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Community-Acquired Pneumonia (CAP) Antibiotic Selection and Management Update

Part II: Evaluation, Risk Stratification, and Current Antimicrobial Treatment Guidelines for Hospital-Based Management of CAP: Outcome-Effective Strategies Based on New National Committee on Clinical Laboratory Standards (NCCLS) Breakpoints and Recent Clinical Studies

—ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) 2002 Consensus Report

Author: **Gideon Bosker, MD, FACEP**, Assistant Clinical Professor, Section of Emergency Services, Yale University School of Medicine, Associate Clinical Professor, Oregon Health Sciences University, Portland.

Peer Reviewers: **Steven M. Winograd, MD, FACEP**, Attending Physician, Emergency Department, Jeannette District Memorial Hospital, Jeannette, PA, St. Clair Memorial Hospital and University of Pittsburgh Medical Center, Pittsburgh, PA; **James A. Wilde, MD, FAAP**, Assistant Professor, Emergency Medicine and Pediatrics, Research Director, Department of Emergency Medicine, Medical College of Georgia, Augusta.

Rational antibiotic decision-making derives from a simple formula: "Use those agents that will cure the patient today and protect the community against antimicrobial resistance tomorrow." Easier to articulate than implement, this "cure and protect" approach to antibiotic selection requires clinicians to select agents that predictably will be active against the expected suite of pathogens causing a particular infection, but without over-extending antibacterial activity to include unlikely pathogens, and in the process, exert unnecessary pressure against organisms that could develop resistance in the future.

Because emergency physicians are responsible for selecting the initial antibiotic regimen for most hospitalized patients with community-acquired pneumonia (CAP), their decisions play an important role in determining clinical success as well as institutional drug resistance patterns. Moreover, it has become clear that the outcomes in patients with CAP can be maximized by using risk-stratification criteria that predict mortality associated with CAP. Associated clinical findings such as hypotension, tachypnea, impaired oxygen saturation, multi-lobar involvement, elevated blood urea nitrogen, and altered level of consciousness are predictive of more serious disease, just as age and acquisition of CAP in a nursing home environment are. These factors may assist emergency physicians in the initial selection of intravenous (IV) antibiotic therapy for hospitalized patients.

In light of important advances, changes, and refinements that have occurred in the area of CAP treatment during the past year—in particular, the introduction of 2002 National Committee on Clinical Laboratory Standards (NCCLS) minimum inhibitory concentration (MIC) breakpoint revisions for ceftriaxone and cefotaxime for treatment of non-meningeal infections caused by Streptococcus pneumoniae*—the authors of this comprehensive review present an evidence-based and updated set of guidelines outlining*

CAP management for the year 2002. Treatment recommendations issued by the Infectious Disease Society of America (IDSA), American Thoracic Society (ATS), and the ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) 2002 Consensus Panel are analyzed for their implications on emergency medicine practice and presented in detail; evidence supporting "cure today, protect tomorrow" treatment guidelines for a wide range of patient subgroups with CAP are outlined in tabular format so they can be incorporated into clinical practice and critical pathways.

Special emphasis has been given to both epidemiological data demonstrating the importance of correct spectrum coverage with specific cephalosporins (ceftriaxone) in combination with a macrolide (azithromycin), or as an alternative, monotherapy with an advanced generation fluoroquinolone (moxifloxacin). The potential for development of antimicrobial resistance through overuse of antibiotics belonging to specific drug classes is highlighted. Finally, the potential benefits of two-drug vs. monotherapeutic (single) drug regimens for treatment of elderly patients with severe CAP associated with Streptococcal bactermia is presented.

—The Editor

ASCAP Consensus Panel Recommendations for Outpatient Management

Despite a general consensus that empiric, outpatient treatment of CAP requires, at the least, mandatory coverage of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis,* as well as atypical organisms (e.g., *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila*), antibiotic selection strategies for achieving this spectrum of coverage vary widely. New treatment guidelines for CAP have been issued by such national associations as the IDSA (2000), the ATS (2001), and the Centers for Disease Control and Prevention Drug-Resistant *Streptococcus pneumoniae* Working Group (CDC-DRSPWG) (2000).

Deciphering the strengths, subtleties, and differences among recommendations issued by different authoritative sources can be problematic and confusing. Because patient disposition practices and treatment pathways vary among institutions and from region to region, management guidelines for CAP in the geriatric patient must be "customized" for the local practice environment. Unfortunately, no single set of guidelines is applicable to every patient or practice environment; therefore, clinical judgment must prevail. This means taking into account local antibiotic resistance patterns, epidemiological and infection incidence data, and patient demographic features.

Patient Management Recommendations. The ASCAP 2002 Consensus Panel concurred that appropriate use of antibiotics requires radiographic confirmation of the diagnosis of CAP. In this regard, physicians should use clinical judgment when ordering chest x-rays, with the understanding that the diagnostic yield of this radiographic modality in CAP is increased in patients with fever greater than 38.5°C; presence of a new cough; and abnormal pulmonary findings suggestive of consolidation, localized bronchoconstriction, or pleural effusion.

Accordingly, a chest x-ray is recommended and encouraged by the ASCAP Consensus Panel, as well as by such national associations as the IDSA, ATS, and American College of Emergency Physicians (ACEP), to confirm the diagnosis of outpatient CAP; however, the panel acknowledges that, on occasion, logistical issues may prevent radiographic confirmation at the time of diagnosis and treatment.

The approach to antibiotic therapy usually will be empiric, and must account for a number of clinical, epidemiological, and unpredictable factors related to antibiotic resistance patterns and respiratory tract pathogens. As a general rule, appropriate antibiotic choice for the patient with CAP requires consideration of strategies that will yield clinical cure in the patient today, combined with antibiotic selection strategies that prevent accelerated

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Editorial Group Head: Valerie Loner
Specialty Editor: Shelly Morrow
Marketing Manager: Schandale Kornegay
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emergence of drug-resistant organisms that will infect the community tomorrow.

Based on the most current clinical studies, the principal six respiratory tract pathogens that must be covered on an empiric basis in individuals with outpatient CAP include: *S. pneumoniae, H. influenzae, M. catarrhalis, C. pneumoniae, M. pneumoniae,* and *L. pneumophila.* In addition, the ASCAP Consensus Panel emphasized that there may be a "disconnect" (i.e., an incompletely understood and not entirely predictable relationship between an antibiotic's MIC level and its association with positive clinical outcomes in CAP). This "disconnect" may be explained by the unique qualities of an antimicrobial, such as tissue penetration and/or pharmacokinetics, patient medication compliance, and other factors.

Double-blinded, prospective clinical trials comparing new generation macrolides vs. new generation fluoroquinolones demonstrate similar outcomes in terms of clinical cure and bacteriologic eradication rates in outpatients with CAP.[1] However, emergence of resistance among *S. pneumoniae* species to new generation fluoroquinolones has been reported in several geographic regions, including the United States, Hong Kong, and Canada, and this may have implications for treatment.

The frequency of drug-resistant *S. pneumoniae* (DRSP) causing outpatient CAP, as estimated by the CDC, is very low (i.e., in the range of 0.14-1.9%). The CDC-DRSPWG cautions against overuse of new generation fluoroquinolones in outpatient CAP, and recommends their use as alternative agents when: 1) first-line therapy with advanced generation macrolides such as azithromycin fails; 2) patients are allergic to first-line agents; or 3) the case is a documented infection with DRSP.[2]

Given concerns about antibiotic overuse, the potential for emerging resistance among DRSP to fluoroquinolones, and the increasing recognition of atypical pathogens as causative agents in patients with outpatient CAP, the panel concurs with the CDC-DRSPWG recommendation advocating macrolides as initial agents of choice in outpatient CAP. The ASCAP Consensus Panel also noted that the Canadian Consensus Guidelines for CAP Management and the 2001 ATS Consensus Guideline Recommendations also include advanced generation macrolides as initial therapy for outpatient CAP.

In this regard, two safe and effective advanced generation macrolides, azithromycin and clarithromycin, currently are available for outpatient, oral-based treatment of CAP (IV azithromycin also is indicated for in-hospital management of patients who are risk-stratified as having more serious diseases). Based on outcome-sensitive criteria such as cost, daily dose frequency, duration of therapy, side effects, and drug interactions, the ASCAP Consensus Panel recommends azithromycin as first-line, preferred initial therapy in CAP, with clarithromycin or doxycycline as an alternative agents; and moxifloxacin, gatifloxacin, or levofloxacin as second-line therapy when appropriate, according to CDC guidelines and other association-based protocols. Among the advanced generation fluoroquinolones, moxifloxacin is preferred by the ASCAP Consensus Panel because it has the most favorable MICs against *S. pneumoniae,* and a more focused spectrum of coverage against gram-positive organisms than levofloxacin or gatifloxacin.

Physicians are urged to prescribe antibiotics in CAP at the time of diagnosis and to encourage patients to fill and begin taking their prescriptions for CAP on the day of diagnosis. Ideally, patients should initiate their first course of oral therapy within eight hours of diagnosis, a time frame that appears reasonable based on studies in hospitalized patients indicating improved survival in patients who received their first IV dose within eight hours of diagnosis. Physicians also are urged to instruct patients in medication compliance, and in the case of short (five-day) courses of therapy, educate their patients that, although they are only consuming medications for a five-day period, the antibiotic remains at the tissue site of infection for about 7-10 days and continues to deliver therapeutic effects during that period.

Either verbal or on-site, reevaluation of patients is recommended within a three-day period following diagnosis and initiation of antibiotic therapy. Follow-up in the office or clinic within three days is recommended in certain risk-stratified patients, especially the elderly, those with co-morbid illness, and those in whom medication compliance may be compromised. More urgent follow-up may be required in patients with certain increasing symptoms, including dyspnea, fever, and other systemic signs or symptoms. Follow-up chest x-rays generally are not recommended in patients with outpatient CAP, except in certain high-risk groups, such as those with right middle lobe syndrome, and in individuals in whom the diagnosis may have been uncertain.

In-Hospital Management of CAP—Monotherapy vs. Combination Therapy: Outcomes Analysis and ASCAP Treatment Guidelines

As emphasized earlier, prompt administration of IV antibiotics in the emergency department (ED) can improve clinical outcomes in patients with CAP. Consequently, once diagnostic tests, including cultures and radiographs (when appropriate), have been performed, initial antibiotic therapy for hospitalized patients should be administered in the ED, especially if delays in getting the patient admitted are anticipated.

Although antibiotic recommendations based on risk-stratification criteria, historical features, sites where the infection was acquired, and other modifying factors play a role, institutional protocols, hospital-based critical pathways, resistance features, and other factors also will influence antibiotic selection. Despite variations in hospital or departmental protocols, certain requirements regarding drug selection for CAP are relatively consistent.

When combination cephalosporin/macrolide therapy is the accepted hospital protocol, among the beta-lactams available, IV ceftriaxone is recommended by the ASCAP 2002 Consensus Panel because of its evidence-based efficacy in moderate to severe CAP, once-daily administration, and spectrum of coverage, and because it is supported by all major guideline panels. One study evaluated antibiotic resistance using data derived from community-based medical practices. Data were gathered from July 1999 to April 2000. Four of the most common isolates were:

M. catarrhalis (27%), *H. influenzae* (25%), *Staphylococcus aureus* (14%), and *S. pneumoniae* (12%); atypical organisms were not assessed.

Among *S. pneumoniae* isolates, levofloxacin exhibited a 4.8% level of resistance; for ceftriaxone, the resistance rate was only 5.8% (based on pre-2002 NCCLS MIC breakpoint). For *Staphylococcus aureus,* both ceftriaxone and levofloxacin inhibited all isolates. And for *M. catarrhalis* and *H. influenzae,* no resistance was observed for either levofloxacin or ceftriaxone. The investigators concluded that levofloxacin and ceftriaxone exhibited equivalent susceptibility/resistance patterns to organisms encountered in CAP.[3]

Although ceftriaxone was introduced to the market in 1985, and despite 18 years of use, its susceptibility to multiple gram-positive and gram-negative isolates has not changed significantly. In this regard, ceftriaxone has retained potent activity against the most commonly encountered enteric species (i.e., *Escherichia coli, Klebsiella pneumoniae, Klebsiella xytocia,* and *Proteus mirabilis*), at a level of 93-99%.[3]

Azithromycin is recommended as the co-therapeutic macrolide agent (i.e., in combination with ceftriaxone) in patients with CAP for the following reasons: 1) it can be administered on a once-daily basis, thereby minimizing human resource costs associated with drug administration; 2) it is the only macrolide indicated for in-hospital, IV-to-oral step-down, monotherapeutic management of CAP caused by *S. pneumoniae, H. influenzae, M. catarrhalis, L. pneumophila, M. pneumoniae, C. pneumoniae,* or *S. aureus*—an important efficacy and spectrum of coverage benchmark; 3) at $19-22 per day for the IV dose of 500 mg azithromycin, its cost is reasonable; 4) the IV-to-oral step-down dose of 500 mg has been established as effective in clinical trials evaluating hospitalized patients with CAP; and 5) azithromycin has excellent activity against *L. pneumophila,* a pathogen commonly implicated in the geriatric patient with CAP. The decision to use azithromycin as a monotherapeutic agent, or in combination with a cephalosporin for initial therapy of CAP, will be determined by intrainstitutional pathways and protocols, based on consensus recommendations and association guidelines as presented in this article.

Critical Pathways and Protocols. When patients with CAP are hospitalized in the intensive care unit (ICU) or there is a significant likelihood of gram-negative infection (i.e., *Klebsiella, E. coli,* or *Pseudomonas aeruginosa*), monotherapy with a macrolide is not appropriate, and the CDC-DRSPWG's recent consensus report stresses the importance of using an IV macrolide in combination with other agents—in particular, third-generation cephalosporins such as ceftriaxone.[4] In these patients, a macrolide should be used in combination with a cephalosporin (i.e., ceftriaxone), and when anti-pseudomonal coverage is necessary, an anti-pseudomonal cephalosporin and/or an aminoglycoside also may be required. Alternatively, an extended spectrum fluoroquinolone such as levofloxacin should be considered, although combination therapy that includes a cephalosporin such as ceftriaxone also has been advocated with this agent in severely ill patients.[4] When anaerobic organisms are suspected, clindamycin or a beta-lactam/beta-lactamase inhibitor is appropriate.

Accordingly, a number of critical pathways for pneumonia therapy recommend use of two-drug therapy for CAP. The therapy typically is the combination of an IV cephalosporin such as ceftriaxone plus a macrolide, which usually is administered, initially, by the IV route when the patient's condition so warrants. Perhaps the important change in CAP treatment since publication of the ATS guidelines in 1993 is the current general consensus, including guidelines presented at the 2001 ATS Scientific Conference, that atypical organisms such as *L. pneumophila, C. pneumoniae,* and *M. pneumoniae* must be covered empirically as part of the initial antibiotic regimen. Whereas previous consensus guidelines indicated that macrolides could be added to a cephalosporin on a "plus-or-minus" basis for initial CAP treatment, it now is felt that coverage of the atypical spectrum, along with coverage of *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* is mandatory.[2] New guidelines from the IDSA, ATS, ASCAP, and CDC now reflect this strategy.

Although virtually all protocols using combination cephalosporin/macrolide therapy specify IV administration of the cephalosporin, guidelines specifying whether initial macrolide therapy should occur via the IV or oral route are less concrete. Recent CDC-DRSPWG guidelines recommend an IV macrolide therapy for patients hospitalized in the ICU, while oral therapy is permissible in conjunction with an IV cephalosporin in the medical ward patient.[4] Because atypical infections such as *L. pneumophila* are associated with high mortality rates, especially in the elderly, and because hospitalized patients with CAP, by definition, represent a sicker cohort, it is prudent and, therefore, advisable that initial macrolide therapy in the hospital be administered by the IV route. The ASCAP Consensus Panel, therefore, recommends IV azithromycin therapy as the preferred initial, empiric agent in combination with ceftriaxone. The Panel acknowledges, however, that some institutions will use IV ceftriaxone in combination with an oral macrolide in non-ICU patients, an approach supported by a number of national panels. In patients on combination cephalosporin/macrolide therapy, step-down to oral therapy with azithromycin can be accomplished when the patient's clinical status so dictates, or when culture results suggest this is appropriate.

Monotherapy vs. Combination Therapy. It should be pointed out that while some consensus panels (ATS Guidelines, 2001) support the use of IV azithromycin monotherapy in very carefully selected hospitalized CAP patients (i.e., those with mild disease), other panels, such as CDC-DRSPWG and the IDSA 2000 Guidelines, support its use specifically as the macrolide component of combination therapy (i.e., to be used in combination with such agents as ceftriaxone).

As emphasized, advanced generation fluoroquinolones also provide a monotherapeutic option for management of CAP, and advocates of this approach argue that these agents, on an empiric basis, provide an adequate spectrum of coverage against expected respiratory pathogens at lower drug acquisition costs. Other experts make the case that although monotherapy for pneumococcal pneumonia is standard practice in many institutions, and is identified as a treatment option in many national association

guidelines, there may be a survival benefit from using a combination beta-lactam and macrolide therapy.[5] To address this issue, a group of investigators evaluated a patient database to determine whether initial empirical therapy with a combination of effective antibiotic agents would have a better outcome than a single effective antibiotic agent in patients with bacteremic pneumococcal pneumonia.

