MRSA therapy (vancomycin 30mg/kg as a single loading dose followed by 15mg/kg q12h, linezolid 600mg q12h)

Doses should be adjusted for abnormal renal function. Trough levels should be obtained for the aminoglycosides and vancomycin. For gentamicin and tobramicin they should be less than 1 microgram, for amikacin they should be less than 4-5 micrograms and for vancomycin they should be between 15-20 micrograms/ml.

Special Pathogens

Empiric treatment should be refined once culture and sensitivity information is returned. Some pathogens that are isolated in patients with HAP or VAP require special consideration because of unusual resistance patterns. *Acinitobacter baumanni* has been implicated in outbreaks of HAP and VAP, particularly in the ICU.[6] Because acinitobacter is found in environmental sites and may be a non-pathogenic colonizer caution must be used in implicating it as a cause of pneumonia unless it is isolated from a normally sterile site or from the blood, or amidst an outbreak. Many strains are highly resistant to antibiotics. The most active agents are imipenem, cefepime, ampicillin/sulbactam, and amikacin. For those strains that are totally resistant to conventional antibiotics, colistin, an antibiotic in use in the '60s but abandoned when less toxic alternatives became available, is recommended in combination with imipemen or ampicillin/sulbactam.

Another organism sometimes recovered from the sputum of hospitalized patients with pneumonia is *Stenotrophomonas maltophilia*. Like acinitobacter, stenotrophomonas is found in the environment and more often colonizes the trachea rather than causes disease; however, it can be a true pathogen particularly in patients with underlying structural lung disease such as cystic fibrosis or in patients on mechanical ventilation.

Stenotrophomonas is best treated with trimethoprin/sulfamethoxazole. **Extended-spectrum beta-lactamase producing strains of enterobacteriaceae (ESBL)** display variable resistance to cephalosporins (e.g. ceftriaxone) and anti-pseudomonal penicillins (e.g. piperacillin/tazobactam). Carbopenems are the most reliable empiric agents against ESBL-producing strains. Ominously, strains of Klebsiella have emerged recently that produce **carbapenemases (KPC)** that bestow the broadest resistance. For such strains, colistin or tigecycline may be the only options.

Prevention

With rates of resistance on the rise and fewer effective antibiotics available, greater efforts need to be made to prevent nosocomial infections including pneumonias. Increasing awareness on the part of healthcare worker of modifiable risk factors has led to reductions of HAP and VAP in those hospitals that have launched such programs . These actions have included increasing compliance with hand-washing protocols using alcohol-based disinfectants, surveillance for introduction of new MDR organisms and isolation of patients so infected. Measures to reduce the risk of VAP include reducing the use of orotracheal intubation by employing non-invasive ventilation techniques whenever possible, careful emptying of contaminated condensates from ventilator circuits, continuous aspiration of subglottic secretions, and keeping patients in the semi recumbent position (30-45 degrees) during enteral feeding. The increasing use of powerful antibiotics, particularly broad-spectrum, highly active agents such as beta-lactam betalactam inhibitor combinations, 3rd and 4th generation cephalosporins, carbopenems (e.g., imipenem-cilastin) and fluoroquinolones has led to an ever increasing cycle of resistant organisms. A program of careful oversight and management of antibiotic use by clinical pharmacists and infectious disease experts (antibiotic stewardship) can minimize the emergence and spread of these problematic pathogens.

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Post-influenza Pneumonia: Everything Old Is New Again

Melina Irizarry-Acosta, MD, and Yoram A. Puius, MD, PhD

The 1918-1919 Influenza pandemic spread worldwide with remarkable speed. Approximately 500 million people were infected, and the death toll was between 50 and 100 million worldwide.

It is hypothesized that a major cause of morbidity and mortality may not have been the viral pneumonitis, but the bacterial superinfection of the susceptible post-influenza lung. Here, we will review the role of bacterial coinfection in past influenza pandemics, and how it relates to the current H1N1 strain of 2009-2010.

Morbidity and Mortality: Lessons from History

A number of scientific accounts elaborated on the role of bacterial superinfection in the 1918-1919 influenza pandemic. In 1921, Opie et al.[1] published an investigation of causes of respiratory diseases in military personnel, investigating an epidemic of influenza affecting 22.7% of more than 50,000 personnel at Camp Pike, Arkansas, with an incidence of pneumonia of 2.9% which was observed to follow one week after the influenza outbreak. The excess mortality, 466 deaths, was attributed to pneumonia: "In a civil hospital there is often great difficulty in deciding, even in the presence of an epidemic, if death from pneumonia is the result of influenza, but at Camp Pike the relation of the heightened death rate to the epidemic has excluded all save a trivial error in determining the relation of fatal pneumonia to influenza."

The group's collection of microbiological and pathological data emphasizes the pervasive presence of *Bacillus influenzae* (*Haemophilus influenzae*) as well as pneumococci, but makes mention of other *Streptococcus* species, *Micrococcus catarrhalis* (*Moraxella catarrhalis*) and even *Bacillus coli* (*E. coli*) as some of the most frequently found pathogens. The isolation of *H influenzae* was so frequent, in almost 80% of cases, that it was thought to be "constantly present." Patterns of bronchitis, bronchopneumonia, and lobar pneumonia were identified in autopsy investigation, and microscopic examination of the lung described destruction of the epithelium as "changes in the bronchial walls [that] destroy the defences against invasion by microorganisms." The authors observed that these findings were similar to previous epidemics, most notably a pandemic of 1889-1890.

These themes recurred in a study published by Vaughan in the same year.[2] Comparing the 1918-19 pandemic with previous outbreaks of influenza, he stated: "The secondary invaders of pathogenic importance are the various forms of the streptococcus and pneumococcus, the meningococcus, the staphylococcus, and probably the tubercle bacillus and the influenza bacillus. In the last epidemic as in that of thirty years previously, the chief complications were bronchitis and pneumonia.."

Also in 1921, McCallum described the pathology of post-influenza pneumonia[3], making similar pathological and bacteriological observations from cases seen in two military camps as well as at Johns Hopkins hospital. In contrast with other scientists that regarded *Bacillus influenzae* as a primary pathogen in the pandemic, he states that "[n]o direct information has been gained as to the nature of the infective agent which...causes the epidemic disease influenza."

The actual causes of influenza-related deaths have been under discussion among the scientific community. One important aspect of the 1918-1919 pandemic, not always seen in other pandemics, was the "W-shaped" death curve, in which influenza mainly targeted infants, young adults (ages 20-40) and the elderly.

A modern rationale for the high numbers of young and otherwise healthy people among the casualties is the "cytokine storm," which leads to respiratory distress syndrome through a hemorrhagic alveolitis. The pathogenic potential of the inflammatory response may have been more severe in pandemic compared to non-pandemic strains, which may explain the difference in mortality. Support for this theory has been found in animal models of infection with a reconstructed 1918 virus, which demonstrated more severe lung pathology, higher mortality, and greater activation of pro-inflammatory and cell-death pathways.[4] An alternative hypothesis is simply that older patients had immunological memory to a related strain which had circulated in 1889, whereas the younger segment of the population lacked these protective antibodies[5].

Other reports, however, describe the mortality from primary pandemic influenza pneumonia as relatively uncommon. Brundage and Shanks[6] discuss the accounts of fatalities in the US, UK and New Zealand. In all three regions the time of death was highly variable, and that those with longer duration of illness were considered to have secondary bacterial infections. *H. influenzae*, pneumococci, hemolytic streptococci and on occasion, staphylococci were considered the main culprits. In 2008,[7] they went on to suggest that the actual infections with influenza were self- limited, but paving the way for lethal bacterial pneumonias, proposing the "sequential infection" hypothesis.

Morens and coworkers[8] reviewed a vast amount of data from the 1918-1919 pandemic which support the role of bacterial superinfections in the morbidity and mortality of pandemic influenza. They evaluated pathological, epidemiological, and microbiological reports published during the pandemic, encompassing a total of 8398 postmortem examinations. They then went on to directly evaluate samples obtained during autopsy from 58 influenza victims during the 1918-19 pandemic.

Lung tissue blocks obtained from autopsies performed during the pandemic, and preserved by the US military showed that, in virtually all cases, there was compelling histological evidence of severe acute bacterial pneumonia, either as predominant pathology or in conjunction with features now known to be associated with influenza virus infection: desquamation of respiratory epithelium of tracheobronchial and bronchiolar tree; dilation of alveolar ducts, hyaline membranes, evidence of bronchial and/ or bronchiolar epithelial repair. There were also changes consistent with either pneumococcal or streptococcal

pneumonia, and some had evidence of staphylococcal pneumonia, in the form of multiple small abscesses. In virtually all cases bacteria were seen in massive numbers.

Published articles from the pandemic period discuss postmortem examination findings as well as epidemiological data. Most agree that without secondary bacterial pneumonia most patients with influenza may have indeed recovered. There is a prevalent description of desquamative tracheobronchitis and bronchiolitis as the primary lesion of early severe influenza- associated pneumonia. This was associated with a sloughing of bronchiolar epithelial cells to the basal layer, hyaline membrane formation in alveolar ducts and alveoli, and ductal dilatation, as described by Opie et al.[1] in 1921. A primary "panbronchitis" gave way to an aggressive invasion of bacteria throughout the denuded bronchial epithelium. In the most severe cases, zones of vasculitis, capillary thrombosis and necrosis surrounding the bronchiolar damage were noted. Despite this, there was also noted a "histopathological asynchrony,"[1] with early epithelial regeneration, capillary repair and occasional fibrosis even in the most fulminant cases. This may be a reason why, despite the severe damage to the tracheobronchial tree that is generally ascribed to influenza-associated pneumonias, there are few reports of chronic respiratory damage noted in survivors.

