Community-Acquired Pneumonia

"NO LONGER THE OLD MAN'S FRIEND"

An Update in the Diagnosis and Management of Community-Acquired Pneumonia

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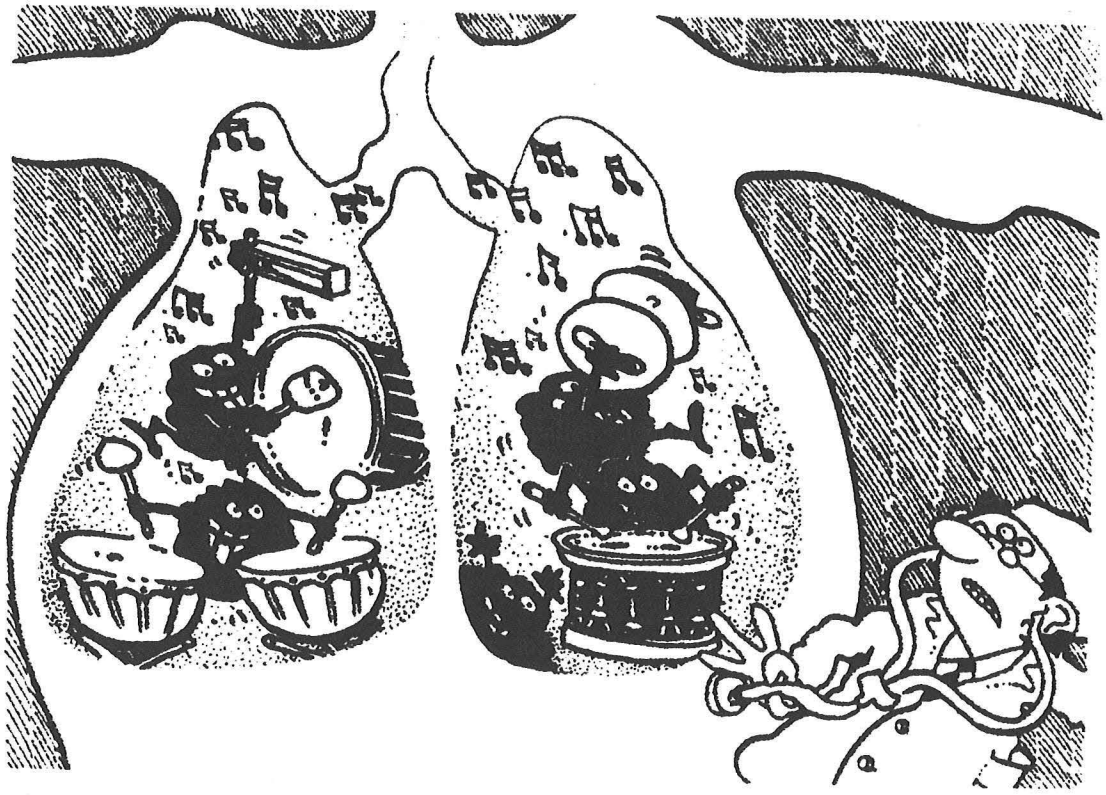

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Biographical Sketch:

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Research Interests and projects: Interstitial Lung Disease with a particular focus in the diagnosis and treatment of sarcoidosis and IPF. This includes epidemiological aspects of ILD including the incidence and prevalence in indigent populations. Current projects involve a clinical trial of gamma- interferon in the treatment of IPF. In addition, a secondary interest in obstructive lung disease particularly asthma.

Introduction:

Pneumonia – "*An infectious disease characterized by inflammation of the lungs, toxaemia of varying intensity, and a fever that usually terminates by crisis" so wrote Sir William Osler in his textbook 'Principles and Practice of Medicine*' in 1910 [1]. The term pneumonia although typically associated with this definition, really applies to community-acquired pneumonia, more commonly referred to as CAP. The term pneumonia is derived from Greek and is defined as: "a disease of the lungs characterized by inflammation and consolidation of the lung as a result of *infection, inhalation of foreign particles or irradiation.*"

At presently, there is no standardized definition of CAP, however, it is generally defined as an "acute infection of the pulmonary parenchyma associated with appropriate symptoms, consistent chest radiographs or auscultatory findings and attributed to patients not hospitalized or residing in a skilled nursing facility for > 14 days prior to the onset of symptoms [2].

Sir William Osler had a great interest in community-acquired pneumonia, a disease that eventually claimed his life. In the first 2 editions of his famous textbook The Principles and Practice of Medicine he described pneumonia as " the Special Enemy of Old Age". It was not until the third edition, that he altered his view to the commonly quoted view of pneumonia as 'the friend of the aged'.

Osler, afflicted by chronic bronchial disease, was subject to recurring bouts of bronchopneumonia during the last six months of his life. On November 1, 1919 he wrote: "No fever since the 16th but the cough persists and an occasional paroxysm- Bouts as bad as senile whooping-cough. One night they nearly blew my candle out! No. 3 pneumococcus and M. Catarrhalis – the organisms. Practically no physical sighs – a little impairment of resonance at bases but no rales or tubular breathing." He lived another eight weeks, his course complicated by an H. flu empyema and died on December 29th, 1919 at the age of 70 having been spared in part, those "cold gradations of decay" so distressing to himself and to his friends[1].

Epidemiology

At the turn of the century using a term John Bunyan ascribed to tuberculosis, Osler wrote, "the most widespread and fatal of all acute diseases, pneumonia, is now the "Captain the Men of Death". It was not until the discovery of antibiotics that a new era in the treatment of infectious disease was begun and the annual mortality from pneumonia fell from 200/100,000 in 1900 to 80/100,000 the year sulfapyridine was introduced reaching its nadir at 28.2/100,000 in 1956 [1]. Despite these inroads community-acquired pneumonia, (CAP) as we know it today remains a disease with significant mortality despite advances made in diagnosis and treatment. This is due in part to a declining in interest in CAP with the continuous advent of stronger and more potent antibiotics [3].

Despite these advances there are a number of reasons that we should maintain a continued interest in this disease and why pneumonia is not the "old man's friend". CAP remains a common and serious illness maintaining its position as the *sixth leading cause of death in the US*, the number *one cause of death due to infectious disease* and the *third most common cause of hospitalization* [4, 5]. In 1998 there were 90,147 deaths due to pneumonia with and age-adjusted death rate of 13 deaths /100,000 [6]. Because pneumonia is not a reportable disease its incidence is based on crude estimates, and it is estimated that 4.8 million cases are reported annually with 1.8 cases/100 persons [4-6]. Recent data from the CDC indicate that there were 1.3 million hospital discharges in 1998 for patients with pneumonia, up from 1.1 million in 1996. In 1997 there were an estimated 1.3 million ER visits for pneumonia. The annual cost of treating CAP is estimated at 9.7 billion, and the primary determinant of cost is length of stay in the hospital [7, 8].

While mortality is < 5% in the outpatient setting it is markedly increased in patients requiring hospitalization with rates averaging 12%. The rates increase almost exponentially in patients with bacteremia, from nursing homes or chronic care facilities, approaching 40% in patients who require admission to the ICU [8].

Based on recently published data, the epidemiology and treatment of pneumonia have undergone a number of changes in the past few years. CAP is now increasingly recognized among older patients and those with co-existing illnesses [4, 9-11]. In addition to this it is now recognized that mortality from this disease is on the rise

with mortality rates having increased by 59% in the United States from 1979 to 1994 [2, 12]. Much of this increase is felt to be secondary to the increased proportion of persons aged > 65 years; however, after adjusting for age the increase is still significantly elevated at 22% suggesting other factors may have a role including a greater proportion of the population < age 65 with underlying chronic medical conditions.

In the last 5 years a number of new antimicrobial agents have become available, for the treatment of CAP and in concert with our new antibiotic armamentarium comes the evolution of new bacterial resistance mechanisms. In the last decade many common respiratory pathogens have become resistant *in vitro* to commonly used antmicrobials. Resistance, occurring by a number of mechanisms has been documented with increasing frequency among *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and a number of gram-negative bacteria [13-18].

This discussion is limited to the *immunocompetent* individual with community-acquired pneumonia as this represents the population most commonly encountered. Those with HIV, organ transplantation, or other immunosuppressive illness are not addressed in this discussion as they are often infected with organisms not frequently found in CAP. However, patients on chronic immunosuppression such as prednisone are included.

In response to the changing epidemiology, increasing antimicrobial resistance and significant mortality associated with CAP the American Thoracic Society (ATS), the Infectious Disease Society of America (ISDA) and the Canadian Infectious Diseases Society (CIDS) have all issued new guidelines for the diagnosis and treatment of CAP in the last 12 months [2, 19, 20]. While guidelines are just that; guidelines – once issued they are advocated as a means to improve quality, decrease costs, reduce variation, and /or foster evidence-based decision making [21, 22]. Once published, guidelines are regarded as standards of care to which physicians are held by many agencies including Medicare and HCFA. Over the past decade a large number of studies supporting the currently issued guidelines have been published and as a result agencies such as Health Care Financing Administration (HCFA) and now the Joint Commission on Accreditation of Health Car Organizations (JCAHO) have selected certain process of care as "quality indicators" and "Core Measures" [23]. This is important to understand because these are areas in which physicians and hospitals will be audited particularly since HCFA estimates $3.5 *billion* dollars was spent on *Medicare* patients with pneumonia in 1993 alone [24, 25]. Outcomes examined in claims data include mortality rates, readmission rates, complication rates, transfers, procedure rates and finally length of stay[24].

Thus the new guidelines attempt where possible to give an evidence-based approach for making the final recommendations most of these recommendations are largely on level I and II evidence. That is evidence obtained from at least on properly randomized controlled trial or evidence obtained from well-designed cohort, case control or non-randomized trials. Interestingly a number of authors were part of more than one guideline committee and many of the recommendations are very similar.

Diagnosis:

A diagnosis of pneumonia is generally entertained on the basis of the initial presentation of a constellation of signs and symptoms followed by radiographic and laboratory testing. Although a number of criteria for clinical, radiographic and laboratory findings have been proposed to identify CAP, there are no perfectly reliable criteria for diagnosis and relatively few studies have examined the value of this approach [2, 26].

1. Clinical Findings:

In any patient that has newly acquired respiratory symptoms of cough, dyspnea, and sputum production, particularly if accompanied by fever and auscultatory findings of abnormal breath sounds and crackles the diagnosis of CAP must be entertained. However, one should be cognizant that in the elderly or those with an inadequate immune response pneumonia can present with confusion, failure to thrive, worsening of an underlying chronic illness or falling down [11, 20, 27]. In these patients fever may be absent, but tachypnea is usually present along with abnormal, physical examination of the chest [28]. In some patients the history may be useful in identifying patients at risk for infections with specific pathogens (Table 1) [19].

Table 1. Clues to the epidemiology and etiology of pneumonia, based on the medical history.

