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Part I of this two-part series on respiratory diseases covered two viral infections, severe acute respiratory syndrome (SARS) and influenza. Part II of this series will focus on a bacterial infection, community-acquired pneumonia (CAP).

—The Editor

Respiratory Disease Update 2004: SARS, Influenza, Community-Acquired Pneumonia—The Emergency Medicine Perspective

Part II: Community-Acquired Pneumonia

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Overview

CAP affects 5.6 million adults annually in the United States, and causes 1.7 million hospitalizations per year.[1] Combined mortality rates for pneumonia and influenza indicate that this is the sixth leading cause of death in the United States, accounting for 83,000 deaths annually. It is the cause for 46% of all deaths from infectious disease.[2] While causative pathogens are identified in fewer than 50% of cases,[3] the specific organisms that require coverage have been identified. The typical organisms include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The atypical organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*.[4] The atypical agent may have a presentation more subacute, with nonproductive cough, and a chest radiograph that appears characteristically worse than the patient's clinical appearance.

This update on the management of CAP addresses the following topics:

1. Appropriate triage disposition from the emergency department (ED);
2. Recommended treatment;
3. The role of newer antibiotics and of antibiotic resistance;
4. Updated testing for specific pathogens; and
5. Use of anticoagulation in the management of the CAP patient.

Disposition from the ED

Fine's landmark study helped to identify patients with CAP who are at low risk of mortality and who can be treated safely on an outpatient basis. The prediction rule stratifies patients into five categories based upon age, sex, coexisting illnesses, physical, and laboratory findings. Patients in Class IV and V require hospitalization, while patients in Class III may be

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managed in a 24-hour stay unit.[5] Patients older than 50 years were assigned automatically to Class II-V. However, patients who were younger than 50 years of age without a history of neoplastic disease, congestive heart failure, renal or liver disease, or cerebrovascular disease, who had normal mental status and vital signs were assigned to Class I and deemed suitable for management as outpatients. Mortality for classes I and II was fewer than 1%. In this study, 6% of patients in Class III, 11% of patients in Class IV, and 17% of patients in Class V, respectively, required intensive care unit (ICU) admission.

The point scale was derived from 14,199 cases and validated in another 38,039.[6] The Pneumonia Patient Outcomes Research Team (PORT) score derived from that study has been cited as suitable for determination of the initial disposition of the patient with CAP.[79] Selection of the initial site of treatment is one of the most important clinical decisions made in the treatment of patients with CAP. The ED plays a key role, as portal of entry for 75% of admissions for pneumonia in the United States.[7]

The Pneumonia PORT Severity Index is listed. (*See Table 1.*) The initial site of treatment must take into account not only the pneumonia severity index, but also any pre-existing social and medical conditions that may compromise the safety of home care. Hypoxemia, inability to take oral medications, severe social or psychiatric problems, or an unstable living situation all mitigate toward hospitalization for CAP.

There are other indicators for predicting mortality in the CAP patient. In one study, predictors of mortality included: patient age older than 65 years, confusion, temperature less than 37° C, respiratory rate greater than 24 breaths/ minute, serum sodium less than 135 mmol/L, BUN greater than 19.6 mg/dL, and pleural effusion on chest radiograph.[8]

Guidelines for ICU admissions also have been proposed, and include a PaO_2 to FiO_2 ratio of less than 250, multilobar infiltrates, and a systolic blood pressure of less than 90 mmHg, septic shock, or need for mechanical ventilation.[9] Another study listed the following risk factors for death due to CAP: at least three lobes affected, a respiratory rate of greater than 30 breaths/minute, the presence of shock, altered mental status, bedridden status, leukocytosis of greater than 14,900, or severe hypoxemia.[10]

Therapeutic Guidelines—Update

Antibiotic treatment guidelines have been adopted by the British Thoracic Society,[11] American Thoracic Society (ATS),[12] Infectious Disease Society of America,[13] the Centers for Disease Control and Prevention's Drug-Resistant Streptococcus Pneumonia Therapeutic Working Group,[14] and by the Antibiotic Selection for Community-Acquired Pneumonia Consensus Panel (ASCAP).[4] Each of these groups recommends a beta-lactam plus a macrolide or an antipneumococcal ("respiratory") fluoroquinolone alone as empiric therapy for patients admitted to a general medicine ward.

For patients with no underlying cardiopulmonary disease, the ATS recommends monotherapy with a macrolide, azithromycin.[9] Data indicate that azithromycin monotherapy is efficacious in treating hospitalized patients with CAP, even in the presence of cardiopulmonary disease and age greater than 65 years[15] and with fewer adverse effects than a regimen of cefuroxime with or without erythromycin.[16] Therapy, however, should take into account local resistance patterns, epidemiological data, and patient demographics.

For patients who need ICU therapy, and for whom Pseudomonas infection is not a significant concern, a combination of a beta-lactam plus a macrolide or a respiratory fluoroquinolone should be used.[7] The empiric therapy for CAP in immunocompetent adults as recommended by the Infectious Diseases Society of America is listed. (*See Table 2.*)

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Table 1. How the Pneumonia PORT Severity Index (PSI) Is Derived

PATIENTS ARE STRATIFIED INTO 5 SEVERITY CLASSES BY MEANS OF A 2-STEP PROCESS.

Step 1. Determination of whether patients meet the following criteria for class I: age < 50 years, with 0 of 5 comorbid conditions (i.e., neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal disease), normal or only mildly deranged vital signs, and normal mental status.

Step 2. Patients not assigned to risk class I are stratified into classes II-V on the basis of points assigned for 3 demographic variables (age, sex, and nursing home residency), 5 comorbid conditions (listed above), 5 physical examination findings (pulse, ≥ 125 beats/min; respiratory rate ≥ 30 breaths/min.; systolic blood pressure, < 90 mmHg; temperature, < 35° C or ≥ 40° C; and altered mental status), and 7 laboratory and/or radiographic findings (arterial pH < 7.35; blood urea nitrogen level ≥ 30 mg/dL; sodium level < 130 mmol/L; glucose level ≥ 250 mg/dL; hematocrit < 30%; hypoxemia by O_2 saturation < 90% by pulse oximetry or < 60 mmHg by arterial blood gas; and pleural effusion on baseline radiograph).

For classes I-III, hospitalization usually is not required. For classes IV and V, the patient usually requires hospitalization. It should be noted that social factors, such as outpatient support mechanisms and probability of adherence to treatment, are not included in this assessment.

PREDICTION RULE SCORING SYSTEM: COMMUNITY-ACQUIRED PNEUMONIA.

If a patient is younger than 51 years and has no coexisting illnesses or no abnormal physical examination findings, then risk class 4. *Otherwise*, circle the following characteristics and add up the score to determine the risk class.

PATIENT CHARACTERISTICS	POINTS
Age	
Man	_____ Age (years)
Woman	_____ Age (years - 10)
Nursing home resident	+ 10
Coexisting illnesses	
Neoplastic disease	+ 30
Liver disease	+ 20
Congestive heart failure	+ 10
Cerebrovascular disease	+ 10
Renal disease	+ 10
Physical examination findings	
Altered mental status	+ 20
Respiratory rate ≥ 30 breaths/min.	+ 20
Systolic blood pressure < 90 mm Hg	+ 20
Temperature < 35° C (95 F) or ≥ 40° C (104° F)	+15
Pulse ≥ 125 beats/min.	+10
Laboratory and radiographic findings (if study performed)	
Arterial pH < 7.35	+30
Blood urea nitrogen ≥ 30 mg/dL	+20
Sodium < 130 mmo/L	+20
Glucose > 250 mg/dL	+10
Hematocrit < 30%	+10
Partial pressure of arterial O_2 < 60 mmHg or O_2 Sat < 90%	+10
Bilateral pleural effusions	+10

Total points = Age + sex correction + sum of above circled points

(*Continued*)

Newer Antibiotics and the Role of Antibiotic Resistance

A drug resistant *S. pneumoniae* is now defined with a breakpoint minimum inhibitory concentration (MIC) of greater than 4 mcg/mL for non-meningeal sources, as adopted by the National Committee on Clinical Laboratory Standards (NCCLS) in January 2002. Susceptibility of pneumococcal isolates to cefotaxime and ceftriaxone in non-meningeal infections now is defined by the NCCLS as follows: susceptible if the MIC is less than 1 mcg/mL, intermediate as an MIC of 2 mcg/mL, and resistant as an MIC of greater than 4 mcg/mL. Cefotaxime or ceftriaxone, therefore, are the preferred parenteral agents for treatment of pneumococcal pneumonia without meningitis with reduced susceptibility to penicillin but with MIC of less than 2 mcg/mL.

Table 1. (Continued) PSI Severity Index with Point Total and Suggested Therapy

CLASS	POINTS	MORTALITY	SUGGESTED THERAPY
Class 1*	< 51	0.1%	Oral antibiotics at home
Class II	(51-70)	0.6%	Oral antibiotics at home—if vomiting/unreliable, then short stay
Class III	(71-90)	0.9%	Oral antibiotics at home—if vomiting/unreliable, then short stay
Class IV	(91-130)	9.5%	Inpatient stay + IV antibiotics
Class V	>130	26.7%	Inpatient stay (ICU) + IV antibiotics

* Younger than 51 years of age and no coexisting illnesses or abnormal physical examination findings.

The new breakpoints mean that nonmeningeal infections formerly deemed intermediately susceptible or resistant can be treated with the usual doses of beta-lactam drugs. They also reflect the feeling that levels of drug in alveolar macrophages, alveolar lining fluid, and epithelial lining cells are more important than serum levels.[7,17]

The following developments relate to the efficacy of antibiotics, and are discussed by class. (*See Table 3.*)

Fluoroquinolones. These are active against greater than 98% of strains of *S. pneumoniae* in the United States.[18,19] In order of most active to least active agents against *S. pneumoniae*, moxifloxacin historically is most active, followed by gatifloxacin and levofloxacin. Gemifloxacin, a new agent, is available as an oral agent only. There has been growing concern regarding the increasing levels of levofloxacin-resistant *S. pneumoniae*, including treatment failures. Increased fluoroquinolone use has been noted to be associated with *S. pneumoniae* resistance since 1999.[20] There has been emerging resistance of both gram-negative organisms and methicillin-resistant *Staphylococcus aureus*.[18] Resistance to fluoroquinolones due to overuse could have possible public policy implications, as they currently are active against category A bacterial agents of bioterrorism such as tularemia, anthrax, and *Yersinia pestis* infections.