The investigators conducted a review of adult bacteremic pneumococcal pneumonia managed in the Methodist Healthcare System, Memphis, TN, between Jan. 1, 1996, and July 31, 2000. Empirical therapy was defined as all antibiotic agents received in the first 24 hours after presentation. On the basis of culture results, empirical therapy was classified as single effective therapy (SET), dual effective therapy (DET), or more than DET (MET). Acute Physiology and Chronic Health Evaluation II (APACHE II)-based predicted mortality (PM), and Pneumonia Severity Index (PSI) scores were calculated.[5]

Two hundred twenty-five subjects met the inclusion criteria for analysis. An additional seven cases of CAP with pneumococcal bacteremia were identified but were excluded from the study because the isolate was resistant to the empirical therapy the patients received. Investigators noted that the subjects who received MET were significantly sicker than the subjects who received SET or DET, as measured by the PSI (P = 0.04) and APACHE II-based PM (P = 0.03). Of special significance was the fact that there was no statistically significant difference in the prevalence of chronic disease states between the SET and DET groups.

Levofloxacin was the most commonly chosen fluoroquinolone (70.4%), with only four subjects treated with ciprofloxacin (one in the SET group, two in the DET group, and one in the MET group, all with no fatalities). Eight subjects who received more than one antibiotic agent as empirical therapy were classified as SET on the basis of the isolate being resistant to azithromycin (five subjects), cefotaxime (two subjects), or combined ticarcillin-clavulanate potassium (one subject). Twenty-nine subjects (12.9%) died. A Kaplan-Meier plot of mortality over time for each antibiotic therapy group demonstrated that mortality with the SET group was significantly higher than with the DET group (P = 0.02; odds ratio [OR], 3.0 [95% confidence interval (CI), 1.2-7.6]). Even when the DET and MET groups are combined, the mortality still was significantly higher in the SET group (P = 0.04; OR, 2.3 [95% CI, 1.0-5.2]). Because only a few subjects received MET and the subjects who received MET were significantly sicker than the other subjects, subsequent analysis is confined to the SET and DET groups.

Because subjects who received SET had a lower PM than those who received DET, a logistic regression model was used to calculate the OR for death of SET vs. DET adjusted for PM, which was 6.4 (95% CI, 1.9-21.7). All deaths occurred in patients with a PSI score higher than 90 (PSI classes IV and V). In subjects with PSI class IV or V CAP who were given SET, the PM-adjusted OR for death was 5.5 (95% CI, 1.7-17.5). Because antibiotic therapy would be expected to have little influence on early deaths, the investigators reanalyzed SET vs. DET groups after excluding all deaths that occurred within 48 hours of presentation (n = 4, 3 in the SET group and 1 in the DET group). Univariate analysis of this subgroup showed a trend to better outcome with DET compared with SET (94% survival vs 85%, respectively; P = 0.06). Multivariate analysis again confirmed that SET was an independent predictor of worse outcome (P = 0.01), with the PM-adjusted odds ratio for death in subjects given SET being 4.9 (95% CI, 1.6-18.3). Subgroup analysis did not show any significant trends to suggest any advantage or disadvantage of any specific antibiotic agents or combinations of antibiotic agents within the SET or DET groups.

While acknowledging its limitations, the results of this retrospective study strongly suggest that bacteremic patients with pneumococcal CAP who receive at least two effective antibiotic agents within the first 24 hours after presentation to a hospital have a significantly lower mortality than patients who receive only one effective antibiotic agent. In fact, among high-risk patients (PSI classes IV or V), receiving only one effective antibiotic agent increases mortality by more than five-fold as compared with patients receiving two effective antibiotic agents. Although these findings need to be confirmed by a prospective study, the authors suggest that current approaches to the empirical therapy of severe CAP may need to be reevaluated.[5] Accordingly, the ASCAP 2002 Consensus Panel evaluated this study and found its results and conclusions—as well as its clinical implications—to be sufficiently compelling to recommend combination therapy with ceftriaxone plus a macrolide as the initial approach-of-choice in managing moderately to severely ill patients suspected of having bacteremia associated with pneumococcal pneumonia.

Extended Spectrum Fluoroquinolones: Intensification of Coverage and Patient Selection

The extended spectrum quinolones moxifloxacin, levofloxacin, and gatifloxacin are indicated for treatment of CAP. Each of these agents is available as an oral and IV preparation. Quinolones have been associated with cartilage damage in animal studies. They are not approved for use in children, adolescents, and pregnant and nursing women.

Moxifloxacin. Among the new fluoroquinolones, moxifloxacin has the lowest MICs against *S. pneumoniae* and more specific gram-positive coverage; therefore, it is recommended by the ASCAP Consensus Panel as the fluoroquinolone of choice—when a fluoroquinolone is indicated—for managing patients with CAP. Moxifloxacin generally is well-tolerated. In clinical trials, the most common adverse events were nausea (8%), diarrhea (6%), dizziness (3%), headache (2%), abdominal pain (2%), and vomiting (2%). The agent is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any quinolone antibiotic. The safety and effectiveness of moxifloxacin in pediatric patients, young adults (older than age 18 years), pregnant women, and lactating women have not been established.

Although reports of clinical problems are rare, moxifloxacin has been shown to prolong the QTc interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QTc interval, patients with uncorrected

hypokalemia, and patients receiving Class lA (e.g., quinidine, procainamide) or Class lll (e.g., amiodarone, sotalol) antiarrhythmic agents due to the lack of clinical experience with the drug in these patient populations. Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QTc interval, including cisapride, erythromycin, antipsychotics, and tricyclic antidepressants, have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded; therefore, moxifloxacin should be used with caution when given concurrently with these drugs.

Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected central nervous system (CNS) disorders or in the presence of other risk factors that may predispose the patient to seizures or lower the patient's seizure threshold.

Gatifloxacin. Gatifloxacin, a broad-spectrum 8-methoxy fluoroquinolone antibiotic, is approved for community-acquired respiratory tract infections, such as bacterial exacerbation of chronic bronchitis (ABE/COPD); acute sinusitis; and CAP. The recommended dose for gatifloxacin is 400 mg once daily for individuals with normal renal function. Dosage adjustment is required in patients with impaired renal function (creatinine clearance less than 40 mL/min).

Gatifloxacin is excreted primarily through the kidneys, and less than 1% is metabolized by the liver. Gatifloxacin may have the potential to prolong the QTc interval in some patients, and due to limited clinical experience, gatifloxacin should be avoided in patients with known prolongation of the QTc interval, in patients with uncorrected hypokalemia, and in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Gatifloxacin should be used with caution when given together with drugs that may prolong the QTc interval (e.g., cisapride, erythromycin, antipsychotics, and tricyclic antidepressants), and in patients with ongoing proarrhythmic conditions (e.g., clinically significant bradycardia or acute myocardial ischemia).

Levofloxacin. Levofloxacin, the S-enantiomer of ofloxacin, is a fluoroquinolone antibiotic that, when compared with older quinolones, also has improved activity against gram-positive organisms, including *S. pneumoniae.* This has important drug selection implications for the management of patients with CAP and exacerbations of chronic obstructive pulmonary disease (COPD). The active stereoisomer of ofloxacin, levofloxacin is available in a parenteral preparation or as a once-daily oral preparation that is given for 7-14 days. Levofloxacin is well-tolerated, with the most common side effects including nausea, diarrhea, headache, and constipation.

Although no significant effect of levofloxacin on plasma concentration of theophylline was detected in 14 healthy volunteers studied, because other quinolones have produced increases in patients taking concomitant theophylline, theophylline levels should be monitored closely in patients on levofloxacin, and dosage adjustments made as necessary. Monitoring also is recommended for patients taking warfarin and quinolones.

When given orally, levofloxacin is dosed once daily, is well-absorbed orally, and penetrates well into lung tissue.[6] It is active against a wide range of respiratory pathogens, including atypical pathogens and many species of *S. pneumoniae* resistant to penicillin.[7,8] In general, levofloxacin has greater activity against gram-positive organisms than ofloxacin and is slightly less active than ciprofloxacin against gram-negative organisms.[9,10]

Levofloxacin is available in both oral and parenteral forms, and the oral and IV routes are interchangeable (i.e., same dose). Levofloxacin generally is well-tolerated (incidence of adverse reactions is less than 7%). Levofloxacin is supplied in a parenteral form for IV use and in 250 mg and 500 mg tablets. The recommended dose is 500 mg IV or orally qd for 7-14 days for lower respiratory tract infections.

Levofloxacin is indicated for the treatment of adults (older than 18 years) with mild, moderate, and severe pulmonary infections, including acute bacterial exacerbation of chronic bronchitis and CAP.[11] It is active against many gram-positive organisms that may infect the lower respiratory tract, including *S. pneumoniae* (including DRSP) and *S. aureus,* and it also covers atypical pathogens, including *C. pneumoniae, L. pneumophila,* and *M. pneumoniae.* It also is active against gram-negative organisms, including *E. coli, H. influenzae, H. parainfluenzae, K. pneumoniae,* and *M. catarrhalis.* Although it is active against *P. aeruginosa* in vitro and carries an indication for treatment of complicated UTI caused by *P. aeruginosa,* levofloxacin does not have an official indication for CAP caused by this gram-negative organism.

Several studies and surveillance data suggest that some newly available, expanded spectrum fluoroquinolones, including levofloxacin (which is approved for PRSP), are efficacious for the treatment of *S. pneumoniae,* including penicillin-resistant strains.[4,12,13] In one study, microbiologic eradication from sputum was reported among all 300 patients with pneumococcal pneumonia treated with oral levofloxacin.[12] In a study of in vitro susceptibility of *S. pneumoniae* clinical isolates to levofloxacin, none of the 180 isolates (including 60 isolates with intermediate susceptibility to penicillin and 60 penicillin-resistant isolates) was resistant to this agent.[13] In addition, a surveillance study of antimicrobial resistance in respiratory tract pathogens found levofloxacin was active against 97% of 9190 pneumococcal isolates and found no cross-resistance with penicillin, amoxicillin-clavulanate, ceftriaxone, cefuroxime, or clarithromycin.

Fluoroquinolones: Resistance Concerns and Over-Extended Spectrum of Coverage. Despite high-level activity against pneumococcal isolates and a formal indication for levofloxacin use in suspected DRSP lower respiratory tract infection, the CDC-DRSPWG recent guidelines do not advocate the use of extended spectrum fluoroquinolones (among them, levofloxacin) for first-line, empiric treatment of pneumonia.

This is because of the following: 1) their broad spectrum of coverage that includes a wide range of gram-negative organisms; and 2) concern that resistance among pneumococci will emerge if there is widespread use of this class of antibiotics. Population-based surveillance in the United States has shown a statistically significant increase in ofloxacin resistance among pneumococcal

isolates between Jan. 1, 1995, and Dec. 31, 1997 (unpublished data, Active Bacterial Core Surveillance, CDC).[4]

The CDC-DRSPWG concerns about inducing fluoroquinolone resistance apply not only to *S. pneumoniae,* but also to other pathogenic organisms.[14,15] Fluoroquinolone use in U.S. hospitals, as measured by inpatient dispensing, is changing over time. Selective pressure exerted by fluoroquinolone use may be related causally to the prevalence of ciprofloxacin-resistant *P. aeruginosa.* In fact, databases support growing concern about emerging fluoroquinolone resistance. In this regard, recent surveillance data indicate that resistance for *P. aeruginosa* to fluoroquinolones is increasing, possibly due to increased use of this drug class.[14,15] To shed light on this possible association, the SCOPE-MMIT network of 35 hospitals tracked inpatient fluoroquinolone dispensing since 1999, and obtained hospital antibiograms to assess for associations between use and resistance rates.

MediMedia Information Technology (MMIT, North Wales, PA) collected data of inpatient-dispensed drugs from each participating hospital information system. Grams of individual fluoroquinolones are converted each quarter to defined daily dose/1000 patient days (DDD/1000PD). Antibiograms testing susceptibility of *P. aeruginosa* to ciprofloxacin were available from 22 hospitals. The relationship between total fluoroquinolone use and percentage resistance for *P. aeruginosa* to ciprofloxacin was assessed by linear regression. Results indicated that total fluoroquinolone use between 1999 and 2001 remained at approximately 140 DDD/1000PD, although mean levofloxacin increased significantly and ciprofloxacin use declined slightly. There was a significant positive relationship between total fluoroquinolone use and resistance to *P. aeruginosa* ($r = 0.54$, $P = 0.01$).

Investigators concluded that mean total fluoroquinolone dispensing in the 35 hospitals studied was stable, although there were significant differences in use between individual fluoroquinolones. It was not yet possible to determine if the relationship was causal or which fluoroquinolones are most likely responsible. The SCOPE-MMIT network will continue to evaluate the quantitative relationships between antibiotic use and resistance as antibiotic use changes over time, and as resistance rates respond to these changes in selective pressure.[14,15]

Fluoroquinolones and MRSA. Methicillin-resistant *S. aureus* (MRSA) represents a persistent problem in antibiotic therapy.[16] There are a variety of well-known risk factors for the development of MRSA in the hospital, including extensive prior broad-spectrum antibiotic use, admission to an ICU, prolonged hospitalization, presence of an indwelling catheter, severe comorbid diseases, surgery, and exposure to MRSA-colonized patients. However, there has arisen a substantial amount of new data that fluoroquinolones are a risk factor for the increase in MRSA. Given the widespread use of oral fluoroquinolones in the community during the past several years, and the increase in community-acquired MRSA, it is prudent to consider the possibility that fluoroquinolone overuse may be associated with increasing emergence of MRSA.[17]

To address this question, one study evaluated prior antibiotic exposure and the development of nosocomial MRSA bacteremia in patients admitted to a 750-bed tertiary care hospital.[17] All patients with nosocomial bacteremias from Jan. 1, 1996, to June 30, 1999, were evaluated. For each patient, investigators documented all antibiotics administered prior to the development of the bacteremia. They performed a case-controlled evaluation comparing fluoroquinolone-exposed patients to non-fluoroquinolone-exposed patients in relation to the development of MRSA bacteremia. A chi-squared analysis and relative risk (RR) were calculated.

A total of 514 nosocomial bacteremias occurred during the study period, with 78 (15%) MRSA cases. The percentage of MRSA bacteremias/nosocomial bacteremias increased from 10% in 1996 to 22% in 1999 ($P < 0.05$). MRSA as a percentage of all *S. aureus* clinical isolates increased from 29% to 40%. Prior fluoroquinolone exposure and MRSA bacteremia rose significantly from 25% of cases in 1986 to 65% of cases in 1999 (40% fluoroquinolone alone and 25% fluoroquinolone and other antibiotics) ($P < 0.05$). Cephalosporin exposure alone and the development of MRSA bacteremia dropped significantly from 50% of cases in 1996 to 0% of cases in 1999 ($P < 0.01$). Overall, 52% of fluoroquinolone-exposed patients developed MRSA bacteremia vs. 8% methicillin-sensitive *S. aureus* (MSSA) bacteremia ($P < 0.05$). In 1996 the RR of fluoroquinolone exposure and the development of MRSA bacteremia was 2.27 (ns), whereas during 1997-99 the RR of fluoroquinolone exposure was significant, ranging from 3.25 to 4.68 ($P < 0.05$). Fluoroquinolone usage increased hospital-wide during the study period.[17]

The study group noted a significant increase in nosocomial MRSA bacteremias in fluoroquinolone-exposed patients and a significant decrease in patients with cephalosporin exposure during the study period. Fluoroquinolone-exposed patients had a 3-4 times greater risk of developing nosocomial MRSA bacteremia than non-fluoroquinolone-exposed patients. Because increasing fluoroquinolone usage may have contributed to the increased selection and development of MRSA bacteremias, the study group implemented policies to limit fluoroquinolone utilization to attempt to control the selection and development of nosocomial MRSA bacteremias in the future.[17]

Selective Fluoroquinolone Use. Based on surveillance data and published studies, the CDC-DRSPWG has recommended that fluoroquinolones be reserved for selected patients with CAP. These experts have identified specific patient subgroups that are eligible for initial treatment with extended spectrum fluoroquinolones. For hospitalized patients, these include adult patients for whom one of the first-line regimens (cephalosporin plus a macrolide) has failed, those who are allergic to the first-line agents, or those who have a documented infection with highly drug-resistant pneumococci (i.e., penicillin MIC = 4 mcg/mL).[18]

Morbidity and Mortality Weekly Report recently reported the increasing levels of fluoroquinolone resistance among *S. pneumoniae*. Ofloxacin-resistance of 3.1% in 1995 had increased to 4.5% in 1997 ($P = 0.02$), whereas levofloxacin-resistance of 0.2% in 1998 was reported to be 0.3% in 1999 (P value not sig-

nificant).[19] The *Morbidity and Mortality Weekly Report* concluded that, "appropriate use of antibiotics is crucial for slowing the emergence of fluoroquinolone resistance."

Empiric Antibiotic Coverage for CAP: Matching Drugs with Patient Profiles

A variety of antibiotics are available for outpatient management of pneumonia. Although the selection process can be daunting, as mentioned, a sensible approach to antibiotic selection for patients with pneumonia is provided by treatment categories for pneumonia generated by the Medical Section of the American Lung Association and published under the auspices of the ATS.[20] This classification scheme helps make clinical assessments useful for guiding therapy, but it also is predictive of ultimate prognosis and mortality outcome.

