Community Acquired Pneumonia

Current Controversies in Treatment

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January 2001

Despite extensive research and review over the past ten years, pneumonia remains the leading cause of death due to infection in North America.[1] Recently, revised and updated guidelines for the treatment of community acquired pneumonia (**CAP**) have been published.[1,2] The following is a commentary on the guidelines developed by the Canadian Infectious Diseases Society (**CIDS**) and Canadian Thoracic Society (**CTS**), highlighting changes, supporting rationale and contrasts with current American recommendations.

What has prompted the development of new guidelines?

Over the past decade several factors have emerged, some of which have improved our understanding of CAP while others have challenged its management. The new recommendations have been developed around two key issues affecting current treatment:

- emerging patterns of **antimicrobial resistance** and the role of both older antibiotics and newer agents
- effective **cost containment** strategies which will not compromise patient care but maintain or improve outcomes

How has emerging resistance impacted proposed therapeutic measures?

- **Reliance on empiric therapy**

Timely, definitive determination of the etiology of CAP is seldom achieved necessitating continued reliance on empiric therapy. In up to 50% of cases the causative agent remains unidentified [3] and error rates in identifying organisms can be as high as 30%.[4] Both *Strep. pneumoniae* and *H. influenzae* are associated with a high rate of false negatives from sputum samples.[5] Clinical and radiographic features may provide clues to etiology but are not consistently reliable in identifying specific organisms.[6,7]

HIGHLIGHTS

- **Timely empiric treatment is still crucial but targeted therapy when possible may reduce costs, side effects, and resistance**
- **Respiratory quinolones offer the advantage of highly efficacious, OD dosed monotherapy for all major pathogens but cost and resistance are potential drawbacks**
- **Penicillin/amoxicillin still adequate for treatment of pneumococcal pneumonia if MIC ≤ 4mg/L**
- **Consider outpatient treatment when feasible and IV-to oral switch therapy with earlier discharge for inpatients**

These gaps in current diagnostic testing have led to a difference in opinion between the American Thoracic Society (**ATS**) and the Infectious Diseases Societies. Due to lack of sensitivity and specificity, the ATS favors empiric therapy over extensive testing. A further argument is that even when the organism is identified and initial empiric therapy changed to target that organism, it does not affect outcome.[8] The Infectious Disease Society of America (**IDSA**) however, emphasizes establishing the etiology whenever possible. Despite lack of documented benefit on outcome, efforts should still be made at pathogen specific therapy in order to potentially:

- reduce microbial resistance with use of narrower spectrum antibiotics
- reduce antibiotic costs by using fewer, more select agents
- reduce unnecessary side effects
- aid understanding of CAP's etiology and treatment

Both sides agree that diagnostic procedures should not delay prompt initiation of appropriate empiric antibiotic treatment which can significantly affect mortality.

- **Importance of chest radiography**

Under most circumstances, chest x-rays are still strongly recommended for routine examination of *all* patients with suspected pneumonia. The advantage of chest radiography is that it strengthens the diagnosis, rules out other possible non-microbial causes (eg. carcinoma) and allows differentiation of acute bronchitis (**AB**). AB is typically viral, does not usually require antimicrobial treatment, and is a chief offender in antibiotic overprescribing and resistance.

- ***Drugs of Choice* for empiric therapy**

The attached chart summarizes the recommendations for empiric therapy. Treatment is largely based on:

- severity of presentation and need for inpatient vs. outpatient treatment
- host factors (co-morbidity)
- etiology of likely pathogens (community vs. institutional acquisition; host factors; local resistance patterns)

The shift has been away from beta lactams and cotrimoxazole in favor of fluoroquinolones (**FQs**), newer macrolides, and combination macrolide/beta lactam therapy. This is mainly due to increasing penicillin resistance and cross resistance in pneumococcal species, beta-lactamase resistance in *H. influenzae* and *M. catarrahalis*, and prevalence of "atypicals" (*Mycoplasma*, *Chlamydia*, and *Legionella pneumonia* species).