Feature	Possible etiologic agent or associated condition
Environmental	
Exposure to contaminated air-conditioning cooling towers; hot tub; recent travel and stay in a hotel; grocery store mist machine; visit to or recent stay in a hospital with drinking water contaminated by *L. pneumophila*	*Legionella pneumophila*
Exposure to infected parturient cats, cattle, sheep, or goats	*Coxiella burneti*
Pneumonia develops after windstorm in an area of endemicity	*Coccidioides immitis*
Outbreak of pneumonia in shelter for homeless men or jail	*Streptococcus pneumoniae, Mycobacterium tuberculosis*
Outbreak of pneumonia in military training camp	*S. pneumoniae, Chlamydia pneumoniae*, adenovirus, *M. pneumoniae*
Outbreak of pneumonia in a nursing home	*C. pneumonia, S. pneumoniae*, respiratory syncytial virus, influenza A virus
Exposure to contaminated bat caves; excavation in areas of endemicity	*Histoplasma capsulatum*
Exposure to turkeys, chickens, ducks, or psittacine birds	*Chlamydia psittaci*
Exposure to mice or mice droppings	Hantavirus
Exposure to rabbits	*Francisella tularensis*
Travel history	
Travel to Thailand or other countries in Southeast Asia	*Burkholderia pseudomallei (melioidosis)*
Immigration from countries with high endemic prevalences of tuberculosis	*M. tuberculosis*
Occupational history	
Health care work	*M. tuberculosis*, acute HIV seroconversion with pneumonia
Tick bite (*Dermacentor variabilis* or *Ixodes dommini* [*scapularis*])	Rocky Mountain spotted fever (rarely complicated by pneumonia), *Ehrlichia* species
Host factor	
Diabetic ketoacidosis	*Streptococcus pneumoniae, Staphylococcus aureus*
Alcoholism	*S. pneumoniae, Klebsiella pneumoniae, S. aureus*, anaerobes
Chronic obstructive lung disease	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
Solid organ transplantation (pneumonia occurring >3 mo after transplantation)	*S. pneumoniae, H. influenzae, Legionella* species, *Pneumocystis carinii* (rarely CMV), *Strongyloides stercoralis*
Sickle cell disease	*S. pneumoniae*
HIV infection and CD4 cell count <200/μL	*P. carinii, S. pneumoniae, H. influenzae, Cryptococcus neoformans, M. tuberculosis, Rhodococcus equi*
B cell defects (e.g., multiple myeloma, Hodgkin's disease)	*S. pneumoniae*
Granulocytopenia	Aerobic gram-negative rod-like bacteria such as *Escherichia coli* or *K. pneumoniae*

In addition one must realize that the physical examination is *neither* sensitive nor specific in the diagnosis of CAP [27, 29-31]. The level of agreement for physical exam findings is variable among physicians. In a study designed to investigate the ability of physicians to detect abnormal auscultatory findings on the basis radiographic abnormalities, interobserver agreement was noted in only 41.5% of cases, decreasing to 25% when the presence of crepitant rales was investigated [31]. In another study [29] involving 52 patients, 25 of whom had pneumonia by radiograph and clinical presentation; the investigators found a sensitivity of 47-69% and specificity of 58-75%. In addition to this the sensitivity and specificity of physical findings showed considerable variability amongst examiners as well as for a given individual examiner in eliciting findings between the right and left lungs. Yet, despite detecting abnormal sounds, the examiner did not think the patient had pneumonia in many cases, attributing the findings to other respiratory disorders. Thus while a chest examination, vital signs and history are probably sufficient to screen for pneumonia, some patients do not have abnormal lung sounds, even in the presence of pneumonia, and furthermore, lung findings can be evanescent and may change substantially, within minutes. The positive predictive value of a clinical diagnosis of pneumonia based on physical examination varied from 53-61% [18, 27]. Hence while clinical findings are important they should not be relied upon solely for diagnosis and it recommended that a chest radiograph be obtained.

2. Chest Radiographs:

All three guidelines recommend that whenever possible chest radiographs be obtained [2, 19, 20]. It can be particularly useful in differentiating CAP from other conditions that may mimic it clinically or can suggest specific etiologies or conditions such as tuberculosis or lung abscess. In addition to this it can identify those with potential complications such as multilobar pneumonia or pleural effusion. Any significant pleural effusion should be sampled, preferably prior to initiation of antibiotic, therapy to rule out a complicated parapneumonic effusion or empyema. Note however, there is no benefit to delaying therapy for a thoracentesis [19, 20]. Pleural fluid should be sent for gram stain, culture, pH, LDH, Glucose, total protein, AFB. Heffner et al, showed in a study of 39 patients with pneumonia and pleural effusion, that a delay in thoracentesis 2-8 days after detection lead to a significant increase in the length of stay (>10 days) and 33% increase in cost [32]. Therefore never let the sun set on a pleural effusion. Patients may initially have a negative chest radiograph and still have evidence

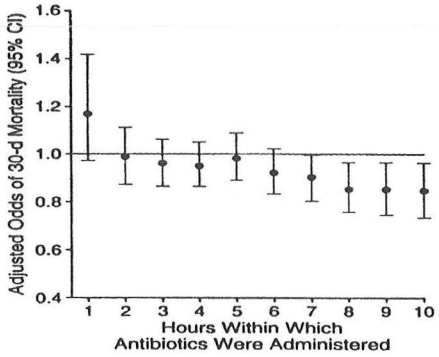
of disease on HRCT however the clinical relevance of these findings are unknown and this is not recommended as an initial diagnostic approach [33].

3. Laboratory:

No prospective studies have identified specific tests to order in patients with suspected CAP. While an effort should be made to identify the etiologic agent one should realize that even with aggressive attempts, an etiologic *diagnosis is made in only 50-60% of patients with CAP.* If the etiologic agent is known therapy can then be focused, more cost effective, with less side effects and concern for developing resistance. However, this goal must be tempered by two findings:

First, if testing leads to a delay in the initiation of appropriate therapy, it may lead to an adverse outcome. A large national Medicare study demonstrated that 30 day mortality is increased when the administration of the first dose of antibiotic therapy was delayed > 8 hours from time of arrival to the hospital [33] (Fig 1).

Figure 1. Relationship of receiving antibiotics within a given time frame and 30-day mortality



In this same national retrospective study of over 14,000 patients' four processes of care were examined to determine whether any of them were associated with lower 30-day mortality. They were: time from hospital arrival to antibiotic administration, blood culture collection before antibiotics, blood culture collection within 24 hours of hospital arrival, and oxygenation assessment within 24 hours of arrival. The administration of antibiotics within 8 hours of arrival and the collection of blood cultures within 24 hours were both associated with improved survival. However many clinical pathways call for administration within 4 hours of arrival and new data yet to be published suggests survival advantage if the antibiotics are given within 3 hours of arrival [24].

Secondly, because the possibility of co-infection particularly with an atypical pathogen is a consideration, the value of overly focused therapy may not cover all involved pathogens. In large population studies, treatment that accounted for atypical pathogen co-infection led to a better outcomes and lower 30 day mortality than treatment regiments that did not account for this co-infection with atypical organisms [34-36].

Sputum Gram Stain:

This is perhaps one of the most controversial tests available for the etiologic diagnosis of CAP. The ATS and ISDA are at odds on this with the ATS recommending that it be considered for inpatients only and done in all seriously ill (ICU) patients [20]. The ISDA recommends it be done for all inpatients using the information to narrow coverage [2]. The ATS does not recommend the gram stain be used for this purpose because it is not sensitive and on can miss co-infecting organisms not seen on gram stain. Like the expression 'all politics is local' all resistance is local so one must be aware of local infection and resistance patterns in determining the significance of findings and treatment. The ATS guidelines suggest that the gram stain results can be used to expand coverage if unexpected organisms e.g., pseudomonas is identified [2, 20]. The reason for this controversy lies in the well-documented limitations to this test,

1. Not all patients can provide an adequate sample (either due to quality or inability to produce sputum.) An acceptable sample is defined as one with < 10 squamous epithelial cells, and > 25 neutrophils per low-power field [2].
2. Interpretation is observer dependent [37].
3. Atypical pathogens cannot be seen.

4. The definition of positive varies from study to study [38]. This alters test characteristics dramatically.
5. A positive result for pneumococcus is poorly predictive of the ability to recover the organism from a sputum or blood culture [39, 40].

However, direct staining for some infections such as *Mycobacterium* sp., endemic fungi, *Legionella spp.*, and *Pneumocystis Carinii* may be useful if these organisms are suspected.

Blood Cultures:

In general blood cultures have a low yield with only 5-11 % of all admitted patients having positive blood cultures. Pneumococcus accounts for 60% of cases of documented bacteremia [11, 41]. However, as stated earlier this was shown to be associated with an increased 30-day mortality in a large cohort of Medicare patients and is considered by HCFA and Medicare as a quality indicator. It is recommended that all hospitalized patients have blood cultures drawn preferably before antibiotic or at least within 8 hours of receiving antibiotics. The primary rational is if positive it is an unequivocal diagnosis from a sterile site; and allows for narrowing of antibiotic coverage [19, 24, 42].

Miscellaneous tests:

Serologic testing and cold agglutinin measurements are not useful in the initial evaluation of patients with CAP and should not be routinely performed. When Legionella is suspected measurement of the urinary antigen is valuable being positive in the majority of patients with *Legionella* serogroup 1 infection [43, 44]. HIV should be considered in those with risk factors [45]. Invasive diagnostic techniques such as transtracheal aspiration, bronchoscopy with protected brush and bronchoalveolar lavage, and direct percutaneous fine needle aspiration of the lung are not indicted in most patients with CAP [2, 46, 47]. Outcome has not shown to be improved by establishing a specific etiologic diagnosis [48, 49].

Atypical vs. Typical CAP:

Clinical features of CAP i.e., symptoms, signs and radiographic findings cannot be used to establish the etiology of pneumonia with any significant degree of sensitivity or specificity. For years pneumonia has been classified into 'atypical' and typical forms. This classification originally arose from the observation that the presentation and natural history of some patients with pneumonia were different compared with those of patients with pneumococcus [50, 51]. Pathogens such as *H. Flu*, *S. Aureus* and gram negative enteric bacteria caused clinical syndromes identical to those produced by *S. pneumoniae* [52]. Yet, other pathogens such as *M. Pneumoniae* [53] and other viral agents have been identified as producing a subacute illness [54, 55]. It has now been documented that some of these agents like *Legionella* species and influenza, can cause a wide spectrum of illness, ranging from a fulminant life-threatening pneumonia to a more subacute presentation [55]. Thus one must be careful in the application of these terms or not use them at all since clinical features alone cannot be used to determine likely etiologic organisms [38, 56-59]. In addition, advancing age and coexisting illnesses frequently affect the clinical presentation of pneumonia. Those over age 65 have a significantly increased risk of mortality from bacteremic pneumococcal disease, and amongst this age group the common clinical features of fever, chills and cough are often obscured, atypical or even absent [27, 50, 60]. This is because it is now known that host factors are just as important as the identity of the etiologic pathogen in defining the presenting signs and symptoms of pneumonia. Thus in those over the age of 65 one must be more diligent in considering this as a possible diagnosis and equally aggressive in its treatment.

Site of Care:

The initial site of care decision is likely to be the single most important clinical decision made by physicians during he entire course of illness for patients with CAP. It has a direct bearing on the intensity of testing, microbiologic evaluation, therapy and costs of treatment [4, 11, 20].