Blood cultures were positive in 70.3% of cases, mostly growing known pneumopathogens such as *Streptococcus pneumoniae* and other streptococci. These were also the primary pathogens reported on cultures of pleural fluid and lung tissue. During the 1918-19 pandemic the incidence of *Staphylococcus aureus* was low, and a significant percentage of identified bacteria were nonpneumopathogens such as viridans group streptococci, *E. coli*, *Klebsiella* and *H. influenzae*, which were seen in coinfection with known pneumopathogens. *Bacillus* (later *Haemophilus*) *influenzae* was the primary coinfector in early symptomatic influenza and was associated with diffuse bronchitis and bronchiolitis. Outbreaks of meningococcal pneumonia were also documented.

An interesting alternative hypothesis for the distribution of influenza-related deaths is provided by Starko. [9] She notes that the doses in which aspirin was prescribed at the time are now known to be toxic, and may have resulted in pulmonary toxicity. Salicyclate overdose may have resulted in pulmonary edema, impairment of mucociliary clearance and increase in protein levels may have predisposed these patients to secondary pulmonary infections.

A makeshift emergency hospital at Camp Funston, Kansas, caring for soldiers sickened by the 1918 flu, as mentioned by Opie et al.[1] (Credit: The National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, D.C. Image number NCP 1603)

Prominent pathogens: Pneumococcus and S. aureus

Two pathogens that deserve special attention for their role in post-influenza pneumonia are *Streptococcus pneumonia* and *Staphylococcus aureus*. These are particularly noteworthy because they occur frequently in the role of superinfecting pathogen, and their virulence often results in significant morbidity and mortality.

In their review of historical culture data of specimens from the 1918-1919 pandemic, Morens et al.[8] *S. pneumoniae* was generally the single most commonly isolated organism, appearing in 1235/5266 positive lung tissue cultures (23.5%), 509/1887 positive blood cultures (27.0%), and 263/1245 pleural fluid cultures (21.1%). Brundage and Shanks[7] cited much of the same data, and argued that the median time to death of 7-11 days in military populations correlated with pneumococcal bacterial superinfection. Klugman et al.[10] generated a startling graph showing that the distribution of days of illness before death from influenza-related pneumonia during the 1918-1919 pandemic precisely reproduced that of untreated pneumococcal pneumonia in the 1920s and 1930s, leading to their conclusion that "similar times to death provide additional evidence that the in?uenza-related pneumonia deaths during the 1918 influenza pandemic were largely due to the pneumococcus."

In 1949, after the influenza virus had already been identified as the etiologic agent of the disease, Maxwell et al.[11] also noted the particular role of pneumococcus in coinfection. They studied cases of known bacterial pneumonia from 1946-7, spanning a time when influenza A was prevalent in the community, as well as during a time described as an "interpepidemic period." They found that "there was a simultaneous infection with pneumococci and influenza virus in about one-half of the human cases of lobar pneumonia studied during an influenza epidemic," suggesting that "bacterial pneumonia is in some way related to recent or concurrent infection with influenza virus."

Studies of later epidemics highlight the pneumococcus as well: patients confirmed to have epidemic influenza in Stockholm[12] (1969-70, 1971-72) showed bacteriologic and/or serologic evidence of pneumococcal infection in 12/116 patients (10%) in 1969-1970, and 37/176 patients (21%) in 1971-72.

However, since the seasonality of pneumococcal infection mirrors that of seasonal influenza, it has been unclear whether the correlation between influenza circulation and invasive pneumococcal disease has been causal. The most recent study of this association, using data in the United States from 1995-2006, found that in?uenza circulation was associated with 11%–14% of pneumococcal pneumonia during periods of elevated in?uenza circulation, with rates of 5%–6% overall.[13]

Vaccination of children with a heptavalent protein–polysaccharide conjugate and adults with a 23-valent polysaccharide vaccine has led to a decline in invasive disease. Pediatric vaccination seems to be associated with a decreased incidence in viral pneumonia due to influenza A, as well as other viral etiologies such as RSV, parainfluenza, and adenovirus, presumably through a "synergism between viral and pneumococcal infection." [14]

The role of *S. aureus* had not historically been as significant. Morens et al.[8] also identified *S. aureus* in autopsy cultures from 1918-1919, in 427/5266 (8.1%) of positive cultures of lung tissue, and 68/1887 (3.6%) of positive blood cultures, and 59/1245 (4.7%) of pleural fluid cultures. During the Hong Kong influenza epidemic of 1968-1969, the bacterial etiology of pneumonia admissions to Grady Memorial Hospital shifted: 25.9% of all pneumonias included *S. aureus*, compared to 10.2% from the previous year[14], although the actual rate of true influenza-*S. aureus* coinfection was not documented.

However, beginning in 2003, *S. aureus*, most notably community-acquired methicillin-resistant *S. aureus* (CA-MRSA), had been noted to be a significant cause of influenza-associated bacterial pneumonia as reported in a small case series[15], with a case fatality rate of 4/15 (26.7%), generally in people without comorbidities. A larger series of cases from the 2006-2007 influenza season[16, 17] confirmed that *S. aureus* pneumonia occurred in younger patients without comorbidities, the strains involved were predominantly CA-MRSA (28 out of 31 *S. aureus* isolates), and documented influenza virus coinfection was associated with a worse outcome. Worse outcomes of CA-MRSA-influenza coinfection have also been seen in the pediatric population.[18]

CA-MRSA pneumonia is often characterized by high fever, hypotension, rapid progression, and a requirement for ventilator support, often with multilobar infiltrates or cavitation.[19] Since it has now been firmly established as a major etiological agent of post-influenza pneumonia, it is worth considering empiric therapy for MRSA in any patient with a severe pneumonia fitting this presentation.[20] Vancomycin has long been considered the drug of choice for MRSA pneumonia; however, several recent retrospective studies and pharmacologic advantages of linezolid – greater penetration into the lung, the ability to shut down production of toxins such as the Panton-Valentine Leukocidin — support the empiric use of linezolid.[19]

The pathology of H1N1 influenza infection has overall been similar to that of prior pandemics.

The current H1N1 pandemic

The role of superinfection in the current H1N1 pandemic (2009-2010) has been extensively studied. The pathology of H1N1 influenza infection has overall been similar to that of prior pandemics,[21,22] with findings including diffuse alveolar damage, pulmonary hemorrhage, and necrotizing bronchiolitis. These results are thought to be due to some combination of direct damage from the virus and the host inflammatory response.

Of interest is the lower fraction of cases in which bacterial superinfection have been evident on pathology: There was no clear evidence of bacterial infection in a series of 5 confirmed H1N1 fatalities from Mexico[21], and only 3 of 21 patients had bacteria seen on histology in a series from Brazil.[22] However, antibiotics were given to many of these patients, possibly decreasing the amount of bacteria detectable on histochemistry alone compared to prior eras.

Other efforts to determine the relative contributions of viral pneumonitis and bacterial superinfection included a study of the immunomodulatory effect of H1N1 on the host[23]. Unsurprisingly, pro-inflammatory cytokines were elevated in the serum of infected patients, much with other strains of influenza. However, when peripheral blood mononuclear cells from H1N1-infected patients were stimulated with *S. pneumoniae*, they produced decreased amounts of TNFα and IFNγ, suggesting a defective cytokine response which may predispose to superinfection.

The use of molecular methods as an adjunct to traditional culture techniques adds another dimension to the estimation of the epidemiology of superinfection. On one hand, it can be argued that it enhances the sensitivity of culture techniques, which is especially important when the routine use of broad-spectrum antibiotics may cause false-negative results, both in culture and in lung pathology. On the other hand, the high sensitivity may result in colonizing organisms in low colony counts (e.g. as in chronic bronchitis) being counted as true pathogens.

With this caveat in mind, the most publicized study of bacterial coinfection in H1N1 found that, by a combination of PCR and immunohistochemistry, a coinfecting organism could be identified in 22/74 fatal cases[24]. The distribution of organisms was comparable to that observed in prior influenza superinfections: *S. pneumoniae* (45%), *S. pyogenes* (27%), *S. aureus* (32%), *Streptococcus mitis* (9%), *H. influenza* (5%), and multiple organisms (18%). (So far, the literature contains only one published report of a definitive coinfection with H1N1 and CA-MRSA.) The editorial note in the study concludes that "[t]he findings in this report indicate that, as during previous influenza pandemics, bacterial pneumonia is contributing to deaths associated with pandemic H1N1" but cautions that "the results cannot be used to assess the prevalence of bacterial pneumonia among patients who have died from pandemic H1N1." A series of 36 pediatric deaths also showed significant coinfections with *S. aureus, S. pneumoniae*, and other Streptococcus species[25].

A molecular study of 199 cases of H1N1 in Argentina allowed for the identification of coinfecting bacteria and viruses by PCR of nasopharyngeal swabs[26]. This study provided the best estimate of superinfection so far, detecting at least one additional potential pathogen in 152/199 (76%) of cases. Clinical outcomes seen in this molecular survey suggested that

coinfection with *S. pneumoniae* (62 cases) was associated with a worse prognosis. Additional bacteria identified included *H. influenzae* (104 cases), methicillin-sensitive *S. aureus* (35), and MRSA (6), as well as a smaller number of cases of *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Serratia marcescens.* These methods also allowed for the identification of coinfecting respiratory syncytial viruses (12 cases), rhinoviruses (5), and coronaviruses (3), adding an entire additional dimension to the possible causes of superinfection.