- **Fluoroquinolone(FQ) -Macrolide -β-Lactam Debate**

Canadian recommendations favor the respiratory FQs. These are highly efficacious bacteriocidal agents that cover all major pathogens and atypicals as well as penicillin-resistant pneumoccocal pneumonia (**PRSP**). Monotherapy is

possible in both out- and inpatient settings and they have the added advantage of OD dosing. Cost is a drawback and increasing resistance a major concern. American guidelines suggest reserving these agents as 2nd line for those who fail or are intolerant of appropriate beta-lactam/macrolide therapy or have PRSP (MIC ≥4mg/L). Alternatively, macrolides could be used first. Macrolides are highly effective, covering all major pathogens and atypicals with the exception of erythromycin for *H. influenzae*. Although they are bacteriostatic with no post-antibiotic effect, they do accumulate intracellularly especially in alveolar macrophages. While monotherapy is possible for select outpatients, combination therapy is usually required (see selection chart). Resistance is currently more prevalent with macrolides and β lactams than with the FQs and cost is an important limitation with the newer agents.

◆ **Clinical relevance of penicillin resistant strep. pneumoniae (PRSP)**

Reported limits of penicillin resistance were originally based on MICs required for treatment of meningitis where antibiotic penetration into the CNS is much more difficult and resultant concentrations much lower than those in serum. Since alveolar concentrations of penicillin are much easier to achieve, breakpoints of resistance *in pneumonia* might be clinically more relevant if reported as:[9]

Sensitive (current MIC = < 0.06 mg/L) changed to < 1.0 mg/L
Intermediate (MIC = 0.1-1.0 mg/L) . . . . . < 2.0 mg/L
Resistant (MIC = > 2.0 mg/L) . . . . . ≥ 4.0 mg/L
***(**MICs remain unchanged in the case of meningitis)**

Several clinical studies have also demonstrated that outcome is unaffected even when penicillin is used in species with resistant susceptibilities (ie MIC 2-4 mg/L).[10,11,12] Advanced age and underlying disease still appear to be the most important factors affecting mortality.[13]

Also emerging in the battle against resistance is the theory of "mutation prevention concentration" or the minimum in vitro concentration of a particular antibiotic needed to prevent resistant mutation within a certain strain of bacteria. The theory in practice may lead to use of higher doses of antibiotics for shorter periods. Studies are ongoing…

How can costs be reduced while maintaining successful outcomes?

◆ **Risk stratification and site-of-treatment**

The decision to hospitalize a patient or treat as an outpatient is perhaps the single most important clinical decision made by the physician during the entire course of illness and has direct bearing on the intensity and cost of both laboratory evaluation and antibiotic therapy. The estimated total treatment cost in hospital for an episode of CAP is $7500 (US), more than 20 times the cost of outpatient treatment.[2] Physicians often overestimate the risk of death leading to the decision to hospitalize.[13] Research over the past decade has lead to a better understanding of the factors affecting risk, prognosis and outcome. Both the IDSA and the Canadian CAP Working Group have endorsed the use of the POST clinical prediction rule, also known as the Pneumonia Severity Index (**PSI**).[14] This is a risk scoring and stratification system based on age, severity of illness, and co-morbidity. It aids in determining which patients are at lower risk of mortality and may be successfully treated as outpatients (Figure 1). Since the system was developed from cohort data and may not take into account individual factors affecting the patient's ability to cope with outpatient care (cognitive and physical limitations, social support etc.), the prediction rule serves as *a guideline only* and should be used along with good clinical judgment.