The most common pathogens responsible for causing CAP include the typical bacteria: *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* as well as the atypical pathogens: *Mycoplasma, Legionella,* and *Chlamydia pneumoniae*.[21] *H. influenzae* and *M. catarrhalis* both are found more commonly in patients with COPD. Clinically and radiologically, it is difficult to differentiate between the typical and atypical pathogens; therefore, coverage against all of these organisms may be necessary. In patients producing sputum containing polymorphonuclear leukocytes, the sputum Gram's stain may contain a predominant organism to aid in the choice of empiric therapy. For most patients, therapy must be entirely empiric and based on the expected pathogens.[22,23]

Therefore, for the vast majority of otherwise healthy patients who have CAP but who do not have comorbid conditions and who are deemed well enough to be managed as outpatients, therapy directed toward *S. pneumoniae, H. influenzae, M. pneumoniae, C. pneumoniae, L. pneumophila,* and *M. catarrhalis* is appropriate. From an intensity and spectrum of coverage perspective, coverage of both the aforementioned bacterial and atypical species has become mandatory.

In these cases, one of the newer macrolides should be considered one of the initial agents of choice. The other monotherapeutic agents available consist of the extended spectrum quinolones, which provide similar coverage and carry an indication for initial therapy in this patient subgroup.

For the older patient with CAP who is considered stable enough to be managed as an outpatient, but in whom the bacterial pathogen list also may include gram-negative aerobic organisms, the combined use of a second- or third-generation cephalosporin or amoxicillin-clavulanate plus a macrolide has been recommended. Another option may consist of an advanced generation quinolone.

Some experts emphasize that in non-smoking adults without COPD (i.e., patients at a low risk for having *H. influenzae*), therapy with erythromycin should be strongly considered.[23] This is a matter of clinical judgment, but in any event, the newer macrolides azithromycin and clarithromycin are recommended in cases of erythromycin intolerance. In patients with COPD, either trimethoprim-sulfamethoxazole (TMP-SMX) or doxycycline usually provides adequate coverage against *S. pneumoniae* and *H. influenzae,* but TMP-SMX will not cover atypical pathogens.

Use of the older quinolones is not recommended for empiric treatment of community-acquired respiratory infections, primarily because of their variable activity against *S. pneumoniae* and atypical organisms. Although the older quinolones (i.e., ciprofloxacin) generally should not be used for the empiric treatment of CAP, they may provide an important option for treatment of bronchiectasis, particularly when gram-negative organisms such as *Pseudomonas* are cultured from respiratory secretions.[24] In these cases, ciprofloxacin should be used in combination with another anti-pseudomonal agent when indicated.

The most important issue for the emergency physician or pulmonary intensivist is to ensure that the appropriate intensity and spectrum of coverage are provided, according to patient and community/epidemiological risk factors. In many cases, especially when infection with gram-negative organisms is suspected or when there is structural lung disease, this will require shifting to and intensifying therapy with an extended spectrum quinolone. However, in most cases of non-ICU patients admitted to the hospital, IV ceftriaxone plus azithromycin IV is recommended, depending on institutional protocols.

In this regard, determining which of these antibiotics (macrolides vs extended spectrum quinolones) should be considered "workhorse" drugs in the ED or hospital setting for initial CAP treatment requires thoughtful analysis that takes into account cost, convenience, spectrum of coverage, host risk factors, and patient risk stratification.

In the case of azithromycin, its five-day duration of therapy; $39-$42 cost per course of treatment; and targeted coverage of *S. pneumoniae, H. influenzae, M. catarrhalis, Chlamydia,* and *M. pneumoniae* must be weighed against the longer duration and slightly greater cost per treatment course for the quinolones and the fact that their spectrum of coverage includes not only the appropriately targeted, aforementioned organisms commonly implicated in CAP, but also extensive activity against gram-negative organisms, which may not always be required, especially in otherwise healthy individuals. This over-extended spectrum of coverage may exert resistance pressure on gram-negative organisms frequently encountered in a hospital setting; therefore, quinolone use should be risk-stratified to an appropriate subset.

Finally, there is an increasing problem in the United States concerning the emergence among hospitalized pneumonia patients of *S. pneumoniae* that is relatively resistant to penicillin and, less commonly, to extended spectrum cephalosporins. These isolates also may be resistant to sulfonamides and tetracyclines.[20,25,26] Except for vancomycin, the most favorable in vitro response rates to *S. pneumoniae* are seen with extended spectrum quinolones. *(See Table 1 for a summary of current recommendations for initial management of outpatient and in-hospital management of patients with CAP.)*

Antimicrobial Therapy and Medical Outcomes. A recent study has helped assess the relationship between initial antimicrobial therapy and medical outcomes for elderly patients hospitalized with pneumonia.[27] In this retrospective analysis, hospital records for 12,945 Medicare inpatients (65 years of age) with

Table 1. ASCAP 2002 Guidelines — Empiric Antimicrobial Therapy of Choice for Outpatient‡ and In-Hospital Management of Patients with CAP

PATIENT PROFILE/ETIOLOGIC AGENTS	FIRST-LINE ANTIBIOTIC THERAPY†	ALTERNATIVE FIRST-LINE ANTIBIOTIC THERAPY
Otherwise Healthy < 60 years of age (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, high likelihood of compliance, and supportive home environment)*	Azithromycin PO	Moxifloxacin PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
Otherwise Healthy > 60 years of age (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, high likelihood of compliance, and supportive home environment)*	Azithromycin PO	Moxifloxacin PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
In-hospital (not in intensive care unit) underlying risk factors or comorbid conditions: In-hospital management (COPD, history of pneumonia, diabetes, etc.)	Ceftriaxone IV plus azithromycin IV†††	Moxifloxacin *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP acquired in the nursing home environment (increased likelihood of gram-negative, *E. coli, Klebsiella pneumoniae*)	Ceftriaxone IV plus azithromycin IV	Moxifloxacin *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP in the elderly individual with chronic alcoholism (Increased likelihood of *Klebsiella pneumoniae* infection)	Ceftriaxone IV plus azithromycin IV	Cefotaxime†† plus erythromycin IV *OR* 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 quinolones and cephalosporins	Ceftriaxone IV plus moxifloxacin *OR* Ceftriaxone IV plus levofloxacin IV	Vancomycin¶ plus azithromycin IV
Severe CAP complicated by structural disease of the lung (bronchiectasis): Increased likelihood of *Pseudomonas* and polymicrobial infection	Cefepime IV plus levofloxacin IV plus/minus aminoglycoside *OR* Ciprofloxacin IV plus aminoglycoside 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 gram-negative and anaerobic infection**)	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, or who resides in, a community or facility with a high reported incidence of methicillin-resistant *S. aureus* (MRSA)***	Moxifloxacin IV plus vancomycin IV *OR* Levofloxacin IV plus vancomycin IV	Gatifloxacin IV plus vancomycin IV
CAP patient with severe pneumonia requiring ICU hospitalization***	Ceftriaxone IV plus levofloxacin IV plus/minus aminoglycoside (*Pseudomonas* strongly suspected) *OR* Ceftriaxone IV plus azithromycin IV plus/minus anti-pseudomonal agent	Cefepime IV plus aminoglycoside IV plus azithromycin IV *OR* Imipenem IV plus aminoglycoside IV plus azithromycin IV

‡ Adapted from references 4, 12, 34-47.
* 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.
§ Quinolones generally are restricted for use in patients > 18 years of age.
¶ If *S. pneumoniae* demonstrates complete resistance to extended spectrum quinolones (very rare), third-generation cephalosporins, and macrolides, then vancomycin may be required as part of initial therapy, although this would be necessary only in rare circumstances.
† 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.
†† Cefotaxime IV should be dosed on a q 8 hours basis when used for treatment of CAP.
††† Some institutions may use oral macrolide therapy for patients with mild-to-moderate CAP.
** When anaerobic organisms are suspected as one of the possible etiologic pathogens in a patient with CAP, clindamycin or a β-lactam/β-lactamase inhibitor (ampicillin/sulbactam, ticarcillin/clavulanate, or ticarcillin/tazobacatam) is recommended.
*** High community prevalence 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 should be considered as component for initial therapy.
§§ Cefotaxime may be substituted for ceftriaxone, although ceftriaxone is preferred because of its once-daily dosing.

pneumonia were reviewed. Associations were identified between the choice of the initial antimicrobial regimen and three-day mortality, adjusting for baseline differences in patient profiles, illness severity, and process of care. Comparisons were made between the antimicrobial regimens and a reference group consisting of patients treated with a non-pseudomonal third-generation cephalosporin alone.

Of the 12,945 patients, 9751 (75.3%) were community-dwelling, and 3194 (24.7%) were admitted from a long-term care facility (LCF). Study patients had a mean age of 79.4 years ± 8.1 years, 84.4% were white, and 50.7% were female. As would be expected, the majority (58.1%) of patients had at least one comorbid illness; and 68.3% were in the two highest severity risk classes (IV and V) at initial examination. The most frequently coded bacteriologic pathogens were *S. pneumoniae* (6.6%) and *H. influenzae* (4.1%); 10.1% of patients were coded as having aspiration pneumonia, and in 60.5% the etiologic agent for the pneumonia was unknown.

The three most commonly used initial, empiric antimicrobial regimens in the elderly patient with pneumonia consisted of the following: 1) a non-pseudomonal third-generation cephalosporin only (ceftriaxone, cefotaxime, ceftizoxime) in 26.5%; 2) a second-generation cephalosporin only (cefuroxime) in 12.3%; and 3) a non-pseudomonal third-generation cephalosporin (as above) plus a macrolide in 8.8%. The 30-day mortality was 15.3% (95% CI, 14.6%-15.9%) in the entire study population, ranging from 11.2% (95% CI, 10.6%-11.9%) in community-dwelling elderly patients to 27.5% (95% CI, 26%-29.1%) among patients admitted from a long-term care facility.[27]

As might be predicted, this study of elderly patients with hospitalization for pneumonia demonstrated significant differences in patient survival depending upon the choice of the initial antibiotic regimen. In particular, this national study demonstrated that, compared to a reference group receiving a non-pseudomonal third-generation cephalosporin alone, initial therapy with a non-pseudomonal plus a macrolide, a second-generation cephalosporin plus a macrolide, or a fluoroquinolone alone was associated with 26%, 29%, and 36% lower 30-day mortality, respectively. Despite the fact that these regimens are compatible with those recommended by the IDSA and CDC, only 15% of patients received one of the three aforementioned regimens associated with reduced mortality rates.

For reasons that are not entirely clear, patients treated with a beta-lactam/beta-lactamase inhibitor plus a macrolide or an aminoglycoside plus another agent had mortality rates that were 77% and 21% higher than the reference group, respectively.

Role of Specific Pathogens in CAP. Prospective studies evaluating the causes of CAP in elderly adults have failed to identify the cause of 40-60% of cases of CAP, and two or more etiologies have been identified in 2-5% of cases. The most common etiologic agent identified in virtually all studies of CAP in the elderly is *S. pneumoniae,* and this agent accounts for approximately two-thirds of all cases of bacteremic pneumonia.

Other pathogens implicated less frequently include *H. influenzae* (most isolates of which are other than type B), *M. pneumoniae, C. pneumoniae, S. aureus, Streptococcus pyogenes, Neisseria meningitidis, M. catarrhalis, K. pneumoniae,* and other gram-negative rods, *Legionella* species, influenza virus (depending on the time of year), respiratory syncytial virus, adenovirus, parainfluenza virus, and other microbes. The frequency of other etiologies, (e.g., *Chlamydia psittaci* [psittacosis], *Coxiella burnetii* [Q fever], *Francisella tularensis* [tularemia], and endemic fungi [histoplasmosis, blastomycosis, and coccidioidomycosis]), is dependent on specific epidemiological factors.

The selection of antibiotics, in the absence of an etiologic diagnosis (Gram's stains and culture results are not diagnostic), is based on multiple variables, including severity of the illness, patient age, antimicrobial intolerance or side effects, clinical features, comorbidities, concomitant medications, exposures, and the epidemiological setting.

Consensus Guidelines for Antibiotic Therapy

Consensus Report Guidelines: Infectious Disease Society of America. The IDSA, through its Practice Guidelines Committee, provides assistance to clinicians in the diagnosis and treatment of CAP. The targeted providers are internists and family practitioners, and the targeted patient groups are immunocompetent adult patients. Criteria are specified for determining whether the inpatient or outpatient setting is appropriate for treatment. Differences from other guidelines written on this topic include use of laboratory criteria for diagnosis and approach to antimicrobial therapy. Panel members and consultants were experts in adult infectious diseases.

The guidelines are evidence-based when possible. A standard ranking system is used for the strength of recommendations and the quality of the evidence cited in the literature reviewed. The document has been subjected to external review by peer reviewers as well as by the Practice Guidelines Committee, and was approved by the IDSA Council in September 2000. *(See Table 2.)*

Centers for Disease Control Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (CDC-DRSPWG) Guidelines. One of the important issues in selecting antibiotic therapy for the elderly patient is the emerging problem of DRSP. To address this problem and provide practitioners with specific guidelines for initial antimicrobial selection in these patients, the CDC-DRSPWG convened and published its recommendations in May 2000.[4] Some of the important clinical issues they addressed included the following: 1) what empirical antibiotic combinations (or monotherapeutic options) constituted reasonable initial therapy in outpatients, in hospitalized (non-ICU) patients, and in hospitalized intubated or ICU patients; 2) what clinical criteria, patient risk factors, or regional, epidemiological features constituted sufficient trigger points to include agents with improved activity against DRSP as initial agents of choice; and 3) what antibiotic selection strategies were most appropriate for limiting the emergence of fluoroquinolone-resistant strains.

Their conclusions with respect to antibiotic recommendations overlap significantly with the IDSA recommendations and the existing ATS guidelines. The specific differences contained in the CDC-DRSPWG primarily involve the sequence in which antibi-

otics should be chosen to limit the emergence of fluoroquinolone-resistant strains, a preference for using combination drug therapy, cautionary notes about using fluoroquinolones as monotherapy in critically ill patients, reserving use of fluoroquinolones for specific patient populations, and detailed guidance regarding the comparative advantages among agents in each class. *(See Table 3.)*

Oral macrolide (azithromycin, clarithromycin, or erythromycin) or beta-lactam monotherapy is recommended by the CDC working group as initial therapy in patients with pneumonia who are considered to be amenable to outpatient management. For inpatients not in an ICU (i.e., medical ward disposition), this group recommends for initial therapy the combination of a parenteral beta-lactam (ceftriaxone or cefotaxime) plus a macrolide (azithromycin, erythromycin, etc.).[4] Hence, one of the most important, consistent changes among recent recommendations for initial, empiric management of patients with CAP is mandatory inclusion of a macrolide (which covers atypical pathogens) when a cephalosporin (which has poor activity against atypical pathogens) is selected as part of the initial combination regimen.

For critically ill patients, first-line therapy should include an intravenous beta-lactam, such as ceftriaxone, and an intravenous macrolide such as azithromycin. The option of using a combination of a parenteral beta-lactam (ceftriaxone, etc.) plus a fluoroquinolone with improved activity against DRSP also is presented. Once again, however, this committee issues clarifying, and sometimes cautionary, statements about the role of fluoroquinolone monotherapy in the critically ill patient, stating that caution should be exercised because the efficacy of the new fluoroquinolones as monotherapy for critically ill patients has not been determined.[4]

Clearly, fluoroquinolones are an important part of the antimicrobial arsenal in the elderly, and the CDC-DRSPWG has issued specific guidelines governing their use in the setting of outpatient and inpatient CAP. It recommends fluoroquinolones be reserved for selected patients with CAP, among them: 1) adults, including elderly patients, for whom one of the first-line regimens (cephalosporin plus a macrolide) has failed; 2) those who are allergic to the first-line agents; or 3) those patients who have a documented infection with highly drug-resistant pneumococci (i.e., penicillin MIC > 4 mcg/mL).

Prevention of Deep Venous Thromboembolism (DVT)

Background. Although antibiotic therapy, oxygenation, and maintenance of hemodynamic status are the primary triad of emergency interventions in elderly patients with pneumonia, there has been an increasing recognition of the risk for venous thromboembolic disease (VTED) incurred by immobilized elderly patients with infections such as pneumonia, especially when accompanied by congestive heart failure (CHF) and/or respiratory failure. Emergency physicians, as well as attending physicians admitting such patients to the hospital, should be aware that the risk of VTED is significant enough to require prophylaxis in elderly patients with CAP who are likely to be immobilized for a period of three days or more (i.e., can ambulate fewer than 10 meters per day), and who have such risk factors as obesity, previous history of VTED, cancer, varicose veins, hormone therapy, chronic heart failure (NYHA Class III-IV), or chronic respiratory failure.[28]

Table 2. IDSA — Year 2000 Guidelines. Empirical Selection of Antimicrobial Agents for Treating Patients with CAP

OUTPATIENTS

- Generally preferred (not in any particular order): doxycycline, a macrolide, or a fluoroquinolone.
- These agents have activity against the most likely pathogens in this setting, which include *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae.*
- Selection should be influenced by regional antibiotic susceptibility patterns for *S. pneumoniae* and the presence of other risk factors for drug-resistant *S. pneumoniae.*
- Penicillin-resistant pneumococci may be resistant to macrolides and/or doxycycline.
- For older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients.