Given these epidemiological and drug resistance trends, at least one panel[4] recommends moxifloxacin as the initial fluoroquinolone of choice when a respiratory fluoroquinolone is deemed appropriate for CAP. Furthermore, recent reports of levofloxacin failures in cases of CAP caused by *S. pneumoniae* are a continuing cause of concern, and other resistance data demonstrating precipitous increases in levofloxacin resistance among *S. pneumoniae* species support the panel's recommendations to avoid levofloxacin as the initial agent selected for empiric management of CAP.

Amoxicillin can be used for treatment of pneumococcal pneumonia involving susceptible strains, but because it is almost always impossible to determine if a strain is susceptible at time of presentation, this agent rarely is used on an empiric basis. If the isolate is penicillin-susceptible, penicillin G may be used. For empiric therapy, ceftriaxone or a respiratory fluoroquinolone may be used.

Macrolides. These are recommended for monotherapy of outpatients with no pre-existing disease and those not previously treated with other antibiotics. An advanced macrolide such as azithromycin or clarithromycin may be used as monotherapy for patients with co-morbid diseases such as diabetes, malignancy, renal failure, or congestive heart failure if they have not been treated previously with antibiotics. Azithromycin and clarithromycin generally are well-tolerated and may be administered once daily. Erythromycin is less active against *H. influenzae*, and causes more gastrointestinal side effects. A macrolide plus a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) is a preferred regimen for outpatients if resistance is an issue, and for hospitalized patients. Approximately 25% of pneumococci show some degree of resistance to macrolides.[18,21] Retrospective analysis indicates that dual therapy including a macrolide reduces mortality associated with bacteremic pneumococcal pneumonia.[22,23]

Ketolides. Destined to play an important role for oral management of CAP in ED patients, ketolides represent a new class of antibiotics with activity against gram-positive cocci that are macrolide-resistant. Recently approved by the FDA for use in CAP, acute bacterial exacerbations of chronic bronchitis (ABE/CB), and acute bacterial sinusitis, telithromycin is active against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, as well as Legionella, Mycoplasma, and Chlamydia species.[24,25] The dose is 800 mg per day.[7] Telithromycin has been investigated intensively for its efficacy and safety in treating outpatients with CAP.

From a pharmacological perspective, the ketolide class, of which telithromycin is an example, is composed of agents that are semisynthetic derivatives of 14-membered macrolides. They were developed specifically to be effective against macrolide-resistant, gram-positive cocci, in particular *S. pneumoniae*. Their enhanced activity against *S. pneumoniae* is facilitated by structural modifications at the positions of 3, 6, and 11-12, which yields modifications and improvements in the pharmacokinetic and antimicrobial activity of the parent compounds.

Antibacterial activity of macrolides and ketolides is dependent on inhibition of bacterial protein synthesis. The main differences between them, however, are that, although macrolides bind to only 1 contact site within the 23S ribosomal subunit (domain V), ketolides bind more avidly to domain V and, in addition, bind to a second site on the 23S subunit (domain II). Telithromycin also has some affinity for the effluxpump.[26,27] These differences explain why ketolides remain active against pathogens with both erm- and mef-mediated resistance.

Table 2. Initial Empiric Therapy for Suspected Bacterial Community-Acquired Pneumonia (CAP) in Immunocompetent Adults

PATIENT VARIABLE	PREFERRED TREATMENT OPTIONS
Outpatient	
Previously healthy	
No recent antibiotic therapy	A macrolide or doxycycline
Recent antibiotic therapy[a]	A respiratory fluoroquinolone alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate
Comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide[b] or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a beta-lactam[c]
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A beta-lactam[c] or a respiratory fluoroquinolone
Inpatient	
Medical ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a beta-lactam[d]
Recent antibiotic therapy	An advanced macrolide plus a beta-lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy).
ICU	
Pseudomonas infection is not an issue	A beta-lactam[d] plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a beta-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is an issue[e]	**Either** 1.) an antipseudomonal agent plus ciprofloxacin, *OR* 2.) an antipseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but the patient has a beta-lactam allergy	**Either** 1.) aztreonam plus levofloxacin[f] OR 2.) aztreonam plus moxifloxacin *OR* gatifloxacin, with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or amoxicillin-clavulanate plus an advanced macrolide
Hospitalized	Same as for medical ward and ICU

[a] That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection.
[b] Azithromycin or clarithromycin
[c] High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.
[d] Cefotaxime, cefriaxone, ampicillin-sulbactam, or ertapenem.
[e] Risk factors for Pseudomonas infection include severe structural lung disease (e.g., bronchiectasis), and recent antibiotic therapy or stay in hospital (especially in the ICU).
[f] Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

In vitro, telithromycin is active against *S. pneumoniae*, including macrolide-resistant strains, as well as *H. influenzae* and *Moraxella catarrhalis*.[28,29] The drug also inhibits Legionella, Mycoplasma, and Chlamydophilia species.[30,31] The drug is given once daily at a dose of 800 mg and appears to be well tolerated while achieving ratios of tissue to plasma of about 500 and 16.8 in alveolar macrophages and epithelial lining fluid, respectively.[32,33]

Data from three randomized, controlled, double-blind CAP trials comparing telithromycin with amoxicillin, clarithromycin, and trovafloxacin suggest that the ketolide is as effective as the comparators.[34-36] Data available to date suggest that the ketolides

Table 3. Year 2004 ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) Guidelines for Management of CAP

PATIENT PROFILE/ETIOLOGIC AGENTS	FIRST-LINE ANTIBIOTIC THERAPY[1,13,14]	ALTERNATIVE FIRST-LINE ANTIBIOTIC THERAPY
Otherwise Healthy Outpatients[13] with CAP (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, no comorbidity, high likelihood of medication compliance, and supportive home environment)[2]	Azithromycin PO	Moxifloxacin[3] PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
Comorbidity Present in Outpatients (Patients deemed to be suitable for outpatient/oral therapy, but comorbid conditions such as chronic alcoholism, diabetes, malignancy, or other risk factors such as age > 60 years are present)	Moxifloxacin PO *OR* Azithromycin PO	Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
In-Hospital Management[14] (not in intensive care unit) in patients with underlying risk factors or comorbid conditions (COPD, alcoholism, history of pneumonia, diabetes, bacteremia, etc.)	Ceftriaxone IV[4] plus azithromycin IV[5]	Moxifloxacin IV (preferred) *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP acquired in the nursing home environment (increased likelihood of gram-negative, *E. coli, Klebsiella pneumoniae*) **and managed in the hospital setting**	Ceftriaxone IV plus azithromycin IV	Moxifloxacin IV *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP managed in the nursing home environment (increased likelihood of gram-negative infection)	Ceftriaxone IV or IM plus azithromycin IV *OR* Levofloxacin IV or PO *OR* Amoxicillin-clavulanate PO plus azithromycin PO	Moxifloxacin PO *OR* Gatifloxacin PO
CAP in hospitalized individual with chronic alcoholism (Increased likelihood of *Klebsiella pneumoniae* infection)	Ceftriaxone IV plus azithromycin IV	Levofloxacin IV *OR* Cefepime IV plus azithromycin IV
Severe bacteremic CAP with documented *S. pneumoniae* species showing high-level resistance to macrolides and/or penicillin, but maintaining high sensitivity to extended spectrum (respiratory) fluoroquinolones and cephalosporins (i.e., ceftriaxone)	Ceftriaxone IV plus moxifloxacin	Ceftriaxone IV plus levofloxacin IV
Severe CAP complicated by structural disease of the lung (i.e., bronchiectasis; high-dose steroid use; cystic fibrosis; immunocompromised host) leading to increased likelihood of *Pseudomonas* and/or polymicrobial infection[12]	Ceftazidime[6] IV plus levofloxacin IV[7] plus aminoglycoside *OR* Ciprofloxacin IV plus ceftazidime IV plus azithromycin IV	Ciprofloxacin IV plus cefepime IV plus azithromycin IV *OR* Imipenem IV plus azithromycin IV plus aminoglycoside
CAP in a patient with suspected aspiration (increases the likelihood of both gram-negative and anaerobic infection)[9]	Ceftriaxone IV plus azithromycin IV plus clindamycin IV	Levofloxacin IV plus clindamycin IV *OR* Levofloxacin IV plus metronidazole IV *OR* Gatifloxacin IV plus clindamycin IV
Severe CAP in a compromised host with a previous hospitalization for MRSA, or who resides in a community or facility with a high reported incidence (> 50%) of methicillin-resistant *S. aureus* (MRSA)[8]	Moxifloxacin IV plus vancomycin IV[8] *OR* Moxifloxacin IV plus linezolide[11]	Levofloxacin IV plus vancomycin IV
CAP patient with severe pneumonia[10] requiring ICU hospitalization[8] *(Pseudomonas* is not suspected)	Ceftriaxone IV plus levofloxacin[7] IV *OR* Ceftriaxone IV plus moxifloxacin IV	Ceftriaxone IV plus azithromycin IV
CAP patient with severe pneumonia requiring ICU hospitalization (*Pseudomonas* considered a possible etiologic agent, alone, or in addition to *S. pneumoniae, H. influenzae, M. catarrhalis,* or atypical pathogens)[12]	Ceftazidime IV[6] plus ciprofloxacin IV plus azithromycin IV *OR* Imipenem IV plus aminoglycoside plus levofloxacin IV[7]	Ceftazidime plus aminoglycoside plus azithromycin IV *OR* Imipenem IV plus aminoglycoside IV plus moxifloxacin IV

[1] First-line therapy recommendations take into consideration cost of the drug (which may vary from one institution to another), convenience of dosing, daily dose frequency, spectrum of coverage, side effects, and risk of drug-drug interactions.