Given the prominent role of bacterial superinfection in morbidity and mortality, the fraction of critically ill H1N1 patients with evidence of bacterial pneumonia is lower than might be expected. Surveys of critically ill patients with H1N1 in Canada[27], Mexico[28], and Spain[29] documented a relatively low rates of detection of bacterial pneumonia after ICU admission, respectively 24.4%, 8%, and 3%. Bacterial pneumonia was not noted to be associated with a poorer outcome, but overall the use of empiric antibiotics was very high. Nosocomial pneumonia has also been noted in these studies[28], and should be considered for any hospitalized patient not improving on appropriate therapy.

Implications for management

The practical application of these data to the current H1N1 pandemic ultimately comes down to a few clinical questions: which H1N1 patients have post-influenza pneumonia, how should they be managed, and how do we prevent or prepare for it?

A textbook description of post-influenza bacterial pneumonia is as follows: "The patients (most often older adults or those with chronic pulmonary, cardiac, and metabolic or other disease) have a classic influenza illness followed by a period of improvement that lasts usually 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest radiograph."[30]

Specifically pertaining to H1N1, Wright et al.[31] also suggest that secondary bacterial pneumonia is more likely to be characterized by a secondary fever after a period of defervescence, a positive sputum Gram stain and/or culture, increased white blood cell count, and a later onset of respiratory compromise.

There are, however, difficulties with applying these generalizations, especially in the setting of the current H1N1 pandemic:

- Cases of infection and death appear to be concentrated in younger patients. Older age may reduce the likelihood of H1N1 infection, possibly due to exposure to related viruses earlier in life[32].
- No data are available to confirm the timing of bacterial infection described above, and bacteria are often cultured on first presentation with H1N1.
- Chest radiography findings in H1N influenza may be unilateral or bilateral, may include consolidations or ground glass opacities[33], and this cannot reliably exclude bacterial pneumonia

Cunha raises issues as to whether antibiotics should be withheld in H1N1 patients unlikely to be superinfected, since it may be rarer than previously thought[34, 35]. He then goes on to propose that patients without lobar or segmental infiltrates on chest radiography may not need antibiotics[36].

So, who is to be treated for bacterial superinfection? It is, perhaps, a tautology to state that a patient who meets criteria for diagnosis of community-acquired pneumonia[20] or healthcare-associated pneumonia[37] should be treated as such.

Patients who are not ill enough to be hospitalized may be considered for oral antibiotic therapy (see Cilley and Silverblatt, in this issue). Superinfection with atypical organisms such as *Mycoplasma*, *Chlamdyophila*, and *Legionella* species is rare and need not be a focus of the regimen, although tetracyclines, macrolides, or fluoroquinolones may cover them incidentally.

Patients ill enough to be hospitalized may be considered for broader-spectrum antibiotics, and risk-stratified for resistant organisms. The high prevalence of CA-MRSA in influenza cases, coupled with the high morbidity and mortality, make it essential that critically ill patients receive therapy to cover MRSA, such as linezolid or vancomycin.

Of course, the optimal method of managing post-H1N1 bacterial pneumonia is prevention. Thus, vaccination against both influenza and *S. pneumoniae* are essential components of preventive health care, as are all age-appropriate vaccinations.

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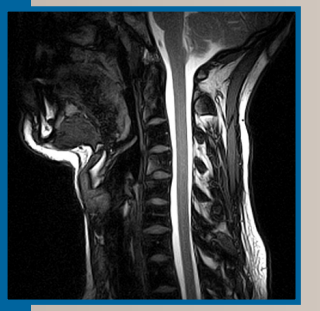

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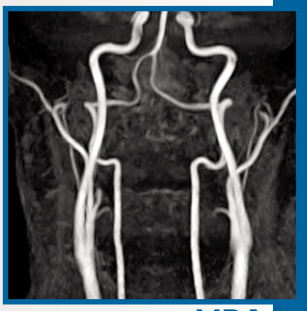

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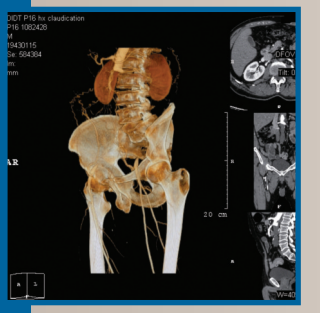

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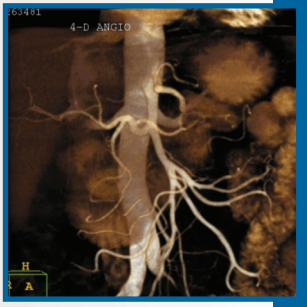

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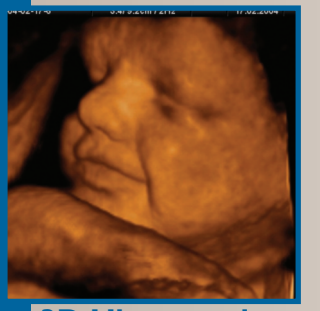

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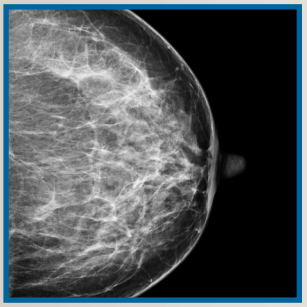

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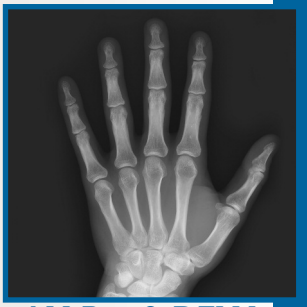

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Community-Acquired Pneumonia In Children

Penelope H. Dennehy, MD

Community-acquired pneumonia (CAP) is one of the most common infections encountered in pediatrics, with an annual incidence of approximately 40 cases per 1000 children in North America.[1] Despite its frequency, CAP in children remains difficult to diagnose, evaluate, and manage because many pathogens may be responsible, co-infections occur frequently, clinical features may vary widely, and laboratory testing to support the diagnosis is limited.

ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

Many pathogens cause pneumonia in children, including bacteria, viruses, and fungi. Because culture of lung parenchyma or pleural fluid requires an invasive procedure, most studies in children have relied on indirect methods such as rapid viral testing or **polymerase chain reaction assay (PCR)** on upper respiratory tract secretions, serology, and/or blood culture to identify the infecting pathogen. Studies that include an intensive search for etiology in hospitalized children with pneumonia identified a likely cause in up to 85% of cases, but an etiologic diagnosis is made in a much smaller proportion of outpatient cases. Due to a reluctance to perform invasive diagnostic procedures on young children, the epidemiology of CAP in children remains poorly defined.

The most common etiologies of pneumonia vary with the age of the patient (Table 1). In neonates, group B streptococcus and gram-negative enteric bacteria are the most common bacterial pathogens and are generally acquired through vertical transmission.[2] Viral pneumonia with cytomegalovirus and herpes simplex virus should be considered even without a suspicious maternal history. *Chlamydia trachomatis* infection, once a common cause of infection in infants, has become much less common through prenatal screening and treatment of maternal infection.

The most common cause of bacterial pneumonia in children older than 3 weeks is *Streptococcus pneumoniae.* Before the pneumococcal vaccine was introduced in 2000, *Streptococcus pneumoniae* accounted for 13 % to 28% of pediatric CAP.[3] Post-licensure epidemiologic studies show that all-cause pneumonia hospitalizations in children under age 2 in the United States have decreased by 39%, providing further evidence of the role of pneumococcus as a major cause of childhood CAP.[1, 4, 5]

Group A streptococcus, *Staphylococcus aureus, Haemophilus influenzae* type b, and *Moraxella catarrhalis* are less common bacterial causes of pneumonia. The organisms *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (formally *Chlamydia pneumoniae*) commonly cause CAP in school-age children and adolescents, although they may infect preschool-age children more commonly than generally recognized. In one study, the age of patients with atypical infection ranged from 9 months to 13 years, with 47% of infections occurring in those aged younger than 5 years.[6] *Bordetella pertussis* should be considered in young or unimmunized children with paroxysmal cough, whoop, posttussive emesis, or apnea. Tuberculosis should also be considered if the patient has suggestive clinical signs, has recently been to an endemic area, or has had contact with an individual with active tuberculosis.

Most cases of CAP in preschool-age children are caused by viruses, including **respiratory syncytial virus (RSV),** adenovirus, parainfluenza 1, 2 and 3, influenza A and B, human metapneumovirus, and rhinoviruses. Preceding viral illness is thought to play a part in the pathogenesis of bacterial pneumonia. A study by Ampofo and colleagues recently showed a strong temporal association between confirmed viral respiratory illness with RSV, influenza, and human metapneumovirus and invasive pneumococcal disease over six winter seasons.[7] Although their data do not prove causation, rates of invasive pneumococcal disease rose in close association with the diagnosis of respiratory viral illnesses each winter season.

Mixed infections may occur in 30% to 50% of children with CAP, including

Streptococcus pneumoniae and a virus, *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae* and *C. pneumoniae*.[3, 6]

Evaluation and Diagnosis

Children with fever, tachypnea, increased work of breathing, and an abnormal respiratory examination require evaluation for pneumonia. Goals of this evaluation include diagnosis and determination of likely etiologies while recognizing limitations of current diagnostic methods.

Table 1. Common Pathogens in Community-Acquired Pneumonia By Age

Age	Etiology	
	Bacterial	Viral
Birth to ≤ 3 months	Group B streptococci Gram-negative enteric bacilli Streptococcus pneumoniae Bordetella pertussis Chlamydia trachomatis Staphylococcus aureus Listeria monocytogenes	Respiratory syncytial virus Influenza A&B Parainfluenza viruses 1, 2 & 3 Human metapneumovirus Rhinovirus Adenovirus
3 months to 5 years	Streptococcus pneumoniae Mycoplasma pneumoniae Chlamydophila pneumoniae Haemophilus influenzae Moraxella catarrhalis Staphylococcus aureus *Streptococcus pyogenes*	Respiratory syncytial virus Influenza A&B Parainfluenza viruses 1, 2 & 3 Human metapneumovirus Rhinovirus Adenovirus
5 years and older	Streptococcus pneumoniae Mycoplasma pneumoniae Chlamydophila pneumoniae Staphylococcus aureus	Influenza A&B

Clinical Assessment

Children with CAP present with various clinical signs and symptoms. Symptoms and signs of pneumonia include fever, cough, tachypnea, nasal flaring, grunting, retractions, poor feeding, irritability, rales, and hypoxia, and the presence of these findings varies depending on the patient's age and the severity of illness. There is often a history of a preceding viral upper respiratory tract infection.

