Infections due to *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have become common in various populations, especially critically ill patients. Although clinicians have been aware of the high mortality associated with *P. aeruginosa* infections, there has been a controversy regarding the mortality directly attributable to *A. baumannii*. Recent data have shown that *A. baumannii* infection is also associated with considerable mortality. Another development with major public health implications is the advancing antimicrobial resistance of *P. aeruginosa* and *A. baumannii* isolates that may be intrinsic or acquired and is mediated with various mechanisms of resistance (production of beta-lactamases or enzymes inactivating aminoglycosides, efflux pumps, lower permeability of the outer membrane, mutations in antibiotic targets, etc.). A broad-spectrum beta-lactam antibiotic, such as imipenem/cilastatin, has been considered as the first choice for *P. aeruginosa* and *A. baumannii* infections. Meta-analyses of data from randomized controlled trials have shown that the addition of an aminoglycoside to a beta-lactam agent does not offer advantages compared to beta-lactam monotherapy; however, this issue needs further clarification in the specific population of patients with *P. aeruginosa* bacteremia. The worrisome pattern of increasing antimicrobial resistance of *P. aeruginosa* and *A. baumannii* isolates (including carbapenem resistant isolates) has led to re-evaluation and use of polymyxins (colistin and polymyxin B) in various parts of the world. In addition, the administration of antimicrobial agents directly into the respiratory tract for the prevention and treatment of ventilator associated pneumonia (VAP) has been under investigation. Also, various agents with novel mechanisms of antibacterial action have been studied; however, there are no clinical data available regarding their effectiveness and safety.