[2] Oral therapy/outpatient treatment recommendations are appropriate only for those otherwise healthy patients with CAP of mild enough severity that they are judged to be suitable candidates for outpatient management with oral antibiotics.

[3] Quinolones are restricted for use in patients > 18 years of age.

[4] Cefotaxime may be used as an alternative to ceftriaxone, although it should be noted that Year 2002 NCCLS breakpoints for cefotaxime apply ONLY when this antibiotic is dosed on a q 8 hr basis, and considerations regarding in-hospital medication administration/compliance must be considered when making such a substitution. In addition, consistently greater susceptibilities by one tube or more have been observed for ceftriaxone vs. cefotaxime in the ARM (Antibiotic Resistance Management) and TSN databases, which support use of ceftriaxone as the agent of choice for co-therapy with a macrolide for CAP, although comparative clinical outcome data are still lacking.

[5] Some institutions may use oral macrolide therapy for patients with mild-to-moderate CAP, but ASCAP Panel recommends initial use of IV azithromycin.

[6] Antipseudomonal agents other than ceftazidime include: piperacillin, piperacillin-tazobactam, imipenem, cefepime, or meropenem. (*Continued*)

Table 3. (*Continued*) Year 2004 ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) Guidelines for Management of CAP

[7] Levofloxacin dosage for hospitalized patients, 750 mg qd.

[8] High community prevalence (> 50%) of previous history of hospitalization, or increasing local incidence of methicillin-resistant *S. aureus* (MRSA) in a patient with a clinical presentation consistent with *S. aureus* pneumonia; vancomycin or linezolid should be considered as component for initial therapy.

[9] When anaerobic organisms are suspected as one of the possible etiologic pathogens in a patient with CAP, clindamycin or a beta-lactam/beta-lactamase inhibitor (ampicillin/sulbactam, tricarcillin/clavulanate, or pipercillin/tazobactam) is recommended.

[10] Two-drug therapy is recommended in severe CAP (non-pseudomonas).

[11] If intolerant to vancomycin.

[12] Three-drug therapy recommended in ICU patients in whom pseudomonas infection is being considered.

[13] If an outpatient with CAP has received a previous course of outpatient, oral therapy with either a beta-lactam (cefuroxime, amoxicillin, amoxicillin-clavulanate, etc.) or a macrolide within the past 3 months, excluding the current episode, a respiratory fluoroquinolone (i.e., moxifloxacin, levofloxacin) is recommended as the initial treatment. Conversely, recent use of a fluoroquinolone should dictate use of either an advanced generation macrolide alone (in outpatients without comorbidities), or the combination of an advanced generation macrolide plus a beta-lactam (in outpatients with comorbidities).

[14] If an inpatient with CAP has received a previous course of outpatient, oral therapy with either a beta-lactam (cefuroxime, amoxicillin, amoxicillin-clavulanate) or an advanced generation macrolide within the past 3 months, excluding the current episode, use of a two-drug combination consisting of ceftriaxone IV plus azithromycin IV still is recommended as initial therapy. Recent use of an oral or IV fluoroquinolone should dictate use of a non-fluoroquinolone regimen, i.e., ceftriaxone IV plus azithromycin IV as the initial inpatient regimen for hospitalized (non-ICU) patients with CAP.

may have an important role to play in the treatment of CAP caused by macrolide-resistant *S. pneumoniae.*

Updated Testing for Specific Pathogens

Chlamydia pneumoniae. Diagnosis of *C. pneumoniae* may be made by demonstration of a four-fold increase in IgG titer or a single IgM titer of greater than 1:16 using a microimmunofluorescence (MIF) or immunohistochemistry test.[37] Alternate methods for diagnosis include tissue culture or a PCR assay of respiratory secretions. Acute and convalescent-phase MIF samples should be studied on the same run on the same ELISA plate.

Streptococcus pneumoniae. There is a pneumococcal urinary antigen test that is acceptable for use in addition to the standard sputum gram stain and culture. The antigen detection assay detects pneumococcal cell wall polysaccharide, which is common to all serotypes. The immunochromatographic membrane test, or ICT, can be performed on a concentrated urine in 15 minutes. The sensitivity ranges from 50-80%, with specificity of approximately 90%.[38,39] The sensitivity in defining bacteremic disease in adults is cited as 70-90%.[7] However, in children, the specificity appears to be much lower, as nasopharyngeal carriers of pneumococci may register falsely positive.[40]

It is notable that a traditional test for pneumococcus, a gram stain and culture of sputum, may have little to no value in the diagnosis and management of the CAP patient. One study of 74 adult patients hospitalized with nonsevere CAP were evaluated with gram stains and sputum cultures. Even with strict criteria of 25 neutrophils and fewer than five squamous epithelial cells per low powered field, gram stain of valid sputum specimens failed to identify the etiologic agent in a single case. Sputum cultures identified an agent in only four cases, all patients responded to appropriate initial antibiotic therapy, without use or knowledge of culture results.[38]

Legionella pneumophila. The preferred diagnostic tests for Legionella are urinary antigen testing and culture of respiratory secretions. The urinary antigen test rapidly detects 80-95% of community-acquired cases. Culture on selective media detects nearly all strains, but takes 3-7 days to complete.[41] Testing may be appropriate in certain epidemiologic settings, for cases in which the cause of CAP is unclear and the patient is not improving on standard CAP therapy.

Viral Agents. Influenza testing is discussed in Part I of this series. Antigen tests for respiratory syncytial virus in adults are insensitive for detecting infection, and are not recommended.

Current literature indicates that with extensive studies, including blood and sputum cultures, bronchoscopy, needle aspirate of pleural fluid, and acute and convalescent serum testing, an etiologic agent diagnosis can be found in approximately 50% of cases of CAP (53/101 cases).[10] Many of these tests are clearly of little or no utility in the emergency setting.

Quality Indicators and Assurance

The ED is the portal of entry for the majority of cases of pneumonia admitted to the hospital. There has been increased emphasis on the administration of antibiotics within four hours of patient arrival. Blood cultures should be drawn and sent prior to antibiotic administration in hospitalized patients. In unselected patients, the yield of blood cultures in determining an etiologic agent in CAP is on the order of 6-11%; however, in the elderly, blood cultures within 24 hours of admission to guide therapy were associated with reduced 30-day mortality.[42] Appropriateness of initial antibiotic selection has come under increased scrutiny as well. Utilization goals are tied closely to accuracy and promptness of initial therapy in the ED.

As well, there has been increasing emphasis on the proper disposition from the ED, including criteria for admission to the hospital and admission to intensive care. It has been estimated that hospitalizations account for 89-96% of pneumonia costs.[3,43]

Length of stay has been shown to be related to three quality-of-care measures: initial administration of antibiotics in the ED, appropriate antibiotic selection, and shortened door to needle time. Initiation of antibiotic therapy in the ED led to shorter hospital stays for CAP by approximately two days in one report.[44]

The following have been listed as quality indicators in the assessment of care of the CAP patient:

1. Antibiotics given in a timely way, within either 4 or 8 hours of hospital admission;

2. Oxygen assessment or therapy within 8-24 hours of hospital arrival;

3. Blood culture drawn prior to antibiotic administration in the hospitalized patient;

4. Administration of antibiotics with activity against all likely causative pathogens, preferably the least expensive efficacious regimen;

5. Counseling patients regarding smoking cessation;

6. Switching from IV to oral antibiotics if clinically improving and hemodynamically stable, with discharge within 24 hours of switching to oral therapy;

7. Chest radiography within 24 hours of hospital admission;

8. Employment of methods to increase vaccination rates against influenza and pneumococcus; and

9. No discharge home for patients who are unstable on the day of discharge.[45]

Discharge Criteria

More rapid and appropriate discharge from the hospital has been shown to save money without compromising patient safety in a recent study. Discharge criteria included ability to take medications by mouth, heart rate less than 100 beats/minute, respiratory rate less than 24 breaths per minute, baseline mental status, and temperature less than 38° C. Systolic blood pressure should be greater than 90 mmHg, and pulse oximetry should be greater than 90% saturation.[46] As well, no other medical reasons for hospitalization should be present. Thirty-day mortality and re-hospitalization, and return to function were similar to the group that was hospitalized longer despite stability of the above.

Studies of Medicare patients in the 1980s indicate that, since the prospective payment system was implemented, there has been a 43% relative increase in patients being sent home either prematurely or in an unstable state.[47] Of patients discharged from the hospital in an unstable state, this group has been documented to show increased mortality on hospital re-admission.[48]

Prevention of Thromboembolic Phenomena

Hospitalization for pneumonia puts the patient at risk for thromboembolic disease, especially when co-morbid conditions such as respiratory failure and congestive heart failure are factored into the equation. The presence of pneumonia itself in patients older than 75 years of age has been deemed to be an indication for prophylaxis against deep venous thrombosis (DVT).[4] This is of particular significance in the presence of respiratory failure of CHF,[49] and has been emphasized in guidelines promulgated by the American College of Chest Physicians.[47] The recent MEDENOX trial noted a 63% decrease after 14 days of treatment with 20-40 mg of enoxaparin daily in the incidence of DVT compared to placebo in patients treated for CHF, pneumonia, or respiratory failure. No increase in frequency of hemorrhage, thrombocytopenia, or any other adverse event was noted, compared to placebo.[49]

Conclusions

Antibiotic therapy should be tailored to treating the most likely pathogens, and also to keeping the therapy from being overly broad and thereby inducing resistant strains of bacteria. Emphasis has been placed on early antibiotic therapy, both to improve mortality and to decrease duration of hospitalization. The house of medicine and the emergency physician in particular may be called upon to assume a greater role in preventative care and public health, especially in regard to immunization, smoking cessation, and recognition of new epidemics.