HOSPITALIZED PATIENTS

- General medical ward
- Generally preferred: an extended spectrum cephalosporin combined with a macrolide or a β-lactam/β-lactamase inhibitor combined with a macrolide or a fluoroquinolone (alone).

INTENSIVE CARE UNIT

- Generally preferred: an extended spectrum cephalosporin or β-lactam/β-lactamase inhibitor plus either a fluoroquinolone or macrolide.

ALTERNATIVES OR MODIFYING FACTORS

- Structural lung disease: antipseudomonal agents (piperacillin, piperacillin-tazobactam, imipenem, or cefepime) plus a fluoroquinolone (including high-dose ciprofloxacin)
- β-lactam allergy: fluoroquinolone ± clindamycin
- Suspected aspiration: fluoroquinolone with or without clindamycin, metronidazole, or a β-lactam/β-lactamase inhibitor

Note: β-lactam/β-lactamase inhibitor: ampicillin-sulbactam or piperacillin-tazobactam. Extended-spectrum cephalosporin: cefotaxime or ceftriaxone. Fluoroquinolone: gatifloxacin, levofloxacin, moxifloxacin, or other fluoroquinolone with enhanced activity against *S. pneumoniae* (for aspiration pneumonia, some fluoroquinolones show in vitro activity against anaerobic pulmonary pathogens, although there are no clinical studies to verify in vivo). Macrolide: azithromycin, clarithromycin, or erythromycin ± with or without.

Table 3. Recommended Year 2000 CDC-DRSPWG Empiric Regimens for Treating Community-Acquired Pneumonia*

Empiric treatment**	Penicillin MIC mcg/mL ≤ 0.06	0.12-1	2	4	≥ 8	Comments
Outpatients						
Macrolide (erythromycin, clarithromycin, or azithromycin)	+++	+	±	-	-	Covers atypical pathogens (*Mycoplasma* species *Chlamydia* species, and *Legionella* species)
Doxycycline (or tetracycline)	+++	++	+	-	-	Covers atypical pathogens; not FDA-approved for children younger than 8 years
Oral β-lactam (cefuroxime axetil, amoxicillin, or amoxicillin-clavulanate potassium)	+++	++	+	-	-	Does not cover atypical pathogens; alternatively, cefpodoxime or cefprozil may be used
Fluoroquinolones (levofloxacin, moxifloxacin, or gatifloxacin)†	+++	+++	+++	++	++	Not first-line treatment because of concerns about emerging resistance; not FDA-approved for use in children; covers atypical pathogens
Hospitalized (Nonintensive Care Unit) Patients						
Parenteral β-lactam (cefuroxime, cefotaxime sodium, ceftriaxone sodium, or ampicillin sodium-sulbactam sodium) plus macrolide (erythromycin, clarithromycin, or azithromycin)	+++	+++	++	±	-	Ceftriaxone and cefotaxime have superior activity against resistant pneumococci in comparison with ampicillin-sulbactam and with cefuroxime.
Fluoroquinolones (e.g., moxifloxacin, levofloxacin, gatifloxacin, or trovafloxacin)†	+++	+++	+++	++	++	See previous comments about fluoroquinolones.
Intubated or Intensive Care Unit Patients‡						
Intravenous β-lactam (ceftriaxone or cefotaxime sodium) plus intravenous macrolide (erythromycin or azithromycin)	+++	+++	++	±	-	Ceftriaxone or cefotaxime are preferred over other β-lactams because of their superior activity against resistant pneumococci; clarithromycin has no intravenous formulation.
Intravenous β-lactam (ceftriaxone or cefotaxime) plus fluoroquinolone (e.g., gatifloxacin, levofloxacin, moxifloxacin, or trovafloxacin)†	+++	+++	++	++	++	Ceftriaxone or cefotaxime are preferred over other β-lactams; see previous comments about fluoroquinolones.
Fluoroquinolones (e.g., moxifloxacin, levofloxacin, gatifloxacin, or trovafloxacin)†	++	++	++	++	++	See previous comments about fluoroquinolones; efficacy of monotherapy for critically ill persons with pneumococcal pneumonia has not been established.

* FDA indicates Food and Drug Administration. Ratings estimate clinical efficacy and in vitro susceptibility among persons with pneumococcal pneumonia. In-depth information on empiric treatment of pneumonia is given by the Infectious Disease Society of America and the American Thoracic Society guidelines.

† The relative antipneumococcal activity of these agents differs slightly, with that of trovafloxacin equal or superior to that of grepafloxacin, which equals that of sparfloxacin, which is superior to that of levofloxacin. Because of new data showing an association with serious liver damage, the FDA issued a public health advisory recommending that trovafloxacin be used only for patients with serious and life- or limb-threatening infections who receive initial treatment in an inpatient health care facility and for whom physicians believe that the benefit of the agent outweighs its potential risk.

‡ Vancomycin hydrochloride may be indicated for the treatment of selected critically ill children with community-acquired pneumonia for whom coverage of drug-resistant *Streptococcus pneumoniae* must be ensured.

** Adaptations made to reflect introduction of new agents since report was published.

From a practical perspective, this subset of patients should be considered strongly for prophylaxis to reduce the risk of VTED. Based on recent studies, the presence of pneumonia in a patient age 75 years or older is, in itself, a criterion for prophylaxis against VTED; when these factors are accompanied by CHF (Class III-IV) or respiratory failure, prophylaxis should be considered mandatory if there are no significant contraindications.[28] It should be added that The American College of Chest Physicians (ACCP) guidelines[29] and International Consensus Statement[30] also cite risk factors for VTED and emphasize their importance when assessing prophylaxis requirements for medical patients.

Evidence for Prophylaxis. The data to support a prophylactic approach to VTED for serious infections in the elderly are growing. The studies with subcutaneous unfractionated heparin (UFH) are inconclusive, although this agent is used for medical prophylaxis. Despite the recognition of risk factors and the availability of effective means for prophylaxis, DVT and pulmonary embolism (PE) remain common causes of morbidity and mortality. It is estimated that approximately 600,000 patients per year are hospitalized for DVT in North America.[31] In the United States, symptomatic PE occurs in more than 600,000 patients and causes or contributes to death in up to 200,000 patients annually.[32]

With respect to the risk of VTED in older patients with infection, one study group randomized infectious disease patients older than age 55 to UFH 5000 IU bid or placebo for three weeks. Autopsy was available in 60% of patients who died. Deaths from PE were delayed significantly in the UFH group, but the six-week mortality rate was similar in both groups. Nonfatal VTED was reduced by UFH. The findings of previous trials of prophylaxis in medical patients have been controversial, as the patient populations and methods used to detect thromboembolism and the dose regimens vary, undermining the value of the findings. Therefore, comparative studies with clearly defined populations and reliable end points were required to determine appropriate patient subgroups for antithrombotic therapy.[33]

The MEDENOX Trial. In response to the need for evidence to clarify the role of prophylaxis in specific non-surgical patient subgroups, the MEDENOX (prophylaxis in MEDical patients with ENOXaparin) trial was conducted using the low molecular weight heparin (LMWH) enoxaparin in a clearly identified risk groups.[131] In contrast to previous investigations, the MEDENOX trial included a clearly defined patient population (patients immobilized with severe chest [cardiopulmonary] disease), and was designed to answer questions about the need for prophylaxis in this group of medical patients and to determine the optimal dose of LMWH.[28]

Patients in the MEDENOX trial were randomized to receive enoxaparin, 20 or 40 mg subcutaneously, or placebo once daily, beginning within 24 hours of randomization. They were treated for 10 days (4 days in the hospital and followed up in person or by telephone contact on day 90 [range, day 83-110]). During follow-up, patients were instructed to report any symptoms or signs of VTED or any other clinical events. The primary and secondary efficacy end points for MEDENOX were chosen to allow an objective assessment of the risk of VTED in the study population and the extent of any benefit of prophylaxis. The primary end point was any venous thromboembolic event between day 1 and day 14. All patients underwent systematic bilateral venography at day 10 or earlier if clinical signs of DVT were observed. Venous ultrasonography was performed if venography was not possible. Suspected PE was confirmed by high probability lung scan, pulmonary angiography, helical computerized tomography, or at autopsy.[28] The primary safety end points were hemorrhagic events, death, thrombocytopenia, or other adverse events or laboratory abnormalities.[28]

A total of 1102 patients were included in the MEDENOX trial, in 60 centers and nine countries. The study excluded patients who were intubated or in septic shock. Overall, the mean age was 73.4 years, the gender distribution was 50:50, and the mean body mass index was 25.0. The mean patient ages, gender distribution, and body mass index were similar in all three treatment groups; there were slightly more males than females in the placebo and enoxaparin 20 mg groups, and more females than males in the enoxaparin 40 mg group, but this difference was not significant. The reasons for hospitalization of randomized patients varied.

The majority of patients were hospitalized for acute cardiac failure, respiratory failure, or infectious disease, with pneumonia being the most common infection in those older than 70

ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) 2002 Consensus Panel Members: Gideon Bosker, MD, FACEP, Section of Emergency Medicine, Yale University School of Medicine and Oregon Health Sciences University, ASCAP Panel Moderator and Chairman, Editor-in-Chief, *Emergency Medicine Reports;* **Charles Emerman, MD, FACEP,** ASCAP Panel Associate Chairman, Chairman, Department of Emergency Medicine, Cleveland Clinic Hospitals and Metro Health Center, Cleveland, Ohio; **Stephen Ernest, PharmD,** Clinical Pharmacist, Infectious Diseases; **John Gums, PharmD,** Professor, Departments of Pharmacology and Medicine, University of Florida, Gainesville; **Dave Howes, MD, FACEP,** Program Director and Chairman, Residency Program, Department of Emergency Medicine, University of Chicago Hospitals and Clinics, Associate Professor, Pritzker School of Medicine; **Kurt Kleinschmidt, MD, FACEP,** Associate Professor, Department of Emergency Medicine, University of Texas Southwestern Medical School, Parkland Memorial Medical Center, Dallas, Texas; **David Lang, DO,** Operations Medical Director, Department of Emergency Medicine, Mt. Sinai Medical Center, Miami, Florida; **Sandra Schneider, MD, FACEP,** Professor and Chairman, Department of Emergency Medicine, University of Rochester/Strong Memorial Hospital, Rochester, New York; and **Gregory A. Volturo, MD, FACEP,** Vice Chairman and Associate Professor, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester.

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years. For the study population as a whole, the most prevalent risk factor in addition to the underlying illness was advanced age (50.4%). By day 14, the incidence of VTED was 14.9% in the placebo group and 5.5% in the enoxaparin 40 mg group, representing a significant 63% relative risk reduction in VTED (97% CI: 37-78%; P = 0.0002).

The primary conclusions of the MEDENOX trial can be applied directly to clinical practice. First, acutely ill elderly medical patients with cardiopulmonary or infectious disease are at significant risk of VTED. Second, enoxaparin, given once daily at a dose of 40 mg for 6-14 days, reduces the risk of VTED by 63%; and third, the reduction in thromboembolic risk is achieved without increasing the frequency of hemorrhage, thrombocytopenia, or any other adverse event compared with placebo. This study strongly suggests that elderly, immobilized patients admitted to the hospital with severe pneumonia, especially if accompanied by respiratory failure or Class III-IV CHF, should, if there are no contraindications to the use of anticoagulants, be considered candidates for prophylaxis with enoxaparin, 40 mg subcutaneously qd upon admission to the hospital to prevent VTED.

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Physician CME Questions

75. Outpatient management requires mandatory coverage of which of the following?
    A. *Streptococcus pneumoniae* and *Haemophilus influenzae*
    B. *Moraxella catarrhalis*
    C. *Mycoplasma pneumoniae*
    D. *Chlamydia pneumoniae* and *Legionella pneumophila*
    E. All of the above

76. Ideally, patients with CAP should initiate their first course of oral therapy within:
    A. eight hours of diagnosis.
    B. 12 hours of diagnosis.
    C. 18 hours of diagnosis.
    D. 24 hours of diagnosis.

77. One of the most important changes introduced by the 2001 American Thoracic Society (ATS) Guidelines for CAP is:
    A. that *Klebsiella pneumonia* should be covered empirically in all cases of CAP.
    B. *Pseudomonas* should be covered empirically in all cases.
    C. atypical organisms, such as *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae,* must be covered empirically as part of the initial antibiotic regimen.
    D. All of the above

78. The results of a retrospective study comparing treatment options for CAP strongly suggest that:
    A. bacteremic patients should be treated routinely with one broad spectrum agent.
    B. bacteremic patients should be treated routinely with three agents.
    C. patients with pneumococcal CAP who receive at least two

effective antibiotic agents within the first 24 hours after presentation to a hospital had a significantly lower mortality than patients who receive only one effective antibiotic agent.

D. All of the above

79. There are a variety of risk factors for the development of MRSA in the hospital. These include:
    A. extensive prior broad-spectrum antibiotic use.
    B. admission to an ICU.
    C. prolonged hospitalization.
    D. presence of an indwelling catheter.
    E. All of the above

80. The the CDC-DRSPWG has recommended that fluoroquinolones be reserved for selected patients with CAP. Such patients would include:
    A. adult patients, including the elderly, in whom one of the first-line regimens (cephalosporin plus a macrolide) has failed.
    B. those who are allergic to the first-line agents.
    C. those who have a documented infection with highly drug-resistant pneumococci.
    D. All of the above

81. Use of the older quinolones, such as ciprofloxacin, is not recommended for empiric treatment of community-acquired respiratory infections primarily because of their variable activity against:
    A. *S. pneumoniae* and atypical organisms.
    B. *E. coli*.
    C. *Klebsiella.*
    D. *H. influenzae*.
    E. All of the above

82. Prospective studies evaluating the causes of CAP in elderly adults have failed to identify the cause in:
    A. 40-60% of cases.
    B. 4-6% of cases.
    C. 14-16% of cases.
    D. 20% of cases.

In Future Issues:

Polypharmacy in the Elderly

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;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art 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;
- and provide patients with any necessary discharge instructions.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Community-Acquired Pneumonia, Part II

ASCAP 2002 Guidelines—Empiric Antimicrobial Therapy of Choice for Outpatient and In-Hospital Management of Patients with CAP

PATIENT PROFILE/ETIOLOGIC AGENTS	FIRST-LINE ANTIBIOTIC THERAPY†	ALTERNATIVE FIRST-LINE ANTIBIOTIC THERAPY
Otherwise Healthy < 60 years of age (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, high likelihood of compliance, and supportive home environment)*	Azithromycin PO	Moxifloxacin PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
Otherwise Healthy > 60 years of age (Patients deemed to be suitable for outpatient/oral therapy, i.e., no systemic toxicity, high likelihood of compliance, and supportive home environment)*	Azithromycin PO	Moxifloxacin PO (preferred) *OR* Levofloxacin PO *OR* Clarithromycin *OR* Gatifloxacin PO
In-hospital (not in intensive care unit) underlying risk factors or comorbid conditions: In-hospital management (COPD, history of pneumonia, diabetes, etc.)	Ceftriaxone IV plus azithromycin IV†††	Moxifloxacin *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP acquired in the nursing home environment (increased likelihood of gram-negative, *E. coli, Klebsiella pneumoniae*)	Ceftriaxone IV plus azithromycin IV	Moxifloxacin *OR* Levofloxacin IV *OR* Gatifloxacin IV
CAP in the elderly individual with chronic alcoholism (Increased likelihood of *Klebsiella pneumoniae* infection)	Ceftriaxone IV plus azithromycin IV	Cefotaxime†† plus erythromycin IV *OR* 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 quinolones and cephalosporins	Ceftriaxone IV plus moxifloxacin *OR* Ceftriaxone IV plus levofloxacin IV	Vancomycin¶ plus azithromycin IV
Severe CAP complicated by structural disease of the lung (bronchiectasis): Increased likelihood of *Pseudomonas* and polymicrobial infection	Cefepime IV plus levofloxacin IV plus/minus aminoglycoside *OR* Ciprofloxacin IV plus aminoglycoside 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 gram-negative and anaerobic infection**)	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, or who resides in, a community or facility with a high reported incidence of methicillin-resistant *S. aureus* (MRSA)***	Moxifloxacin IV plus vancomycin IV *OR* Levofloxacin IV plus vancomycin IV	Gatifloxacin IV plus vancomycin IV
CAP patient with severe pneumonia requiring ICU hospitalization*	Ceftriaxone IV plus levofloxacin IV plus/minus aminoglycoside (*Pseudomonas* strongly suspected) *OR* Ceftriaxone IV plus azithromycin IV plus/minus anti-pseudomonal agent	Cefepime IV plus aminoglycoside IV plus azithromycin IV *OR* Imipenem IV plus aminoglycoside IV plus azithromycin IV

‡ Adapted from references 4, 12, 34-47.
* 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.
§ Quinolones generally are restricted for use in patients > 18 years of age.
¶ If *S. pneumoniae* demonstrates complete resistance to extended spectrum quinolones (very rare), third-generation cephalosporins, and macrolides, then vancomycin may be required as part of initial therapy, although this would be necessary only in rare circumstances.
† 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.
†† Cefotaxime IV should be dosed on a q 8 hours basis when used for treatment of CAP.
††† Some institutions may use oral macrolide therapy for patients with mild-to-moderate CAP.
** When anaerobic organisms are suspected as one of the possible etiologic pathogens in a patient with CAP, clindamycin or a β-lactam/β-lactamase inhibitor (ampicillin/sulbactam, ticarcillin/clavulanate, or ticarcillin/tazobacatam) is recommended.
*** High community prevalence 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 should be considered as component for initial therapy.
§§ Cefotaxime may be substituted for ceftriaxone, although ceftriaxone is preferred because of its once-daily dosing.