Although most present with fever and respiratory symptoms, such as cough and tachypnea, some children with pneumonia present with less classic symptoms, such as abdominal pain, nausea, vomiting, or chest pain. Abdominal pain may occur in patients with basilar pneumonia and at times is the most prominent complaint and may be mistaken for appendicitis. In a study of children admitted for abdominal pain, pneumonia was ultimately found to be causative in 1.6% of patients.[8]

Wheezing and exacerbation of underlying asthma are symptoms more typically encountered in patients with pneumonia caused by viruses and atypical bacteria such as *Mycoplasma pneumoniae* and *C. pneumoniae*. Symptoms such as headache, low-grade fever, pharyngitis, and cough usually precede signs of lower respiratory tract infection by 5 to 7 days in patients with atypical bacterial pathogens.

Multiple studies have sought to identify clinical variables that can be used to make an accurate clinical diagnosis of pneumonia. These studies found that no single clinical variable offers significant accuracy, although tachypnea has the highest sensitivity (45%-80%) and specificity (54%-75%).[9-11] Combining tachypnea, rales, and increased respiratory effort raises the specificity for a clinical diagnosis of pneumonia to 84%, but lowers the sensitivity to only 43%, thus missing a significant portion of patients with pneumonia, since the majority of patients do not have all three findings on examination.[11] A 1997 Canadian study concluded that the absence of tachypnea, crackles, decreased breath sounds, and respiratory distress effectively excludes pneumonia. [9] However, a subsequent study found that the sensitivity and specificity of these guidelines were only 45% and 66%, respectively. [12] The absence of crackles or rales does not preclude the diagnosis of pneumonia. Other signs of increased work of breathing, such as nasal flaring and retractions, increase the likelihood of pneumonia but are not highly sensitive or specific, as bronchiolitis may present similarly.

The **World Health Organization (WHO)** suggests that tachypnea and retractions are the most accurate signs for identifying pneumonia and should be used to guide management in areas with limited access to radiography. The WHO defines tachypnea as 50 breaths/min in infants 2 to 12 months of age, 40 breaths/min in children aged 1 to 5 years, and 20 breaths/min in children aged 5 years and older. Respiratory rate should be measured over 60 seconds due to variations in respiratory rate from periodic breathing and behavioral factors.

No single clinical sign reliably predicts hypoxia, although inability to breastfeed, grunting, or central cyanosis suggests it.[13] Oxygen saturation should be measured in patients with respiratory distress or ill appearance.

Laboratory and Radiologic Assessment

In outpatients the diagnosis of CAP does not generally require laboratory studies or radiographs. Patients requiring hospitalization typically undergo diagnostic evaluation, although a standard laboratory work-up has not been defined.

Most studies do not demonstrate a higher likelihood of bacterial infection in patients with high temperature or elevated white blood cell count.[3, 14] Acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate have low specificity for bacterial pneumonia.[3]

Blood cultures may provide useful microbiologic data, including antibiotic sensitivities, and are often obtained in hospitalized children with suspected pneumonia. However, with the use of the Hib and pneumococcal conjugate vaccines, the risk of bacteremia is extremely low in outpatients older than 2 months of age with uncomplicated CAP.[15, 16] The rate of positive blood cultures may be higher in hos-

Table 2. Antimicrobial Therapy in Community-Acquired Pneumonia Based on Age

Age	Therapy		
	Outpatient	**Inpatient**	**Inpatient Complicated Pneumonia**
Birth to 30 days	Not recommended	IV ampicillin + gentamicin	IV ampicillin + cefotaxime*
4 weeks to ≤ 3 months	Oral erythromycin# or azithromycin if *C. trachomatis* or *Bordetella pertussis* is suspected or confirmed	IV cefotaxime or ceftriaxone ± ampicillin§	IV cefotaxime or ceftriaxone ± ampicillin§*
3 months to 5 years	**Preferred:** high-dose oral amoxicillin ± azithromycin^ **2nd line:** oral clindamycin or oral third generation cephalosporin (cefdinir or cefpodoxime)	**Preferred:** IV ampicillin ± azithromycin^ **2nd line:** IV clindamycin or cefotaxime or ceftriaxone	**Preferred:** IV clindamycin + cefotaxime or ceftriaxone **2nd line:** IV vancomycin + cefotaxime or ceftriaxone
5 years and older	**Preferred:** azithromycin ± high-dose oral amoxicillinë **2nd line:** oral clindamycin or oral third generation cephalosporin (cefdinir or cefpodoxime)	**Preferred:** IV ampicillin ± azithromycin^ **2nd line:** IV clindamycin or cefotaxime or ceftriaxone	**Preferred:** IV clindamycin + IV cefotaxime or IV ceftriaxone **2nd line:** IV vancomycin + IV cefotaxime or IV ceftriaxone

* IV vancomycin or clindamycin should be considered if there is concern for MRSA.
\# Erythromycin is generally avoided in patients aged 6 weeks or younger because of an association with pyloric stenosis.
§ Add ampicillin if Listeria is suspected.
^ Consider adding azithromycin if symptoms persist despite ampicillin.
ë Azithromycin monotherapy may be used if there is a high level of suspicion for atypical pathogens. If the patient does not improve after 48 hours of treatment, high-dose amoxicillin may be added.

pitalized patients or those with pneumonia complicated by empyema.

Testing outpatients with uncomplicated CAP to determine etiology generally is not indicated. Hospitalized patients with pneumonia are often tested for cohorting purposes or to facilitate selection of antibiotic therapy. Bacterial cultures of nasopharyngeal secretions have low accuracy because upper airway flora may differ significantly from lower airway pathogens.[9] Older patients may be able to produce a sputum sample for Gram stain and culture. Sputum cultures must be interpreted cautiously, however, due to potential contamination with colonizing oropharyngeal flora. A high-quality sputum specimen should have few squamous epithelial cells (≤10 per high-powered field) and numerous white blood cells (≥25 per high-powered field) on Gram stain. Patients with symptomatic pleural effusions should have pleural fluid obtained prior to antibiotic administration, when possible. Gram stain and bacterial culture of pleural fluid should always be performed in patients with pneumonia who have had pleural fluid drainage.

Rapid tests are often used for RSV and influenza, while cultures are often available for parainfluenza, adenovirus, and other pathogens. Testing for human metapneumovirus and multiplex PCR assays for a panel of respiratory viruses are also available in some laboratories. Because multiple studies have demonstrated a high prevalence of co-infections or superinfections, isolation of a virus does not rule out the possibility of bacterial infection.[6, 17, 18]

Chlamydia trachomatis (in neonates) and *C. pneumoniae* can be detected via PCR although prolonged shedding can occur causing PCR tests remain positive outside a period of active disease. Both of these pathogens can otherwise be diagnosed by acute and convalescent serologies. For neonates and young infants direct fluorescent antibody testing can also be used on conjunctival and respiratory specimens for the diagnosis of *Chlamydia trachomatis*.

Mycoplasma pneumoniae is the most reliably detected by serologic testing in paired specimens obtained 2 to 3 weeks apart; a fourfold or greater rise in the antibody titers indicates a recent or current infection. Unfortunately, results of serologic testing rarely are available in time to influence clinical management. PCR testing is also available for the diagnosis of *M. pneumoniae* in some laboratories.

Although often considered the gold standard for diagnosis of pneumonia, chest radiography is not essential to diagnose pneumonia, particularly in outpatients. A 2005 Cochrane review found no evidence that chest radiographs improve outcome in ambulatory children with acute lower respiratory tract infections.[19] Chest radiography should be considered in highly febrile patients without another identifiable source especially those with tachypnea or a peripheral leukocytosis.[20] Confirmatory chest radiography is not necessary, however, in patients with classic findings of community-acquired pneumonia such as high fever, tachypnea and rales on physical examination. Imaging should be considered in patients when the diagnosis is unclear, in those not responding to antibiotic therapy, and in those with possible complications such as pleural effusion or empyema. In patients with complications of pneumonia, chest ultrasound or chest computed tomography may further guide management.

Certain chest radiography findings in patients with pneumonia can suggest a particular etiology although studies suggest that chest radiographs alone do not accurately differentiate between etiolo-

gies.[3] Bacterial pneumonia tends to be lobar although *Staphylococcus aureus* can cause a patchy bronchopneumonia. Viral and atypical bacterial pathogens, such as *Mycoplasma pneumoniae*, tend to cause interstitial infiltrates on chest radiography. However, atypical bacterial pathogens occasionally cause lobar infiltrates. Small parapneumonic effusions can also be seen with bacterial, viral, or atypical pneumonia. Severe bacterial pneumonias can cause loculated effusions or empyemas. Hilar lymphadenopathy and nodular disease suggest tuberculosis, or endemic mycoses such as *Histoplasma* or *Coccidiodes*. Pneumatoceles are often seen in pneumonias caused by *S. aureus* and occasionally *Streptococcus pneumoniae*.