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Physician CME Questions

21. Quality indicators demonstrated to decrease length of hospital stay for patients with community-acquired pneumonia include:
    A. initial antibiotic treatment in the emergency department.
    B. appropriate antibiotic selection.
    C. shortened door-to-needle time.
    D. All of the above

22. An otherwise healthy outpatient with CAP reasonably may be treated with any of the following as a monotherapy antibiotic *except*:
    A. Levofloxacin
    B. Amoxacillin
    C. Clarithromycin
    D. Azithromycin

23. Which diagnostic test does *not* match the organism?
    A. Urine antigen—pneumococcus
    B. Urine antigen—legionella
    C. Acute and convalescent sera—*C. pneumoniae*, viruses
    D. Gram stain—*C. pneumoniae*

24. Which of the following are factors found in one study to be predictors of mortality in CAP patients?
    A. Age greater than 65 years
    B. Respiratory rate greater than 24 breaths/minute
    C. Pleural effusion on chest radiograph
    D. BUN greater than 19.6 mg/dL
    E. All of the above

25. Which of the following statements is true regarding antibiotics used to

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

treat CAP?

A. Moxifloxacin historically has been the fluoroquinolone agent most active against *S. pneumoniae*.
B. Increased fluoroquinolone use has been noted to be associated with *S. pneumoniae* resistance since 1999.
C. Erythromycin is less active against *H. influenzae*.
D. A macrolide plus a beta-lactam is a preferred regimen for outpatients if resistance is an issue.
E. All of the above.

26. Which of the following factors is *not* a factor in discharge criteria for patients with CAP?
    A. Ability to take medications by mouth
    B. Temperature greater than 38° C
    C. Pulse oximetry greater than 90% saturation
    D. Respiratory rate less than 24 breaths/minute

27. Ketolides such as telithromycin are a new class of agents that are active against gram-positive cocci that are macrolide-resistant.
    A. True
    B. False

28. Which of the following is the suggested therapy for Class IV patients based on the PORT severity index?
    A. Oral antibiotics at home
    B. An inpatient stay in the ICU plus IV antibiotics
    C. An inpatient stay plus IV antibiotics
    D. A short hospital stay only if the patient is unreliable or experiences vomiting.

29. Antigen tests for respiratory syncytial virus in adults are insensitive for detecting infection and are not recommended.
    A. True
    B. False

30. Common organisms associated with CAP include all of the following *except*:
    A. *Legionella pneumophila*
    B. *Moraxella catarrhalis*
    C. *Escherichia coli*
    D. *Chlamydia pneumoniae*

Correction

In the March 22, 2004, issue, a reference was listed incorrectly. The correct reference should be:

20. White HD. Thrombolytic therapy in the elderly. *Lancet* 2000;356:2028-2030.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports 2004 NEPA Award Winner

Emergency Medicine Reports received a 2004 First Place award in the Best Single-Topic Newsletter category from the Newsletter and Electronic Publishers Foundation for the two-part article on immigrant medicine published Feb. 10 and Feb. 24, 2003. The authors of the winning article are Mary Meyer, MD, Danica Barron, MD, and Carter Clements, MD. The article was edited by Gideon Bosker, MD, and Shelly Morrow Mark.

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In Future Issues: **Facial Trauma**

CME Answer Key

21. D	26. B
22. B	27. A
23. D	28. C
24. E	29. A
25. E	30. C

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Respiratory Illness, Part II

How the Pneumonia PORT Severity Index (PSI) is Derived

PATIENTS ARE STRATIFIED INTO 5 SEVERITY CLASSES BY MEANS OF A 2-STEP PROCESS.

Step 1. Determination of whether patients meet the following criteria for class I: age < 50 years, with 0 of 5 comorbid conditions (i.e., neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal disease), normal or only mildly deranged vital signs, and normal mental status.

Step 2. Patients not assigned to risk class I are stratified into classes II-V on the basis of points assigned for 3 demographic variables (age, sex, and nursing home residency), 5 comorbid conditions (listed above), 5 physical examination findings (pulse, ≥ 125 beats/min; respiratory rate ≥ 30 breaths/min.; systolic blood pressure, < 90 mmHg; temperature, < 35° C or ≥ 40° C; and altered mental status), and 7 laboratory and/or radiographic findings (arterial pH < 7.35; blood urea nitrogen level ≥ 30 mg/dL; sodium level < 130 mmol/L; glucose level ≥ 250 mg/dL; hematocrit < 30%; hypoxemia by O_2 saturation < 90% by pulse oximetry or < 60 mmHg by arterial blood gas; and pleural effusion on baseline radiograph).

For classes I-III, hospitalization usually is not required. For classes IV and V, the patient usually requires hospitalization. It should be noted that social factors, such as outpatient support mechanisms and probability of adherence to treatment, are not included in this assessment.

PREDICTION RULE SCORING SYSTEM: COMMUNITY-ACQUIRED PNEUMONIA.

If a patient is younger than 51 years and has no coexisting illnesses or no abnormal physical examination findings, then risk class 4. *Otherwise*, circle the following characteristics and add up the score to determine the risk class.

PATIENT CHARACTERISTICS	POINTS
Age	
Man	_____ Age (years)
Woman	_____ Age (years - 10)
Nursing home resident	+ 10
Coexisting illnesses	
Neoplastic disease	+ 30
Liver disease	+ 20
Congestive heart failure	+ 10
Cerebrovascular disease	+ 10
Renal disease	+ 10
Physical examination findings	
Altered mental status	+ 20
Respiratory rate ≥ 30 breaths/min.	+ 20
Systolic blood pressure < 90 mm Hg	+ 20
Temperature < 35° C (95 F) or ≥ 40° C (104° F)	+15
Pulse ≥ 125 beats/min.	+10
Laboratory and radiographic findings (if study performed)	
Arterial pH < 7.35	+30
Blood urea nitrogen ≥ 30 mg/dL	+20
Sodium < 130 mmo/L	+20
Glucose > 250 mg/dL	+10
Hematocrit < 30%	+10
Partial pressure of arterial O_2 < 60 mmHg or O_2 Sat < 90%	+10
Bilateral pleural effusions	+10

Total points = Age + sex correction + sum of above circled points

CLASS	POINTS	MORTALITY	SUGGESTED THERAPY
Class 1*	< 51	0.1%	Oral antibiotics at home
Class II	(51-70)	0.6%	Oral antibiotics at home—if vomiting/unreliable, then short stay
Class III	(71-90)	0.9%	Oral antibiotics at home—if vomiting/unreliable, then short stay
Class IV	(91-130)	9.5%	Inpatient stay + IV antibiotics
Class V	>130	26.7%	Inpatient stay (ICU) + IV antibiotics

* Younger than 51 years of age and no coexisting illnesses or abnormal physical examination findings.

Initial Empiric Therapy for Suspected Bacterial Community-Acquired Pneumonia (CAP) in Immunocompetent Adults

PATIENT VARIABLE	PREFERRED TREATMENT OPTIONS
Outpatient	
Previously healthy	
No recent antibiotic therapy	A macrolide or doxycycline
Recent antibiotic therapy[a]	A respiratory fluoroquinolone alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate
Comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide[b] or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a beta-lactam[c]
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A beta-lactam[c] or a respiratory fluoroquinolone
Inpatient	
Medical ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a beta-lactam[d]
Recent antibiotic therapy	An advanced macrolide plus a beta-lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy).
ICU	
Pseudomonas infection is not an issue	A beta-lactam[d] plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a beta-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is an issue[e]	**Either** 1.) an antipseudomonal agent plus ciprofloxacin, *OR* 2.) an antipseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but the patient has a beta-lactam allergy	**Either** 1.) aztreonam plus levofloxacin[f] OR 2.) aztreonam plus moxifloxacin *OR* gatifloxacin, with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or amoxicillin-clavulanate plus an advanced macrolide
Hospitalized	Same as for medical ward and ICU

[a] That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection.
[b] Azithromycin or clarithromycin
[c] High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.
[d] Cefotaxime, cefriaxone, ampicillin-sulbactam, or ertapenem.
[e] Risk factors for Pseudomonas infection include severe structural lung disease (e.g., bronchiectasis), and recent antibiotic therapy or stay in hospital (especially in the ICU).
[f] Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

Year 2004 ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) Guidelines for Management of CAP