IDSA—Year 2002 Guidelines. Empirical Selection of Antimicrobial Agents for Treating Patients with CAP

OUTPATIENTS

- Generally preferred (not in any particular order): doxycycline, a macrolide, or a fluoroquinolone.
- These agents have activity against the most likely pathogens in this setting, which include *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae.*
- Selection should be influenced by regional antibiotic susceptibility patterns for *S. pneumoniae* and the presence of other risk factors for drug-resistant *S. pneumoniae.*
- Penicillin-resistant pneumococci may be resistant to macrolides and/or doxycycline.
- For older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients.

HOSPITALIZED PATIENTS

- General medical ward
- Generally preferred: an extended spectrum cephalosporin combined with a macrolide or a β-lactam/β-lactamase inhibitor combined with a macrolide or a fluoroquinolone (alone).

INTENSIVE CARE UNIT

- Generally preferred: an extended spectrum cephalosporin or β-lactam/β-lactamase inhibitor plus either a fluoroquinolone or macrolide.

ALTERNATIVES OR MODIFYING FACTORS

- Structural lung disease: antipseudomonal agents (piperacillin, piperacillin-tazobactam, imipenem, or cefepime) plus a fluoroquinolone (including high-dose ciprofloxacin)
- β-lactam allergy: fluoroquinolone ± clindamycin
- Suspected aspiration: fluoroquinolone with or without clindamycin, metronidazole, or a β-lactam/β-lactamase inhibitor

Note: β-lactam/β-lactamase inhibitor: ampicillin-sulbactam or piperacillin-tazobactam. Extended-spectrum cephalosporin: cefotaxime or ceftriaxone. Fluoroquinolone: gatifloxacin, levofloxacin, moxifloxacin, or other fluoroquinolone with enhanced activity against *S. pneumoniae* (for aspiration pneumonia, some fluoroquinolones show in vitro activity against anaerobic pulmonary pathogens, although there are no clinical studies to verify in vivo). Macrolide: azithromycin, clarithromycin, or erythromycin ± with or without.

Recommended Year 2000 CDC-DRSPWG Empiric Regimens for Treating Community-Acquired Pneumonia*

Empiric treatment**	Penicillin MIC mcg/mL ≤ 0.06	0.12-1	2	4	≥ 8	Comments
Outpatients						
Macrolide (erythromycin, clarithromycin, or azithromycin)	+++	+	±	-	-	Covers atypical pathogens (*Mycoplasma* species *Chlamydia* species, and *Legionella* species)
Doxycycline (or tetracycline)	+++	++	+	-	-	Covers atypical pathogens; not FDA-approved for children younger than 8 years
Oral β-lactam (cefuroxime axetil, amoxicillin, or amoxicillin-clavulanate potassium)	+++	++	+	-	-	Does not cover atypical pathogens; alternatively, cefpodoxime or cefprozil may be used
Fluoroquinolones (levofloxacin, moxifloxacin, or gatifloxacin)†	+++	+++	+++	++	++	Not first-line treatment because of concerns about emerging resistance; not FDA-approved for use in children; covers atypical pathogens
Hospitalized (Nonintensive Care Unit) Patients						
Parenteral β-lactam (cefuroxime, cefotaxime sodium, ceftriaxone sodium, or ampicillin sodium-sulbactam sodium) plus macrolide (erythromycin, clarithromycin, or azithromycin)	+++	+++	++	±	-	Ceftriaxone and cefotaxime have superior activity against resistant pneumococci in comparison with ampicillin-sulbactam and with cefuroxime.
Fluoroquinolones (e.g., moxifloxacin, levofloxacin, gatifloxacin, or trovafloxacin)†	+++	+++	+++	++	++	See previous comments about fluoroquinolones.
Intubated or Intensive Care Unit Patients‡						
Intravenous β-lactam (ceftriaxone or cefotaxime sodium) plus intravenous macrolide (erythromycin or azithromycin)	+++	+++	++	±	-	Ceftriaxone or cefotaxime are preferred over other β-lactams because of their superior activity against resistant pneumococci; clarithromycin has no intravenous formulation.
Intravenous β-lactam (ceftriaxone or cefotaxime) plus fluoroquinolone (e.g., gatifloxacin, levofloxacin, moxifloxacin, or trovafloxacin)†	+++	+++	++	++	++	Ceftriaxone or cefotaxime are preferred over other β-lactams; see previous comments about fluoroquinolones.
Fluoroquinolones (e.g., moxifloxacin, levofloxacin, gatifloxacin, or trovafloxacin)†	++	++	++	++	++	See previous comments about fluoroquinolones; efficacy of monotherapy for critically ill persons with pneumococcal pneumonia has not been established.

* FDA indicates Food and Drug Administration. Ratings estimate clinical efficacy and in vitro susceptibility among persons with pneumococcal pneumonia. In-depth information on empiric treatment of pneumonia is given by the Infectious Disease Society of America and the American Thoracic Society guidelines.

† The relative antipneumococcal activity of these agents differs slightly, with that of trovafloxacin equal or superior to that of grepafloxacin, which equals that of sparfloxacin, which is superior to that of levofloxacin. Because of new data showing an association with serious liver damage, the FDA issued a public health advisory recommending that trovafloxacin be used only for patients with serious and life- or limb-threatening infections who receive initial treatment in an inpatient health care facility and for whom physicians believe that the benefit of the agent outweighs its potential risk.

‡ Vancomycin hydrochloride may be indicated for the treatment of selected critically ill children with community-acquired pneumonia for whom coverage of drug-resistant *Streptococcus pneumoniae* must be ensured.

** Adaptations made to reflect introduction of new agents since report was published.

Supplement to Emergency Medicine Reports, May 6, 2002: "Community-Acquired Pneumonia (CAP) Antibiotic Selection and Management Update. Part II: Evaluation, Risk Stratification, and Current Antimicrobial Treatment Guidelines for Hospital-Based Management of CAP: Outcome-Effective Strategies Based on New (NCCLS) Breakpoints and Recent Clinical Studies." —*ASCAP (Antibiotic Selection for Community-Acquired Pneumonia) 2002 Consensus Panel Report* Author: **Gideon Bosker, MD, FACEP**, Assistant Clinical Professor, Section of Emergency Services, Yale University School of Medicine, Associate Clinical Professor, Oregon Health Sciences University, Portland.

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The care of a trauma patient is demanding and requires adequate preparation, rapid access to equipment and resources, and skilled personnel. The system of trauma care is very important to provide rapid, thorough, and comprehensive care to each patient. Second in urgency only to the stabilization of the airway, shock in a trauma patient requires not only rapid stabilization, but also knowledge of pathophysiology and current trends and controversies associated with fluid resuscitation. This article will review methods for improving the efficiency of a trauma resuscitation, whether the physician practices in a high acuity, level I trauma center or a small, rural hospital. The authors also review the pathophysiology and stabilization of a trauma patient who presents in shock. The controversies associated with fluid resuscitation are presented, and future trends are discussed.

—The Editor

Initial Phase of Trauma Management and Fluid Resuscitation

Authors: **John P. Pryor, MD,** Assistant Professor of Surgery, Division of Traumatology and Surgical Critical Care, Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia; **Richard J. Pryor, MD,** Clinical Assistant Instructor, Department of Emergency Medicine, Upstate Medical University, Syracuse, NY; **Perry W. Stafford, MD, FACS, FAAP, FCCM,** Director, Trauma and Surgical Critical Care; Assistant Professor of Pediatric Surgery, Department of Pediatric General and Thoracic Surgery, Children's Hospital of Philadelphia, PA.

Peer Reviewer: **Howard A. Werman, MD,** Associate Professor of Clinical Emergency Medicine, The Ohio State University College of Medicine and Public Health; Medical Director, MedFlight, Columbus, OH.

Introduction

Resuscitation, from the Latin *resuscitare*—to reanimate or revive, has many definitions, depending on what type of clinical system is considered. In trauma care, it refers to all of the diagnostic and therapeutic maneuvers that are used to treat patients who have been seriously injured. Physiologically, it defines the restoration of normal blood volume, blood pressure, and organ perfusion. On a cellular level, the term is used to describe successful restoration of the balance between oxygen utilization and cellular function. In all cases, resuscitation is considered the reversal of shock.

Orchestrating and managing a trauma resuscitation demands a thorough understanding of the physiology of shock, expert physical diagnosis ability, skill with complex procedures, ability to think rationally in chaotic situations, compassion, and fortitude. Those who become proficient in the process find no other situation in medicine more rewarding. However, obtaining the knowledge, learning the skills, and becoming confident in leading a resuscitation is demanding and often exhausting.

Thousands of resuscitations are undertaken every day in the United States, most in hospitals not designated as trauma centers. Despite years of refinement in the practice of trauma resuscita-

tion, there are many controversies about how best to manage patients who sustain significant trauma. Treatments that have been considered dogma, such as early and aggressive fluid administration for patients in shock, have been challenged recently. New technologies, such as ultrasound and high speed computed tomography (CT), have increased the ability to effectively diagnose and treat hemorrhagic shock. Advances in biochemistry, such as artificial blood substitutes, nearly are realities in modern day resuscitation. All of these aspects make trauma resuscitation an evolving and controversial arena for physicians.[1]

Conducting a Resuscitation

In the 1970s, regionalization of trauma care was proposed and the country's first trauma center was created at the University of Maryland. Regional trauma centers have allowed the field of trauma to mature, and have provided the research data that support the current management of multiple system trauma. However, a large percentage of trauma patients still are treated at hospitals that are not designated trauma centers. Therefore, it is important for all providers of emergency care to be facile in the techniques of resuscitation.

The Trauma Bay. The ideal location to perform a resuscitation is a specialized room in the emergency department (ED), set aside for trauma resuscitation. The most important requirement is that the room is large. The space must allow for several practitioners, x-ray machines, ventilators, ultrasound, procedure trays, and the stretcher. Procedure trays that are movable are most convenient. Trays should be set up with airway equipment, chest tube instruments, central venous line kit, and intravenous/blood-draw equipment. *(See Figure 1.)* The trays then can be moved toward or away from the stretcher as they are needed. The head of the stretcher should have an airway station stocked with suction, oxygen, intubation, and surgical airway supplies. The room should have at least two suction canisters (preferably more) that function well. Lighting is very important, and a dedicated operating room (OR) light should be placed above the stretcher to aid in complex procedures. A recorder table large enough for a flow sheet and a phone should be placed away from the patient. Extra supplies need to be readily available, either placed in open shelves or hung on hooks. Cabinets with doors are inconvenient and confusing, even if the contents of the cabinets are labeled. The supplies should be kept away from the patient, to reduce clutter and provide more room for the practitioners to work.

The physical location of the room within the hospital also is important, although this usually is dictated by the existing infrastructure. The room ideally is situated near the CT scanner and angiography room for fast transportation. Easy access to the OR and intensive care unit (ICU) also is important. If an elevator is needed to transport patients to one of these facilities, a key or call system should allow the trauma team immediate access to and control of the elevator. Efforts should be made to locate the room away from other patients in the ED, or to have a physical partition that will decrease the noise of the resuscitation. These considerations are most practical in centers that treat a significant number of trauma patients; however, the concepts are useful for any hospital ED.

Some institutions advocate direct transport of the most critical patients to an OR, avoiding time in the trauma resuscitation room altogether. This requires the hospital to have the resources of an immediately available OR and a triage system that accurately identifies patients who would benefit from bypassing the trauma bay. Several groups have shown that this management scheme may reduce time from arrival to operative incision, and may increase survival beyond predicted rates.[2] Patients who have benefited from direct transport include those with penetrating abdominal wounds, persistent hypotension with significant mechanisms of injury, and uncontrolled external hemorrhage.

Resuscitation Physicians. Depending on the hospital, and sometimes the time of day, trauma resuscitations are performed by different clinicians. Although trauma is a surgical specialty, resuscitation in the ED is a skill that is shared among surgery, anesthesia, and emergency medicine personnel. Among the specialties, there is variation in the training level of physicians participating and leading the effort. It is clear that the most efficient and well-run trauma systems take advantage of a collaborative effort by all specialties at all training levels. Systems and hospitals differ greatly in the way physicians are used in resuscitations. One center may have an on-call trauma team with in-house

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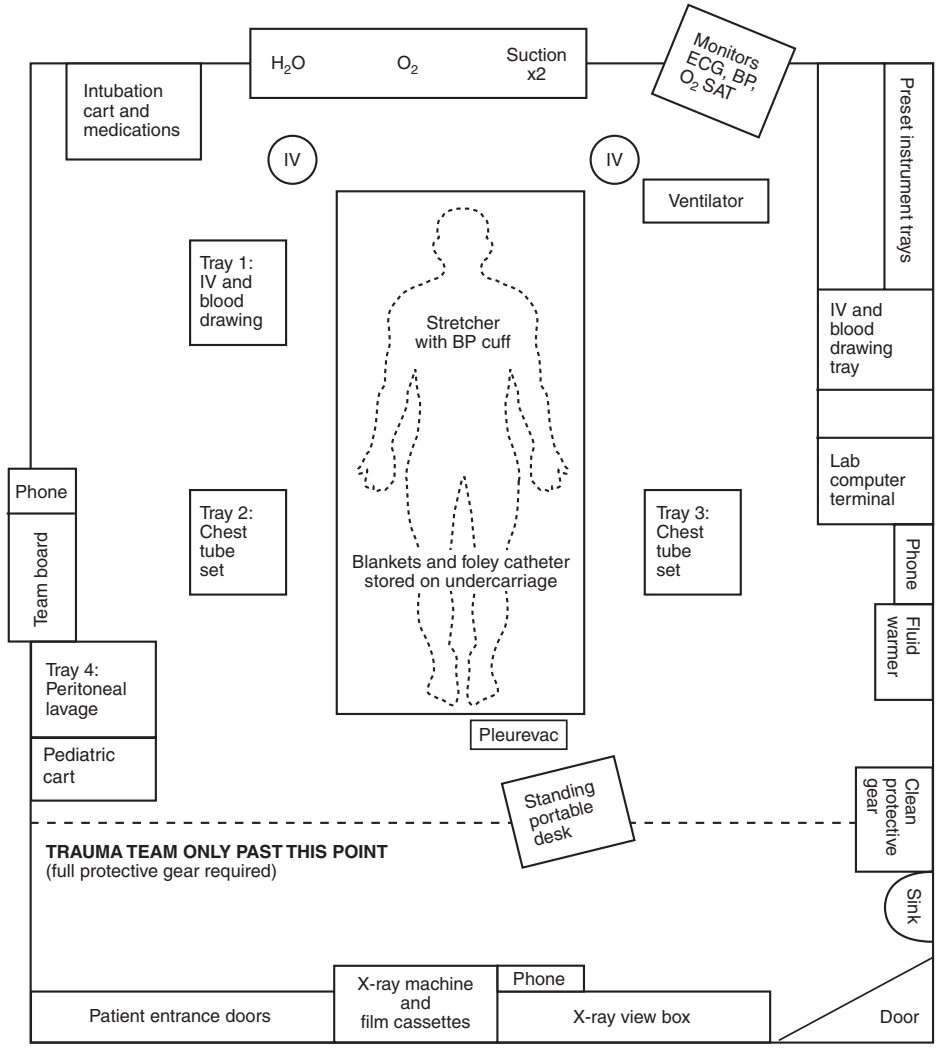
Figure 1. Layout of a Trauma Resuscitation Area



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attending surgeon coverage, while another may have one emergency medicine attending as the resuscitator, with others called to the hospital as needed. There is some evidence that an in-house, on-call trauma surgeon significantly decreases time to complete diagnostic tests, time to the OR, and costs of resuscitation.[3] However, it has not been shown that the morbidity or mortality of trauma patients is changed when surgical residents perform the initial resuscitations with attending surgeons called in from home. Some institutions have developed a system in which the emergency medicine physicians perform the entire initial resuscitation, and only involve a surgeon when an operative procedure is needed. Most institutions, however, utilize a combination of residents from surgery and emergency medicine to make up the resuscitation team.