Risk Stratification of Patients with CAP:

Understanding the prognosis of a disease allows physicians to inform patients regarding the expected natural history of an illness, potential complications, and the probability of successful treatment. It is important to understand the prognostic indictors of CAP since; it ranges from rapid recovery without functional impairment

to serous morbid complications and death. The ability to predict these medical outcomes has a major impact on management and the decision to hospitalize or treat as and outpatient. The estimated cost of CAP managed in the hospital is $7500, [4, 7, 61] > 20 fold higher than outpatient therapy.

A number of independent risk factors for either increased mortality or risks of a complicated course of CAP have been identified [20, 27, 42, 62-64]. Many of these factors were identified by Osler in the pre-antibiotic era and remain today [4, 9, 65-69]. The ATS guidelines suggest that when multiple risk factors coexist, hospitalization should be strongly considered [20]. The decision to admit is based on the art and science of medicine, as social issues must also be considered. These include issues such as availability of outpatient support services, ability to tolerate oral intake, compliance issues, and so on. In general there is a wide geographic variation in hospital admission rates for CAP [70] and physicians typically overestimate the risk of death leading to unnecessary admissions [71] (Table 2-3), while in other studies they have failed to recognize patients as being severely ill at time of presentation [71, 72].

Table 2: Overestimation of Mortality

Risk of 30-day Mortality in Low-Risk CAP Patients

Estimated Risk	Outpts.	Inpts.	Observed Mortality
>5%	5%	41%	<1%

When the estimated risk of death was >5%, low-risk patients were 6 times more likely to be hospitalized

Table 3: Factors Independently associated with hospitalization

Factor*	Odds Ratio	95% CI
Medical trainee	69.0	16.2-293.7
Estimating 30-d risk of Patient death >5%	18.4	6.1-55.7
Respiratory distress	12.7	4.0-40.5
Preexisting medical Problems	7.0	2.6-18.7
Emergency medicine Specialty	5.8	1.3-25.1

Numerous studies have identified and validated risk factors for mortality in CAP [2, 42, 62]. These risk factors can be categorized by clinical history, physical, laboratory and radiographical risk factors. (Tables 4-6)

Risk Factors associated with Increased Mortality

Table 4: History [63, 73-80]

1. Age > 65 years
2. Comorbid Conditions
   a. Lung Disease: COPD or Bronchiectasis
   b. Cardiac: CHF
   c. Liver Disease: Cirrhosis or alcohol abuse
   d. Renal Disease: failure or insufficiency
   e. Endocrine: Diabetes or Malnutrition
   f. Neurological: Cerebrovascular disease
   g. Miscellaneous: Neoplasm or spleenectomy
3. Hospitalization within the last year

Table 5: Physical Findings [60, 70-73, 76, 78, 79]

1. Respiratory Rate ≥ 30
2. Diastolic BP ≤ 60mmHg
3. Systolic BP ≤ 90mmHg
4. Pulse ≥ 125/min
5. Temperature <35C or ≥ 40C
6. Confusion/decreased level of consciousness
7. Extrapulmonary sites of infection

Table 6: Laboratory and Radiographic risk factors [63, 75, 76, 79, 81-83]

1. WBC < 4 X 10^9/L or > 30X 10^9, or an absolute neutrophil count below 1 X 10^9
2. Pa_{O2} < 60mmHg or Pa_{CO2} > 50mmHg on Room air
3. Serum Creatinine > 1.2 mg/dl or BUN of > 20mg/dl
4. Hematocrit < 30% or hemoglobin < 9mg/dl
5. Arterial pH < 7.35
6. Evidence of Sepsis as manifested by a metabolic acidosis, or coagulopathy
7. Multilobar involvement, cavitation, pleural effusion or rapid radiographic spread

In the initial guidelines a number of risk factors were identified based on 'expert opinion' and subsequent studies have not validated these criteria. Since that time, the British Thoracic Society (BTS) and the Pneumonia

Research Outcomes Team (PORT) have both identified risk factors used to stratify patients according to risk that have been well validated in subsequent studies. The two studies are complimentary in that the BTS study identifies high-risk patients so their severity of illness is not underestimated and the PORT trial is focused on recognizing low risk patients so their severity of illness is not overestimated [63, 72, 82]. These risk factors have primarily been defined for inpatients and have not been studied in a large number of outpatients (Table 7 and Fig. 2).

Table 7: British Thoracic Society Prognostic Rules

Rule 1: Two of the three present represents a 21X increased risk of death

- Respiratory Rate ≥ 30x /min
- Diastolic Blood Pressure ≤ 60mmHg
- Blood Urea Nitrogen (BUN) > 7mMol/L (19.1mg/dl)

Rule 2

- Mental confusion instead of BUN

The BTS rule (Table 7) was derived based on 453 inpatients with CAP [84] and independently validated in 246 inpatients with CAP [72, 82]. Initially the rule only included respiratory rate, diastolic blood pressure and BUN however a fourth variable, confusion, was added to the rule and in one study, patients with any two of the four factors had a 36-fold increase in mortality compared to those without these findings [72]. In the same study, the BTS rule identified 19 patients as severely ill who subsequently died, while clinicians identified only 12 of the 19 high risk patients based on their initial clinical assessment. Thus it is felt that there is value for the BTS rule to identity high-risk patients in a simple and reliable fashion [20]. Subsequent studies have shown Rule 1 to be 89% sensitive and 79% specific and Rule 2 to be less sensitive at 39% and very specific 94% [72, 82].

The other commonly quoted and well-validated prediction rule comes from the Pneumonia Patient Outcomes Research Team (PORT). This study used a derivation co-hort of 14,199 inpatients with CAP in 4 different institutions and was independently validated in 38,039 inpatients with CAP and again in 2,287 inpatients and outpatients prospectively enrolled in the PORT cohort study [71]. This is a two-step process used to identify those patients at low risk for mortality and the only rule that has been tested in an independent cohort of patients [85] (Fig. 2).

Step 1. (Fig 2)
In step 1, patients are classified as risk class I if they are ≤ 50 years old, have none of 5 comorbid conditions (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or renal disease), and have normal or mildly deranged vital signs.

Step 2. (Fig 2., Table 8)
In step 2 all patients not assigned to risk class I are stratified into classes II-IV on the basis of points assigned for 3 demographic variables, 5 comorbid conditions, 5 physical examination findings, and 7 laboratory or radiographic findings [71]. Point assignments correspond with the different classes (Fig. 2). In the derivation and validation of this rule mortality was found to be low for risk classes I-III (0.01-2.8 %), moderate for risk class IV (8.2-9.3%) and high for risk class V (37-31.1%) [71] (Table 8). Based on this, the investigators suggest that patients in risk class I and II be considered for outpatient treatment while those in class III were potential candidates for outpatient treatment but may need brief inpatient observation, while traditional inpatient care should be provided for patients in classes IV and V. Note no attempt was made to use this to define need for admission to the ICU. The authors extrapolated this data to suggest that admission for inpatient care could be reduced by as much as 31%. It was also noted in subsequent reports that [71] 1% of patients recommended for outpatient care died and 4.3% admitted to an ICU. If the strategy were amended to include traditional inpatient care for any patient with hypoxemia (defined as Pa O2 <60mm Hg or O2 saturation < 90%) at the time of presentation the reduction in inpatient care would have been slightly less dramatic but the number of ICU admissions for inpatients who were initially recommended for outpatient care, would have been reduced.

While the authors have extrapolated the data to define need for hospitalization, the prediction rule was actually derived to define *mortality risk.* In addition, it was never prospectively tested during development for the

purpose of defining need for hospitalization. However, prospective studies have been performed that suggest it may have some use for this purpose [86, 87]. In the first study ER physicians were educated about the rule and encouraged to treat those in risk classes I-III as outpatients. The outcomes for those treated at home during this intervention phase were compared to the outcomes for historical control subjects form the time period immediately preceding the intervention. The percentage treated as outpatients was higher during the intervention period than the control period (57 vs. 42% a relative increase of 36%; P=. 01). None of those treated in the intervention period died but 9% of patient's initially discharged according to the rule subsequently required admission [71].

A more recent study known as the CAPITAL study [87] designed to examine a critical pathway for the diagnosis and treatment of pneumonia was conducted in 19 Canadian hospitals. The emergency departments were randomized to one of two groups; one group was to use a critical pathway that included the prediction rule and the other to conventional management. Once again physicians in the intervention group were encouraged to discharge those patients in risk classes I-III but physician judgment was allowed to override the rule. Overall 1743 patients were enrolled in the study and in the intervention hospitals there was an 18% reduction in admissions (31 vs. 49% $P < 0.013$) yet the morbidity and mortality did not differ between the two groups. Because the pathway contained a number of interventions the impact of a single factor such as the PORT prediction rule could not be evaluated [87].

There are several caveats that should be kept in mind when considering the use of prediction rules: First, they tend to oversimplify the manner in which physicians interpret predictor variables as each variable has a "threshold" for being a poor prognostic finding. For example in the PORT approach, a patient with diastolic BP of 59 mmHg falls into the same stratification as a patient with a diastolic BP of 25 mmHg even though they have a different severity of illness. Secondly, predication rules tend to overlook the importance of patient preferences in clinical decision-making. This is demonstrated by observations that the majority of patients with CAP do not have their site preferences for care solicited even though many have been shown to prefer outpatient care to inpatient care [88].

Recommendations Regarding Admission Decisions are:

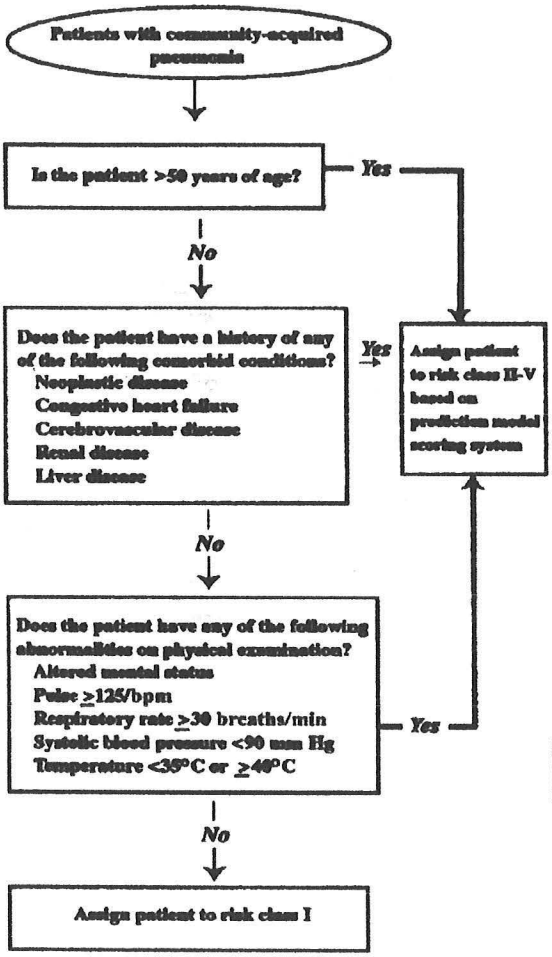
1. Use prediction rules to **support** NOT replace physician decision-making. E.g. neuromuscular disease is not included in the prediction rule but they have an increased likelihood of worse prognosis due to their inability to clear secretions.
2. Factors other than severity of illness must be considered, such as ability to maintain oral intake, history of substance abuse, ability to carry out activities of daily living.
3. The final decision remains and "art of medicine" decision that cannot be easily made by any existing prediction models [20].