PATIENT PROFILE/ETIOLOGIC AGENTS	FIRST-LINE ANTIBIOTIC THERAPY[1,13,14]	
Otherwise Healthy Outpatients[13] with CAP (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, no comorbidity, high likelihood of medication compliance, and supportive home environment)[2]	Azithromycin PO	Moxifloxacin[3] PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
Comorbidity Present in Outpatients (Patients deemed to be suitable for outpatient/ oral therapy, but comorbid conditions such as chronic alcoholism, diabetes, malignancy, or other risk factors such as age > 60 years are present)	Moxifloxacin PO *OR* Azithromycin PO	Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
In-Hospital Management[14] (not in intensive care unit) in patients with underlying risk factors or comorbid conditions (COPD, alcoholism, history of pneumonia, diabetes, bacteremia, etc.)	Ceftriaxone IV[4] plus azithromycin IV[5]	Moxifloxacin IV (preferred) *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP acquired in the nursing home environment (increased likelihood of gram-negative, *E. coli, Klebsiella pneumoniae*) **and managed in the hospital setting**	Ceftriaxone IV plus azithromycin IV	Moxifloxacin IV *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP managed in the nursing home environment (increased likelihood of gram-negative infection)	Ceftriaxone IV or IM plus azithromycin IV *OR* Levofloxacin IV or PO *OR* Amoxicillin-clavulanate PO plus azithromycin PO	Moxifloxacin PO *OR* Gatifloxacin PO
CAP in hospitalized individual with chronic alcoholism (Increased likelihood of *Klebsiella pneumoniae* infection)	Ceftriaxone IV plus azithromycin IV	Levofloxacin IV *OR* Cefepime IV plus azithromycin IV
Severe bacteremic CAP with documented *S. pneumoniae* species showing high-level resistance to macrolides and/or penicillin, but maintaining high sensitivity to extended spectrum (respiratory) fluoroquinolones and cephalosporins (i.e., ceftriaxone)	Ceftriaxone IV plus moxifloxacin	Ceftriaxone IV plus levofloxacin IV
Severe CAP complicated by structural disease of the lung (i.e., bronchiectasis; high-dose steroid use; cystic fibrosis; immunocompromised host) leading to increased likelihood of *Pseudomonas* and/or polymicrobial infection[12]	Ceftazidime[6] IV plus levofloxacin IV[7] plus aminoglycoside *OR* Ciprofloxacin IV plus ceftazidime IV plus azithromycin IV	Ciprofloxacin IV plus cefepime IV plus azithromycin IV *OR* Imipenem IV plus azithromycin IV plus aminoglycoside
CAP in a patient with suspected aspiration (increases the likelihood of both gram-negative and anaerobic infection)[9]	Ceftriaxone IV plus azithromycin IV plus clindamycin IV	Levofloxacin IV plus clindamycin IV *OR* Levofloxacin IV plus metronidazole IV *OR* Gatifloxacin IV plus clindamycin IV
Severe CAP in a compromised host with a previous hospitalization for MRSA, or who resides in a community or facility with a high reported incidence (> 50%) of methicillin-resistant *S. aureus* (MRSA)[8]	Moxifloxacin IV plus vancomycin IV[8] *OR* Moxifloxacin IV plus linezolide[11]	Levofloxacin IV plus vancomycin IV
CAP patient with severe pneumonia[10] requiring ICU hospitalization[8] *(Pseudomonas* is not suspected)	Ceftriaxone IV plus levofloxacin[7] IV *OR* Ceftriaxone IV plus moxifloxacin IV	Ceftriaxone IV plus azithromycin IV
CAP patient with severe pneumonia requiring ICU hospitalization (*Pseudomonas* considered a possible etiologic agent, alone, or in addition to *S. pneumoniae, H. influenzae, M. catarrhalis,* or atypical pathogens)[12]	Ceftazidime IV[6] plus ciprofloxacin IV plus azithromycin IV *OR* Imipenem IV plus aminoglycoside plus levofloxacin IV[7]	Ceftazidime plus aminoglycoside plus azithromycin IV *OR* Imipenem IV plus aminoglycoside IV plus moxifloxacin IV

1 First-line therapy recommendations take into consideration cost of the drug (which may vary from one institution to another), convenience of dosing, daily dose frequency, spectrum of coverage, side effects, and risk of drug-drug interactions.

2 Oral therapy/outpatient treatment recommendations are appropriate only for those otherwise healthy patients with CAP of mild enough severity that they are judged to be suitable candidates for outpatient management with oral antibiotics.

3 Quinolones are restricted for use in patients > 18 years of age.

4 Cefotaxime may be used as an alternative to ceftriaxone, although it should be noted that Year 2002 NCCLS breakpoints for cefotaxime apply ONLY when this antibiotic is dosed on a q 8 hr basis, and considerations regarding in-hospital medication administration/compliance must be considered when making such a substitution. In addition, consistently greater susceptibilities by one tube or more have been observed for ceftriaxone vs. cefotaxime in the ARM (Antibiotic Resistance Management) and TSN databases, which support use of ceftriaxone as the agent of choice for co-therapy with a macrolide for CAP, although comparative clinical outcome data are still lacking.

5 Some institutions may use oral macrolide therapy for patients with mild-to-moderate CAP, but ASCAP Panel recommends initial use of IV azithromycin.

6 Antipseudomonal agents other than ceftazidime include: piperacillin, piperacillin-tazobactam, imipenem, cefepime, or meropenem. (*Continued*)

7 Levofloxacin dosage for hospitalized patients, 750 mg qd.

8 High community prevalence (> 50%) of previous history of hospitalization, or increasing local incidence of methicillin-resistant *S. aureus* (MRSA) in a patient with a clinical presentation consistent with *S. aureus* pneumonia; vancomycin or linezolid should be considered as component for initial therapy.

9 When anaerobic organisms are suspected as one of the possible etiologic pathogens in a patient with CAP, clindamycin or a beta-lactam/beta-lactamase inhibitor (ampicillin/sulbactam, tricarcillin/clavulanate, or pipercillin/tazobactam) is recommended.

10 Two-drug therapy is recommended in severe CAP (non-pseudomonas).

11 If intolerant to vancomycin.

12 Three-drug therapy recommended in ICU patients in whom pseudomonas infection is being considered.

13 If an outpatient with CAP has received a previous course of outpatient, oral therapy with either a beta-lactam (cefuroxime, amoxicillin, amoxicillin-clavulanate, etc.) or a macrolide within the past 3 months, excluding the current episode, a respiratory fluoroquinolone (i.e., moxifloxacin, levofloxacin) is recommended as the initial treatment. Conversely, recent use of a fluoroquinolone should dictate use of either an advanced generation macrolide alone (in outpatients without comorbidities), or the combination of an advanced generation macrolide plus a beta-lactam (in outpatients with comorbidities).

14 If an inpatient with CAP has received a previous course of outpatient, oral therapy with either a beta-lactam (cefuroxime, amoxicillin, amoxicillin-clavulanate) or an advanced generation macrolide within the past 3 months, excluding the current episode, use of a two-drug combination consisting of ceftriaxone IV plus azithromycin IV still is recommended as initial therapy. Recent use of an oral or IV fluoroquinolone should dictate use of a non-fluoroquinolone regimen, i.e., ceftriaxone IV plus azithromycin IV as the initial inpatient regimen for hospitalized (non-ICU) patients with CAP.

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Acute Pain Management: An Emergency Department Perspective

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Introduction

Although chronic pain management seems to receive the lion's share of published literature, acute pain management issues recently have come to the forefront now that regulatory agencies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), American Pain Society (APS), National Committee for Quality Assurance (NCQA), and Center for Medicare/Medicaid Services (CMS) have made this a priority with regard to education, measurement, assessment, and documentation. Since acute pain management is protean in nature, the focus of this report consciously will be to avoid such topics as procedural sedation, alternative nonpharmacologic adjuncts, medication pharmacokinetics, sickle cell pain crisis management, cancer pain management, and physician liability in withholding analgesic treatment.

Historical Perspective

Prior to the 19th century, pain management was well documented but perhaps not as well understood with regard to the neurobiology of pain. Nevertheless, China's Xia Dynasty (2140-1711 BC) described pain as the simple disruption of *chi*—life energy. Ancient Egypt and India were clear in their interpretations that pain was related to demons, gods, and spirits of the dead. Hippocrates first described the four humors (i.e., blood, phlegm, black bile, and yellow bile) and how their imbalance would lead to painful conditions. Plato and Aristotle furthered that notion by stating that there must be a peripheral stimulus to create the imbalance, followed by an internal emotional experience. In addition, Judeo-Christian teachings (through the books of Job and Genesis and the story of the crucifixion) have created an inseparable relationship between pain/suffering and the human condition.[1,2]

More traditional teachings were first described in the 19th century. Serturner in 1804 first described the importance of the plant extract *somniferus opium* in alleviating painful conditions. Syringes and medicinal extracts were available widely and were unrestricted. Subsequently, self-medication soon contributed largely to the budding science of addiction, tolerance, dependence, and toxicity. Pharmaceutical companies became very active at the turn of the century, with Bayer making aspirin and morphine analogs available for purchase for purchase by consumers. In 1914 Congress instituted the Narcotic Control Act, mostly in an attempt to gain some control of the narcotic craze.[1,3]

Livingston in 1943 illustrated that a noxious stimulus needs to be generated peripherally, then transmitted centrally to the spinal cord and, ultimately, to the brain for further processing. In 1950, pain was designated a disease state and soon after Noordenboos described myelinated ("fast system") and unmyelinated ("slow system") nerves. Melzack and Wall in 1965 proposed the gate theory of hyperstimulation, attenuation, and spinal level inhibition. The International Association for the Study of Pain first defined pain in 1986. Issues related to pain and analgesia had an illustrious history and during the past 25-30 years have generated recent renewed interest.[1,2,4]

Neuroanatomic, Physiologic, and Biologic Considerations

In the acute pain model, a mechanical, chemical, and/or thermal stimulus incites a cascade of events by activating receptors. Following a minor stimulus, an electrical impulse is transmitted and propagated via myelinated A-delta fibers and/or unmyelinated c-fibers. This electrical impulse may dissipate, be attenuated,

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or be part of a reflex (withdraw) arc. If the stimulus is large enough, a chemical release can occur, creating an "inflammatory soup" consisting of bradykinins, phospholipids, histamine, substance P, endorphins, nitric oxide (NO), serotonin, and other mediators. These chemicals can sustain the stimulation and /or attenuate the impulse depending on receptor regulation, past experiences, concurrent medications, disease states, etc. The electrical impulse travels to the dorsal horn of the spinal cord where further modulation occurs as some of the information is transmitted via the spinothalamic tracts to the cortex. Much facilitation and remodeling occurs at the cortical, subcortical, and spinal levels prior to reflex, peripheral, motor, and/or emotional responses. Neuroplasticity theories describe the nervous system's capability to fluctuate, adapt, and reset some of these integration processes as one develops and matures. For example, patients exhibit widely different pain thresholds even if the pain stimulus is highly controlled in a laboratory setting.

Locally, sodium (Na) and calcium (Ca) channels affect electrical impulse transmission and this likely is illustrated by the effect that carbamazepine (Na channel blockade) has on neuralgic pain. Endogenous opioids such as enkephalins, dynorphins, and endorphins have affinity for specific receptors (mu, kappa, delta, sigma, and epsilon) located centrally as well as at the spinal cord level. Receptors, and to a lesser degree channels, are extremely dynamic structures that can exert their own control by concentration variability on the end organ, differing affinities for the same ligand depending on their location and their ability to be up- or down-regulated. In addition to local effects, opioids can stimulate the release of more active substances such as serotonin, Norepi, and GABA, which in turn can act locally and systemically. Lastly, the vasoactive substances such as bradykinin, histamine, and prostaglandins also contribute to the pain experience by causing smooth muscle spasm, increasing blood flow, inciting capillary leakage, and ultimately creating inflammation.[5-8]

Nonnarcotic Analgesics

Nonallopathic alternative methodologies require specific review that is beyond the scope of this article. They have not been as rigorously studied as the pharmacological agents, but nevertheless have been used clinically for quite some time. These include acupuncture, massage, hypnosis, and manipulation. Other nonpharmacologic methods include ultrasound, transcutaneous electrical nerve stimulation (TENS), and biofeedback.