Management

Management of children with CAP depends on the severity of disease and the patient age. All febrile neonates should be hospitalized and undergo a complete evaluation for serious bacterial infection, including blood, urine, and cerebrospinal fluid cultures. Antibiotic therapy with ampicillin and cefotaxime or gentamicin should be initiated to cover suspected pathogens, including group B streptococcus and *Escherichia coli* and *Listeria monocytogenes*. Afebrile, well-appearing infants with presumed *C. trachomatis* pneumonia can be managed as outpatients with macrolide therapy and close followup.[9] Children older than 3 months with CAP can be managed as outpatients if they are not hypoxic, in respiratory distress, or dehydrated.[21] Hospital admission should be considered for patients younger than three months of age, patients with underlying disease (sickle cell disease, immunocompromised host, etc.), those with oxygen saturation of less than 92% on room air, those with severe respiratory distress or grunting, or dehydration or inability to take oral fluids and antibiotics, or if follow-up can not be assured. Outpatients should be seen 24 to 48 hours after diagnosis to monitor response to therapy and assess for complications such as empyema.

Choosing which children to treat with antibiotics is difficult as there are few criteria to accurately differentiate between viral and bacterial pneumonia. Many researchers suggest close follow-up without antibiotic therapy for young children with mild disease, in whom a viral etiology is more likely.[21] If antimicrobial therapy is used, the choice of antibiotic is based on the most likely pathogen(s) in the patient's age group. (Table 2)

Although often considered the gold standard for diagnosis of pneumonia, chest radiography is not essential to diagnose pneumonia, particularly in outpatients.

In outpatients aged 3 months to 5 years, oral amoxicillin 80 to 90 mg/kg/day divided 2 or 3 times daily is effective against most *Streptococcus pneumoniae* and is considered first-line therapy.[22] High-dose amoxicillin is typically chosen to account for the possibility of resistant *Streptococcus pneumoniae*, whose resistance can be overcome at higher drug concentrations. In patients with penicillin allergy an appropriate alternative treatment is clindamycin which provides excellent pneumococcal coverage. Oral third-generation cephalosporins or macrolide can also be considered for patients with penicillin allergy. However it is important to note that these antibiotics are not as effective anti-pneumococcal agents as penicillins and macrolide resistance among pneumococcal strains is increasing.[23] A macrolide may be added to amoxicillin, as atypical infections may be more common in younger children than generally recognized.

For outpatient management of children over age 5 years, azithromycin is typically the drug of choice due to the prevalence of atypical pathogens. Azithromycin 10 mg/kg/day on day 1 followed by 4 additional days of 5 mg/kg/ day is usually effective, although some experts suggest a 7- to 10-day course.[24] In the United States, approximately 15% of *Streptococcus pneumoniae* show resistance to macrolides; therefore, if the patient does not improve after 48 hours of treatment, high-dose amoxicillin may be added.[25]

Antimicrobial choice for inpatients is usually empiric and depends on the patient's age and most likely pathogen. Ampicillin, ampicillin-sulbactam, and cephalosporins such as ceftriaxone may be used in hospitalized children.[24] Fluoroquinolones are rarely used in young children. Trimethoprim-sulfamethoxazole is suggested by the WHO as first-line therapy for treatment of CAP in cases that are not severe, although a Cochrane review has shown it to be less effective than amoxicillin.[26]

Methicillin-resistant *Staphylococcus aureus* (MRSA), while not a common cause of CAP, can cause a necrotizing pneumonia, especially in conjunction with influenza.[27] In cases where MRSA is suspected, clindamycin or vancomycin should be added. Clindamycin has been shown to be effective against MRSA, but local patterns of antibiotic susceptibility can vary. [28] Clindamycin should be considered for severe or necrotizing pneumonia in hospitalized patients if the frequency of clindamycin resistance among local MRSA isolates is less than 15%. If the frequency of clindamycin resistance is $\geq$ 15%, vancomycin should be used.

Levofloxacin is a fluoroquinolone effective against most resistant pneumococcal strains and atypical pathogens such as *Mycoplasma pneumoniae*.[29] These atypical pathogens should be considered in older patients as well as those with wheezing. Levofloxacin has broad coverage which makes it a useful therapy in patients with resistant isolates or significant drug allergies. While concerns of tendon rupture and other musculoskeletal injuries have prevented the approval of fluoroquinolones for children under age 18 data support safety in these patients.[30]

Patients with persistent symptoms or failure to improve after 48 hours should receive an initial or repeat chest radiography to detect a new or evolving pleural effusion. Some patients have small parapneumonic effusions that require no intervention, while others have significant bacterial infection in the pleural space that requires drainage. Current evidence favors surgical drainage within 48 hours of moderate large or large or loculated effusions, but prospective clinical trials are lacking.[31]

Prevention

The leading causes of vaccine-preventable pneumonia in the United States are *Streptococcus pneumoniae* and influenza. Since routine childhood immunization with **pneumococcal conjugate vaccine (PCV7)** began in the United States in 2000, the overall incidence of invasive pneumococcal disease has decreased.[5, 26] These declines have been tempered by concern about the emergence of other pathogens or other pneumococcal serotypes, including invasive serotypes such as 19A.[32, 33] On February 24, 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed by the FDA for prevention of invasive pneumococcal disease caused by the 13 pneumococcal serotypes covered by the vaccine, including invasive serotypes such as 19A.[34]

In 2004-05, routine immunization for influenza was recommended for children aged 6 to 23 months. During seasons with a good match between vaccine and circulating influenza strains, efficacy approaches 70% to 90%.[35] In 2003-04, a year without good match, the protective effect for children 6 months to 8 years was only 23% and 51 % against influenza-like illness and bacterial or viral (including influenza) pneumonia, respectively.[36] This study found that previously unvaccinated children under the age of 8 years require 2 doses for maximal protection against influenza. The current recommendations for influenza vaccine now recommend annual immunization for children aged 6 months to 18 years.[37] Children younger than age 9 years should receive two doses 4 weeks apart during their first immunization year.

Conclusions

CAP represents a common and challenging pediatric problem. Diagnosis may be difficult because of limited laboratory testing, the broad range of pathogens, and the frequency of co-infections. Treatment typically targets the likely pathogen based on the patient's age. Future goals are to identify the most effective antimicrobial treatments for patients with community-acquired pneumonia, to establish guidelines for treatment of children with CAP, to assess the impact of antimicrobial resistance, and to understand the long-term impact of immunization campaigns, especially against *Streptococcus pneumoniae* and influenza, on the development of CAP in children.

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Persistent Non-Cancer Pain Management In the Older Adult

Maria Tomas, MD, and Noel Javier, MD

MO, an 83-year old woman with spinal stenosis, osteoarthritis, hypertension, and hypothyroidism, presented with a three week history of left hip and lower back pain. She described the pain as dull, non-radiating, and not associated with paresthesia, numbness, or bladder dysfunction. Radiographs of the spine and hip confirmed osteoarthritis and suggested spinal stenosis. Initial management strategies included initiation of acetaminophen up to 3 grams per day, application of cold and hot packs, referral to physical therapy, therapeutic exercise, and application of a lidocaine patch to the left hip.

Pain is a complex phenomenon derived from sensory stimuli and modified by individual memory, expectations, and emotions. It has been defined by The International Association for the Study of Pain has defined "pain" as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1,2]

Older adults more frequently experience persistent pain than younger adults, typically from musculoskeletal disorders including arthritis and spinal stenosis, which are further complicated by medical comorbidities. The prevalence of pain, ranging from mild to severe, may be as high as 50% in community-dwelling older adults and 80% in long-term care residents.[3,4] Sawyer reported that nearly 75% of community-dwelling older adults complained of pain, and half reported decreased function.[5] Pain contributes to diminished quality of life, functional decline, recurrent falls, social isolation, depression, impaired cognition, sleep disturbance, polypharmacy, caregiver distress, and increased healthcare costs and resource utilization.

Pain is classified by its duration: 1) acute pain, which results from an illness or injury that is time-limited and of recent onset; 2) subacute pain, which usually lasts for up to three months; and 3) chronic pain, which persists for longer than three months.[2,6,7] Pain is also classified by underlying pathophysiologic mechanism: 1) nociceptive pain, 2) neuropathic pain, 3) mixed pain, and 4) psychogenic pain.[3] Nociceptive pain is derived from stimulation of pain receptors. It is divided into somatic (skin and deep tissues) and visceral pain (internal organs). Neuropathic pain results from peripheral or central nervous system pathology, while the mixed type is a combination of both nociceptive and neuropathic. Psychogenic pain is modified by the presence of psychological disorders.[3] For this patient, the pain is nociceptive-somatic, caused by osteoarthritis and spinal stenosis.

A thorough assessment is crucial to understanding the causes of chronic pain. This assessment includes a comprehensive history, physical examination, neurologic assessment, psychological evaluation, and appropriate diagnostic testing. Commonly used pain scales include but are not limited to visual analog, faces, numerical, and verbal descriptor scales.[3,8]

Management of chronic pain combines pharmacologic and non-pharmacologic interventions. Although older adults are more likely to experience adverse reactions, analgesic drugs are safe. The rule of starting low and going slow is generally followed and is appropriate, especially for medications known to have extensive side-effect profiles.[3,9,10] Table 1 highlights the most common opioid, non-opioid, and adjuvant medications for pain management.

In 1986, the **World Health Organization (WHO)** developed a stepwise treatment guide for cancer-associated pain, known as the WHO analgesic ladder. Its use has been extended to other kinds of pain, including persistent pain from non-cancer causes.[10,11] For intermittent mild pain, it is recommended to begin treatment with non-opioid analgesics. Acetaminophen is generally preferred over NSAIDs due to a narrower adverse effect profile and is recommended as first-line therapy for pain.[9] A mild opioid (e.g., hydrocodone, oxycodone) may be added for persistent mild to moderate pain, and may be titrated to a higher potency opioid (e.g., morphine) for moderate to severe pain.