◆ **Timely administration of antibiotics**

Timely administration of empiric antibiotics can significantly reduce mortality. A recent landmark study showed that administration within the first 8 hours of presentation could reduce mortality by up to 20%.[15] Efforts should be aimed at giving antibiotics as soon as possible and avoiding unnecessary delays caused by diagnostic testing such as specimen collection and gram stain results. If possible, initial doses should be given in the ER prior to admission to the ward. [16]

◆ **IV-to-oral switch therapy**

Recent years have seen the introduction of several improved oral antibiotics that achieve higher or more persistent serum and tissue concentrations than their predecessors, making oral therapy more feasible. Switch therapy can significantly reduce costs of both drugs and ancillary administration equipment and nursing time. Earlier discharge is also possible, further reducing hospital costs and freeing up acute care beds. Many clinical studies including several RCTs have demonstrated favorable outcomes after an IV-to-oral switch with few relapses requiring re-hospitalization and/or return to IV therapy.[17, 18] IV-to-oral conversion can occur within 48-72 hours of initial IV therapy provided:[1,2]

- patient does not require intensive care and is hemodynamically stable
- patient's condition is improving clinically (ie. resolution of fever, reduction in WBCs, cough, respiratory distress)
- patient's GI tract is functioning normally and they are able to take oral meds
- oral antibiotic formulation has good bioavailabilty and the same or similar spectrum of activity as IV agent

Discharge can be considered for patients meeting the above criteria as well as:[6]

- WBC ≤ 12 $x10^9$/L
- stable co-morbid illness
- normal oxygenation (for patients with COPD = pO2 >60 mm Hg and pCO2 <45 mm Hg)

Recent studies have looked at even earlier conversion, i.e. within one day or after one dose of appropriate IV therapy. Other studies are looking at hospitalized patient groups which could be treated solely with oral therapy.[19]

What is the bottom line regarding CAP?

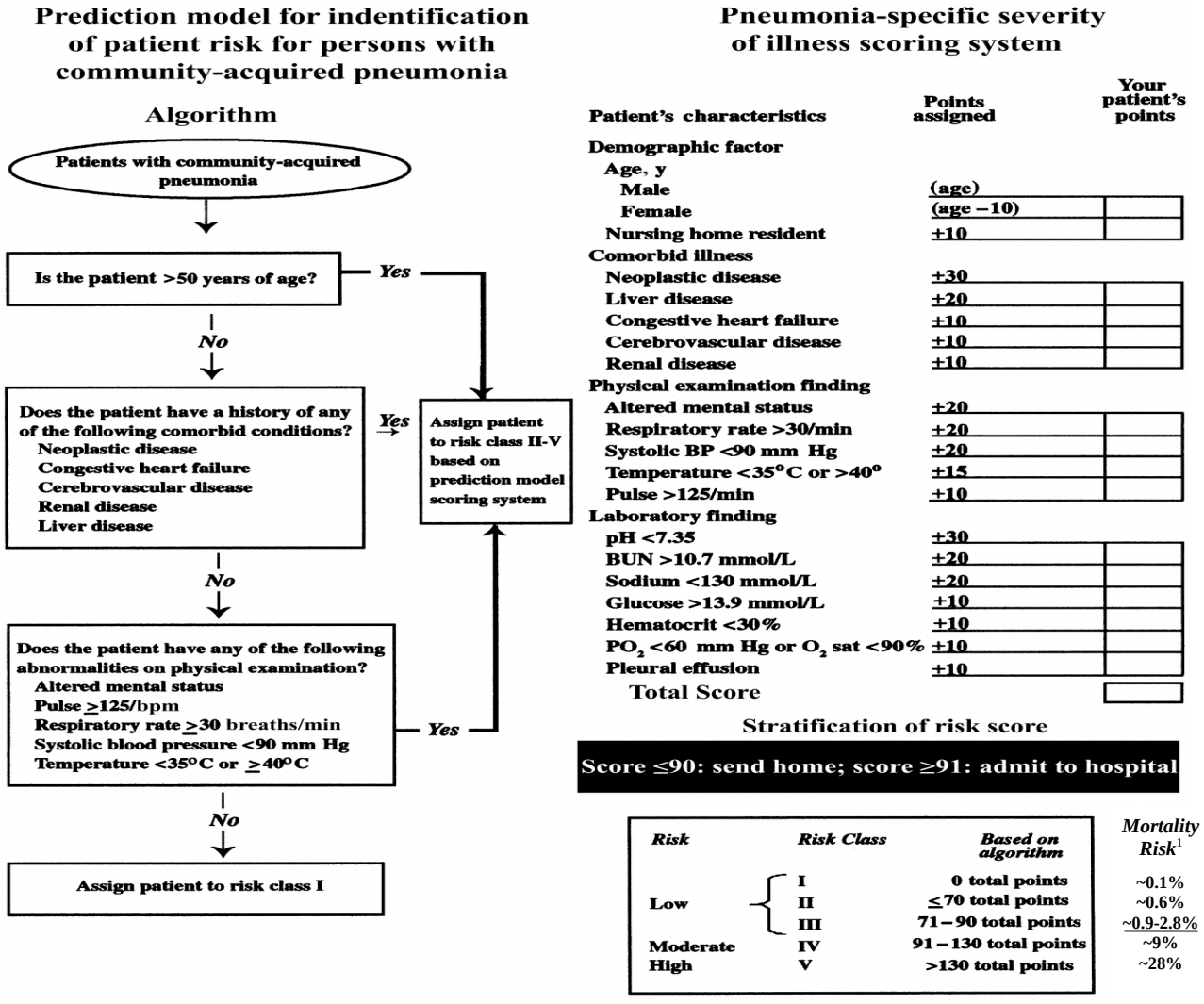
When all is said and done, there is no one optimal way to treat CAP. Management of few conditions in medicine remains so controversial. It remains to be seen which of the newer antibiotics will emerge the preferred agents as they jockey for position in our current era of antimicrobial resistance. Hang on for the ride...