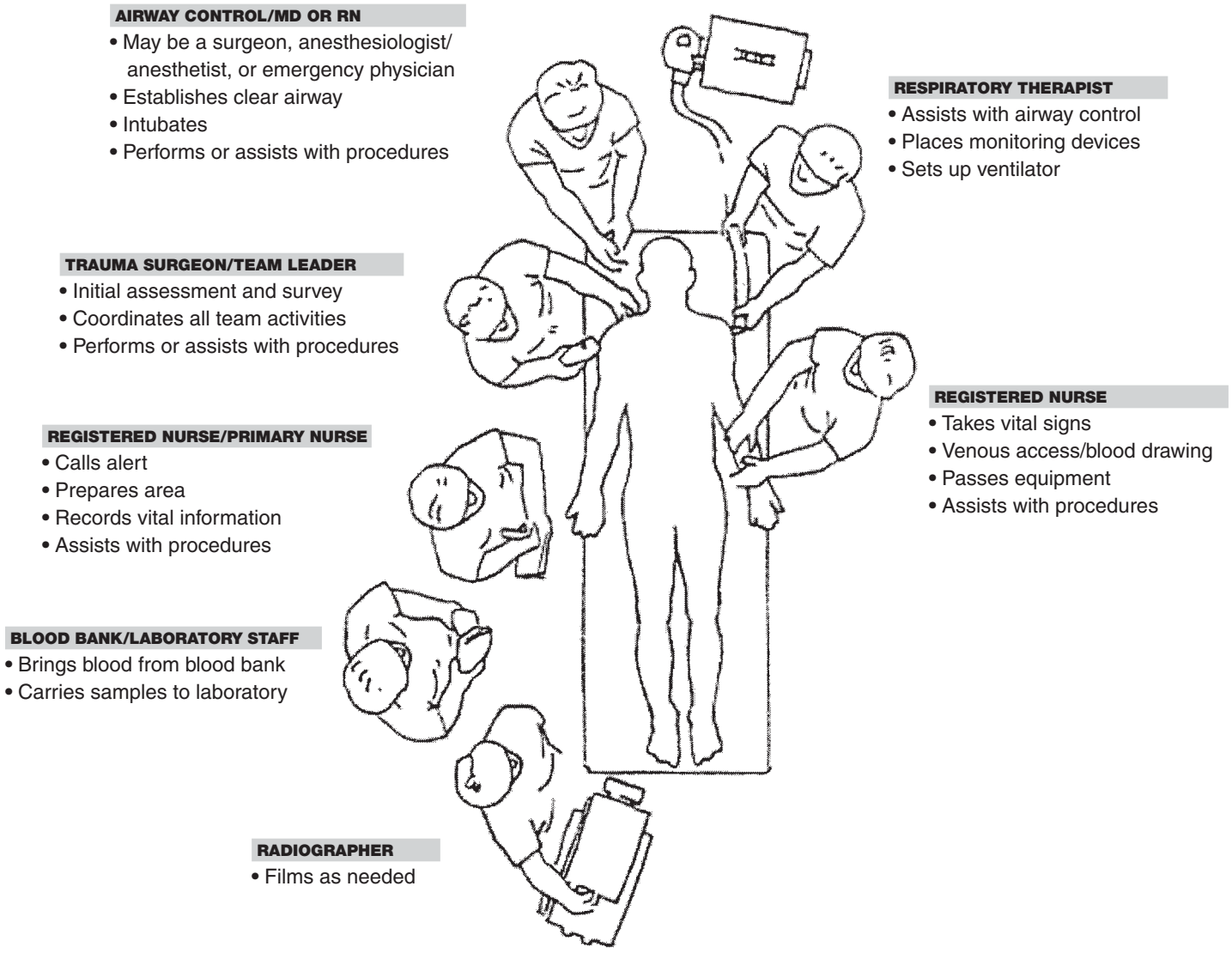
Paradigms of Resuscitation. There are two general types of resuscitation, depending on the location and personnel available to the patient. A *vertical resuscitation* completes diagnostic and therapeutic tasks in a step-by-step fashion. Vertical resuscitations often occur in hospitals with limited personnel resources, in multiple casualty incidences where clinicians are divided among patients, or when a patient arrives without notification and a single physician must initiate care. This form of resuscitation utilizes sequential examination and interventions by a single practitioner. For example, an emergency medicine physician in a community hospital would perform all assessments and procedures. Therefore, airway would be assessed, and if it was not secure, intubation would be performed before the breathing assessment could take place. Tasks are assigned to non-physicians according to their abilities. In many smaller hospitals, physician assistants or nurse practitioners may be able to perform procedures such as chest tube insertion. The physician team leader must direct the resuscitation, as well as participate directly in patient care. This is an organized and effective way to deliver care, but it is slow and burdensome to the practitioner.

A *horizontal resuscitation* is a collective effort by several practitioners working at the same time. It is the model most often seen in trauma centers where there are several physicians, nurses, and technologists available. *(See Figure 2 for one example.)* In this type of scenario, one physician can perform the primary and secondary assessments in their entirety. When an issue is found, such as a need for a chest tube, a second physician, if available, can perform the procedure as the first physician resumes the assessment. This allows multiple assessments and interventions to be accomplished at the same time. The advantage is that the initial diagnosis and treatment is accomplished quickly and completely. The major disadvantage is that the situation can get chaotic and unorganized if a team leader fails to assume control.

The Trauma Resuscitation Team. Success of a horizontal resuscitation depends on each member of the team understanding and executing his or her role while a clearly identified team leader keeps control and makes treatment decisions. The team consists of a command physician (team leader), airway practitioner, trauma nurse, recorder, chaplain, respiratory technologist, radiology technologist, and housekeeping staff. If available, additional physicians may perform assessments and procedures under the direction of the command physician. Each member of the team has directed responsibilities, and all are under the control of the command physician.

An identified command physician has been shown to enhance performance and improve efficiency of trauma resuscitation.[4] This physician can be a senior resident or an attending physician from either emergency medicine or surgery. The command

Figure 2. Positions and Roles of the Trauma Team Members During a Horizontal Resuscitation



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physician is positioned depending on the availability of other practitioners. If there are multiple practitioners to assist with the resuscitation, the command physician stands at the foot of the bed, away from the stretcher. If staffing permits, the team leader should not take on procedures or other tasks that will focus attention away from the entire process. Other duties of the command physician include communicating with the OR, radiology, and consulting physicians. This physician will make all decisions about what tests will be done and in what order, what fluids to run, when to transfuse blood, and which procedures to perform. In cases of multiple patients, the leader may need to oversee more than one patient at a time. This can be done if other capable physicians are performing the assessments and procedures on the multiple patients.

If a physician other than the team leader is available to act as assessment physician, he or she primarily is responsible for performing the primary and secondary surveys defined by the Advanced Trauma Life Support (ATLS) course of the American College of Surgeons. Often, a junior resident fills this role. The assessor will verbalize findings loudly so that the recorder, team leader, and team members can hear clearly. Initially, this physician stands to the patient's right, near the head. The team leader occasionally may direct certain parts of the exam to be done in a different order, such as getting a gross neurological exam before the patient is intubated for airway control. After completing the exam, the assessor becomes available to help with procedures or other tasks. The assessing physician has the responsibility of documenting his or her physical findings as a trauma admission physical exam.

The airway team is situated at the head of the bed and consists of one or two airway practitioners and a respiratory technologist. The practitioners may include a senior resident, trauma/critical

care fellow, nurse anesthetist, attending emergency medicine physician, or an anesthesiologist. A second person is extremely helpful in cases of complicated airway management. The airway team, along with the assessing physician, will evaluate the airway for patency. If intubation is required, the airway team temporarily takes control of the resuscitation and directs other members of the team to position the patient, administer medications, and call for additional equipment, if necessary. In situations in which the airway is stable, the team will initiate oxygen therapy and elicit a history from the patient. Important aspects of the history include circumstances of the trauma, past medical history, past surgical history, medications, allergies, and when the patient last ate or drank. All of this information is relayed to the recorder and team leader.

If a procedure physician, other than the command physician, is available, he or she initially is positioned on the patient's left and away from the stretcher. Procedures are done at the discretion of the team leader, and include chest tube placement, central venous line insertion, splinting, and ultrasound exams. All procedures are done under the best possible sterile conditions, although OR conditions seldom are present in complex resuscitations. All procedures done by the procedure physician are recorded in the medical record as procedure notes.

One or two trauma nurses are positioned on either side of the patient. The initial responsibilities of the nurses include initiating electrocardiogram (ECG), oximetry, and blood pressure monitoring. Intravenous (IV) access is assessed quickly, and inadequate or missing IVs are converted to large-bore, free-flowing lines. The patient's clothes are removed and placed into a bag, and valuables are collected and catalogued. The trauma nurses are responsible for hanging fluids and setting rates, as determined by the team leader. They have the responsibility of checking blood and assuring that it is administered properly. They may assist in blood draws and administer medications, such as tetanus prophylaxis and antibiotics. Experienced trauma nurses seldom need much direction, and are adept at anticipating tasks and accomplishing them with a high skill level.

The recorder often is a nurse; however, in multiple patient scenarios, anyone who is familiar with the flow sheet can record. All aspects of the resuscitation are recorded to keep a complete record of assessments and treatments. In addition to vital signs and exam findings, the flow sheet should record decisions and events, such as "orthopedics contacted" or "patient vomited." This allows a clear and full picture of what happened during the resuscitation for later review. The team leader has a responsibility to review the trauma flow sheet for accuracy after the resuscitation is over.

A chaplain or social worker is an indispensable part of the trauma team. This person can be a minister from any denomination, and acts as a liaison between the family, patient, and the rest of the trauma team. The initial responsibility of the chaplain is to positively identify the patient and to make contact with the patient's family. The chaplain acts as the primary contact for the family and relays basic information to family members before they arrive at the hospital. Of course, the chaplain also has the role of spiritual leader for the patient and family, and frequently fills the role of counselor. A formal chaplain's note, including information about family contacts, is very helpful to physicians caring for a patient after he or she is transferred from the trauma bay.

A radiology technologist facile with the special requirements of trauma patients can streamline the radiographs taken in the bay. All members of the team should wear lead aprons under their gowns, so that radiographs may be taken while other tasks are completed. An overhead, movable x-ray machine is the fastest and most convenient way to perform radiographic procedures in the trauma bay; however, mobile machines can accomplish the same goals.

Housekeeping often is overlooked as a crucial part of the trauma team. Cleanliness is of the utmost importance, since the same stretcher and equipment may be used to treat several patients each day. Speed also is important, since a dirty bay cannot be used for the next trauma patient who arrives. A fast and efficient housekeeping team can avert many problems in busy centers.

Barrier Precautions. All personnel involved in the direct care of trauma patients must exercise universal precautions against body fluid exposure. The rate of HIV and hepatitis in trauma patients is significantly higher than in the general public, and has been reported to be as high as 19% in some centers.[5] Even in institutions with low rates of communicable disease, no one safely can determine who is and who is not infected with such pathogens. The standard barrier precautions include a hat, face mask, eyewear, gown, gloves, and shoe covers. Even in a busy center with a strict barrier precaution policy, one analysis showed only 89% of practitioners were compliant with the policy.[6] Unannounced trauma arrival is the situation that leads most often to a breach in compliance with precautions. Personnel should be instructed to take the time to put on protective gear, even if it means a one-minute delay in treating the patient.

Physiology of Hemorrhage and Shock

The goal of trauma resuscitation is to stabilize the patient and reverse shock. Hemorrhagic shock is caused by the loss of both circulating blood volume and oxygen-carrying capacity. The most common clinical etiologies are penetrating and blunt trauma, gastrointestinal bleeding, and obstetrical bleeding. Humans are able to compensate for significant traumatic hemorrhage through various neural and hormonal mechanisms. Modern advances in trauma care allow many patients to survive when the adaptive compensatory mechanisms become overwhelmed.[7]

Although there are many clinical causes of shock, the basic cellular derangement in all types involves an imbalance of oxygen utilization. Whenever cellular oxygen demand outweighs supply, both the cell and the organism are in shock. Cells that are not provided with enough oxygen shift from aerobic to anaerobic metabolism. Anaerobic metabolism is much less efficient in producing adenosine triphosphate (ATP) from fuel sources, but it can act to preserve cell function temporarily when there is inadequate oxygen supply.[8] The by-product of anaerobic metabolism is lactic acid, and accumulation of lactate will cause metabolic acidosis. Thus, the amount of lactate, or the severity of acidosis, can be used as a clinical marker of shock.

On a multicellular level, the definition of shock becomes more difficult because not all tissues and organs will experience the same amount of oxygen imbalance for a given clinical disturbance. Clinicians struggle daily to adequately define and monitor oxygen utilization on the cellular level and to correlate this physiology to useful clinical parameters and diagnostic tests.[9]

There are well-described responses to acute loss of circulating volume. The end result of these responses is that they systematically divert circulating volume away from non-vital organ systems so that blood volume is conserved for vital organ function. Acute hemorrhage causes decreased cardiac output and decreased pulse pressure. These changes are sensed by baroreceptors in the aortic arch and atrium. With a decrease in the circulating volume, neural reflexes cause an increased sympathetic outflow to the heart and other organs. The response is an increase in heart rate, vasoconstriction, and redistribution of blood flow away from certain non-vital organs such as the skin, gastrointestinal tract, and kidneys.

Concurrently, there is a multisystem hormonal response to acute hemorrhage. Corticotrophin-releasing hormone is stimulated directly, eventually leading to glucocorticoid and beta-endorphin release. Vasopressin from the posterior pituitary is released, causing water retention at the distal tubules. Renin is released by the juxtamedullary complex in response to decreased blood pressure, leading to increased aldosterone levels and, eventually, to sodium and water resorption. Hyperglycemia commonly is associated with acute hemorrhage. This is due to a glucagon- and growth hormone-induced increase in gluconeogenesis and glycogenolysis. Circulating catecholamines relatively inhibit insulin release and activity, leading to increased plasma glucose.

In addition to these global changes, there are many organ-specific responses. The brain has remarkable autoregulation that keeps cerebral blood flow constant over a wide range of systemic mean arterial blood pressures. The kidneys can tolerate a 90% decrease in total blood flow for short periods of time. With significant decreases in circulatory volume, intestinal blood flow is reduced dramatically by splanchnic vasoconstriction. Early and appropriate resuscitation may avert damage done to individual organs as adaptive mechanisms act to preserve the organism.

The physiologic aim in trauma resuscitation is to stabilize or reverse these physiologic derangements in patients who are in shock. This is accomplished by arresting ongoing hemorrhage, restoring circulating volume, providing oxygen-carrying capacity, and correcting other pathology that ultimately interferes with oxygen delivery (i.e., tension pneumothorax, pericardial tamponade).

Resuscitation Fluid

It perhaps is obvious that the fluid of choice for patients in hemorrhagic shock is blood. However, blood and blood products are not available in the field, and often not during the immediate phase of resuscitation. In types of shock other than hemorrhagic (e.g., septic shock), the patient's hemoglobin level may be even higher than normal, disqualifying blood as an adequate resuscitation fluid. In the absence of blood, there is controversy about what type of substitute fluid should be given, how it should be given, and how much should be used. New technologies and advances in the field of artificial blood have delivered some potential products that may be viable as blood substitutes in the future.[10]

Colloid vs. Crystalloid. Determining the optimal replacement fluid for patients in shock has been controversial since 1918, when fluid resuscitation first was reported to improve outcome in patients with hypovolemia.[11] Physicians realized early on that adequate resuscitation from hemorrhagic shock required the restoration of both circulating volume and oxygen-carrying capacity in the form of red blood cells. Much of the early research demonstrated the improvement in survival after hemorrhage when animals were resuscitated with both lactated Ringer's solution and blood.

During the time of the Vietnam War, complications of resuscitation—most notably, pulmonary dysfunction and renal failure—were appreciated. Many investigators began to search for a resuscitation fluid that could provide intravascular volume while limiting the accumulation of water in the interstitium, especially the lungs. Human albumin was a logical empiric choice, since it provided the intravascular space with oncotic pressure and did not readily cross the capillary membrane. Indeed, early animal studies showed that it remained in the vascular space, raised oncotic pressure, and even improved survival after hemorrhagic shock in some animal studies.[12] Human studies showed that exogenous administration increased serum albumin concentration and increased the oncotic pressure in the blood. Although these finding were encouraging, the effects of albumin were shown to be reversed completely 24 hours after administration.[13] More concerning, patients resuscitated with colloid after major trauma had a worse clinical course, remained on the ventilator longer, and had significantly worse intrapulmonary shunt than those who received crystalloid infusion.[14] Subsequent research has failed to determine if colloid is superior or inferior to crystalloid resuscitation in patients with hemorrhagic shock in regard to survival, pulmonary complications, and resuscitative time.

A large, evidence-based review of more than 82 studies comparing colloid to crystalloid resuscitation recently was reported by a group at McMaster University.[15] The meta-analysis revealed no overall difference in mortality, pulmonary edema, or length of stay between patients resuscitated with primarily colloid vs. crystalloid solutions. In a subgroup analysis, trauma patients who were resuscitated with colloid had a slightly increased relative risk of death, although with a poor confidence interval. The authors conclude that to show definitively a significant difference in mortality between the treatments, a randomized, prospective trial would have to include more than 9000 patients. Based on this and other available evidence, colloid resuscitation does not confer any benefit over crystalloid in hemorrhagic resuscitation. In addition, it does have certain disadvantages. It is a human blood product and is capable of transmitting infectious agents, although the risk is relatively small. It is expensive compared to lactated Ringer's solution, and has a limited shelf life. Therefore, colloid resuscitation cannot be recommended for routine use in the resuscitation of patients with hemorrhagic shock.

Blood. Most blood banks in the United States no longer provide whole blood for transfusion. Donated whole blood is separated into packed red blood cells (PRBCs) and plasma. Plasma from several donors is used to pool platelets, cryoprecipitate, and other special products, such as concentrated factor VIII.