Fig. 2. Pneumonia –specific severity-of-illness scoring system and factors associated with the decision to admit a patient with CAP to the hospital[71]

STEP 1.

Prediction model for indentification of patient risk for persons with community-acquired pneumonia

Algorithm



STEP 2

Pneumonia-specific severity of illness scoring system

Patient's characteristics	Points assigned	Your patient's points
Demographic factor		
Age, y		
Male	(age)	
Female	(age −10)	
Nursing home resident	+10	
Comorbid illness		
Neoplastic disease	+30	
Liver disease	+20	
Congestive heart failure	+10	
Cerebrovascular disease	+10	
Renal disease	+10	
Physical examination finding		
Altered mental status	+20	
Respiratory rate >30/min	+20	
Systolic BP <90 mm Hg	+20	
Temperature <35°C or >40°	+15	
Pulse >125/min	+10	
Laboratory finding		
pH <7.35	+30	
BUN >10.7 mmol/L	+20	
Sodium <130 mmol/L	+20	
Glucose >13.9 mmol/L	+10	
Hematocrit <30%	+10	
PO_2 <60 mm Hg or O_2 sat <90%	+10	
Pleural effusion	+10	
Total Score		

Stratification of risk score

Score ___90: send home; score ___91: admit to hospital

Risk	Risk Class	Based on algorithm
Low	I	0 total points
	II	≤70 total points
	III	71–90 total points
Moderate	IV	91–130 total points
High	V	>130 total points

Table 8. Mortality by Risk Class [71]

I. .01-.04%
II. 0.6-0.7%
III. 0.9-2.8%
IV. 8.2-9.3%
V. 27-31.1%

Definition of Severe Community-Acquired Pneumonia and Need for Admission to the ICU

In the past decade severe community acquired pneumonia has been established as a clinical syndrome of it is own with specific features of risk, epidemiology and outcome. As a result it requires a distinct clinical approach and initial antimicrobial treatment [67, 89, 90].

In general severe CAP is considered as pneumonia requiring ICU admission and approximately 10% of all hospitalized patients with CAP fall into this category [91, 92]. The mortality of these patients is especially high, typically reaching 20-50% [48, 49, 89, 90, 93, 94]. However, precise criteria behind the decision to admit to the ICU are essentially undetermined and there is no universally accepted definition of severe pneumonia. Despite this, it is imperative that this patient population be recognized early on in their course of CAP with prompt initiation of therapy directed at likely etiologic pathogens. This is a strategy that has been associated with reduced mortality if patients have a clinical improvement within 72 hours [49].

The original ATS guidelines published in 1993 identified nine criteria for severe illness and the presence of any one was used to define severe CAP. Subsequent studies evaluating these criteria have demonstrated that they are overly sensitive and not very specific with a low positive predictive value for admission to the ICU. In fact, using these criteria as many as 65-68% of all admitted patients would be defined as having severe CAP and be admitted to the ICU [36, 49, 95].

A subsequent study using multivariate analyses divided the nine criteria for sever CAP into five "minor" criteria that could be present on admission and four "major" criteria that could be present on admission or later in the hospital stay [95] (Table 9).

Table 9: Overview of 10 Severity Criteria for the Assessment of Severe CAP[95]

Baseline (**"minor"**) criteria assessed at admission

1. Respiratory Rate > 30/min
2. Severe respiratory failure (Pao2/Fio2 < 250)
3. Bilateral involvement in chest radiograph
4. Involvement of ≥ 2 lobes in chest radiograph (Multilobar involvement)
5. Systolic blood pressure < 90mmHg
6. Diastolic blood pressure < 60 mmHg

"Major" Criteria assessed at admission **or** during clinical course

1. Requirement for mechanical ventilation
2. Increase in the size of infiltrates by ≥ 50% in the presence of clinical nonrepsonse to treatment or deterioration (progressive infiltrates)
3. Requirement of vasopresors > 4 H (septic Shock)
4. Serum creatinine ≥ 2mg/dl or increase of ≥ 2mg/dl in a patient with previous renal disease or acute renal failure requiring dialysis (renal failure)

The inclusion of the baseline criteria (minor) in the analysis revealed that only 3 parameters remained independently associated with the need for ICU admission: They are:

1. Systolic BP < 90 mmHg
2. Multilobar involvement
3. Pao2/Fio2 <250

Of these three variables only Systolic blood pressure < 90 mmHg and multilobar involvement were independent predictors of death. Among the major criteria mechanical ventilation, septic shock and renal failure remained independent predictors of severe pneumonia while only mechanical ventilation and septic shock were independently associated with death. Using a rule that required the presence of either two of three minor criteria or one of one of three major criteria the authors were able to improve upon the sensitivity and specificity of these prognostic indicators of severity and mortality[95] (Tables 10-11).

Table 10.

OPERATIVE CHARACTERISTICS OF THREE PREDICTION RULES FOR SEVERE CAP CONSISTING OF BASELINE (MINOR) CLINICAL VARIABLES*

Rule	Sensitivity n (%)	Specificity n (%)	PPV n (%)	NPV n (%)
One of three	28/60 (47)	182/284 (64)	28/130 (22)	182/214 (85)
Two of three	20/60 (33)	268/284 (94)	20/36 (56)	268/308 (87)
Three of three	2/60 (3)	284/284 (100)	2/2 (100)	268/308 (83)

* Criteria: systolic blood pressure < 90 mm Hg, multilobar involvement, Pa_{O_2}/Fi_{O_2} < 250 at admission.

Table 11

OPERATIVE CHARACTERISTICS OF TWO PREDICTION RULES FOR SEVERE CAP*

Rule	Sensitivity n (%)	Specificity n (%)	PPV n (%)	NPV n (%)
First rule	47/60 (78)	268/284 (94)	47/63 (75)	268/281 (95)
Second rule	49/60 (82)	258/284 (91)	49/75 (65)	258/269 (96)

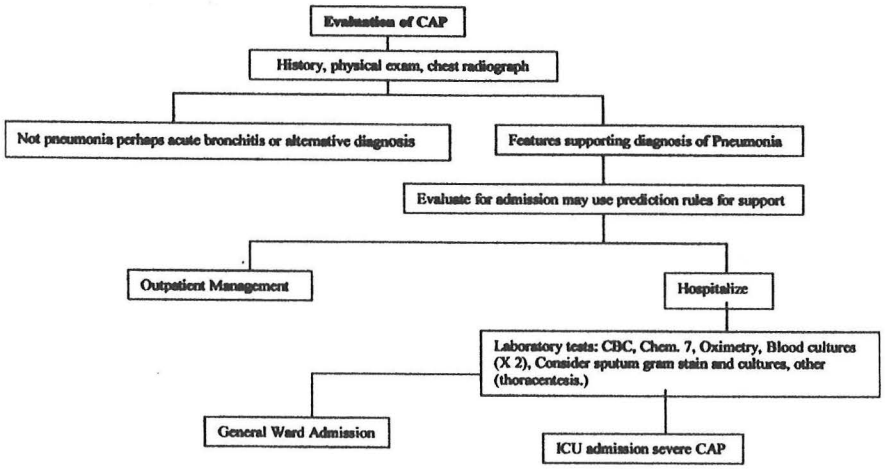
Definition of abbreviations: PPV = positive predictive value; NPV = negative predictive value.

* First rule: two of three baseline (minor) clinical parameters: systolic blood pressure < 90 mm Hg, multilobar involvement, Pa_{O_2}/Fi_{O_2} < 250 at admission; or one of two major parameters: requirement of mechanical ventilation, septic shock, renal failure.

Second rule: two of three baseline (minor) clinical parameters: systolic blood pressure < 90 mm Hg, multilobar involvement, Pa_{O_2}/Fi_{O_2} < 250 at admission; or one of three major parameters: requirement of mechanical ventilation, septic shock, renal failure.

By using rule 2 (Table 11) the sensitivity and specificity were markedly increased. However this proposed rule remains imperfect because the performance relying only on baseline clinical criteria was limited. Even so the proposed rule can serve as a useful counter part to the prediction rule put forth by Fine et al, [71] in the PORT study. If validated in an independent population this may be a more accurate definition of severe CAP. Other findings suggesting severe illness such as the BTS rule, namely confusion and BUN > 19.6 mg/dl are useful in evaluating this population [84].

Fig 3. Evaluation of CAP



Treatment:

The treatment of any infectious disease can be directed or empiric. Directed therapy assumes that one knows the specific etiologic organism whereas the latter approach is an educated guess. The obvious advantages with directed therapy include a reduction in polypharmacy, reduced costs, and a lower incidence of adverse drug reactions, and less antibiotic selection pressure. Given the obvious one may inquire why use empiric therapy at all? The answer lies in the disease itself, the pathogens involved, and our limitations in regards to diagnostic testing. Although frequently regarded as a single homogeneous entity, CAP is in reality a complex of syndromes whose causative pathogens and ultimate outcomes depend on the host, severity of illness and site where care is administered. All these determine the type of therapy rendered [3].

While a rapid etiologic diagnosis is optimal in the management of any infectious process, we know that in CAP the responsible pathogen remains unidentified in as many as 50-60% of patients despite extensive diagnostic testing [65-67, 96-98]. This is likely due to a number of factors including the presence of unusual pathogens that go unrecognized (fungi, Coxiella, viral infections), the presence of a noninfectious mimic of

CAP such as sarcoid and prior treatment with antibiotics [20]. Currently there is no single test available that can identify all potential pathogens and of the available tests each has its share of limitations as discussed earlier.

One problem in particular is the inability to detect commonly encountered pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella spp.*, and respiratory viruses. This is further compounded by the fact that it is now generally believed that often more than one pathogen is involved in CAP [65, 66, 99, 100]. This concept of *microbial synergy* has been recognized for years in other infections, such as peritonitis, intra-abdominal abscess and diabetic foot infections. One pathogen may inhibit the interaction of host defenses with other pathogens, or provide essential nutrients, or alter the local microenvironment so other pathogens can thrive [3, 101]. For example, the association of *Staphylococcus aureus* and *Haemophilus influenzae* infections in the same patient, for example, may be explained by the fact that the staphylococci produce nicotinamide dinucleotide, which is necessary for the *H. influenzae* to grow [3, 102]. Data supporting likely co-infection with atypical pathogens in CAP have been derived by serologic testing, or documentation of four-fold rise in titers to *M. pneumoniae, C. pneumoniae,* or *Legionella spp.*, with some of these diagnoses having even been made with single high acute titers [66, 69]. Since may of these diagnoses have not involved testing for the surface antigens of these pathogens, or cultures of respiratory secretions, the clinical significance of the serologic data remains unclear.

Thus the major variables influencing the spectrum of etiologic agents and the initial approach to therapy are: (1) severity of illness at initial presentation, (2) the presence of coexisting illness, and (3) the presence of identifiable clinical risk factors for drug-resistant and unusual pathogens (Table 12).