We wish to acknowledge those who have assisted in the development & review of this newsletter: Dr. K. Williams (Inf. Disease), Dr. T. Laubscher (Family Medicine), Y. Shevchuk (U. of S. - C. of Pharmacy), & the *RxFiles* Advisory Committee. *S. Downey BSP, B. Jensen BSP & L. Regier BSP, BA*

Table 1: Specific Therapy for Selected Pathogens in Community Acquired Pneumonia

Pathogen	Therapy	Comments
Streptococcus pneumoniae ◆Penicillin sensitive (MIC<0.1mg/L) ◆Intermediate (MIC≤ 1mg/L) ◆Resistant (MIC≥ 2mg/L) CAP with high level resistance and associated meningitis	Oral penicillin V, amoxicillin, cephalosporin, or macrolide Amoxicillin 500mg TID; cefuroxime axetil 500mg BID Pen G 2MU IV q6h; cefotaxime 1g IV q8h; ceftriaxone 1g IV q24h; Respiratory fluoroquinolone (levofloxacin or moxifloxacin; MICs for moxifloxacin better than levofloxacin) Vancomycin (1st choice) or respiratory FQ (not studied in CNS)	◆~ >80% of isolates still sensitive (MIC <0.1mg/L) ◆~4% high level resistance in SK (MIC ≥ 2mg/L)[20] ◆~90% cross resistant to cotrimoxazole,~ 60% to cefuroxime, ~20% to macrolides
Haemophilus influenzae	2nd or 3rd G cephalosporin or βlactam/lactamase inhibitor	◆ ~ 30% of isolates βlactamase +
Moraxella catarrhalis	2nd or 3rd G cephalosporin or βlactam/lactamase inhibitor	◆ >90% of isolates βlactamase +
Respiratory anaerobes	βlactam/lactamase inhibitor or levofloxacin + either clindamycin or metronidazole; moxifloxacin alone	
Staphylococcus aureus ◆Methicillin sensitive ◆Methicillin resistant	 Cloxacillin Vancomycin	
Enteric gram –ve bacilli	3rd or 4th G cephalosporin +/- aminoglycoside	
Pseudomonas aeruginosa	Antipseudomonal βlactam + either aminoglycoside or ciprofloxacin	No synergy with ciprofloxacin
Legionella species	Macrolide +/- fluoroquinolone or rifampin	
Chlamydia pneumoniae	Macrolide or doxycycline	
Mycoplasma pneumoniae	Macrolide or doxycycline	