Adjuvants or coanalgesics are agents that can be used alone or more typically as an aid for providing synergy while employing one of the more traditional analgesics—opioids. These would include the inhalants, nonsteroidal antiinflammatories (NSAIDs), aspirin, acetaminophen, corticosteroids, anticonvulsants, antidepressants, benzodiazepines, and muscle relaxants.

As a group, muscle relaxants afford some efficacy over placebo in multiple clinical trials. The studies are in general somewhat difficult to interpret because of issues involving sample size, uniformity in comparable pain syndromes (acute vs chronic), subjective nature of the syndrome, and measurement standardization (for example, how is muscle spasm defined). The mechanism of action for the muscle relaxants is largely unknown but it is hypothesized that they affect the cortical and subcortical levels to produce sedation. They likely impart decreased muscular response and activity from the alpha and delta neuron inputs that are controlled from the cortex. The prototype comes from the benzodiazepine class—diazepam (Valium). An incomplete list of muscle relaxants includes: carisoprosodol (SOMA), chlozoxazone (Parafon Forte), cyclobenzaprine (Flexeril), metaxolone (Skelaxin), methocarbamol (Robaxin), and orphenadrine (Norflex). Anticholinergic effects and decreased therapeutic indices tend to make some of these agents a bit more difficult to use safely. Orphenadrine and cyclobenzaprine can be used parenterally, which gives them a slight edge for acute management, but their side effect profiles would suggest that perhaps they are not the safest in this class of drugs. One recent trial would suggest what many already believe that adding a muscle relaxant to an NSAID affords no real clinical benefit and definitely exposes the patient to side effects, adverse events, and drug-drug interactions.[3,9]

Local and regional anesthetic agents play a major role given the sheer volume of lacerations and wounds that are cared for in an acute care setting. They are fairly safe when their respective therapeutic ceilings are respected. The amide family includes lidocaine, mepivacaine, and bupivicaine. Their dosages vary by the specific drug and by the procedure being performed. For instance, top-end

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dosages for lidocaine vary with a Bier block (1 mg/kg), high volume (3-5 mg/kg), and local infiltration with epinephrine (7 mg/kg). Their toxicities can span from perioral paresthesias and agitation to seizures and cardiovascular collapse. Hepatic microsomes are responsible for their primary degradation.

The esters include procaine and tetracaine. They are metabolized via the RBC cholinesterase and pseudocholinesterase pathways. Over all, the esters have a safer profile than the amides because of their higher therapeutic index. The esters are less available and, hence, tend to be more expensive. They are less likely to cause the toxicities sometimes seen with the amides when accidental toxic doses have been administered.

Nitrous oxide has been used for years in varying concentrations. A 50:50 premixed tank commonly is available, which precludes the need to have an analyzer and mixing apparatus when using the prior method of having two separate tanks that needed mixing at time of administration. Its exact mechanism of action is unknown but it likely exerts its effects as a dissociative agent at the subcortical level. Its primary strength is in procedural sedation because it can be readily turned on and off by the patient and is quickly washed out from the pulmonary circulation. It acts as an amnestic as well as a mild analgesic agent. It has been recommended and used in multiple emergency situations and procedures: prehospital setting, ischemic chest pain, pain crisis, lumbar puncture, foreign body removal, abscess incision and drainage, and arterial puncture to list a few. Self-administration by mask provides both positive and negative features to this modality. Diffusion hypoxemia is unusual with the premixed tanks but a required scavenger unit and the abuse potential make this method a bit more cumbersome from an operational standpoint. Lastly, when used alone, its safety profile is good but once again when used as an adjunct with benzodiazepines and/or narcotics the risk for deep sedation and/or anesthesia is real.[3,10,11]

Ketamine is a parenteral dissociative agent that exerts itself at the thalamocortical level. It is a phencyclidine (PCP) derivative. Although it has been used widely in veterinary practice for longer, ketamine has been used in human clinical practice for about 30 years. Its strength is for procedural sedation since the IV form has a fairly short half-life. Almost as a rule, patients will be able to maintain their protective reflexes and will be afforded some mild cardiorespiratory stability with this medication. Additionally, via sympathetic stimulation it can provide smooth muscle relaxation that probably explains its utility for bronchospastic patients experiencing acute respiratory failure.

This is a very lipophilic substance and, hence, its therapeutic response is in approximately 5 minutes for IM and 1 min for IV administration. It is water-soluble, and the starting doses are 4 mg/kg IM and 2 mg/kg IV. Atropine or glycopyrrolate can be used for those patients with extra secretions to further guard the respiratory tree during administration. The use of adjuncts such as benzodiazepines, nitrous oxide, and/or narcotics along with ketamine requires a good working knowledge of the additive effects, synergism, and the potential toxicities.

Although it is a fairly safe medication, it too has its relative and absolute contraindications. Since it can increase intraluminal pressure and, therefore, affect intraocular, intracranial, and abdominal pressures, one might have to choose an alternative therapeutic modality. Other side effects and idiosyncratic reactions have been documented. Unpleasant reactions to emergency phenomena can be minimized by educating all caretakers and family members to appropriate recovery. The use of midazolam to emergency phenomena has been proposed, but recent literature would suggest that it is not necessary and probably not worth the risk in coadministering these two agents. Chest wall rigidity is not reversible but can be attenuated by giving the correct IV dose slowly. If it does occur, then time and supplemental oxygen and assisted breathing are very likely the most that will be needed. Laryngospasm is another nonreversible complication but occurs infrequently. By being aware of preprocedure laryngeal secretions and either using an anticholinergic medication or choosing an alternative modality, the physician can minimize this adverse event.

Acetaminophen first was used in 1878 and, other than its excellent antipyretic activity, it also has some mild analgesic properties when used alone. It has a fairly safe therapeutic index when used as intended, but a delay in diagnosing its toxicity can prove fatal. Its primary mechanism of action is via centrally mediated cyclooxygenase inhibition. In addition, it has little peripheral anti-inflammatory activity and has no effect on platelet function. The therapeutic ceiling is about 4 gm/day in a healthy adult. Lastly, tolerance, dependence, and addiction are not issues with acetaminophen.

Acetylsalicylate (ASA) became widely used after 1899. It has equianalgesic and equiantipyretic effects similar to acetaminophen. Its strength comes from its anti-inflammatory and antiplatelet activity. It inhibits prostaglandin synthesis at the cyclooxygenase level at a similar point to where other NSAIDs effect their control. The toxicity profile tends to hinder its wider use in that it decreases mucus secretions, disrupts the gastrointestinal (GI) mucosal barrier, decreases platelet stickiness, decreases glomerular filtration rate (GFR), and can precipitate bronchospasm. Currently, ASA is being widely used for those patients predisposed to atherosclerotic disease or documented atherosclerotic end organ disease states.

NSAIDs exert their effect at the cyclooxygenase level and avoid the lipooxygenase pathway similar to ASA. Some medications within this class have been shown to block at higher levels on the arachidonic pathway, but what clinical significance this bears is unclear. The primary toxicity is related to the cyclooxygenase inhibition that in turn affects the GI mucosa protective barrier and the GFR. The topical preparations have not been well studied and currently are not yet used widely, although the ability for this type of modality with good penetration could have significant clinical impact for acute injuries. Combining NSAIDs with other agents such as narcotics or muscle relaxants for oral use makes sense since effecting analgesia via two separate pathways allows for less total dose of either agent—synergism without toxicity.

The NSAIDs have been grouped based on the acid derivatives—acetic and propionic. Indomethacin (acetic acid prototype) has potent analgesic and anti-inflammatory properties exhibited by its effectiveness with certain arthropathies like gout.

Ibuprofen (propionic acid prototype) at higher end doses also can serve as an effective analgesic and anti-inflammatory agent. The pharmacology of most NSAIDs is quite similar except for dosing schedule, therapeutic half-life, and therapeutic ceiling. Ibuprofen has the following characteristics: rapid GI absorption, non-sedating, no respiratory depression, and no dependency or tolerance. Its therapeutic ceiling is about 2400 mg/day for healthy adult patients, but gastropathy can occur at doses above 1800 mg/day. Complications with phenytoin and warfarin also can occur due to the NSAID's ability to displace those agents from protein binding sites. This displacement could effectively increase each of their therapeutic as well as toxic effects.

Ketorolac is another NSAID agent that can be administered by either parenteral or oral routes. It has become a widely used medication in acute painful conditions in part due to its clinical effectiveness but also due to its relative convenience of administration. It has been studied in the acute care setting for the following diagnoses: renal colic, tension headache, migraine, gout, and skeletomuscular syndromes. Administered at 30 mg/kg either IM or IV, it has been shown to have similar clinical effects as morphine sulfate 10 mg in one study. The pediatric dose is about 0.5 mg/kg but has not been studied well in infants and toddlers. Due to the impact on GFR, the dose needs to be decreased for patients older than 60 years of age, those with known or suspected renal insufficiency, and those with acute or chronic dehydration. Lastly, a rebound pain phenomenon has been documented in patients who receive a parenteral dose but then fail to be treated aggressively prior to ketorolac's first therapeutic half-life.[3,12]

The cyclooxygenase-2 (COX-2) inhibitors (rofecoxib/celecoxib) have been a heavily marketed subclass of NSAIDs that act by preferentially inhibiting the COX-2 isoform. This in turn impacts inflammation and pain. This isoform is found throughout the body but its counterpart COX-1 is found in higher concentrations at the GI mucosa, platelet surface, and glomerular apparatus. The premise is that one can selectively inhibit the prostaglandin synthesis that impacts pain while sparing the toxicity typically encountered by the usual NSAIDs. Although the literature does support the use of these COX-2 inhibitors for subacute and chronic inflammatory processes, the emergency medicine literature still is scant in advocating their use in the acute care setting unless otherwise dictated by individual patient characteristics and preferences.