Table 12: Modifying Factors that increase Risk of Infection with Specific Pathogens [10, 20, 103]

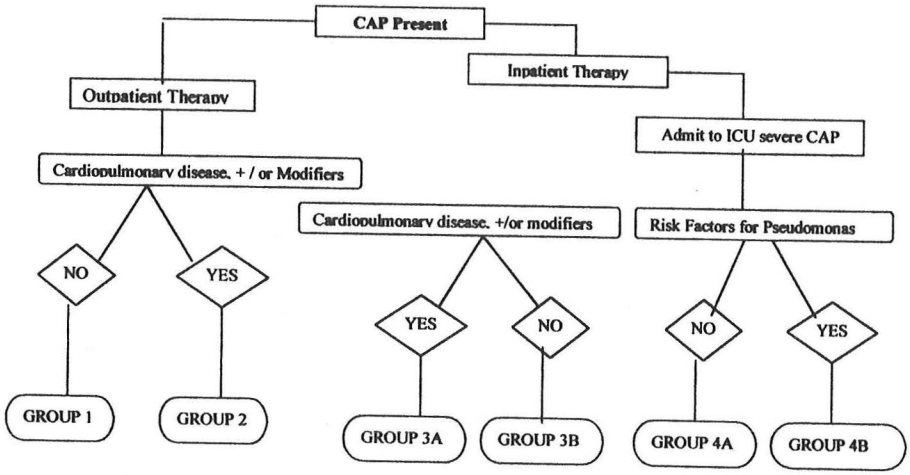
Penicillin-resistant and drug-resistant Pneumococci
Age > 65 yr
β-Lactam therapy within the past 3 months
Alcoholism
Immune- suppressive illness (including therapy with corticosteroids)
Multiple medical comobidities
Exposure to a child in a day care center
Enteric Gram-negatives
Residence in a nursing home
Underlying cardiopulmonary disease
Multiple medical co morbidities
Recent antibiotic therapy
Pseudomonas aeruginosa
Structural lung disease (bronchiectasis)
Corticosteroid therapy (> 10mg prednisone per day)
Broad-spectrum antibiotic therapy for > 7 d in the past month
Malnutrition

Knowledge of this spectrum and patient population being treated is the <u>key</u> to deciding "empiric" therapy. Further stratification of patients in to four groups (Fig 4) on the basis of 1) site of therapy (outpatient, inpatient, ICU); 2) the presence of coexisting cardiopulmonary disease; and 3) the presence of modifying risk factors (Table 12) further narrows the spectrum and assists with antibiotic selection. Smoking history was not taken into consideration in the ATS and ISDA guidelines because *H. Influenzae* is covered in all the recommended regimens. However smoking is an important part of the history as it is independently associated with an increased risk of invasive pneumococcus and increased mortality [104].

Previous guidelines used age as a major discriminating factor among patients to define bacterial etiology. Subsequent studies have not supported this, showing that age alone, in the absence of comorbid illness, has little impact on the bacterial etiology of CAP [10, 68, 105]. In fact the only pathogen whose impact may be affected by age alone is drug-resistant *Streptococcus pneumoniae* (DRSP), with a number of studies showing that age > 65 by itself is a specific independent risk factor for other organisms [17, 106]. In defining the bacteriology of CAP, the most likely etiologic pathogens for each category were examined, adding new information about the emerging resistance of common CAP pathogens such as pneumococcus, *H.*

influenzae, and *M. catarrhalis* [13-16, 18, 92, 107]. Regardless of all the various possibilities *S. pneumoniae* is by far and away the most common organism (60% of patients) accounting for 2/3 of deaths in CAP [3, 108].

Figure 4. Stratification of patients identified as having CAP [20]



Specific Pathogens by Patient Subset: (TABLES 13-16)

Table 13: Group 1: Outpatients, NO cardiopulmonary disease or modifying factors*

Organisms	**Therapy**
Streptococcus pneumoniae *Mycoplasma pneumoniae* *Chlamydia pneumoniae* (alone or as Mixed infection) *Haemophilus influenzae* Respiratory viruses Miscellaneous *Legionella spp.* *Mycobacterium tuberculosis* Endemic Fungi	Advanced Generation Macrolide: Azithromycin or Clarithromycin# OR Doxycycline@

*Excludes HIV patients,
Erythromycin is NOT active against H. influenzae,
@ Many isolates of S. pneumoniae are resistant to tetracycline and it should be used only if the patient is allergic to or intolerant of macrolides

This group is essentially comprised of healthy individuals without risk factors. Recommended therapy is with an advanced generation macrolide. Erythromycin is not nearly as well tolerated and is not active against *H. Flu* (increased risk in smokers). However, if the patient is a nonsmoker in this group and *H. flu* is not a concern Erythromycin can certainly be used. While coverage with a fluoroquinolone would be effective it is felt to be unnecessary and could promote overuse of a valuable class of antibiotics. Thus it is not recommended as first line therapy in this particular group by both the ATS and the Canadian guidelines recently issued. It is listed in the ISDA guidelines but they do not differentiate between types of outpatients i.e., those with and without comobidities.

Although most patients with pneumonia are treated as outpatients the etiology of pneumonia in this group of patients has not been well studied. Pneumococcus is the most commonly identified pathogen (9-20%) when sputum samples are taken; while *M. Pneumoniae* is the most common organism (13-37% of all episodes) identified when serologic testing is performed [64, 109, 110]. *Legionella spp.* has also been documented with rates varying from 0.7-13% of all patients. In addition, the incidence of viral infections is variable, but in one series was documented as high as 36%[111]. In many of these studies the importance of bacterial pathogens is understated because may of the outpatients did not have sputum specimens collected. Mortality in this population is very low (<1-5%) [42, 71].

TABLE 14 Group 2: Outpatient WITH cardiopulmonary disease and/or other modifying factors

Organisms	Therapy
Streptococcus pneumoniae (including DRSP)*	β- Lactam (oral cefpodoxime,
Mycoplasma pneumoniae	Cefuroxime,
Chlamydia pneumoniae	High-dose amoxicillin,
Mixed infection (bacteria plus	Amoxicillin/clavulanate;or
atypical pathogen or virus)	Parenteral ceftriaxone
Haemophilus influenzae	Followed by oral cefpodoxime
Enteric gram-negatives	**PLUS**
Respiratory viruses	Macrolide or Doxycycline
Miscellaneous	**OR**
Moraxella catarrhalis, Legionella spp.	Antipneumococcal fluoroquinolone (used alone)
Aspiration (anaerobes) Mycobacterium tuberculosis	
Endemic Fungi	

*DRSP – Drug resistant pneumococcus

This more complex group of outpatients can be managed either with a β-Lactam/ macrolide combination or monotherapy with an antipneumococcal quinolone. For most patients the ease of use of one drug daily will make the quinolone option more appealing, and can at times be cheaper in cost [87]. The Canadian guidelines further suggest that the fluoroquinolone be reserved for those who have either been on prednisone or antibiotics in the previous 3 months. Although pneumococcus remains the most likely pathogen, resistance to penicillin and other agents (macrolides, Bactrim) is more likely in this population and this should be considered in the antibiotic selection. In addition if the patient is from a nursing home, then aerobic gram-negative infection is possible and can include the *Enterobacteriaceae* such as *Escherichia coli*, or *Klebsiella spp.*, and even *P. aeruginosa* if bronchiectasis is present [20]. In the presence of poor dentition or if a history of neruologic illness, impaired consciousness, or a swallowing disorder aspiration with anaerobes must be considered and clindamycin also be considered as a therapy. Mortality in this group is also low (< 5%), but as many as 20% or this group initially treated as outpatients may require subsequent hospitalization[71].

Table 15: **Group 3**: Inpatients NOT in the ICU

Organisms	Therapy
3A: Cardiopulmonary Disease and /or Modifying Factors (Includes Nursing home residents)	
Streptococcus pneumoniae (including DRSP)	Intravenous β- Lactam
Haemophilus influenzae	(Cefotaxime, Ceftriaxone,
Mycoplasma pneumoniae	Ampicillin/sulbactam,
Chlamydia pneumoniae	High-dose ampicillin)
Mixed infection (bacteria plus	**PLUS**
atypical pathogen or virus)	Intravenous or oral Macrolide or Doxycycline
Enteric gram-negatives	**OR**
Aspiration (anaerobes)	Intravenous Antipneumococcal fluoroquinolone
Respiratory viruses	(used alone)
Legionella spp.	
Miscellaneous	
M. Tuberculosis, Endemic fungi, P. Carinii	
3B: No Cardiopulmonary Disease and /or Modifying Factors	
Streptococcus pneumoniae (including DRSP)	Intravenous Azithromycin alone
Haemophilus influenzae	If macrolide allergic or intolerant
Mycoplasma pneumoniae	Doxycycline AND a β-lactam
Chlamydia pneumoniae	
Mixed infection (bacteria plus	**OR**
atypical pathogen or virus)	Montherapy with an
Respiratory viruses	Antipneumococcal fluoroquinolone
Legionella spp.	
Miscellaneous	
M. Tuberculosis, Endemic fungi, P. Carinii	

Most patients requiring hospitalization will have some risks for DRSP, enteric gram-negative or underlying cardiopulmonary disease. These factors influence likely etiologic pathogens with *S. pneumoniae*, *H. influenzae*, and atypical pathogens most commonly identified. There is good evidence to suggest that these patients can be treated with either a β-lactam/macrolide combination or montherapy with an antipneumococcal fluoroquinolone [112, 113]. The macrolide provides additional coverage for any atypical organisms present. In patients with risk factors for aspiration or living in a nursing home, anaerobes should be covered by using ampicillin/sulbactam, or high-dose ampicillin, (defined as 1gm q 8 hours) or other active β-lactams [20].

For the admitted patient without any modifying risk factors or cardiopulmonary disease data suggest that IV Zithromax alone is efficacious; however, few admitted patients fall into this category [114, 115]. This therapy has been effective for admitted patients with CAP including those with pneumococcal bacteremia. In this group the most likely pathogens are S. *pneumoniae, H. influenzae, M. pneumoniae, C.* pneumoniae, viruses, and possibly *Legionella spp.* Mortality rates in this group as a whole have been reported at 5-25%, with most deaths occurring in the first 7 days [42, 96]. One caveat is that TB should be of particular concern in those who have been born in foreign countries with high rates of endemic illness, alcoholics, and elderly who reside in nursing homes.

Table 16: Group 4: Severe CAP patients admitted to the ICU

Organisms	Therapy
4A: NO Risks for Pseudomonas aeruginosa	
Streptococcus pneumoniae (Including DRSP) *Legionella spp.* *Haemophilus influenzae* Enteric gram-negative bacilli Staphylococcus aureus *Mycoplasma pneumoniae* Respiratory viruses Miscellaneous *Chlamydia pneumoniae* *Mycobacterium tuberculosis* Endemic Fungi	Intravenous β-lactam (Cefotaxime, Ceftriaxone) PLUS EITHER Intravenous macrolide (Azithromycin) OR Intravenous fluoroquinolone (**not** alone)
4B: Risks for Pseudomonas aeruginosa	
ALL of the above PLUS *Pseudomonas aeruginosa*	Selected intravenous antipseudomonal β-lactam (Cefipime, imipenem, Meropenem, pipercillin/tazobactam) **PLUS** Intravenous antipseudomonal Quinolone (ciprofloxacin) **OR** Selected intravenous antipseudomonal β-lactam (Cefipime, imipenem, Meropenem, pipercillin/tazobactam) PLUS intravenous aminoglycoside **Plus either** Intravenous macrolide (Azithromycin) **OR** Intravenous nonpseudomonal Fluoroquinolone

This group has the highest mortality and is stratified on the basis of their risk of pseudomonas infection. While gram-negative organisms have often been identified in patients with severe CAP the most commonly identified organisms remain *S. Pneumoniae*, *Legionella spp.*, and *H. influenzae*, with some reporting *S. aureus* as a common pathogen [9, 89, 90, 116]. In addition, atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* can lead to severe illness. *An important point to be aware of is that while the antipseudomonal β-lactams would be*

just as effective in any of the groups calling for β-lactams they are not recommended for any other groups due to the increased risk of developing antimicrobial resistance particularly to pseudomonas. The role of antipneumococcal fluoroquinolone montherapy in severe CAP is yet to be established. Published trials have involved too few patients admitted to the ICU and the proper dosing and efficacy of the new quinolones for severe CAP is unknown. Hence the guidelines suggest that they either be used as a replacement for a macrolide or be part of a combination regimen, usually with a β-lactam in those with risk for pseudomonas infection. The addition of a β-lactam will also ensure adequate therapy of pneumonia complicated by meningitis, since the efficacy of quinolone montherapy in this setting is unknown. If a patient has a β-lactam allergy then aztreonam combined with an aminoglycoside and an antipneumococcal fluoroquinolone is acceptable.