Figure 1. Pneumonia Severity Index (PSI) Scoring System (from Mandell LA et al. Canadian guidelines for initial management of community acquired pneumonia: an evidence-based update by the CIDS and the CTS. Clin Infec Dis 2000; 31: 383-421, reference 64)



Community Acquired Pneumonia – Empiric Antibiotic Selection Prepared by: Sharon Downey, Brent Jensen, Loren Regier - www.sdh.ck.ca/**RxFiles –JAN/2001**

Patient Characteristics	Likely Pathogens	Recommended Empiric Antibiotics *Current Consensus*		Specific Agents & Sample Adult Dosages	$ per 10 d	Comments
OUTPATIENTS		**Canadian**[2]	**American**[1]			
No modifying factors	◆Strep. pneumoniae ◆Mycoplasma pneum. (not as prevalent in the elderly) ◆Chlamydia pneumoniae	1st – Macrolide 2nd - Doxycycline	◆Macrolide ◆Doxycycline ◆Respiratory FQ *no particular order of preference although suggest reserving FQs for: ◆more severe cases with co-morbidity ◆those intolerant or failed on alternates ◆PRSP - penicillin resistant Strep.pneum (MIC ≥4mg/L)	Erythromycin base 250mg po qid Erythromycin PCE 333mg po tid Clarithromycin 500mg po bid Azithromycin 500mg po **Day1**; then 250mg po **Days 2-5** ***due to long t½ , 5 day tx ≈ 10 days with alternate agents Doxycycline 100mg po bid ▼Levofloxacin 500mg po od ✘ ▼ Moxifloxacin 400mg po od Amoxicillin 500mg po tid Amox/clav 875mg po bid Cefuroxime axetil 500mg po bid Cefprozil 500mg po bid	10 25 78 *41[5d] 17 66 66 14 55 76 79	◆compared to erythromycin, newer macrolides more costly but better GI tolerance & ↓ dosing frequency ◆3-5 day tx with azithromycin? ◆Doxycycline preferred over TCN due to better GI tolerance and bioavailabilty & BID dosing ◆Ciprofloxacin not recommended – poor Strep. coverage/resistance ◆Cephalosporins not recommended because lack coverage of atypicals ◆Penicillin still OK for Strep. pneu if MIC ≤4 mg/L (~80% of isolates); amoxicillin preferred due to better bioavailability, longer t1/2, ↓ dosing frequency, more favorable MICs
COPD – no recent antibiotics or oral steroids within past **3** months	Above plus: ◆H. influenzae	1st – New Macrolide 2nd – Doxycycline				
COPD – recent antibiotics or oral steroids within past **3** months	Above plus: ◆H.influ, βlactamase + ◆Legionella pneumophilia (rare in SK) ◆Gram -ve rods	1st – Respiratory FQ 2nd – Macrolide + Amox/clav or 2ndG cephalosporin				
Nursing home resident, outpatient management (if hospitalized, treat as below)	◆Strep. pneumoniae ◆H. influenzae ◆Gram –ve rods ◆aspiration pneumonia	1st – Respiratory FQ 2nd – Macrolide + amox/clav 3rd – Macrolide + 2ndG Cephalosporin				
HOSPITALIZED INPATIENTS						
General Ward admission	◆Strep. pneumoniae ◆Chlamydia pneumoniae ◆H. influenzae ◆Legionella pneumophilia	1st – Respiratory FQ 2nd –2nd,3rd,4thG Ceph + macrolide	1st – 3rdG Ceph + macrolide or FQ alone 2nd – Cefuroxime + macrolide or azithromycin alone	Levofloxacin 500mg IV q24h (or levofloxacin/moxifloxacin **po** as above) Cefuroxime 750mg IV q8h Cefotaxime 1g IV q8h Ceftriaxone 1g IV q24h Erythromycin 500mg IV q6h Azithromycin 500mg IV q24h **x5d** (or **po** as above) Tazocin 3.375g IV q6h (**dose/cost of oral agents above**)	450 (66) 110 200 350 165 105 710	◆Cdn CAP group favor monotherapy with FQs; US IDSA favors reserving FQs 2nd line due to ↑ resistance ◆choice of 2nd, 3rd, or 4th generation cephalosporin dependent on local resistance ◆adjust doses for severity/renal fx. ◆IV penicillin (2MU IV q6h) or ampicillin (1-2g IV q6h) still OK for *Strep. pneum* if MIC ≤4mg/L
ICU	Above plus: ◆Enteric gram – rods	1st – IV Respiratory FQ + 3rdG Ceph or β lactam/lactamase-Inh 2nd –IV macrolide + 3rdG Ceph or βlactam/lactamase Inh	◆3rdG Ceph or βlactam/lactamase Inh + macrolide ◆ respiratory FQ instead of macrolide			
ICU, risk of Pseudomonas (Cystic Fibrosis, HIV, structural lung disease, bronchiectasis)	Above plus: ◆Pseudomonas species	1st – antiP FQ + antiP βlactam or AMG 2nd – triple IV therapy: ◆antiP βlactam ◆AMG ◆macrolide	◆ antiP βlactam + macrolide ◆ antiP FQ + AMG	Ciprofloxacin 400mg IV q12h Ceftazidime 2g IV q12h (or 1-2g q8h) Imipenem 500mg IV q6h Gentamicin 3-7mg/kg IV q24h Tobramycin 3-7mg/kg IV q24h (**dose/cost of oral agents above**)	660 315 985 60 90	◆Aminoglycoside cost based on 5mg/kg x70kg adult, normal renal fn; 3-5mg/kg if elderly, debilitated 5-7mg/kg if younger, normal CrCl 7mg/kg for more severe infection ◆Tobra > gent for Pseudomonas
Aspiration Pneumonia	◆Oral anaerobes	1st – Amox/clav +/- macrolide 2nd – FQ + clindamycin or metronidazole	◆βlactam/lactamse Inh ◆FQ + clindamycin or metronidazole	Clindamycin 300mg po qid 600mg IV q8h Metronidazole 250mg po tid 500mg IV q12h (**dose/cost of other agents as above**)	59 96 <10 24	◆Moxifloxacin has anaerobic & atypical coverage and could potentially be used as sole agent ◆po bioavailability: metronidazole~100%; clindamycin~90%