Narcotic Analgesics

The opioid class of medications originally was isolated from the unripe seed capsules of the opium plant (Papever somniferum). The prototype morphine sulfate receives it name from the Greek god of dreams—Morpheus. Four medicinal isolates have been extracted from the opium plant: morphine, codeine, papaverine, and noscaprine. In 1939 meperidine first was synthesized, and in 1951 nalorphine was the first antagonist identified. The opioid mechanisms of action are protean since they involve multiple receptor sites and can be up- or down-regulated. In treating patients with acute pain crises, this group of medications alone or in synergy with other modalities allows physicians to help in relieving the pain and suffering experienced by so many patients treated in EDs.[1,3]

The non-therapeutic effects of opioids play a major role in acute care management, especially when safety, toxicity, and monitoring issues are discussed. From a cardiovascular stance, most opioids have little direct cardiovascular effect when given judiciously. Fentanyl has the least direct myocardial depressant effects, at therapeutic doses but all the narcotics when given in toxic doses or administered too rapidly can depress the myocardium as well as cause hypotension. Since some of the medications in this class have different histamine releasing effects such as allergic reactions, local reactions, and bronchospasm, gradual administration is essential during medication delivery and monitoring. The GI adverse reactions usually are related to the dysphoria (sigma receptor mediated) that often is associated with narcotic administration. In addition, the decreased peristalsis affects not only stomach emptying but also constipation. Both the histamine and nausea responses can be alleviated either prophylactically or abortively with the appropriate medications.[3]

The central nervous system (CNS) is where opiates exert their primary toxic non-therapeutic effects. The miotic pupillary response is due to hyperstimulation of the parasympathetic tracts innervating the iris as well as the ciliary body. The medulla houses the chemotactic trigger zone (CTZ). This area can become overstimulated and cause nausea as well as hyperemesis. This is the same proposed mechanism of action for apomorphine and ipecac. Lastly, the pons and medulla contain the respiratory drive apparatus that predominantly is influenced by the carbon dioxide (CO_2) concentration. Narcotics depress respiratory drive by negatively impacting the CO_2-sensing mechanism that in turn allows for hypoventilation, hypoxemia, and CO_2 retention (CO_2 narcosis).[3]

The opiates' primary therapeutic effects are due to their impact on the mu, kappa, and delta receptors at various CNS end organ sites. They exert their control at the primary afferents, dorsal roots, spinothalamic tracts, and medial thalamic nuclei. The mesolimbic system has a complex role in determining mood- and reward-based activity. Dopamine in conjunction with the regulation/sensitization of the mu, kappa, delta, and sigma receptors plays an important role in a patient's sense of euphoria, dysphoria, and/or possible drug-seeking behavior patterns. The medulla has a cough center that can be inhibited by the antitussives—narcotics and their analogs (dextromethorphan). Basic science pain research constantly is adding to knowledge of receptors and receptor end organ concentrations, plasticity, and regulation as it impacts neurobiology, neurochemistry, and neuroimmunology.[3]

Morphine sulfate is the prototypical agent in this category and, hence, equianalgesic doses are based on this opiate. Note that MS no longer is an accepted abbreviation due to safety initiatives that have addressed medication errors due to confusion between sound-alike or look-alike medications—magnesium sulfate and morphine sulfate. Several narcotics are administered via multiple routes: IV/IM/PO (additional discouraged abbreviations). The intramuscular route is painful, not very predictable as to time of onset, and poorly titrated. This tends to be the theme

with most intramuscular narcotics, although some have the added advantage of being given via a subcutaneous (SC) route. In general, acute pain management usually requires some form of ongoing assessment/reassessment and this factor alone makes intramuscular administration much more challenging, although its convenience makes this route of administration understandable. Patient-controlled analgesia (PCA) allows patients more control of their pain crisis management, but the emergency medicine literature has not convinced clinicians that the inherent risks as well as inconveniences for staff are enough to supplant current practice. Also note that some PCA standing orders primarily generated for postoperative pain management are inadequate for some emergency pain management situations due to the nature of the syndrome being treated. To control a patient's pain crisis, the physician often can require immediate higher doses than allowed by PCA protocols. Lastly, hydroxyzine (not to be given IV), along with other similar agents, can help blunt or block some of the common narcotic adverse reactions by providing anxiolytic, antihistamine, and antispasmodic properties.

Morphine sulfate has a high volume of distribution and is mostly protein bound in the plasma. Liver glucuronidation provides the initial steps in degrading morphine in that only one-third of this plasma protein-bound products remain functionally active. Both parenteral as well as oral formulations are available and widely prescribed. As in most cases, the intravenous route allows for titration, less pain, access for reversibility, and shorter onset time.

Hydromorphone (Dilaudid) has an earlier onset time and shorter therapeutic half-life than morphine. In addition, due to its high solubility and, hence, concentration, it can be given by a subcutaneous route. This imparts significant advantages to the patient as well as to the staff administering the medication. Patients with strict volume restraints who require repeat dosing of narcotics can be treated more easily when given these small volumes of medication.

Propoxyphene (Darvon) is somewhat of a controversial narcotic since patients are exposed to potentially serious side effects without being provided any significant advantages over what currently is available. Toxicity from an overdose is especially challenging to treat and often requires large amounts of naloxone to reverse.[13]

Codeine alone has a fairly classic opiate side effect profile with regard to constipation, nausea, and emesis. Despite this, when in combination with acetaminophen (Tylenol with codeine), it has reasonable efficacy for mild to moderate pain syndromes. Its liquid formulation makes it particularly useful for children who are unable to swallow tablets. Similar to other narcotics, it too has reasonable antitussive properties.

Hydrocodone is a semisynthetic derivative of codeine and is a good analgesic for moderate pain crises. It also comes in a myriad of mixed formulations that might include antiemetics, antihistamines, decongestants, and expectorants, to name a few. When hydrocodone is combined with acetaminophen or other NSAIDs, it becomes quite effective because mechanistically the analgesic effects are working through two different pathways. This synergy or coanalgesia also allows for less individual drug toxicity since in theory the patient might receive pain relief at lower doses than if either one drug was used alone.

The effects of Tramadol (Ultram) primarily are mediated via mu receptors. Although some patients believe that it is not a narcotic, it does indeed have some tolerance, dependence, and toxicity profiles consistent with traditional narcotics. It characteristically has underperformed in pain management when compared to combination medications such as NSAIDs and narcotics (hydrocodone/acetaminophen or aspirin/codeine). Lastly, tramadol has to be given special consideration since it also causes monoamine reuptake inhibition. Given its risk profile and less-than-ideal efficacy for moderate or severe pain management, tramadol has not been shown to have a well-defined role in emergency medicine.[9]

Meperidine (Demerol) first was synthesized in 1939 but has become the most widely used narcotic in the United States. It has one-eighth the potency of morphine and does have oral and parenteral formulations. It has several shortcomings when compared to morphine and other narcotics. From a cardiovascular standpoint, meperidine has atropine-like and negative inotropic effects. It lacks the antitussive effects that are provided by codeine and morphine. In addition, meperidine can have a marked histamine release. Administering meperidine when a patient currently is taking a (MAOI) or a selective serotonin reuptake inhibitor (SSRI) is a recipe for toxicity. Lastly, meperidine is readily metabolized to the not only toxic, but also therapeutic, metabolite normeperidine. Its therapeutic half-life is 30 hours. The CNS toxicity can present with nervousness, hallucinations, psychosis, and status epilepticus.

Fentanyl (Sublimaze) is a near-ideal narcotic for acute pain management for several reasons. It is a highly concentrated substance that has a very similar profile to that of the prototype morphine except that it has a much shorter therapeutic half-life (90 minutes) and is safer. It is almost entirely metabolized by the liver. Fentanyl has no histamine-releasing effects found commonly with other narcotics. In addition, it causes no myocardial depression. Other than the usual narcotic side effects, one of its unique disadvantages is that, if given too rapidly and at higher end initial doses, it can cause muscle rigidity. This side effect is not easily reversed since it does not mechanistically follow the mu receptor pathway. Avoidance is the best way to preventing it from occurring. If it does occur, supportive care and time are the best and only therapies. One other disadvantage is that since it has such a relatively short therapeutic half-life, the clinician needs to recall that rebound pain or having gaps in pain control is a suboptimal method of pain management.

The agonist-antagonist group includes medications such as butorphanol (Stadol) and nalbuphine (Nubain). These agents exercise their therapeutic effect by antagonizing the mu receptors and stimulating the kappa receptors. Their theoretical strengths rest in the fact that respiratory drive and addiction control centers are not directly impacted. Note that although receptor physiology might suggest this to be true, patients are naturally much more complex and abuse potential and toxic overdose still are possible. This class of medications has not been well studied in the emergency medicine literature. One major disadvantage to these agents, in

this author's opinion, is that if a patient is not forthcoming regarding his or her narcotic use or if the medication history was not accurately obtained, then an acute narcotic withdrawal may be precipitated. Lastly, once these medications are used, one is subsequently limited in that using traditional mu receptor narcotics will be rendered ineffective due to the antagonism.