Non-pharmacologic interventions for pain management include, but are not limited to physical therapy, therapeutic exercise, cognitive-behavioral therapies, heat and cold therapy, massage, acupuncture, trigger-point therapy, biofeedback, relaxation training, **and transcutaneous nerve stimulation (TENS)**.[3,8]

After a month, MO's lumbosacral and left hip pain continued, only partially relieved with acetaminophen. She was in enough pain to be limited in her activities and felt she needed a stronger analgesic regimen. A combination of hydrocodone-acetaminophen (Vicodin) was started. She was told about possible opioid side effects and a bowel regimen was prescribed.

Opioid analgesics exert their action on opiate receptors, and modulate the ascending and descending pain-related pathways. When mild to moderate pain is not relieved with non-opioid analgesics alone, a fixed-dose combination of opioid with acetaminophen or NSAID may be used. If the maximum safe acetaminophen or NSAID dose is reached without adequate pain relief, one may opt to switch to a non-combination opioid preparation to avoid toxicity.

After initiation of analgesia with opioids, patients should

be closely monitored for drug efficacy and side effects, with careful dose titration for pain relief. The most common and persistent side effect of opioids is constipation. A bowel regimen, such as a bulking agent or stimulant laxative, is therefore added. Other side effects include nausea, vomiting, delayed gastric emptying, bladder dysfunction, pruritus, sexual dysfunction, sedation, impaired cognition, delirium and fatigue.[10,12] Respiratory depression, muscle rigidity and myoclonus are seen with higher doses of opioids.

After three weeks, MO reported continued pain in spite of regularly dosed Vicodin. She was then started on long acting morphine every twelve hours, in addition to a short acting morphine as needed for breakthrough pain. She had substantial improvement with this regimen.

Higher potency opioids such as morphine may be used to relieve moderate to severe pain. Opioids are prescribed around the clock for continuous pain.[11] For opioid-naïve patients, short-acting opioids are initiated every three to four hours as needed. Then the total number of short-acting opioid doses is calculated over 24 hours and divided in two or three doses for the transition to the long-acting agent. The new rescue dose is approximately 10% to 15% of the total daily dose and scheduled as often as every hour, as needed to achieve immediate analgesia. Long-acting opiods should never be started in opioid-naïve patients.

After a few months of good control on scheduled morphine, MO reported a return of continuous pain. She had also developed back spasms. She was referred to a spine surgeon for further evaluation and management, possibly to include corticosteroid injection or neurolytic blockade if warranted. Subsequent spinal MRI ruled out any nerve involvement. MO refused corticosteroid injection as this afforded minimal relief

Table 1. Pharmacologic Agents in Persistent Pain Management

Drug	Recommended Starting Dosage	Comments
NON-OPIOIDS		
Acetaminophen	325-500 mg q4hrs 500 mg – 1g q6hrs	Maximum dose of 3 g. Reduce dose to 50%-75% with liver disease and alcoholics
Celecoxib	100 mg daily	Higher doses associated with GI and cardiac effects
Naproxen sodium	220 mg bid	GI and kidney effects. Less cardiotoxic
Ibuprofen	200 mg tid	GI, kidney, antiplatelet effects
Diclofenac sodium	50 mg bid or 75 mg ER daily	Higher cardiovascular risk due to COX-2 inhibition
Opioids		
Hydrocodone (eg Lorcet, Vicodin, Lorta, Norco, Vicoprofen)	2.5-5 mg q4-6 hrs	Daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs
Oxycodone (eg Percocet, OxyIR, Percodan, Tylox)	2.5-5 mg q4-6 hrs	Useful for acute, recurrent, breakthrough, or episodic pain. Limitations similar to hydorcodone in fixed dose combinations
Oxycontin	10 mg q12 hrs	Usually started after calculating cumulative short acting oxycodone doses over 24 hrs
Morphine immediate release (MSIR, Roxanol)	2.5-10 mg q3-4 hrs	Effective for acute, subacute, and chronic pain
Morphine sustained release (MS Contin, Avinza, Kadian)	15 mg q8-12 hrs	Caution in kidney impaired patients Significant interactions with food and alcohol
Hydromorphone (Dilaudid)	1-2 mg q3-4 hrs	For breakthrough or around the clock dosing
Methadone (Dolophine)		Variable half-life. Non-linear dose equivalents. Prescribed by experienced clinicians. Not a first line agent.
Transdermal Fentanyl	12-25 mcg/h patch q48-72 hrs	Peak effect takes 18-24 hrs. Started only after initial dose determined by effects of immediate release opioids
ADJUVANTS		
Tricyclic antidepressants (Desipramine, Nortriptyline)	10 mg at hs	Anticholinergic effects
Duloxetine (Cymbalta)	20 mg daily	Cause dizziness, cognitive deficits. Drug-drug interactions
Venlafaxine (Effexor)	37.5 mg daily	Dose-related increases in blood pressure and heart rate
Gabapentin (Neurontin)	100 mg at hs	Causes sedation, ataxia, edema
Pregabalin (Lyrica)	50 mg at hs	Causes sedation, ataxia, edema
Prednisone, Methylprednisolone, Dexamethasone	Dose depending on the type of steroid	Monitor for fluid retention, glycemic effects, bone demineralization
Lidocaine 5% patch	1-3 patches for 12 hours on and 12 hours off	Monitor for rash or skin irritation
Baclofen (Lioresal)	5 mg tid	Muscle relaxant. Causes muscle weakness, sedation, urinary problems
Tramadol (Ultram)	12.5-25 mg q4-6 hrs	Mixed opioid and SNRI. Caution with monoamine oxidase inhibitors. Caution with liver and kidney impairment

when given in the past. Low dose baclofen was added to a higher morphone dose.

Adjuvant drugs, including antidepressants, anticonvulsants, and other agents that alter neural membrane potentials, ion channels, cell surface receptor sites, synaptic neurotransmitter levels and other pain signal processes help address pain particularly of a neuropathic nature.[3,8,9] Other drug classes, including corticosteroids, muscle relaxants, benzodiazepines, calcitonin, bisphosphonates, topical analgesics and cannabinoids have been used as co-analgesics for pain management.

In this case, baclofen, a gamma aminobutyric acid B agonist, was chosen and found to be helpful. It is often instituted in patients with severe spasticity resulting from CNS injury and demyelinating conditions. Common side effects include dizziness, somnolence, and gastrointestinal symptoms. Discontinuation after prolonged use requires slow tapering to prevent delirium and seizure.

Corticosteroid injection was offered to this patient as a co-analgesic. These injections can be effective for rheumatic conditions, autoimmune arthropathies, and vasculitides. Corticosteriods are also used in cancer-related bone pain, nerve compression, and bowel obstruction. The well-known side effects and serious toxicity of short and long term use of corticosteroids often limit their use. Currently, there is no clear evidence to guide us regarding initiation, dosing and duration of epidural steroid injections. Treatment decisions should be determined in part by patient preference.[14]

Over the next few days, MO reported that she was doing well with the new regimen of high dose morphine and baclofen in addition to physical therapy and the use of hot and cold packs.

Chronic use of opioids, when medically indicated, is not generally associated with addictive behavior. Under-treatment of pain, however, may result in "pseudoaddictive behavior" wherein a patient complains of pain and requests for opioids or dose escalation. This can be avoided through active listening, careful pain assessment, titration, and monitoring of the narcotic regimen.[10]

In Summary:

1. Pain is a prevalent symptom affecting as many as 50% of community-dwelling older adults.
2. Pain affects quality of life, functional status, cognition, mood, sleep, and well-being.
3. A multimodal approach to pain management consists of both non-pharmacologic and pharmacologic interventions.
4. Prescribing analgesics is safe and effective in older persons if done judiciously by starting low and titrating slowly while monitoring closely for potential side effects.

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Health By Numbers
Rhode Island Department of Health • David Gifford, MD, MPH, Director of Health
Edited by Samara Viner-Brown, MS

Rhode Island Child Death Review: Sudden Infant Death and Sudden Unexpected Infant Deaths, 2008-2009

Stephen C. Meersman, PhD, and Monica J. Schaberg, MD, MPH, FAAP

In the United States, in 2006, sudden infant death syndrome (SIDS) was the 3rd leading cause of death in infants under 1 year of age (behind congenital malformations (1st) and disorders relating to prematurity/low birth weight (2nd); and ahead of results of maternal complications of pregnancy (4th); and accidents-unintentional (5th)).[1] In Rhode Island, during 2008-2009, SIDS is the 2nd leading cause of death for children under 1 year of age. (Figure 1) SIDS is defined as the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, which includes performing a complete autopsy, examination of the death scene, and review of the clinical history.[2]

Improved postmortem examination and testing have resulted in improved cause of death determination in some infants with metabolic or cardiac disorders, but many causes are undetermined.[3] To recognize this trend, the term **sudden unexpected infant deaths** or **deaths in infants (SUID or SUDI)** has been introduced. Most recent estimates are that 4,600 SUID deaths occur annually in the US, 50-80% of which can be classified as SIDS.[5] Because of the inability to determine actual single cause of some SUID cases, many states report these deaths as "undetermined" or modify death certificates to include environmental findings such as "undetermined – co-sleeping" or "SIDS – co-sleeping". Because of a resulting code or diagnostic shift, SIDS rates are declining while undetermined/unspecified/unknown are reported more often.[3, 4]

The most important risk factors for SIDS/SUID are: prone sleeping position, sleep on a surface not designed for infants, bed-sharing, maternal and/or paternal smoking, excessive environmental temperature, premature birth, and concurrent respiratory illness. [5, 6, 7] The first three are thought to contribute to accidental asphyxia, and the occurrence of strangulation associated with inappropriate sleep surface has resulted in the reporting of some of these deaths as **accidental suffocation and strangulation in bed (ASSB)**. [3 5] Since 2007, the **Office of the State Medical Examiner (OSME)** has adopted death scene investigation and scene re-enactments in order to more fully understand factors contributing to SUID in R.I. infants. Recent detailed review of deaths in infants under one year of age has revealed a pattern of SUID which lends itself to intervention.

