TABLE 153-4 RISK FACTORS FOR EARLY DETERIORATION IN CAP

Multilobar infiltrates	Hypoalbuminemia
Severe hypoxemia (arterial saturation <90%)	Neutropenia
Severe acidosis (pH <7.30)	Thrombocytopenia
Mental confusion	Hyponatremia
Severe tachypnea (>30 breaths/min)	Hypoglycemia

Among patients with scores of ≥3, mortality rates are 22% overall; these patients may require ICU admission.

It is not clear which assessment tool is superior. Whichever system is used, these objective criteria must always be tempered by careful consideration of factors relevant to individual patients, including the ability to comply reliably with an oral antibiotic regimen and the resources available to the patient outside the hospital.

Neither PSI nor CURB-65 is accurate in determining the need for ICU admission. Septic shock or respiratory failure in the emergency department is an obvious indication for ICU care. However, mortality rates are higher among less ill patients who are admitted to the floor and then deteriorate than among equally ill patients monitored in the ICU. A variety of scores have been proposed to identify patients most likely to have early deterioration **(Table 153-4)**. Most factors in these scores are similar to the minor severity criteria proposed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) in their guidelines for the management of CAP.

ANTIBIOTIC RESISTANCE

Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Misuse of antibiotics results in increased antibiotic selection pressure that can affect resistance locally or even globally by clonal dissemination. For CAP, the main resistance issues currently involve *S. pneumoniae* and CA-MRSA.

S. pneumoniae In general, pneumococcal resistance is acquired (1) by direct DNA incorporation and remodeling resulting from contact with closely related oral commensal bacteria, (2) by the process of natural transformation, or (3) by mutation of certain genes.

The minimal inhibitory concentration (MIC) cutoffs for penicillin in pneumonia are ≤2 μg/mL for susceptibility, >2–4 μg/mL for intermediate, and ≥8 μg/mL for resistant. A change in susceptibility thresholds resulted in a dramatic decrease in the proportion of pneumococcal isolates considered nonsusceptible. For meningitis, MIC thresholds remain at the former higher levels. Fortunately, resistance to penicillin appeared to plateau even before the change in MIC thresholds. Pneumococcal resistance to β-lactam drugs is due solely to low-affinity penicillin-binding proteins. Risk factors for penicillin-resistant pneumococcal infection include recent antimicrobial therapy, an age of <2 years or >65 years, attendance at day-care centers, recent hospitalization, and HIV infection.

In contrast to penicillin resistance, resistance to macrolides is increasing through several mechanisms. *Target-site modification* caused by ribosomal methylation in 23S rRNA encoded by the *ermB* gene results in high-level resistance (MICs, ≥64 μg/mL) to macrolides, lincosamides, and streptogramin B–type antibiotics. The *efflux mechanism* encoded by the *mef* gene (*M phenotype*) is usually associated with low-level resistance (MICs, 1–32 μg/mL). These two mechanisms account for ~45% and ~65%, respectively, of resistant pneumococcal isolates in the United States. High-level resistance to macrolides is more common in Europe, whereas lower-level resistance predominates in North America.

Pneumococcal resistance to fluoroquinolones (e.g., ciprofloxacin and levofloxacin) has been reported. Changes can occur in one or both target sites (topoisomerases II and IV) from mutations in the *gyrA* and *parC* genes, respectively. In addition, an efflux pump may play a role in pneumococcal resistance to fluoroquinolones.

Isolates resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered MDR strains. The propensity for an association of pneumococcal resistance to penicillin with reduced susceptibility to other drugs, such as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole, also is of concern. In the United States, 58.9% of penicillin-resistant pneumococcal isolates from blood are also resistant to macrolides.

The most important risk factor for antibiotic-resistant pneumococcal infection is use of a specific antibiotic within the previous 3 months. Therefore, a patient's history of prior antibiotic treatment is a critical factor in avoiding the use of an inappropriate antibiotic.

CA-MRSA CAP due to MRSA may be caused by the classic hospital-acquired strains or by the more recently identified, genotypically and phenotypically distinct community-acquired strains. Most infections with the former strains have been acquired either directly or indirectly by contact with the health care environment and would now be classified as HCAP. However, in some hospitals, the CA-MRSA strains are displacing the classic hospital-acquired strains—a trend suggesting that the newer strains may be more robust and blurring this distinction.

Methicillin resistance in *S. aureus* is determined by the *mecA* gene, which encodes for resistance to all β-lactam drugs. At least five *staphylococcal chromosomal cassette mec* (*SCCmec*) types have been described. The typical hospital-acquired strain usually has type II or III, whereas CA-MRSA has a type IV SCC*mec* element. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline in addition to vancomycin and linezolid. However, the most important distinction is that CA-MRSA strains also carry genes for superantigens, such as enterotoxins B and C and Panton-Valentine leukocidin, a membrane-tropic toxin that can create cytolytic pores in polymorphonuclear neutrophils, monocytes, and macrophages.

Gram-Negative Bacilli A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter **(Chap. 186)**. Fluoroquinolone resistance among isolates of *Escherichia coli* from the community appears to be increasing. *Enterobacter* species are typically resistant to cephalosporins; the drugs of choice for use against these bacteria are usually fluoroquinolones or carbapenems. Similarly, when infections due to bacteria producing extended-spectrum β-lactamases are documented or suspected, a fluoroquinolone or a carbapenem should be used; these MDR strains are more likely to be involved in HCAP.

INITIAL ANTIBIOTIC MANAGEMENT

Since the etiology of CAP is rarely known at the outset of treatment, initial therapy is usually empirical, designed to cover the most likely pathogens **(Table 153-5)**. In all cases, antibiotic treatment should be initiated as expeditiously as possible. The CAP treatment guidelines in the United States (summarized in Table 153-5) represent joint statements from the IDSA and the ATS; the Canadian guidelines come from the Canadian Infectious Disease Society and the Canadian Thoracic Society. In all these guidelines, coverage is always provided for the pneumococcus and the atypical pathogens. In contrast, guidelines from some European countries do not always include atypical coverage based on local epidemiologic data. The U.S./Canadian approach is supported by retrospective data derived from administrative databases including thousands of patients. Atypical pathogen coverage provided by the addition of a macrolide to a cephalosporin or by the use of a fluoroquinolone alone has been consistently associated with a significant reduction in mortality rates compared with those for β-lactam coverage alone.

Therapy with a macrolide or a fluoroquinolone within the previous 3 months is associated with an increased likelihood of infection with a resistant strain of *S. pneumoniae*. For this reason, a fluoroquinolone-based regimen should be used for patients recently given a macrolide, and vice versa (Table 153-5).