Overall 10% of admitted patients with CAP are admitted to the ICU and pneumococcus is the primary offending organism presenting up to 1/3 of all patients [49, 67, 89, 90]. Controversy remains regarding the true incidence of gram-negative infection in patients with CAP, since diagnostic testing that involves sputum culture cannot always distinguish between colonization and true infection.

Antibiotic Selection:

The purpose of the guidelines is to provide a rational and manageable approach to the initial antimicrobial management of CAP. Obviously all scenarios cannot be accounted for. The new guidelines [2, 19, 20] base antibiotic selection on: assessment of place of therapy, presence of coexisting cardiopulmonary disease and modifying risk factors (Table 12). These factors have now been better defined in a number of published studies and are fairly well validated [89, 117, 118]. Additional factors to remember in using this approach include the timing of initial therapy, which affects 30-day mortality as discussed earlier [24]. Since etiologic diagnosis is often not possible in this time period given testing and laboratory limitations, a relatively broad-spectrum antibiotic should be given initially. This not only assures timely therapy but can also provide coverage for the possibility of mixed bacterial and atypical pathogen infection.

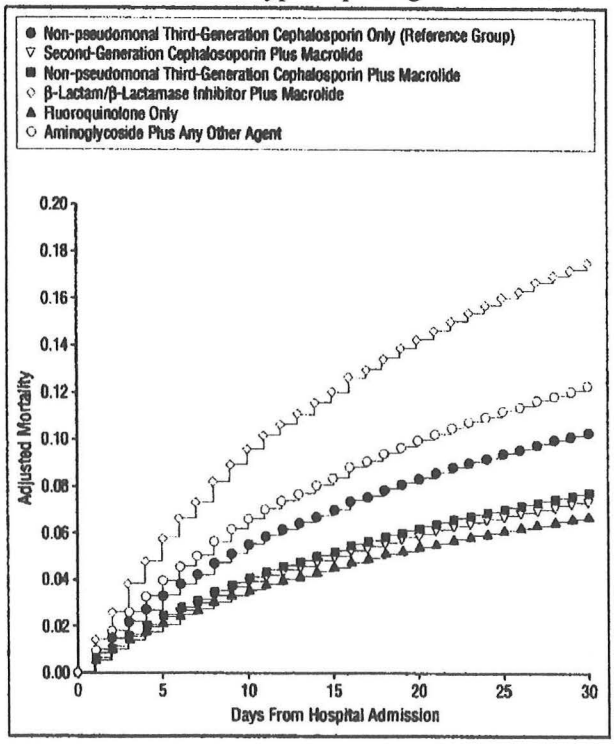


Fig.5. Effect of Antimicrobial Resistance: on 30-day mortality in Hospitalized Elderly Patients

In this era of evidence-based medicine, what evidence do we have that these recommendations are any more effective than prescribing antibiotics at random? Data from both outpatient and inpatient populations have shown that empiric therapy based on guidelines generally leads to a better outcome than if non-guideline therapy is used [34-36]. Gleason et al. studied outpatients and documented the value of macrolide montherapy for patients < age 60 with and without comorbid illness and found that macrolide montherapy was often effective for older patients with comorbid illness [34]. This was not recommended by the guidelines as it was felt the finding did not negate the need for more broad-spectrum therapy in other outpatients. This was primarily because in the study, the patients who were treated according to the guidelines were few in number and were more severely ill than those treated with non-guideline therapy, and they received montherapy with a β-lactam or Bactrim alone without the addition of a macrolide as recommended in the current guidelines.

In addition to this Bactrim and second-generation β-lactams were given without thought to atypical agents in the original guidelines. Bactrim has also been shown to have a high level or resistance to pneumococcus in general and is not used in any of the new guidelines.

Gordon et al., examined 4,500 patients admitted to the hospital and not the ICU, and found that therapy according to the guidelines led to a lower mortality than if non guideline recommended therapy was used, although the mortality was lowest for patients who received a macrolide plus a β-lactam [36].

In a Medicare study of nearly 13,000 patients, the use of a second or third generation cephalosporin with a macrolide, or the use of a quinolone, were therapy regimens associated with reduced mortality compared withal other regimens [35]. There studies lend some support to the potential importance of atypical pathogens and the need for therapy directed at this possibility (Fig 5).

Antimicrobial Resistance

An increasing concern over the past several years has been the increasing incidence of antimicrobial resistance among the various respiratory pathogens. This is not a theoretical consideration by has practical implications as well. There is an increased risk of using inappropriate initial antibiotic therapy or possibly less effective alternative treatment. Healthcare costs increase because of the need for alternative drugs that may be more costly and/or the need for increased duration of hospital stays associated with resistant infections [3, 108, 119]. In reviewing antimicrobial resistance associated with CAP the major changes in susceptibly have occurred in *S. pneumoniae* and Enterobacteriaceae.

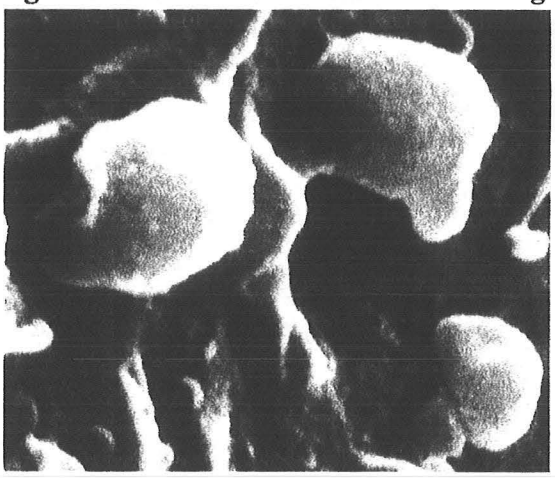
As a reference point, the National Committee of Clinical Laboratory Standards defines a strain with a MIC to penicillin of < 0.06 mμg/ml as sensitive, 0.1 to 1mμg/ml as intermediate, and ≥ 2.0 mμg as resistant [120].

This issue can be examined from three angles: (1) changes in the susceptibility of these pathogens to antibiotics, (2) clinical relevance and (3) treatment implications.

1) Changes in susceptibility:

It has been known for over 100 years that *Streptococcus pneumoniae* is the most important bacterial pathogen of the respiratory tract in both adults and children. Because of the large number of infections caused by this organism, the development of resistance has changed our approach to empiric therapy and prophylaxis. The pneumococcus is a gram-positive coccus that appears microscopically under favorable growth conditions as pairs or chains. A polysaccharide capsule surrounds each organism. Antigenic differences in the capsule separate *S. pneumoniae* into 90 different serotypes [121]. Capsular variability allows different subtypes to avoid immune detection by antibodies previously generated through infection or immunization. Thus in the absence of subtype – specific antibody, the capsule permits the organism to avoid phagocytosis and therefore represents an important virulence factor. Some capsular types are less immunogenic. A second significant virulence factor is the ability to adhere to mucosal linings. If mucociliary clearance is impaired, colonization is followed by rapid replication and clinical infection. Although not capable of producing significant systemically active toxins, the pneumococcus vigorously activates inflammatory mediators (IL-6, IL-8), which are then responsible for the bulk of systemic symptoms and local tissue damage [121-123] (fig. 6).

Fig 6. Pneumococcal Adherence to the Lung wall



Scanning electron micrograph of a pneumococcus attaching to a human lung cell. Pneumococci do not make pili or fimbriae in order to adhere to cells. Rather they decorate their cell wall with proteins that bind to human cell carbohydrates or the PAF receptor, creating a direct contact between bacteria and human cell over a large area.

Fig 7: Frequency of Invasive Pneumococcal Isolates to Various agents[133]

After WWII the wide spread use of penicillin for pneumococcal pneumonia reduced the fatality rate of CAP from 30% to 5% in some studies [62, 124]. However, in 1967 the first case of penicillin-resistant pneumococcus was identified in an Australian patient [3, 124-126]. Significant high-level penicillin resistance was not considered a major problem until the early 1980's in Europe and in the early 1990's it began to be reported in the US [106, 127-130]. In addition to penicillin resistance, multidrug resistant Pneumococci are now becoming more commonplace with resistant isolates having now been reported from virtually every continent. In the US recent data show an increase in resistance of penicillin among pneumococcal isolates, from less than 5% before 1989 to greater than 35% in 1997 [131, 132].

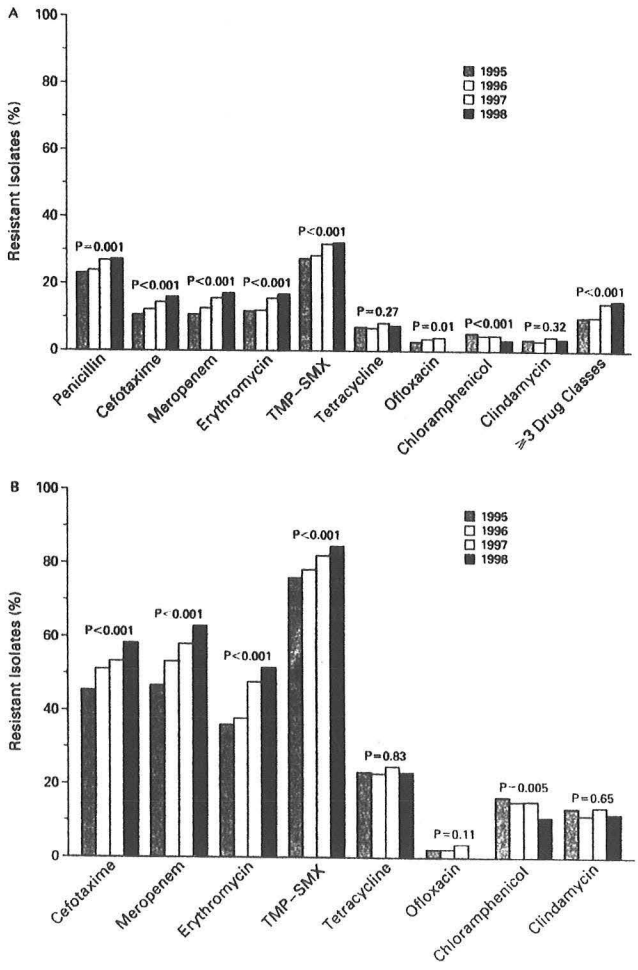


Figure 1. Frequency of Resistance of Invasive Pneumococcal Isolates to Various Agents According to Year, 1995 through 1998, for Selected Counties in the United States.

