Chapter 4
Resistance of Gram-Negative Bacilli to Antimicrobials

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4.1 Background and Epidemiology of the Emerging Problem World Wide with Multiresistant Gram-Negative Bacilli

At the beginning of the twenty-first century, we now find ourselves experiencing a taste of what life was like prior to the advent of the antibiotic age in the twentieth century. We are again faced with life-threatening infections for which there are very few antibiotic options for treatment. However, unlike the previous century, these infections are often caused by gram-negative pathogens (Hujer et al., 2004).

An important factor in the upswing in antibiotic resistance are intensive care units (ICU), which have been deemed “factories for creating, disseminating and amplifying resistance to antibiotics (Carlet et al., 2004).” A majority of patients in the ICU receive antibiotics during their stay, often in combination to attempt to circumvent the development of resistance. For example in the latest report from the National Nosocomial Infections Surveillance (NNIS) System, there was a 47% increase in Klebsiella pneumoniae resistant to third-generation cephalosporins isolated in the ICUs in the USA in 2003 compared to the previous four years (CDC, 2004). Furthermore, this study revealed a 20% increase in quinolone resistance in Pseudomonas aeruginosa.

Another factor contributing to the increase in antibiotic resistance involves the increasing age of the general population of Western countries. With increasing frequency, geriatric patients reside in long-term care facilities (LTCF). Among the residents of LTCFs, one of the foremost causes of morbidity and mortality is infection (Hujer et al., 2004). The most frequently prescribed antibiotics in LTCFs are oral and parenteral cephalosporins. The excessive use of these antibiotics has caused the emergence of gram-negative pathogens that are resistant to third-generation cephalosporins to become endemic in LTCFs. Many of these patients have an indwelling bladder catheter that can become colonized with a resistant organism (Hujer et al., 2004). A number of hospital outbreaks involving ESBL-producing Enterobacteriaceae have been attributed to patients coming to the hospital out of nursing homes (Bradford et al., 1995; Rice et al., 1990, 1996; Schiappa et al., 1996). An epidemiological survey in Chicago showed that 35 out of 55 hospitalized patients infected or colonized with ceftazidime-resistant Enterobacteriaceae had been admitted to the hospital from a LTCF (Wiener et al., 1999). These studies suggest that
patients in LCTFs serve as a reservoir for antibiotic resistance that then gets transferred into the hospital setting along with the patient. Several multidrug resistant pathogens are of specific concern. Whereas prior to the 1990s *Acinetobacter baumannii* were almost universally susceptible to broad spectrum antibiotics, during this decade they became increasingly resistant to penicillins, cephalosporins, fluoroquinolones and aminoglycosides (Bergogne-Berezin and Towner, 1996). Thus in recent years, many of these antimicrobials are no longer reliable for treatment of infections caused by this organism. Most notable is the increase in resistance to the carbapenems which are caused by a variety of β-lactamases and changes in penicillin-binding proteins (PBPs) (Nordmann and Poirel, 2002). There are now reports of multidrug resistant *A. baumannii* strains that are susceptible only to polymixin B and colistin (Levin et al., 1998).

The problem of antibiotic resistance has gained recognition in the mainstream media as well as in scientific publications. Before the problem can be tackled, the mechanisms must be understood. The present threats of resistance to currently available therapies for infections with gram-negative bacteria are outlined in this chapter.

### 4.2 Mechanisms of Resistance

#### 4.2.1 New β-Lactamases

Production of β-lactamase is the most common resistance mechanism against β-lactam antibiotics in gram-negative bacteria. These enzymes hydrolyze the β-lactam ring of all classes of β-lactam antibiotics, thus inactivating the drug. β-lactamases had been observed in bacterial strains long before penicillin was available for use in the treatment of bacterial infections (Abraham and Chain, 1940). Because most β-lactamases share an active site Ser-XX-Lys motif with PBPs, it is thought that serine β-lactamases evolved from PBPs as protection against β-lactam antibiotics produced by molds in the environment (Ghuysen, 1991).

Over the last 20 years many new β-lactam antibiotics have been developed that were specifically designed to be resistant to hydrolysis by β-lactamases. However, with each new class of β-lactam antibiotics that has been used to treat patients, new β-lactamases have emerged that caused resistance to that drug. The first plasmid-mediated β-lactamase, TEM-1 was initially described in the early 1960s in a single *Escherichia coli* isolate from a patient in Greece (Datta and Kontomichalou, 1965). Since that time, TEM-1 has spread worldwide and is now found in many different species of Enterobacteriaceae, *P. aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*. Following the increased use of the oximino-cephalosporins in the early 1980s, extended-spectrum β-lactamases (ESBLs) emerged. Following the increased use of β-lactam/β-lactamase inhibitor combinations containing clavulanic acid in the late 1980s, inhibitor-resistant TEM enzymes emerged. Following the increased use of cephamycins in the early 1990s, plasmid-mediated AmpC-type enzymes emerged. Finally, following the increased use of carbapenems in the late 1990s, carbapenemases have emerged.