Methods

The **Rhode Island Child Death Review Team (RICDRT)** reviewed deaths of infants (birth through < 1 year of age) that occurred in Rhode Island during 2008-2009. Only cases reported to the OSME were reviewed. Out-of-state deaths were not included. Detailed analysis was done on those cases classified as SIDS, SUID, and undetermined. These data are provisional.

Demographic, clinical, and death scene information was abstracted from source documents contained in the OSME record including autopsy and toxicology reports, police reports, perinatal records, existing medical records, Newborn Developmental Risk Assessments, primary care records, and other information as available.

Results

During 2008-2009 there were 88 deaths of infants 0 to 1 year of age (48 in 2008, 40 in 2009). Forty were due to the effects of extreme prematurity, 22 to an undetermined cause (15 of the 22 had a specific notation of SIDS or SUID on the death certificate), 15 to congenital disorders, 10 to perinatal complications, and 1 to homicide. (During this period, no deaths resulted from falls, fire, drowning, **motor vehicle accidents (MVA)**, or infection.) (Figure 1)

In depth analysis was done on the 22 undetermined. Twelve of the infants (55%) were female, six (27%) were breastfed, and 21 (95%) died within the first 6 months of life. Regarding sleep related risk factors: 15 (68%) were co-sleeping with one or more adults, 8 (36%) were sleeping in a prone position, and 17 (77%) were sleeping on structures not designed for infant use; e.g., futons, couches, waterbeds, loungers, and other sleep surfaces designed for adult use. At least 14 (64%) had a suitable crib or bassinette available at the time of death; 3 (14%) of the infants did not have a surface designed

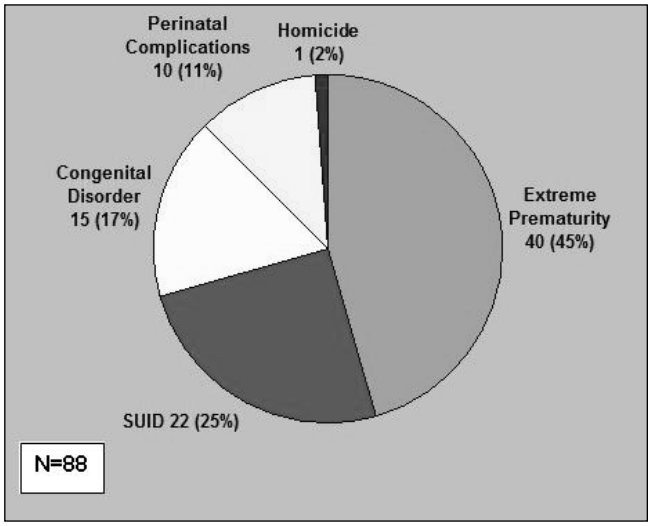

Figure 1. Rhode Island Infant Deaths, Age 0 to 1, 2008-2009.

for proper sleep available; and in 5 (23%) cases, the availability was unknown. Information pertaining to alcohol, cigarette, and/or drug use was incomplete so it was not possible to determine the importance of these factors.

All newborns are screened prior to discharge from the birth hospital for risk factors that can impact development as part of the Department of Health's Newborn Developmental Risk Assessment Program. Risk-positive mothers and babies are offered home visits. Of the 22 infants with SUID, 19 (86%) were risk positive. Most of the infants, 17 (77%), were covered by public insurance (RiteCare/Medicaid), 4 (18%) by commercial plans, and 1 infant was uninsured. There were no known previous cases of SIDS or SUID in these families. (Table 1)

Table 1. Rhode Island Sudden Infant Death and Sudden Unexpected Infant Death Characteristics, Infants 0 to 1 Year of Age, 2008-2009

		2008	2009	N	%
Total		**13**	**9**	**22**	**100**
Gender	*Male*	7	3	**10**	45%
	Female	6	6	**12**	55%
Age (in Months)	<1	3	2	**5**	23%
	1 to <2	4	1	**5**	23%
	2 to <3	2	4	**6**	27%
	3 to <4	1	2	**3**	14%
	4 to <5	1	0	**1**	5%
	5 to <6	1	0	**1**	5%
	6 to <7	1	0	**1**	5%
	7 to <8	1	0	**1**	5%
Bed Sharing	1 or More Adults	8	7	**15**	68%
	None	5	2	**7**	32%
Baby's Sleep Surface	Surface Designed for Infant Sleep (ie.-Crib, Bassinette, Playpen)	3	2	**5**	23%
	Surface Not Designed for Infant Sleep (ie.-Adult bed, Couch, Chair, Sling)	10	7	**17**	77%
Other Sleep Structure Available	Crib or Bassinet	7	7	**14**	64%
	None	2	1	**3**	14%
	Unknown	4	1	**5**	23%
Sleep Position	**Supine**	5	0	**5**	23%
	Prone	2	6	**8**	36%
	In Arms	2	2	**4**	18%
	Other	2	0	**2**	9%
	Unknown	2	1	**3**	14%
Breast Feeding	Yes	5	1	**6**	27%
	No	8	8	**16**	73%
Birth Weight <2500 grams	Yes	2	3	**5**	23%
	No	11	6	**17**	77%
Neonatal Risk Assessment Positive	Yes	11	8	**19**	86%
	No	2	1	**3**	14%
Insurance	RiteCare/Medicaid	9	8	**17**	77%
	Commercial Insurance	3	1	**4**	18%
	None	1	0	**1**	5%
Manner of Death (Death Certificate)	Undetermined	11	6	**17**	77%
	Undetermined (with additional SIDS or SUID Notation)	8	4	**12**	55%
	Natural	2	3	**5**	23%
	Natural (with additional SIDS or SUID Notation)	1	2	**3**	14%

Discussion

Increasingly, investigators are applying a triple-risk model in describing the confluence of events that lead to SIDS/SUID and ASSB deaths.[5] The model provides a framework to understand the interaction of multiple risk factors for death: infants who may be vulnerable for unknown reasons, at a particular developmental phase when external environmental factors can conspire to cause death. In Rhode Island's population, the most common risk factors were: age under 6 months (95%), surfaces not designed for infant sleep (77%), non-supine sleeping positions (64%), and bed-sharing (68%). It should be noted that at least 64% (14 of the 22 cases) had a suitable sleep structure available for use in the household at the time of death. Of the 22 cases, 21 (95%) had at least one identified unsafe sleep environment risk factor and 16 (73%) had 2 or more (e.g. prone sleep, surface not designed for infant sleep, or co-sleeping with 1 or more persons).

Populations generally considered most vulnerable include low-income families (82% had public or no health insurance), birth weights under 2500 grams (23% of infants), and risk-positive status at newborn developmental risk screenings (86% of infants). These screenings provide a potential opportunity for focused individual-level intervention by home visitor support programs, such as First Connections (a program of the RI Department of Health and Department of Human Services).

All primary care providers should reinforce parents' understanding and knowledge of proper sleep conditions for their infants, particularly in the first year of life. Additional education and outreach to infant

caregivers may increase awareness of SIDS / SUID /ASSB and help to reduce the number of sleep-related deaths. Additionally, making a safe sleep structure available for the families who don't have one would be useful, but not sufficient if the family does not use the structure.

The information presented here pertains to infant **mortality** in Rhode Island. The short and long-term **morbidity** associated with unsafe sleep arrangements is unknown except by anecdote: transport of infants suffering "near miss" events or acute life threatening events (ALTEs) some of which might be attributable to inappropriate sleep situations. The RI CDRT will continue to review child deaths to identify risk factors, trends, and priorities for prevention. Comprehensive and systematic review of child death data can inform policy change and the development of prevention strategies with the goal of reducing child morbidity and mortality.

Submitted by the SUID subcommittee for the CDRT:

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The authors have no financial interests to disclose.

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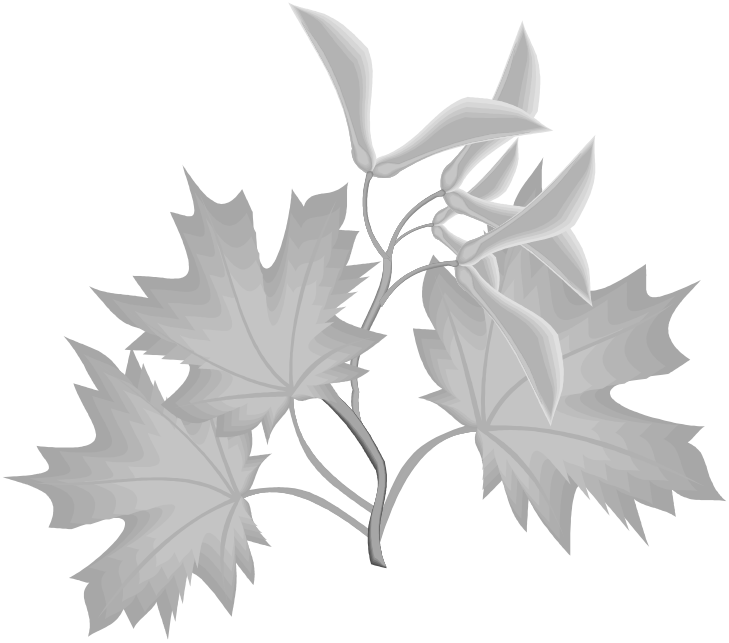


Information for Contributors, *Medicine & Health/Rhode Island*

Medicine & Health/Rhode Island is peer-reviewed, and listed in the *Index Medicus*. We welcome submissions in the following categories.