Blood typing is the act of determining the antigens—A, B, or O—that are present on the cell surfaces of the red blood cells of the specimen. Blood type A, therefore, designates the specimen as having type A antigens on the cell surface. A second major antigen is the Rhesus (Rh) factor. Rh incompatibility is much less severe than incompatibility of ABO antigens. The major morbidity of Rh incompatibility is when an Rh-negative, pregnant woman is induced to develop Rh antibodies by exposure to Rh-positive blood. These induced antibodies will not have an effect on the patient, but may cross the placenta during pregnancy and result in a lysis syndrome of the fetal cells if the fetus is Rh-positive.

Although ABO and Rh represent the major antigens, they are only a few of the great number and variety of antigens that may be present on blood cell surfaces. To avoid incompatibility reaction of these minor antigens, blood from specific donors and recipients is mixed to determine if minor incompatibility exists; this is called a crossmatch.

The safest transfusion, and the one that is of least risk to the recipient, is when blood is typed for major antigens and crossmatched for minor antigens. This process can take more than an hour to perform. For patients who need immediate resuscitation for severe trauma, blood must be available before a formal type and crossmatch can be done. For this purpose, banked type O, Rh-negative blood is kept for immediate use. Men can receive Rh-positive blood without significant risk, since Rh incompatibility is relatively minor in males. Of course, type O blood contains A and B antibodies, which can react against the recipient's native cells. This reaction generally is not clinically relevant unless the amount of type O blood transfused is greater than four units within a short period of time. As soon as possible, type-specific, crossmatched blood should be exchanged for O-negative blood for transfusing. This illustrates the importance of sending a blood sample for type and crossmatch soon after the patient arrives in the resuscitation area.

Transfusion Triggers. The decision to transfuse blood is made after consideration of the mechanism of injury and the patient's hemodynamic status, response to crystalloid infusion, and premorbid status. In general, all trauma patients in shock should first receive crystalloid infusion (up to two liters).[16] Most often, this is administered in the field, and the physiologic response to the fluid can be assessed. If hemodynamic instability continues and there is significant blood loss, transfusion is begun immediately. In adults, two units of type O-negative blood are transfused wide open, preferably through a fluid warmer. Women of childbearing age should receive Rh-negative blood, whereas men may receive Rh-positive blood. A sample is sent concomitantly for typing and crossmatching. After each transfusion, the clinical situation is reassessed. Ongoing blood loss will necessitate continuous replacement with blood and crystalloid.

Patients who are not acutely exsanguinating, but have an anemia secondary to blood loss, also must be evaluated with special concern for their premorbid medical status. Several large studies have refuted the idea that there is a threshold hemoglobin or hematocrit that should prompt transfusion in the stable patient.[17,18] One recent large, randomized, multicenter study showed that receiving transfusions to a hemoglobin threshold of 9 g/dL conferred no physiologic or clinical benefit to patients when compared to those who were maintained at 7 g/dL.[19] In some groups, such as young patients with less severe illness (Acute Physiology and Chronic Health Evaluation [APACHE II] scores < 20), the mortality was higher in the group that was maintained at 9 g/dL. Other groups of patients, specifically ones with acute myocardial infarction and unstable angina, showed some benefit from maintaining a transfusion threshold of 9 g/dL. This study is the most definitive evidence that no single number is a universal transfusion trigger for patients with euvolemic anemia.

Some patients may require a large amount of transfusion in a relatively short period of time. Frequently, these patients can stress the capabilities of the hospital and area blood banks. Patients with massive transfusions are at higher risk of dying from their injuries. Independent predictors of mortality in these situations include persistent hypotension, inotrope requirement intra-operatively, and the need for aortic cross-clamping. However, the amount of transfused units has been shown not to be an independent predictor of a bad outcome, and the need for massive resuscitation cannot be used as an indicator to discontinue care.[20]

Plasma, Platelets, and Other Factors. Partitioning blood into cells and products increases efficiency and allows for the greatest benefit for the most patients from the donated pool. However, in trauma, the ideal blood product would be whole, unfractionated blood. This is due to the unique situation in trauma in which the patient requires not only volume and red cell mass, but also coagulation factors. Therefore, during large volume transfusions of PRBCs, decisions must be made as to which other blood products are to be given. Traditionally, patients were given fresh frozen plasma (FFP) and blood in a fixed ratio of two units FFP for every 4-6 units of PRBCs. Although this is a good estimate, the need for continued transfusion of plasma is determined by the clinical situation. Patients with ongoing bleeding and an elevated prothrombin time (PT) should receive additional FFP transfusions. Those without persistent bleeding do not necessarily need to have an abnormal PT corrected. Often, the limiting factor in following laboratory values for assessment of coagulopathy is the delay in getting results from the lab.

Platelets are pooled from several donors to form one unit. This unit often includes platelets from six donors; hence, it is referred to as a "six-pack" or "super pack." Platelets are suspended in plasma and, therefore, contain a small amount of other coagulation factors in addition to the cells. Transfusion triggers for platelets have been abandoned, along with thresholds for red cell transfusion. Platelet counts below $100/mm^3$ are common in severe trauma, and only patients with ongoing bleeding are candidates for transfusion.

Cell-saver Techniques. Autologous blood that can be collected and re-infused provides the best physiologic fluid resuscitation. Several "cell-saver" techniques have been developed to recycle lost blood. A cell-saver device, set up and managed by a certified perfusionist, collects blood through a suction device, admixes with heparin, washes the cells, and allows reinfusion. Large amounts of lost blood can be salvaged in this manner. In addition to providing whole blood and avoiding the risks of donated blood, salvaging autologous blood significantly decreases the cost of resuscitation by avoiding the use of expensive banked blood.[21] Cell-salvaging techniques also can be applied to situations in which the formal cell-saver apparatus is not available. Modification of chest tube collection devices has allowed collection and re-infusion of blood from hemothoraces to be performed at the bedside, without the need for cell-washing and treatment devices.

Hypertonic Saline. Hypertonic saline is a 7% NaCl solution that often is combined with dextran to form a hyperosmolar fluid used for resuscitation. The hypertonicity draws interstitial fluid into the vascular space, causing the effective fluid accumulation in the vessels to be greater than the volume of saline injected. Since saline is freely diffusable, the effect is transient unless a large, non-diffusable molecule, such as dextran 70, is added to maintain oncotic pressure within the lumen.[22] Hypertonic saline (7%)-dextran 70 (HSD) has been used clinically in situations in which large volumes of resuscitation fluid are not available or desirable.[23] Such situations include prehospital resuscitation, combat zones, pediatric resuscitation, and in patients with concomitant severe head injuries. However, there has been no conclusive evidence that hypertonic saline offers any short- or long-term benefit over standard crystalloid resuscitation. A role for hypertonic saline may exist in patients with shock and concomitant head injury. One group has shown that survival was better in this patient population when HSD was used instead of normal saline in the prehospital phase of resuscitation.[24] Further trials are needed to confirm HSD as a standard treatment option.

Delayed Fluid Resuscitation. There is some evidence that over-aggressive fluid resuscitation may be detrimental, especially in patients who have penetrating abdominal or thoracic injury. Animal studies suggest that there may be two stages of bleeding in penetrating injury. The first acute stage of bleeding occurs when the missile or knife disrupts a vessel. With hemorrhage, arterial blood pressure decreases, a clot begins to form at the arterotomy, and the arterial wall goes into spasm. This leads to a significant decrease (or even complete cessation) of bleeding from the site.[25] Aggressive resuscitation with non-blood fluids will increase the arterial pressure, and thereby disrupt the clot that has formed at the bleeding site.[26] There also is evidence that crystalloid resuscitation will dilute clotting factors and lower viscosity, leading to further leaking around the vessel injury. These factors lead to a secondary bleed that some investigators suggest is the cause of significant morbidity and mortality in patients with this type of injury. In 1994, one group reported a prospective, randomized trial that compared immediate vs. delayed resuscitation for patients with penetrating torso trauma.[27] Patients who received no prehospital resuscitation, followed by delayed hospital resuscitation, had an improved mortality over patients who received standard care. The numbers of postoperative complications, such as respiratory failure and renal failure, also were significantly less. Although there have been many criticisms of this larger study, it illustrates that there may be real complications with large volumes of crystalloid resuscitation for trauma patients. The American College of Surgeons recommendations for trauma resuscitation have not changed since the 1994 report, and initial infusion of lactated Ringer's or normal saline remains the standard of care as the initial treatment of hemorrhagic shock.[28]

Blood Substitutes. An oxygen-carrying, oncotic, non-toxic, non-infectious fluid that is abundantly available, cheap, has an indefinite shelf life, and is easy to use always has been desired. The early attempts were to infuse a hemoglobin solution, referred to as "stromal free hemoglobin." Although the solution effectively carried oxygen, it had several major problems. Free hemoglobin is a potent scavenger of nitric oxide (NO) and causes significant vasoconstriction. In addition, the solutions increase the production of toxic oxygen metabolites, resulting in neurotoxicity and renal failure.[29,30]

Modifications of the free hemoglobin have resulted in several hemoglobin-based, oxygen-carrying compounds (HBOCs) that someday may overcome the problems with stromal free hemoglobin.[31] Biochemical schemes to decrease the NO scavenging properties include "hiding" the reactive hemoglobin moiety by polynitroxylation (PN), cross-linking molecules with diaspirin (DCLHb), and polymerizing several molecules together (polyHb).[32] Currently, some of these products are being used in clinical trials, although all continue to have some clinical limitations.[33] Two recent trials using HBOCs for acute resuscitation of trauma patients were conducted. A group from the University of Colorado has used a polymerized hemoglobin, poly SFH-P, in patients requiring emergent blood transfusion for trauma or emergent surgery. Thirty-nine patients received more than six units of poly SFH-P, with a maintenance of the circulating hemoglobin level despite significantly decreasing red cell mass. Oxygenation and oxygen delivery also were preserved. There were no deaths in this series, and there was a conspicuous lack of side effects such as vasoconstriction or renal dysfunction.[34] Thus, a viable blood substitute with minimal clinical side effects soon may be practical. At present, however, such agents are used only in clinical trials.

Endpoints of Resuscitation

Control of hemorrhage, restoration of adequate circulation, and reversal of shock are the goals of resuscitation. Determining exactly when these have been accomplished sometimes is difficult. Clinical indicators of adequate resuscitation include measures of end organ perfusion. However, these clinical markers can be misleading, and various biochemical indices now are being used to determine when adequate tissue perfusion has been achieved.

Traditionally, clinical measures such as heart rate, blood pressure, and urinary output have been used to judge reversal of

shock. Several studies have demonstrated that even with return of normal vitals signs, tissue oxygen imbalance can continue.[35] This is a state of compensated shock, which is common in young, otherwise healthy patients. The potential consequence of prolonged tissue under-perfusion is systemic inflammatory response syndrome, adult respiratory distress syndrome, and multiple organ failure. Therefore, there is a need to assess the reversal of shock on a cellular basis.

Several laboratory methods for assessing cellular oxygen balance have been utilized, including base deficit, lactate level, and mucosal pH monitoring.[36] Base deficit is an indirect measure of lactate production and is a fast, reliable indicator of shock. Several groups have shown that both the degree of base deficit and the time it takes to resolve correlate with the degree of shock.[37] One researcher showed that a base deficit of more than -15 in a patient younger than age 55 without a head injury was a significant marker for mortality after trauma.[38] Others have shown that the persistence or worsening of a base deficit is the best predictor of continued hemorrhage or ongoing shock.[39]

Since the base deficit is a calculated number, it is prone to errors in interpretation. Although lactic acidosis is the most common cause, other conditions can cause an increased base deficit. Hyperchloremic acidosis may result from over-resuscitation with normal saline, secondary to a loss of bicarbonate in the renal tubules. This results in an anion gap acidosis that is not caused by increased lactate production. Thus, it often is helpful to measure the amount of lactate directly instead of relying on the calculated base deficit. The lactate level in trauma patients has been shown to correlate with the depth of shock and to predict mortality.[40] Specifically, it has been shown that patients who have a normal lactate level within 48 hours of injury are much more likely to survive than those who have a persistent lactic acidosis.[41] Therefore, lactate is a good measure of the reversal of shock in the acute period. Lactate levels should be assessed at admission and every 6-12 hours during the acute phase of resuscitation.

Another method for measuring specific tissue perfusion is gastric tonometry. The pHi is the measured pH of the gastric mucosa. This is done clinically with a balloon sensor that is placed into the stomach in a manner similar to a nasogastric tube.[42] Gastric pH falls rapidly and in proportion to splanchnic under-perfusion, and is a very sensitive marker of ongoing oxygen imbalance at the tissue level. One group has used the pHi as an end point of resuscitation of trauma patients, using pHi greater than 7.3 as a marker for adequate tissue perfusion.[42] Although the technique and technology are available, no clear advantage has been shown for using pHi compared to analyzing more simple endpoints, such as lactate determination.

Determining when resuscitative efforts have been successful includes a clinical and biochemical assessment. Patients with stabilizing blood pressure and heart rate, adequate urine output, and appropriate mental status are believed to be clinically resuscitated from shock. Measurement of the base deficit and lactate levels will unveil ongoing tissue under-perfusion in patients with compensated shock. Assessing the trend of the base deficit and lactate level can help predict the risk of mortality in patients with significant trauma. New technologies, although encouraging, currently show little benefit over other, more traditional measures of organ perfusion.

Special Situations

Closed Head Injury. Hemorrhagic shock with concomitant closed head injury (CHI) portends a poor prognosis. One of the worst prognostic indicators for recovery after CHI is significant and persistent hypotension. Treatment of the CHI in these situations is aimed at restoring blood pressure, controlling bleeding, and assuring adequate cerebral perfusion pressure (CPP). When faced with the dilemma of CHI and persistent hypotension, diagnosis and treatment of the hemorrhage always takes precedence. Therefore, an unstable patient with evidence of intra-abdominal bleeding and a severe CHI would be taken directly to the OR for exploratory laparotomy, deferring the head CT scan until after bleeding is controlled and circulating blood volume is restored. A secondary concern is cerebral swelling and increasing intracranial bleeding. Although these conditions may be exacerbated by aggressive fluid resuscitation, adequate volume should not be withheld in patients who are in shock. Some have advocated using hypertonic saline in these patients, to provide adequate vascular volume while limiting the excess water administration. One prospective, randomized trial found that hypertonic saline was successful in providing volume while controlling intracranial pressure.[43]

Spinal Cord Injury. Spinal cord injury may superimpose neurologic shock onto hemorrhagic shock. Unstable patients with a known spinal cord injury first must be treated as if the hemodynamic instability is secondary to blood loss. Paraplegia or tetraplegia can impede the diagnosis of abdominal injury significantly by masking physical exam findings. The treatment for both types of shock is aggressive fluid administration, and this should be started on arrival. If ongoing bleeding eventually is excluded, and the patient is felt to have isolated neurologic shock, then vasopressors are indicated after adequate volume loading. Patients with neurologic shock are vasodilated inappropriately and often bradycardic due to a loss of sympathetic tone. Dopamine is the drug of choice, because it will cause vasoconstriction, increased chronotropy, and increased inotropy. Phenylephrine, a pure alpha agonist, also may be added to counteract the severe vasodilation.

The Elderly Patient. Although it is true that elderly patients have less physiologic reserve, more premorbid conditions, and less ability to compensate for injury, it is not true that age alone predicts morbidity and mortality in trauma. Several physiologic parameters are compromised in the older patient, including vascular compliance, myocardial reserve, and bone strength.[44] However, it has been shown that the elderly can respond to resuscitation after serious insults, and that age alone should not be used as marker for determining futile care.[45]

Initial management of the elderly is the same as for younger patients. Early determination of premorbid conditions, medications, and previous surgery is more urgent than usual. Heart disease is the leading premorbid condition that puts elderly patients

at higher risk for complications following even minor trauma. A diligent search for a history of myocardial infarction or unstable angina may explain early hemodynamic instability in the face of trivial injury. The use of beta-blockers is widespread, and this may inhibit the patient from developing an appropriate tachycardia after injury. Coumadin, aspirin, and anti-platelet drugs are some of the many medications that cause these patients to be anticoagulated at the time of injury, putting them at risk for significant bleeding complications.[46] All elderly patients who arrive unresponsive are assumed to be taking such medications until laboratory confirmation, or until an adequate accurate history is found.

The Pediatric Patient. Pediatric patients initially are treated in the same manner as adult patients in regard to primary and secondary assessments and interventions. The difference is the child's physiological response to injury and the anatomical and clinical differences in treating a pediatric patient. Children have certain characteristics that make trauma resuscitation more difficult. First, communication is not always possible to the extent that it is with an adult patient. The physical exam findings become more important, and the clinician relies more on objective signs of injury than on chief complaints. The blood volume of children obviously is less, predisposing them to accelerated exsanguination. The relatively large body surface area contributes to rapid heat loss during resuscitation. Technical procedures can be more difficult in the child, especially venous access and endotracheal intubation.