Panel A includes all isolates; panel B includes only penicillin-resistant isolates (minimal inhibitory concentration, ≥0.12 μg of penicillin per milliliter). TMP-SMX denotes trimethoprim–sulfamethoxazole. Susceptibility data from New York are excluded; the total number of isolates is 12,045. Use of ofloxacin was discontinued after 1997. P values are derived with the chi-square test for trend.

Recently Whitney et al. [133] published an article from the Active Bacterial Core Surveillance Program of the CDC examining the emergence of drug resistant strains of pneumococcus in the United States. Cases of invasive *streptococcus pneumoniae* were monitored in Portland, Oregon; San Francisco County, California; greater Minneapolis and St. Paul; greater Baltimore; greater Atlanta; five counties in Tennessee; Rochester, New York; and the state of Connecticut; a total population of 16.5 million. Surveillance began in 1995 and continued through 1998. By 1998 there was a cumulative incidence of invasive pneumococcal disease of 23/100,000, and 4013 cases of invasive *Streptococcus pneumoniae* reported;

of which 24% were resistant to penicillin. Factors associated with an increased risk for DRSP were age < 5 yrs (OR 2.3), white race (OR 1.6) and living in the southeast (OR 3.6). These findings agreed with the results from other authors [127, 134] and give credence to the concerns regarding increasingly resistant organisms. Serotype 7 in particular accounted for 78 % of penicillin-resistant strains - a common strain found in young children who tend to be carriers. Fortunately a new vaccine for this age group is now available and includes serotype 7. White race is thought to be a surrogate for social economic status implying that they are more likely to seek medical attention and demand antibiotics [135-137]. Geographic variation may be related to the spread of resistant clones, local patterns of antimicrobial use, other as yet other undetermined factors. Other risk factors for DRSP have also been identified and discussed earlier in this paper (Table 12) [106, 138, 139].

Between 1995 and 1998 the proportion of isolates that were resistant to penicillin increased from 21-25% (Fig 7). During the same time period the lowest concentration of Penicillin that inhibited the growth of 90% of pneumococcal isolates (MIC_{90}) increased from 1μg/ml to 2μg/ml, and the proportion of isolates for which the MIC of penicillin was at least 4μg/ml increased from 5 to 7% ($P<0.001$) [133]. There were also significant increases from 1995 to 1998 in the proportion of isolates that were resistant to many of the other antimicrobial agents testing including the other β-lactam agents (Fig. 7). Pneumococcal resistance to beta-lactams is caused solely by the presence of low-affinity penicillin-binding proteins (PBP's) [133]. Note if DRSP is suspected first generation cephalosporins, cefaclor, loacarbef, and Bactrim should NOT be used.

Macrolide resistance (61% in high-level resistant penicillin isolates) can occur either by target-site modification mediated by one or more enzymes or an efflux pump, mediated by the *mef* gene [3, 140]. These two mechanisms account for approximately 45 and 55 % of resistant isolates respectively.

Interestingly, there was decline in the proportion of chloramphenicol-resistant isolates form 1995-1998 in both penicillin-susceptible and penicillin- resistant strains. In addition the overall proportion of isolates that were resistant to three or more drug classes increased significantly from 9-14% ($P< 0.001$, Fig 7) [133]. No isolates were resistant to vancomycin however it should be reserved for patients with high-level resistance who are failing other therapies or are suspected to have meningitis.

The fluoroquinolones have assumed an important role in the management of CAP due to the development of new agents with excellent antipneumococcal activity. The advantages include broad-spectrum coverage including gram-positive, gram-negative, and atypical pathogens, with a single agent, once a day [141]. Quinolones penetrate well into the lungs often achieving levels higher than serum levels at sites such as the epithelial lining fluid and alveolar macrophages [141]. In addition they are highly bioavaliable achieving similar levels with oral and intravenous therapy. This attractive feature allows for certain patients with moderately severe illness to be treated with oral therapy out of the hospital and may permit the hospitalized patient to switch to oral therapy allowing for early discharge.

Table 17: Activity of New Quinolones MIC_{90} against Penicillin-Susceptible and Resistant S. Pneumoniae

Drug	PCN-S	PCN-I	PCN-R
Levofloxacin	2	2	2
Trovafloxacin	0.25	0.25	0.25
Gatifloxacin	0.5	0.5	0.5
Clinafloxacin	0.5	0.5	0.5
Moxifloxacin	0.25	0.25	0.25

There are a number of new antipneumococcal fluoroquinolones available (Table 17) for the therapy of CAP [141]. Among the new quinolones only levofloxacin, and gatifloxacin (Tequin) are available for both intravenously and orally, while the other two agents are available only orally, but intravenous formulations of moxifloxacin and gemifloxacin are being developed. Drug related toxicity has limited the usefulness of some of these agents; with some drugs having more class related toxicities. For example photosensitivity is a particular problem with sparfloxacin and GI upset and neurotoxicity with Sparfloxacin. Severe liver toxicity has been reported with trovafloxacin and as a result its use has been virtually halted. This effect can theoretically occur with any quinolone, but appears to be more common with this particular agent. Unfortunately, this was not evident in registration trials or in early clinical experience, suggesting the need to monitor all new agents for this possible effect [141]. Among the agents the MIC values for pneumococcus vary

from 0.12 to 2.0 mg/dl. Antipneumococcal activity is variable with moxifloxacin being the most active down to levofloxacin the least active (Table 17). *In vitro* differences however do not appear to have a clinical impact since all approved agents demonstrate efficacy in CAP [141-143]. These differences may lead to different rates of resistance and clinical success in the future, if pneumococcal resistance to these agents becomes more common.

In 1998 fluoroquinolone resistance was uncommon [144-146]. However, there was a 50% increase in the proportion of isolates that were resistant to ofloxacin from 2.6% to 3.8% (P=0.01) (Fig 7) leading to a concern that resistance to other fluoroquinolones will become more common. Another recent report also documented that 2.9% of pneumococcal isolates from adults were ciprofloxacin resistant and that 4.1% of isolates with high-level resistance to penicillin were quinolone (ciprofloxacin) resistant [146]. When ciprofloxacin resistance was present in *vitro* resistance to the newer quinolones was also present. Fluoroquinolone resistance has been found to be due to mutations in the genes encoding subunits of topoisomerase IV and DNA gyrase A [145]. While nearly all isolates resistant to levofloxacin were also resistant to trovafloxacin only a single mutation need be present for levofloxacin resistance to occur but a mutation must be present at both sites for resistance to trovafloxacin to occur [145]. It is believed that resistance to the quinolones will be slow in developing because of a more complex resistance mechanism.

Recently the FDA has approved a new class of antibiotics the Oxazolinidones. The only available drug in this class is linazolid. It acts by inhibiting bacterial protein synthesis by a unique mechanism and has no cross-resistance to other agents. It is an exciting class in that it is active against MRSA, DRSP and VRE (BOTH faecium and faecalis). Its indication is for nosocomial pneumonia, CAP, complicated skin/soft tissue infections, and VRE. It is fairly well tolerated with nausea, diarrhea, anemia and thrombocytopeina being the more common side effects [147]. This is not recommended of the routine use of CAP, as this should be a drug to keep in mind when the current armamentarium is exhausted.

2. Clinical Relevance and Treatment Implications of Antimicrobial Resistance:
The clinical relevance of antimicrobial resistance in pneumococcus has been hotly debated; with the primary question being do β-lactams still have a role to play in the treatment of this organism? The answer is not black and white particularly when mortality is the outcome measure. A number of studies have failed to show any change in mortality, using currently defined levels of resistance in patients infected with resistant or sensitive organisms, after controlling for comorbid illness, although patients with resistant organisms may have a more prolonged hospital stay [3, 13, 14, 148]. One study has shown that complications such as empyema are more common in patients with penicillin-nonsusceptible organisms even though the majority received adequate therapy. In Spain where there is a very high incidence of DRSP there has been a reported trend towards higher mortality but it was not statistically significant [17].

Part of the answer may lie in the definition of the MIC. A CDC study has shown that a clinically relevant break point for resistance to penicillin is an MIC ≥4 μg/mL [16]. In all the studies resistance at this level was associated with marked increase in mortality in-patients with invasive disease, excluding patients dying in the first 4 days [16]. At this level of resistance an alternative to penicillin should be used although routine therapy with vancomycin is rarely needed [149].

With macrolides the answer is less clear because there is little data to indicate whether *in vitro* resistance to macrolides results in clinical failure. These agents are thought likely to be effective for organisms with penicillin MIC values of ≥ 2mg/L [133, 150]. This is possibly because macrolides penetrate into respiratory secretions, and other relevant tissue sites of infection at extremely high levels overcoming the MIC. In addition most macrolide resistance is due to an efflux mechanism, not a ribosomal mechanism, with the efflux mechanism being associated with a substantially lower MIC value that the ribosomal mechanism [150]. Thus by achieving such high concentrations in the tissue resistance is overcome. In the current guidelines macrolides are used alone only in the absence of risk for DRSP (Table 12) and enteric gram-negative organisms. There are case reports of patients with macrolide-resistant pneumococcal bacteremia requiring hospitalization after oral

therapy but most of these patients would not have been candidates for monotherapy according to current recommendations [150-153].

Examining our local epidemiology, a study of pneumococcal disease in Texas[154] found that the overall incidence of disease was 22/100,000. The highest incidences were in children < 2 and adults ≥ 65 years of age. The most common diagnosis was pneumonia (66%) and 20% of isolates were nonsusceptible to penicillin with rates of hospitalization and death increasing with age. The incidence of pneumococcal disease was highest amongst African Americans and those of low income. Theses rates were found to be similar to rates reported for other counties[14, 134, 155-158]. The results of this study suggest that the rate of disease in urban areas of the United States has been relatively stable over the last decade despite the increased prevalence of nonsusceptible strains of *S. pneumoniae*[134, 156] (Fig 8).

Figure 8: Incidence of invasive S. Pneumoniae in Dallas [154]

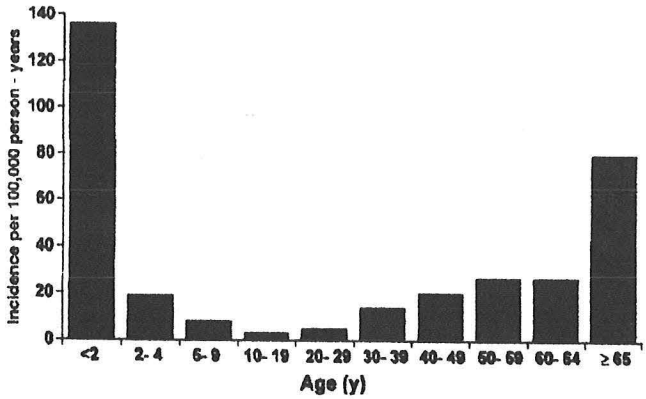


Figure 1. Age-specific incidence of invasive *Streptococcus pneumoniae* disease in Dallas County, Texas, 1995.