Macrolide = erythromycin, clarithromycin, azithromycin; **Newer macrolide** = clarithromycin, azithromycin; **Respiratory FQs (fluoroquinolones)** = levofloxacin, moxifloxacin (NOT ciprofloxacin unless Pseudomonas suspected); **TCN** = tetracycline; **2ndG Ceph** (cephalosporin) = cefuroxime, cefprozil…**3rdG Ceph** = cefotaxime, ceftriaxone, cefixime (oral)…**4thG Ceph** = cefepime ; **Amox/clav** = amoxicillin+clavulanate; **βlactam/lactam Inh (inhibitor)** = Amox/clav (oral), pipercillin/tazobactam, ticarcillin/clav; **AMG** = aminoglycoside (tobramycin>gentamicin against Pseudomonas); **antiP (antipseudomonal) βlactam** = imipenem, ceftazidime, pipercillin/tazobactam; **antiP (antipseudomonal) FQ** = ciprofloxacin; **PRSP** = penicillin resistant Strep. pneumoniae (ie MIC >4mg/L). **Dosages** – may require adjustment for severity/renal fx., etc. **Treatment duration** variable (typically 7-14 days or 4-5 days post-improvement; longer if complicated; 2-3 weeks treatment suggested for Legionella, also for C. pneumoniae and M. pneumoniae due to risk of relapse.)
= EDS in SK; ✘ = non-formulary in SK; ▼= prior approval required for Department of Indian Affairs (DIA) coverage; **Cost = approximate $ drug cost per 10 days** unless noted otherwise.

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