Perhaps the most significant difference between adult and pediatric blunt trauma is that the vast majority of pediatric patients can be resuscitated and ultimately treated non-operatively. Whereas quick decisions are made about whether to operate immediately on adults, pediatric patients very rarely will need an emergent procedure. Blunt injuries to the spleen, liver, kidney, and pancreas, which in the past mandated surgery, now are being treated non-operatively with great success.[47] Currently, the diagnostic test of choice is CT scan, which not only will identify injuries, but also classify them. All grades of liver, spleen, and kidney injuries can be managed non-operatively, depending on the hemodynamic stability and the patient's physiologic response to resuscitation. Pediatric surgeons often will transfuse up to 40 cc/kg of blood products in an effort to stabilize children before reverting to laparotomy for even severe injury, because exploration has been shown to increase blood loss and transfusion requirement over successful, non-operative management. Therefore, children with all grades of injury should be treated based on their physiologic response to resuscitation. If the hemodynamics stabilize after transfusion, observation continues in the ICU. If the child fails and continues to be unstable, laparotomy is indicated.[48] In penetrating trauma this is not true, and children are similar to adults in the indications and need for prompt surgery.

Conclusion

The most critical aspect of trauma resuscitation is preparation. A specified room and easily accessible equipment and resources are critical factors for the smooth functioning of a trauma team, even in the most rural setting. Assigned responsibilities and easy access to equipment required for procedures facilitate an efficiently run trauma resuscitation. Knowledge of the acute presentation of patients in shock and techniques for rapid resuscitation enables the physician to confidently facilitate the rapid stabilization of a trauma patient. In addition, knowledge of the controversies and alternatives for fluid resuscitation guide the critical decisions that must be made early in the patient's clinical course.

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Physician CME Questions

To earn CME credit for this issue of Trauma Reports, *please refer to the enclosed Scantron form for directions on taking the test and submitting your answers.*

1. Physiologic mechanisms in hemorrhagic shock include:
   A. a shift from anaerobic to aerobic metabolism.
   B. increased splanchnic circulation.
   C. decreased oxygen utilization in peripheral tissue.
   D. insulin surge.

2. Which of the following is an absolute indication for blood transfusion?
   A. Persistent tachycardia
   B. Physiologic instability with ongoing blood loss
   C. Blood pressure of 140 mm/Hg
   D. Hemoglobin less than 7 g/dL

3. A patient with evidence of both hemorrhagic and neurologic shock is treated best initially with which of the following?
   A. Phenylephrine
   B. Crystalloid and dopamine
   C. Crystalloid only
   D. Dopamine only

4. The most accurate measure of adequate clinical resuscitation is:
   A. normal lactate level.

B. base deficit of -1.
C. return of normal vital signs.
D. urine output of more than 1 cc/kg/hr.

5. The primary role of the command physician in a horizontal trauma resuscitation configuration is:
   A. recording events on the flow sheet.
   B. initiating ECG, oximetry, and blood pressure monitoring.
   C. airway control and overall management.
   D. keeping control and making treatment decisions.

6. Which of the following is true for patients with hemorrhagic shock and closed head injury?
   A. Craniotomy takes precedence over all other interventions.
   B. Laparotomy takes precedence over craniotomy.
   C. Decreasing intracerebral pressure with mannitol is the first priority.
   D. CT scan of the head should be performed before laparotomy.

7. What drug is every elderly trauma patient assumed to be taking until proven otherwise?
   A. Beta-blocker
   B. Coumadin
   C. ACE inhibitor
   D. Valium

8. In a vertical resuscitation:
   A. the command physician oversees the activities of other staff.
   B. clinicians are assigned one specific responsibility.
   C. resuscitation time generally is longer than in horizontal resuscitation.
   D. chest tube placement is completed before the secondary survey is started.

9. Pediatric trauma patients differ from adults in that:
   A. blood transfusion is more common in children.
   B. head injuries are less common in children.
   C. non-operative management of injuries is more common in children.
   D. the primary and secondary surveys have different steps.

CME Objectives

Upon completing this program, the participants will be able to:

a.) Quickly recognize hemorrhagic shock and the appropriate responses to it;
b.) Be educated about resuscitation fluids and when fluids should be administered or withheld;
c.) Understand the most efficient way of conducting a trauma resuscitation;
d.) Understand factors that affect resuscitations in patients who are elderly or pediatric, or who have closed head or spinal cord injuries; and
e.) Recognize the goals and endpoints of resuscitation.

10. Which fluid is most appropriate to use during the initial phase of a trauma resuscitation?
   A. Colloid
   B. Crystalloid
   C. Hypertonic saline
   D. Poly SFH-P

In Future Issues:

Pelvic Fractures

BIOTERRORISM WATCH
Preparing for and responding to biological, chemical and nuclear disasters

Traumatized health care providers may need stress counseling in horrific aftermath of bioterror attack

A severe test for a mentally tough profession

In a finding that is likely relevant to many other states, a recent tabletop exercise in Columbus, OH, found that the health care system may be better prepared to deal with bioterrorism victims than the traumatized frontline providers who give them care.

The exercise was conducted by the Ohio Senior Interagency Coordinating Group in Columbus.

After running a scenario involving intentional release of pneumonic plague at a rock concert, emergency preparedness officials discovered there was little in place to address the mental health needs of doctors and nurses in the horrific aftermath. In the exercise, an attack with *Yersinia pestis* resulted in 332 fatalities, 720 hospitalizations, and 4,300 people who were examined and released.

"How do you handle all of the nurses and doctors who have seen many, many deaths, who have tried to decrease panic by remaining calm, and who have survived this huge confusion and turmoil?" asks **Kay Ball**, RN, MSA, CNOR, FAAN, a participant in the exercise and perioperative consultant and educator at K & D Medical in Lewis Center, OH. "What about their mental health? That is something that we found that we are weak in. We really have to develop that better."

The hypothetical event began Friday, March 15, when a popular regional band performed at Shawnee State University in Portsmouth, OH. Approximately 2,000 students and community members went to see the band, which is known for its use of smoke and visual enhancements, according to the scenario. **(See tabletop timeline, p. 3.)**

"[The terrorists] aerosolized the agent in a fogging system and that is how it was spread throughout the building." says **Darren Price**, exercise training officer with the state of Ohio Emergency Management Agency in Columbus.

The players take their seats

The exercise had four groups of about nine people, each working at different tables as the events unfolded. The groups were health / medical, law enforcement, fire / emergency medical services, and government. An audience of about 150 people was on hand to observe and evaluate the exercise.

"The whole purpose was to determine our strengths and weaknesses through the disaster that happened," says Ball, who served as facilitator and discussion leader of the health / medical group. "The planning committee will meet and analyze what we learned from this, and then we will bring back everybody who participated."

The scenario was divided into three phases: incubation, response, and recovery. Each phase received about an hour of discussion at the tables, and all players received updated information at the same time. **(See tabletop tips, p. 2.)** The scenario was necessarily arbitrary but designed to

This supplement was written by Gary Evans, editor of *Hospital Infection Control.* Telephone: (706) 742-2515. E-mail: gary.evans@ahcpub.com.

test the state's resources at many levels, Price notes.

"Anytime, you are dealing with tabletop exercises there are a lot of assumptions and artificialities built in just to make it flow," he says. "We ask [participants] to bring their emergency operations procedures and plans, and to actually react based upon their plan."

While the exercise is still being analyzed, the mental health needs for medical providers became apparent in playing out the scenario. Part of the problem is the historic perception that health care workers must not succumb to the emotional toll of patient care, Ball says.

"Even in surgery today, if we lose a patient on the table, there is nothing really in place to talk about the trauma the practitioners are going through," she says. "We just think that we are these stalwart people and we can't crumble under emotional strains. That was one of the [identified] weaknesses."

In contrast, firefighters and emergency medical service workers had a more thorough stress debriefing process than their hospital-based counterparts.

"Within the hospitals themselves we really don't have the mental and spiritual health that we need," she says.

Moreover, the scenario projected widespread "psychological manifestations" in the affected area, with students withdrawing from school and residents reluctant to return to their homes. Bioterrorism response planners brainstormed about how to fight the problem, including bringing in celebrities and public officials to show it was safe to return to the stricken area.

The scenario included a short delay in determining the etiological agent, with chaos building before plague was confirmed as the infecting pathogen. Even with the new emphasis on bioterror education, that scenario is fairly realistic because so few clinicians have seen infections caused by the potential bioterrorism pathogens.

"The first problem was what kind of a bug was it?" Ball says. "Where do we send the cultures, and how fast can we get them back?

The scenario also had many students leaving on spring break. Given the anticipated exodus of people from the community — particularly into the neighboring states of Kentucky and West Virginia — there was no attempt to set up mass quarantine areas, Price says. Instead the national stockpile of antibiotics was called up and confirmed or suspect cases were treated and isolated.

"We looked at the issue of quarantine and determined it was not really feasible," he says. "You would have these large [quarantine] circles everywhere. We moved more toward isolation [of patients] at that point."

While identifying a weakness in mental health care, the planners found communications were strong between groups, there were no turf battles, and additional resources became available quickly.

"One of the strengths that we found was that we were able to get supplies in and to call in extra people," Ball says. "We were able to pull in lots of people very rapidly. We are learning how to work more with all of the other diverse factions."

Indeed, the exercise was set in a rural area so that resources would be taxed, reaching thresholds that would trigger state response, Price adds.

"We're better prepared today than we were yesterday," he says. ■

Bioterror tips for running a tabletop

Planners of a recent bioterrorism tabletop exercise in Columbus, OH, **(see cover story for more information)** offered the following tips for participants in the exercise:

- The scenario is plausible, and events occur as they are presented.
- There are no hidden agendas or trick questions.
- All players receive information at the same time.
- There is not a "textbook" solution. Varying viewpoints and possible disagreements are anticipated.
- Respond based on your knowledge or current plans and capabilities.
- Current agency or department policies and procedures should not limit discussion and development of key decisions.
- The outcome is neither intended to set precedents or reflect an organization's final position on specific issues.
- Assume cooperation and support from other responders and agencies.
- Speak up! Talk to your colleagues and ask questions. This is your chance to learn how other agencies in your community would respond in an emergency. ■

Dire straits: Plague released at concert

Tabletop scenario from first case to aftermath

Highlights of a recent bioterrorism tabletop exercise run by planners in Ohio **(see cover story for more information)** included the following timeline of events:

Sunday, March 17, 2002, Portsmouth, OH

8:00 a.m.: At the emergency department (ED) of Southern Ohio Medical Center (SOMC), a doctor has just come on duty and sees her first patient, a 22-year-old woman. The patient's sister says the woman has been complaining of chest pain and has a temperature of 102 degrees F. The sister worries that the patient may have caught the "bug" through her position at the Shawnee State University (SSU) dormitory mailroom where she works part time. A rapid flu test shows a negative result.

The physician is suspicious in light of the national anthrax cases five months earlier and orders a sputum and blood culture. Transport assistance is requested for sending the cultures to the Ohio Department of Health (ODH) laboratory for anthrax testing. The woman is admitted. The Portsmouth City Health Department and Scioto County District Board of Health are notified of the situation. In turn, the ODH and Ohio Emergency Management Agency (EMA) duty officer are called.

2:00 p.m.: The 22-year-old woman admitted to SOMC earlier this morning develops severe respiratory complications and dies. A full autopsy is ordered, and the physician awaits the preliminary results of the sputum and blood cultures. As the day progresses, local emergency medical services (EMS) become overwhelmed with patients presenting with flu-like symptoms. People presenting with the most severe symptoms, including high fever and difficulty breathing, are hospitalized; however, with many more sick waiting in the ED, the hospital beds and wards are filling rapidly.

5:00 p.m.: Traffic around SOMC becomes impassible, and several ambulances are severely hindered. Medical facilities request security assistance from local law enforcement agencies.

10:00 p.m.: Six patients admitted during the day with the severe flu-like symptoms also die. New cases continue to arrive at SOMC with an increase in the number of patients reporting each hour.

Monday, March 18

8:00 a.m.: Overnight, a public health emergency was declared in Scioto County. A request was made by Scioto County Health, via the Scioto County EMA and elected officials for state support in the growing crisis.

A Level 2 emergency status is reached in Scioto County. The state assessment room is activated to support the events in Scioto County.

10:00 a.m.: The preliminary tests of clinical specimens taken from the 22-year-old woman who died Sunday are complete. The ODH Lab notifies the local health departments that the specimens have tested negative for *Bacillus anthracis.* The laboratory begins rule-out testing for other pathogens.

3:00 p.m.: Epidemiological evidence points to an event three days earlier as a common activity of the majority of new patients. On Friday, March 15, a popular regional band performed at SSU in Portsmouth. The band is well known for use of visual enhancements. Approximately 2,000 students and community members attended the concert.

4:00 p.m.: Hospital supplies are insufficient to meet demand. Fifteen additional patients have died, and 111 are listed in critical condition. Reports now include similar symptoms among several health care workers and first responders. SOMC hospital beds are full.

5:30 p.m.: ODH Lab staff notifies Scioto County local health officials that the 22-year-old patient's cultures are preliminarily positive for *Yersinia pestis.* Local health officials inform local health care professionals and EMS personnel that, in order to prevent the spread of disease, patients having confirmed pneumonic plague should be isolated until sputum cultures are negative for *Y. pestis* bacilli.

Those suspected of having pneumonic plague should be isolated for 48 hours after antibiotic treatment begins.

Wednesday, March 27

It has been 10 days since the first victims arrived at SOMC and local clinics. There have been no further cases of illness identified in Scioto County in the past seven days.

Waiting for signs of recovery

Resources begin to flow into the area as a result of national public outreach. Visitors, however, avoid the area and the impact of the event on the local economy becomes apparent as local businesses are slow to reopen.

The psychological manifestations associated with this event are widespread. Although school reopens, many students withdraw from classes for the quarter. Local residents, still frightened and shocked, look to local and state officials for guidance as they attempt to return to normalcy. ■

Winds of war: Researchers track airborne anthrax

A strikingly rapid and wide dispersion

Struck by the surprising level of aerosolization after merely opening an envelope, Canadian researchers are now using a spore surrogate to study how airborne anthrax silently spreads within an office building, *Bioterrorism Watch* has learned.

Researchers are using *Bacillus globigii* spores to simulant the movements of *Bacillus anthracis* in a one-story research building at the Defence Research Establishment Suffield (DRES) at the Canadian Forces Base in Suffield, Alberta, says **Kent Harding,** chief scientist at DRES. "We will be looking at movement between actual offices along corridors using the *B. globigii* as a simulant. It is a spore-like material that is a well-accepted simulant used to assess and challenge biological detection apparatus." The DRES is on the cutting edge of bioterrorism research; scientists there were studying the dispersion of anthrax from envelopes prior to Sept. 11 and its aftermath. In response to an anthrax hoax mailing in Canada in February 2001, the DRES conducted a study last year using an 1,800 cubic foot test chamber to represent an office space. "We had a hoax letter in this country that closed down a major federal office building," he says. "We were interested in [determining] had it been a real infectious material in the envelope, what was the extent of the risk? We went to the scientific literature and really didn't find anything."

It was hypothesized that opening an envelope constituted a "passive form of dissemination" that would produce minimum aerosolization of spores unless additional energy was added via panic behavior or strong airflows, the researchers stated.[1]

"Our scenario was in a chamber, which was conducive to studying the movement of materials on air currents." Harding says. "An individual was given a stack of envelopes and told to keep opening them until powder fell out. When that happened, [he or she] stood quietly by the desk and didn't move for 10 minutes. We just looked at the movement of material around the room, just simply as a consequence of opening the envelope and pulling out a piece of standard 8½ by 11 paper folded in three." Almost immediately upon opening the envelope, a significant aerosol concentration was observed in the area of the "desk." It declined slowly over the 10-minute sampling period, but the high-resolution slit sampler plates used to measure the release became densely packed with bacterial colonies. In the study, significant numbers of respirable aerosol particles were released upon opening envelopes containing 0.1 g or 1.0 g of *B. globigii* spores. A potentially deadly dose could be inhaled within seconds of opening an anthrax spore-filled envelope. Also, the aerosol quickly spread throughout the room so that other workers, depending on their exact locations and the directional airflow within the office, would likely inhale doses. There was very heavy contamination on the back and front of clothing worn by the test subject.

"There was a large dose presented to the person opening the envelope, which was not unexpected," Harding says. "But what was surprising was the very rapid and extensive movement around that room simply as consequence of the movement of normal air currents. It distributed around the room very quickly and in fairly high quantity."

The researchers also found that the spores could escape from a sealed envelope, a phenomenon that caught U.S. investigators off-guard during the 2001 attacks. "We did note that in a standard envelope sealed in the usual way — just with licking the glue on the back of — that there are substantial openings on the back of the envelope," he says. "In fact, the 'envelope people' design them that way so you can get a letter opener inside. Spores did escape from those openings, but we never quantified that and never referred to it to anything more than an anecdotal manner."

The Centers for Disease Control and Prevention (CDC) in Atlanta was apparently unaware of the study during the initial stages of the U.S. anthrax attacks. Whether it would have made any difference is impossible to say, though some wonder if it would have resulted in more aggressive treatment of postal workers.[2] Regardless, the CDC decision to administer antibiotics to a broad range of people, not just those in the immediate exposure area, is reinforced by the study, Hawkins says. The Canadian researchers have now fully briefed the CDC about the study and their ongoing research.

References

1. Defence Research Establishment Suffield. Kournikakis B, Armour SJ, Boulet CA, et al. Risk assessment of anthrax threat letters. September 2001. *Technical Report DRES TR-2001-048*.

2. Brown D. Agency with most need didn't get anthrax data. *Washington Post*, Feb. 11, 2002:A / 03. ■