 of severe sepsis, fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems, and amikacin—either alone or in combination—are the safest choices pending susceptibility data.

INFECTIONS CAUSED BY MISCELLANEOUS GENERA

Species of *Hafnia*, *Kluyvera*, *Cedecea*, *Pantoea*, *Ewingella*, *Leclercia*, and *Photorhabdus* are occasionally isolated from diverse clinical specimens, including blood, sputum, urine, cerebrospinal fluid, joint fluid, bile, and wounds. These organisms are rare and usually cause infection in a compromised host or in the setting of an invasive procedure or a foreign body. Cephalosporinases from *Kluyvera* have been implicated as the progenitors of CTX-M ESBLs.

187 *Acinetobacter* Infections

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Infections with bacteria of the genus *Acinetobacter* are established as a significant problem worldwide. *Acinetobacter baumannii* is particularly formidable because of its propensity to acquire antibiotic resistance determinants. Endemic infections caused by strains of *A. baumannii* resistant to multiple antibiotic classes, including carbapenems, are a serious concern in many specialized hospital units, especially intensive care units (ICUs). The foremost implication of infection with carbapenem-resistant *A. baumannii* is the need to use "last-line" antibiotics such as colistin, polymyxin B, or tigecycline; these options have the potential to render these bacteria resistant to all available antibiotics.

DEFINITION

Acinetobacter species are oxidase-negative, nonfermenting, short, gram-negative bacilli. They were traditionally thought of as nonmotile—a characteristic from which the genus name was derived (from the Greek *akineto*, meaning "nonmotile"). However, recent work has shown that *Acinetobacter* organisms demonstrate motility under certain growth conditions. The bacteria grow well at 37°C in aerobic conditions on a range of laboratory media (e.g., blood agar). Some species may not grow on MacConkey agar. Differentiation of *Acinetobacter* species is difficult with the means typically available to most clinical microbiology laboratories, including commercial semiautomated identification systems. The commonly used matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) systems are undergoing evaluation for species-level identification of *Acinetobacter*. DNA–DNA hybridization is a method used for speciation in reference laboratories. Naturally occurring oxacillinase genes (bla_{OXA}) have been identified in several *Acinetobacter* species, and their detection by polymerase chain reaction can aid in species identification.

ETIOLOGY

Widely distributed in nature, *Acinetobacter* species can be found in water, in soil, and on vegetables. *Acinetobacter* is a component of the human skin flora and is sometimes identified as a contaminant in blood samples collected for culture. Fecal carriage can be detected in both healthy and hospitalized individuals. However, despite the ubiquity of some *Acinetobacter* species, the natural habitat of the most clinically important species, *A. baumannii,* remains to be fully defined.

EPIDEMIOLOGY

A. baumannii infections have been diagnosed in patients on all inhabited continents. The vast majority of infections occur in hospitalized patients and other patients with significant health-care contact. Outbreaks of carbapenem-resistant *A. baumannii* are particularly problematic. A significant issue is the introduction of carbapenem-resistant *A. baumannii* into hospitals as a result of medical transfers, especially from hospitals where the organism is highly endemic.

The Americas In 1991 and 1992, outbreaks of carbapenem-resistant *A. baumannii* infection occurred in a hospital in New York City. Subsequently, numerous other hospitals in the United States and South America have had outbreaks of carbapenem-resistant *A. baumannii*. Infections with *A. baumannii* among military personnel from the United States and Canada injured in Iraq or Afghanistan were widely observed beginning in 2002. *Acinetobacter* was one of the most common causes of bloodstream infections and bone and soft tissue infections after war-related injury. An epidemiologic investigation revealed that *A. baumannii* could be grown from environmental sites in field hospitals and that the environmental strains were closely related genotypically to clinical isolates.

Europe *A. baumannii* infections have posed a substantial clinical challenge in many parts of Europe since the early 1980s. Three clones (European clones I, II, and III) have been the predominant causes of *A. baumannii* infection in hospitals in Europe. Carbapenem resistance in *A. baumannii* is a significant issue in many European countries, most notably the United Kingdom, Greece, Italy, Spain, and Turkey.

Asia, Australia, the Middle East, and Africa Although surveillance data are sparse from many countries in these regions, problems with carbapenem-resistant *A. baumannii* abound. Community-acquired infections are well described in northern Australia and some parts of Asia. These infections may be more likely in men >45 years of age who have histories of cigarette smoking, alcoholism, diabetes mellitus, or chronic obstructive airway disease. Community-acquired strains are more susceptible to antimicrobial agents than are hospital-acquired strains, but the clinical presentation of community-acquired disease is quite distinct and is characterized by overwhelming infection with severe pneumonia, septic shock, and multiorgan failure.

PATHOGENESIS

A. baumannii colonizes patients exposed to heavily contaminated hospital environments or to the hands of health care workers in these locations. Emerging data suggest that the organism can be found in the air in rooms of patients infected with *Acinetobacter*. Colonization of the upper airways in mechanically ventilated patients may lead to nosocomial pneumonia. Colonization of the skin may lead to central line–associated bloodstream infection, catheter-associated urinary tract infection (UTI), wound infection, or postneurosurgical meningitis. Throat carriage and microaspiration may be involved in the pathogenesis of community-acquired pneumonia due to *A. baumannii*.

Much less is known about the virulence mechanisms of and host responses to *A. baumannii* than about these aspects of other pathogenic gram-negative bacteria. Because of the emergence of multidrug-resistant strains, including those resistant to all available antibiotics, the impetus to study *A. baumannii* pathogenesis has grown. Novel targets for antibacterial drug development are desperately required, and drugs that have antivirulence mechanisms may provide new therapeutic options. Specific virulence mechanisms in *A. baumannii* include iron acquisition and transport systems; outer-membrane protein A (OmpA), which mediates mammalian cell adhesion, invasion, and cytotoxicity through mitochondrial damage and initiation of caspase-dependent apoptosis; lipopolysaccharide (LPS); and proteins important in the formation of biofilm on abiotic and biotic surfaces. Biofilm formation on abiotic surfaces is dependent on a pilus assembly system, which in turn is controlled by a traditional two-component regulatory system mediated by *bfmR*. Also important in biofilm formation are a gene that encodes a biofilm-associated protein (Bap); OmpA; the quorum-sensing gene *abaI*, which controls the secretion of 3-hydroxy-C_{12}-homoserine lactone; and the *pga* locus, which is essential for the production of the polysaccharide poly-β-1,6-*N*-acetylglucosamine. Most recently, a global virulence regulator known