Pediatric pain management deserves some specific discussion, mostly from an educational standpoint. The literature is now replete with evidence about several facts: newborn (neonate) and infant children feel pain; neurological pain pathways have plasticity; toddler and preschool children can describe their pain experience; and children require medication based on weight. Morphine and fentanyl are possibly the narcotics of choice for children. The advantages to IV medication and titration already have been discussed. Synergism or coadjunctive therapy with anxiolytics is powerful but requires vigilance in maintaining skills to optimize therapeutic effects without exposing the child to potentially serious toxicity. Sleep-inducing agents or medications that cause sleepiness are not analgesics and should be used sparingly if at all when administering narcotics.[14-17]

Pediatric patients have therapeutic as well as toxic responses based on the plasma concentrations of the narcotic administered. This in turn directly is related to the liver degradation and/or plasma clearance properties of the medication. The majority of children being treated for acute painful conditions are not preterm or neonate babies, nor do they have liver or kidney disease. The total plasma clearance is age-dependent and as follows: preterm infants 0.5-3 mL/kg/min; preschool children 20-40 mL/kg/min; and adults 10-20 mL/kg/min. Therefore, other than the neonate, children and adolescent patients have equal or higher plasma clearance rates than adults and hence are at no higher risk for narcotic toxicity. This would suggest that due to plasma clearance, increased cardiac output, decreased circulation time, and increased muscular vascularity, that usual starting doses such as morphine 0.1 mg/kg or fentanyl 2 mcg/kg are possibly low doses for acute pain crisis management.[18]

Pain Assessment and Response: Patient/Provider

A patient's pain response is dependent on prior experiences, age, and even gender. A health care provider might find a 27 guage needle puncture to be minor and yet a patient of the same age and gender who is not a health care worker might find it unbearable. In addition, cultural differences, emotional states, and the nature of the injury or illness also play a role in the final pain response. When the patient's appearance, behavior, and personal characteristics are factored in, there is a very complex and unique pain response. The limbic system plays a significant role in inhibition or heightening of these final responses. Note that patients might find a bladder mini-catheterization and an IV catheterization equally painful but the former causes much more distress—anxiety, embarrassment, and fear. Lastly, physiologic parameters such as heart rate, respiratory rate, skin exam, blood pressure are extremely patient-dependent and can vary further with different injury or illness states.[16,19,20]

Some patients may be so agitated by their pain crisis that their pain management becomes the center of their emergency department evaluation and treatment. Other patients are reluctant to ask or complain about their pain syndromes. They might, in fact, choose not to bother staff, to accept their pain as a natural part of their condition, to believe that other much sicker patients need care, to be too proud to complain, or to believe that this what they deserve. Furthermore, once analgesic treatment has begun, patients vary even more in their expectations of how and when the medication is supposed to work.

Patient ethnicity and pain management has become a hotbed of research and discussion. Appropriate assessment tools and retrospective analyses probably have made some of these studies less than ideal but nevertheless bring the subject matter to the forefront. Several investigators have described some differences in analgesic treatment patterns among health care workers given differences in patient ethnicity. The striking similarity among several of these studies is that most patients were under-treated for their illness or injury. Once again, the difficulty has been in conducting a study that looks specifically at patient and provider pain assessments before and after treatment. In addition, one would have to account for disparity that exists in language, culture, region, provider characteristics, and patient characteristics.[21-23]

So how can providers better treat their patients' painful conditions? The literature is less than forthcoming in stating the "how to?" Patient education should focus on the importance of treatment and that analgesia plays a key role toward their healing, recovery, and overall health. Just as important is for providers to be educated as to safety, monitoring, assessment, and some basic pharmacokinetics of the medications prescribed. Less tangible and yet just as important provider issues would include understanding that there is not one appropriate pain behavior, understanding that providers are likely to underestimate a patient's pain level, being aware that patients can experience a real emotional component to their painful condition, and discounting statements such as "opiates are inappropriate unless patients are in severe pain."

Pediatric patients have a traditional pain pathway response in that they sequentially go through perception, interpretation, and expression. Within that context their responses vary depending on their developmental level. Recall that behavioral as well as physiologic response has been studied in preterm, neonate, infant, toddler children. Within one week of life, whether premature or not, children can differentiate degrees of invasiveness of procedures. In addition, their behavioral and physiologic responses may or may not be in parallel, depending on the procedure. The literature has not been able to define clearly whether or not normal consciousness and complete myelination occurs simultaneously or even in parallel. Degree of neuroplasticity does exist because some children have reflexive memory (Pavlov) and yet others can alter their pain response positively or negatively if a parent is present or not. Older infants and toddlers have mostly reflexive total body responses that can be stereotypical, anger based, but is most commonly withdrawal. Preschool children keenly recognize strangers, restraint, and separation.

They experience guilt, anxiety, and punishment. Older, school-age children need to feel in control, have general body awareness, can fantasize, and are cognitively more developed. Adolescent patients (Piaget) can develop more formal operations such as thought, reason, and socialization. They may lack more mature coping skills, but due to their articulate language skills, can fool the health care provider into believing they are more prepared for the pain crisis.[14,17,24-26]

Scales and Scores

The available list for pain scales or scores is lengthy. Their reliability and validity have been studied to some degree, depending on the population and scientist testing the scale. The visual analog scale (VAS) is one commonly accepted and utilized scale but others do exist: numerical descriptor scale (NDS), numerical rating scale (NRS), word descriptor scale (WDS), verbal rating scale (VRS), and facial descriptor scale (FDS). Several validation studies have found that independent of adult age, gender, and etiology of painful condition, clinically relevant differences in pain scales occurred with changes in about 16 mm (0-100 mm), 1.6 cm (0-10 cm), or 2 (VAS 0-10). In choosing the right scale, individual patient characteristics and capabilities such as mental status, visual perception, language skills, and literacy will impact the success of the scale in establishing the most correct score. A provider asking the patient for a number between 0-10 and the patient responding in some format seems to have the highest success rate in obtaining what the patients believe to be their current pain score. Children, too, have been evaluated on scales. They require different scales that are developmentally appropriate. Preschool and school age children have the ability to comprehend stair-step or rank scales and, if solicited, can contribute an amazing amount of detail about their pain crisis. In addition, parental VAS or VDS contribute little to the child's assessment. In fact, their scores tend to overestimate the child's score. Health care workers, as with adult patients, tend to underestimate a child's pain score.[19,23,26-31]

Patient Satisfaction and Pain Control

Several investigators have pursued the link between pain management and patient satisfaction. This is an ambitious undertaking given that pain assessment is fairly subjective and patient satisfaction is very subjective. The latter requires that patients' perceptions and expectations be addressed in some manner. Although pain relief alone will not dictate a patient's satisfaction with pain management, a moderate linear relationship does exist between pain relief and patient satisfaction. In fact, a threshold change in pain score probably exists that would impact a patient's satisfaction regardless of the raw score is 2/10, 5/10, or even 7/10 at the start. In other words, some patients can be very satisfied with their pain management even if they are dispositioned from the emergency department in moderate pain—a goal this author would not advocate. Even scripting has a role in patient satisfaction with regard to pain management. Despite patients being in moderate pain they felt that as long as their clinician demonstrated concern in statement and action about the painful condition, they were very satisfied with their overall pain management. It seems likely that pain relief alone is loosely correlated with patient satisfaction but that the concern and action of taking care of a patient's painful condition, even if not very successful, is more important when addressing patient satisfaction.[6,27,32]

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Physician CME Questions

To earn CME credit for this activity, you must return the enclosed evaluation form and fax it to 1-800-850-1232.

1. Which of the following is the most accurate in describing a common pathway for stimulus generation, propagation, and transmission?
   A. A chemical reaction occurs peripherally whereby local vasoactive mediators are released and affect their control at the spinal and cortical levels.
   B. Following electrical impulses, a cascade of events takes place locally that initiates a fixed response at the spinal cord, cortex, and periphery.
   C. A local stimulus almost always relays information to the cortex, requiring some kind of peripheral response.
   D. A significant local stimulus not only creates a local chemical reaction but also an electrical impulse that is attenuated/inhibited at multiple levels along the arc thru the central nervous system.

2. Which of the following statements about adjuvants/coanalgesics is most accurate?
   A. Nitrous oxide is an excellent adjuvant for pain control because it is easily administered, requires minimal caretaker involvement, and has endorphin agonist properties.
   B. The muscle relaxants are widely marketed and prescribed because their mechanism of activity has been elucidated and their side effect profile is very favorable.
   C. The use of NSAIDs and opioids makes sense since pain production could involve both arachidonic acid as well as mu receptor pathways.
   D. Since xylocaine (Lidocaine) has a proven safety record at multiple doses and has an antidote, it can be administered without much concern for toxicity.

3. Which of the following best describes ketamine's strengths during procedural sedation?
   A. Patients can safely self-administer this agent via a mask and because of its lipophilic characteristic it is readily turned on and off.
   B. Its GABA effects make it particularly well suited for alleviating anxiety typically associated with procedures.
   C. Rarely will a clinician require an adjunct when employing ketamine because at therapeutic doses it is a very effective dissociative agent.
   D. It is a highly titratable substance that mechanistically works similar to propofol.

4. Which of the following statements regarding narcotic opioids is most accurate?
   A. Naloxone (Narcan) is the antidote of choice for reversing the histamine effects often seen with narcotic administration.
   B. Normeperidine is the toxic metabolite of meperidine (Demerol) that accumulates with repeat dosing.
   C. Fentanyl is the prototypical agonist-antagonist agent that has a relatively long therapeutic half-life.
   D. Hydromorphone (Dilaudid) is commonly used as an intramuscular narcotic because it is highly concentrated and has mild anesthetic properties.

5. With regard to the clinician's ability to assess patient's pain, which of the following is most accurate?
   A. In assessing a preschool child's pain score, it is most accurate to average the scores of the child's parent(s) and the nurse.
   B. Patients who exhibit fear or anger responses to their painful conditions are generally unable to quantify their pain score and hence physiologic indicators become the next best predictors.
   C. All health care workers can agree that renal colic is a painful condition and, hence, patients with this condition should receive a standard dose of narcotics early on during their evaluation.
   D. With developmentally appropriate scales, clinicians now have fairly reliable and valid tools with which to assess a patient's pain score.

CME Answer Key:
1. D; 2. C; 3. C; 4. B; 5. D

Emergency Medicine Specialty Reports
CME Objectives

To help physicians:
- understand acute pain in the emergency department setting;
- identify agents for acute pain control;
- identify the factors involved in a patient's pain response.

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