Contributions

Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files (jpeg, tif, or pdf).

Creative Clinician

Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

Point of View

Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

Advances in Pharmacology

Authors discuss new treatments. Maximum length: 1200 words.

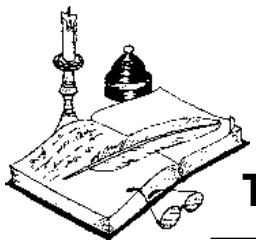
Advances in Laboratory Medicine

Authors discuss a new laboratory technique. Maximum length: 1200 words.

Images in Medicine

Authors submit an interesting Image, with a 300-400 word explanation.

For the above articles: Please submit an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, Joan Retsinas, PhD, e-mail: joan.retsinas@gmail.com For additional information, phone: (401) 272-0422.



Physician's Lexicon

The Celestial Bodies: The Moon, Sun and Stars

Well before laboratory medicine yielded insights into the prognosis of human disease and provided prophetic hints of the future, astrology declared that the configuration of the stars and the movements of the sun and moon foretold the character and destiny of humans and their ailments. It is not surprising, therefore, that so many terms, some medical, have lexical roots in the Greek and Latin words for the celestial bodies.

The Greek and Latin words for moon, *men* and *mensis,* have given rise to a cluster of words such as mensal, menology, all pertaining to the moon or to aspects of the lunar cycles. In medical vocabulary the following words are encountered, based upon the similarity between lunar and uterine bleeding cycles: menstruation, menstruum, menopause (*pausis*, Greek, meaning to cause to cease.). The related Greek word *meniskos* (as in medical terms such as meniscus and meniscocyte, an obsolete term for a sickle-cell) describes a lunar crescent.

Akin to the Latin *mensis* is the companion word, *mensus,* meaning a measure as in technical words such as mensuration, measure, commensurate, dimension, immense and meter.

The name of the moon goddess in Latin is *Luna*; and many medical nouns and adjectives stem from this name, including lunacy, lunatic (moonstruck), Lunaria (moonwort) and semilunar.

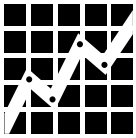
Moon-associated words are more common in medical vocabulary than are words pertaining to the sun. Nevertheless there are a number of terms derived from the Greek root, *helio-,* meaning the sun, and the Latin, *sol.*

General words using the root, *helio*, include heliofugal (flying away from the sun), heliocentric, heliotrope (plants of the borage family such as the Jerusalem artichoke, plants that turn toward the sun); and biomedical words such as helium, heliotherapy, heliophobia (fear of sunlight). The similar Greek root, *helix*, means a spiral as in words such as helicopter (literally, a spiral-wing.)

The Latin, *sol*, gives rise to English terms such as solar, sultry, solstice, parasol; and medical terms such as solar plexus and Solanaceae (nightshade plants).

The Greek word for star, *astron*, has given rise to medical words such as astrocyte [star-shaped cell), astrocytoma, astrobiology and astroid (star-shaped), but not astragalus, the ankle bone, which is derived from a Greek word meaning oyster-shell.

– Stanley M. Aronson, MD



Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	July 2009	12 Months Ending with July 2009		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	182	2,428	231.1	3,097.5
Malignant Neoplasms	182	2,285	217.5	6,222.5
Cerebrovascular Diseases	35	421	40.1	799.5
Injuries (Accidents/Suicide/Homicde)	61	570	54.2	9,477.5
COPD	47	492	46.8	312.0

Vital Events	Reporting Period		
	January 2010	12 Months Ending with January 2010	
	Number	Number	Rates
Live Births	978	12,298	11.5*
Deaths	414	9,178	8.6*
Infant Deaths	(1)	(76)	6.2#
Neonatal Deaths	(14)	(77)	6.3#
Marriages	210	6,217	5.8*
Divorces	307	3,257	3.1*
Induced Terminations	335	4,119	334.9#
Spontaneous Fetal Deaths	49	708	57.6#
Under 20 weeks gestation	(43)	(623)	50.7#
20+ weeks gestation	(6)	(85)	6.9#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,050,788

(c) Years of Potential Life Lost (YPLL)

Note: *Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

THE RHODE ISLAND MEDICAL JOURNAL

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Ninety Years Ago, July 1920

In "A Review of the Goitre Situation," [read before the St. Joseph's Hospital Staff Association], J. James Shaughnessy, MD, considered the problem especially prevalent in southern Minnesota, where he had trained: "There the word goitre was almost a household word and we had occasion to observe goiters of every type …It was common … to observe practically every female member of many families showing enlarged thyroids." He had found the condition even in newborns. The author hypothesized that one cause lay in "the chemistry of the water supply and of the soil." He noted: "…the use of the x-ray is being advocated and it is claimed that results follow. With its use the writer has no personal experience."

An Editorial, "The Mental Defect," questioned a ruling of the Penal and Charitable Board, which barred a young girl from the School for Feeble Minded. The girl was "obviously a mental defect and so found after examination by a competent psychiatrist." The reason lay with her residency-status. "…her mother and father, dead or unknown for nearly 15 years, were not residents of this State…" The girl lived with an aunt who was a resident of RI; nevertheless, the board ruled that the girl was not a resident and consequently not eligible for admission. The Editor concluded: "While such a ruling may be in strict accordance with the law, it opens up the interesting speculation as to what the ruling will be when the Board has to decide what shall be done with the progeny of such a case: if such a one be not safeguarded against the acts which her mentality cannot guard against."

In "Chronic Cases and Irregular Practitioners," the Editor decried the claims of faith-healers. Even if the healer's care didn't directly harm the patient, it might deter him from seeking more effective care. "For example, an individual suffering, without knowing it, from chronic simple glaucoma, will experience 'good and bad' days. Should such a case follow the advice as given by this clergyman not to expect an immediate cure, but to continue to the faith and to pray diligently, much valuable time would be lost and vision sacrificed." The Editor went on to blame medical professionals' "lack of interest in chronic diseases." The physician, after the diagnosis, often drops the case "because, forsooth, he has no cure." The Editor: "So much can be done in incurable cases by relieving symptoms, and physicians fail in their duty when they coldly disregard the chronic case and pass it on to whatsoever irregular healer may be encountered."

Fifty Years Ago, July 1960

Robert H. Felix, MD, Director, National Institute of Mental Health, NIH, gave the Ninth Annual Arthur Hiler Ruggles Oration: "Recent Developments in Mental Health Research." He credited Congress for major advances in mental health, especially Congressman John Fogarty (D-RI), "…who, with great wisdom and foresight has consistently supported mental health activities." Dr. Felix cited the improved understanding of the brain and central nervous system, the trends in psychological and sociological approaches, research in the process of aging, and early diagnostic programs.

In "Hospital Admission X-Rays in Detection of Tuberculosis, Theodore L. Badger, MD, Harvard Medical School, recounted statistics: in 1956, in the United States, there were 14,000 deaths from tuberculosis, 69,000 new cases, and a reservoir of 400,000 cases. The reservoir included "recalcitrants." "While these people will not report their TB, they will be hospitalized for cardiac or other disease, and a hospital admission x ray will pick them up as tuberculosis cases." He judged these x-rays "more than twice as productive as mass community screening." In Boston, 75% of all reportable TB cases were reported from hospital x-ray programs.

In "Isolation Perfusion of Body Regions in the treatment of Cancer: Experimental and Clinical Observations," Lester L. Vargas, MD, William P. Corvese, MD, Clarence H. Soderberg, MD, John D. Pitts, MD, Thomas Forsythe, MD, and Herbert Fanger, MD, used two groups of "unselected mongrel dogs." They concluded: "Regional perfusion of the pelvis or of an extremity with an extracorporeal circulation affords a method of utilizing high doses of cytotoxic drugs with minimal danger of systemic poisoning."

An Editorial, "Only 1 Negative Vote," deplored the legislative passage of a proposal allowing "chiropractic physicians to render 'medical care' to recipients of public assistance." (Governor Del Sesto vetoed the measure.)

In "Summary of Medical, Public Health and Allied Legislation before the RI General Assembly, January Session, 1960," the Committee on Public Laws of the RIMS noted that the General Assembly passed, and the Governor vetoed, "a proposal for a legislative commission to study the need for a medical school, with a $5,000 appropriation."

Twenty-Five Years Ago, July 1985

Stanley M. Aronson, MD, in "The Private Physician and the Public Health," introduced this issue, focused on public health. He cited the first four cases of cholera reported, in July 1832. Afterward, a voluntary committee of RI physicians agreed to issue a report to authorities. Their report cited 4 requirements for safety: "temperance, cleanliness, ventilation, fearlessness." Yet cholera persisted; quarantine and sanitary measures were "patently ineffective." In August 3, 1849, President Zachary Taylor proclaimed a national fast day. In 1856 Providence appointed Dr. Edwin Snow as its first Superintendent of Health. When he retired in 1884, the 28-year old Charles Value Chapin, trained at Bellevue, took over. He served until 1931. Dr. Charles Fischer was appointed to head the Rhode Island Board of Health in 1878.

On the "President's Page," Herbert Rakatansky, MD, asserted "RI is Behind the Times," which he judged a compliment. Specifically, the state had only two major alternative delivery systems (RIGHA and Ocean State), and no for-profit hospitals. (In Georgia, by contrast, 25% of hospitals were for-profit.)

John Tierney, Deputy Director, RI Department of Health, contributed "The Cannon Years: 1961-1984." "His most significant and enduring contribution as Director of Health was cultivating a spirit of professionalism and scientific inquiry."

H. Denman Scott, MD, Director, Department of Health, contributed "Contemporary Issues in Public Health."

"Inside the Rhode Island Department of Health: Special Report," outlined the organizational structure of the Department.

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