Clinical Response to treatment:

There is no standard regarding length of treatment for pneumonia however, on the basis of clinical response to therapy patients may be categorized into three groups. There is good data now to suggest that by dividing patients into these groups patients can possibly be discharged much earlier than previously believed. At present patients are treated with IV antibiotics for 7-10 days.

1. Patients with early clinical response:

It is recommended that those falling in this category should be considered for rapid switch to oral therapy, followed by rapid hospital discharge. This decision is based on an assessment of clinical response, evaluating symptoms of cough, sputum production, dyspnea, fever and leukocytosis. Once the patient has stabilized they are eligible for discharge and up to half of all patients are eligible on hospital day 3 [159]. Studies have shown that an early switch reduces hospital stay, cost and in some instances improves outcomes [159, 160]. One of the initial concerns of this approach was the ability to attain the same drug levels with oral therapy as with intravenous therapy. Two approaches have been investigated (a) Sequential therapy – switch to agents that achieve comparable serum levels either intravenously or orally such as doxycycline, linezolid, and most quinolones [161]. (b) Step-down therapy – where the switch to oral therapy is associated with a decrease in serum levels. This involves agents such as the β-lactams, and macrolides. Clinical success has been documented with either a sequential or step-down approach [66, 159].

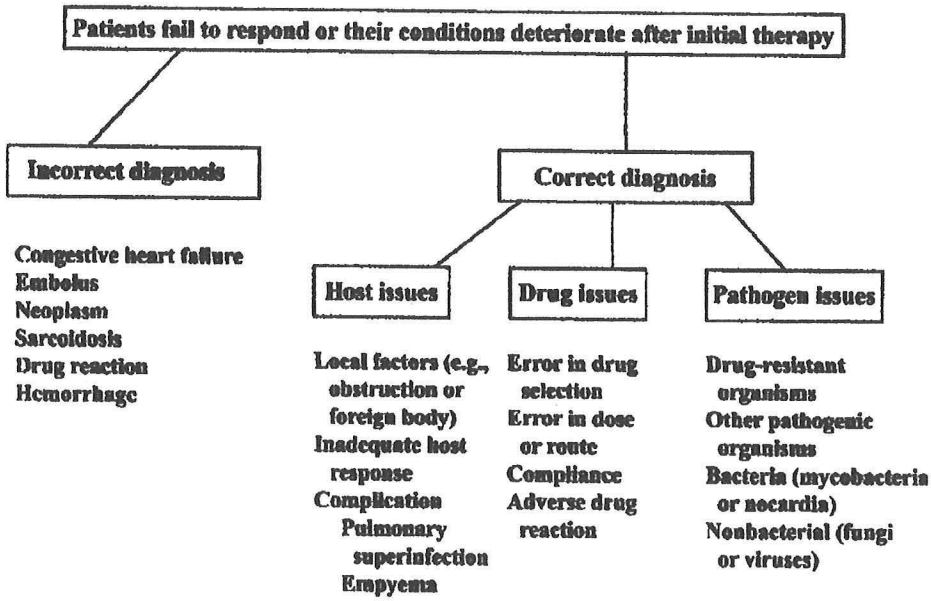
Patients should be switched to oral therapy if they meet ***four*** criteria:

a. Improvement in cough and dyspnea
b. A febrile on two occasions 8 hours apart
c. Decreasing WBC
d. Functioning GI tract [159, 160].

Since compliance is a key issue, switch agents should be chosen with a minimum of side effects, and once or twice daily dosing. Obviously some patients may continue to require hospitalization due to unstable coexisting illnesses, such as diabetes or congestive heart failure or social needs etc [162, 163]. There is no need to repeat a chest radiograph prior to discharge in a patient who is clinically improving. It typically takes 4-6 weeks for a chest radiograph to show resolution. A repeat radiograph is recommended during a follow up office visit 4-6 weeks later to establish a new radiographic baseline and to exclude the possibility of malignancy associated with CAP particularly in older smokers [164, 165].

2. Patients with a lack of clinical response, which should be defined at Day 3 of hospitalization
3. Patients with clinical deterioration, which can occur as early as after 24-48 hours of therapy.
Patients in the above 2 categories need to be reevaluated for host and pathogen factors, along with a reevaluation of the initial diagnosis and a search for possible complications such as empyema. Because of the natural course of treatment response, therapy should not be changed in the first 72 hours unless there is a marked clinical deterioration or if bacteriologic data necessitates a change [159, 160]. Assessment of a nonresponding patient should take into account the possibilities outlined below in figure 9.

Figure 9. Approach to Non-Resolving Pneumonia



Tests appropriate to the individual disease entities should be used to exclude noninfectious possibilities. Specific examples include ventilation-perfusion lung scans and in selected cases PA grams, bronchoscopy or open-lung biopsy to diagnose a variety of noninfectious causes. Some host factor that might influence the range of pathogens includes HIV, cystic fibrosis, neoplasm, recent travel and unusual exposures. Infection caused by an unsuspected organism must always be a concern, an aggressive search should be undertaken if this is suspected to be the case.

PREVENTION:
This discussion would be incomplete if the issue of prevention were not addressed. In general prevention can be thought of in terms of patient related factors, external factors and chemoprophylaxis as the key to decreasing the morbidity and mortality associated with CAP.
Patient related factors: Include making sure patients receive the influenza and pneumococcal vaccine (discussed below)

-Avoidance of tobacco and alcohol use as both have been associated with an increased risk of CAP [91, 104]. Even passive smoke may increase the risk of CAP while alcohol depresses various proinflammatory cytokines and depresses cell-mediated immunity.

-Adequate nutrition – malnourished individuals have depressed cell-mediated immunity
-Dental status – poor dentition can increase the pneumonia due to increase numbers of bacteria in the oropharynx
-Underlying comorbidities

External factors: Influenza vaccine for caregivers
Chemoprophylaxis: Antiviral to prevent influenza-amantadine, rimantadine, neruaminidase inhibitors

Influenza Vaccine:

Advances in virology, basic immunology, and clinical infectious disease have made significant advances in our ability to prevent respiratory diseases through the use of effective vaccines. Despite this, each year, some 50,000 to 90,000 adults die in the US due to influenza, pneumococcal disease and other vaccine preventable illnesses [166, 167]. This is in stark contrast to 500 children that succumb to vaccine preventable disease [166]. Differences related to underlying immune response, physiological reserve and comorbid conditions account for a large portion of this difference. However, disparate and inadequate applications of available vaccine technologies to adult population are also likely to blame as well.

Influenza occurs in an epidemic fashion with 20,000 to 40,000 deaths/epidemic and predisposes toward invasive pneumococcus infection [168, 169]. The vaccine is modified yearly to reflect the anticipated strains in the upcoming season. Standard trivalent inactivated virus (two type A strains and 1 type B strain) is administered to over 60% of adults greater than 65 years in the US. However, less than 30% of at risk individuals under the age of 65 are vaccinated yearly. The vaccine is 70-90% protective in healthy individuals under 65, when the strains are well matched [168]. In older individuals (>65) the vaccine is less efficacious, yet still offers substantial benefit with 30-40% protection against disease, 50-60% efficacy in avoidance of hospitalization, and 80% efficacy in preventing death. In one meta-analysis of 20 studies, the vaccine was shown to reduce the occurrence of pneumonia by 53%, and mortality by 68% [168]. Concern about side effects has limited the use of the vaccine by some but the vaccine does not contain live virus and cannot cause influenza. Reactions include local soreness at the injection site, which may last up to 2d, and is generally mild and not disabling, systemic symptoms of fever, malaise and myalgias beginning 6-12 hours after vaccination and lasting for 1-2 days [170]. The Guillain-Barre syndrome, which has been clearly associated only with the 1976 swine influenza vaccine, has not been associated with other vaccines since then [171].

Recommendations for *Influenza* vaccine:

1. Age > 65 years.
2. Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions.
3. Adults and children with chronic cardiopulmonary disorders.
4. Adults and children who require regular medical follow-up or hospitalization in the preceding year because of chronic metabolic diseases (including DM), renal dysfunction, hemoglobinopathies or immunosuppression.
5. Persons who can transmit influenza to those at high risk: Included are healthcare personnel, employees, of nursing homes, or chronic care facilities.
6. Pregnant women in the second and third trimester during flu season.

Pneumococcal Vaccine:

The pneumococcal polysaccharide vaccine has been available in one form or another for > 20 years. Though the vaccine is primarily recommended for those > age 65, and those with underlying cardiopulmonary disease, many clinicians debate its effectiveness in these groups and widespread application has lagged far behind influenza vaccination [166, 167]. Despite the staggering statistics of approximately 40,000 US deaths annually, and 1.2 million deaths worldwide, (many of which occur in the elderly) [166], only 30% of patients over the age over the age of 65 are vaccinated and only 20% of those at risk under the age of 65 at risk. This is most likely related to the perceived efficacy of the vaccine.

The vaccine is composed of 23 capsular polysaccharides derived from the most prevalent of the 90 identified strains. The downside is that such immunizing antigens are processed in T-cell independent manner, with minimal immunological memory and with induction of somewhat limited humoral immune response. Efficacy has been inconsistently demonstrated in placebo-controlled trials in patients with chronic illness, but case control methodology has documented effectiveness in the range of 56-81% [172, 173]. Efficacy has also been documented by serotype prevalence studies for bactermic illness, but not for nonbacteremic pneumonia [172, 173]. In the immunocompetent patient over 65 effectiveness has not been well documented [172, 173]. Unfortunately, protective antibody levels decline to near pre-vaccination levels in older persons over a 3-5 year period. This has lead to the current recommendations of considering revaccinating after 5 year if the patient is at risk of a fatal infection.

Current recommendations for Pneumovax are:

1. All individuals ≥ 65 years.
2. All individuals with risk factors for pneumonia.
3. Single revaccination after 5 years for:
    a. Asplenia
    b. Immunocompromised state
    c. Patients older than 70, vaccinated more than 5 years previously

Summary:

The last guidelines by the ATS and CIDS, were published in 1993. In the last 1-year updated recommendations have now been issued by the American Thoracic Society (6/01), the Canadian Infectious Disease Society and Infectious Diseases Society of America (1/00). The original guidelines were based primarily on 'expert opinion'. However, over the last 10 years a number of studies have now provided either proved or disproved some of these earlier recommendations leading to more evidenced based guidelines. In the current update, several new important developments have been noted and discussed above.

1. Decision analysis for hospitalization or intensive care.
2. Clinical relevance of emerging resistance among respiratory pathogens particularly DRSP.
3. The availability of newer generation macrolides.
4. New-generation fluoroquinolones.
5. New class of antibiotics, linezolid.
6. The desirability and feasibility of intravenous to oral sequential antimicrobial therapy.
7. Renewed attention to the prevention of CAP.

Clearly we have certainly made significant advances but there are still questions that remain to be definitively answered, such as:

1. How long should therapy be continued?
2. Should duration of therapy be related to severity of initial illness?
3. What role does antibiotic resistance play in the outcome of patients with CAP?
4. Will newer diagnostic method improve our ability to define etiologic pathogens of CAP and will this lead t improved outcomes?
5. What are the best criteria for hospitalization?
6. How will antibiotic choices and guidelines for empiric therapy impact future patterns of antibiotic resistance?
7. Is atypical pathogen co infection common and if so is it prevalent all the time or are there temporal and geographic variables to consider?

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