Chapter 9
RESISTANT PATHOGENS:
Emergence and Control

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INTRODUCTION

Antibiotic resistance is one of the most prominent and vexing problems in intensive care medicine. Physicians are now encountering

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bacterial infections that are essentially untreatable. Scores of articles cite escalating rates of antimicrobial resistance and novel mechanisms of resistances in both nosocomial and community settings. These findings have led some to predict that we are rapidly approaching the "post-antibiotic era" (1). Whether this is the actual case or not, antimicrobial resistance is particularly problematic in the intensive care unit (ICU) (2-5). Ventilator-associated pneumonias (VAPs) involve some of the most highly resistant bacteria (6, 7), making empiric and specific antimicrobial choices challenging. In this chapter, we initially review genetic and biochemical mechanisms of antimicrobial resistance. We then discuss the epidemiology of antibiotic-resistant organisms causing VAP and discuss specific bacteria implicated in hospital acquired pneumonia (HAPs), particularly in ICUs settings. Finally, we outline measures to control or limit nosocomial antimicrobial resistance.

GENETICS OF ANTIMICROBIAL RESISTANCE

Bacteria have evolved a number of mechanisms to protect themselves from antibiotics. Antimicrobial resistance can be acquired from a number of genetic events ranging from chromosomal mutation to acquisition of exogenous DNA.(8-12) Mutations in chromosomal DNA can alter structural genes or regulatory elements (10, 12). In addition to chromosomal mutations, bacteria can acquire resistance genes via exchange of DNA with other microbes (10). Genetic material can be exchanged through transformation (uptake of naked DNA from the environment), transduction (transfer mediated by bacteriophage) or conjugation (exchange of DNA via plasmids or transposons) (10). Transformation and transduction occur mainly between members of the same species, and exert modest effects on antibiotic resistance. Transfer of antimicrobial resistance genes by plasmids (self-replicating, extrachromosomal circular DNA elements) or transposons (mobile DNA elements) may cross species and even genus lines (10).

MECHANISMS OF ANTIMICROBIAL RESISTANCE

Resistance to antimicrobial agents occurs by three general mechanisms:

1. Enzymatic inactivation or modification of the antimicrobial agent
2. Alteration of the primary site of action
3. Reduced access of the antimicrobial agent to the site of action

*Table 1. Examples of resistance mechanisms and their genetic bases**

Antibiotic(s)	Mechanisms	Genetic Basis	Example Organisms
β-lactams			
Penicillins Cephalosporins Monobactams Carbapenems	Altered penicillin-binding protein targets	Chromosomal	**S. aureus** **S. pneumoniae** *Escherichia coli* *P. aeruginosa*
	Reduced permeability	Chromosomal	*P. aeruginosa* *Enterobacter* *S. marcescens* *K.pneumoniae*
	β-lactamase inactivation	Chromosomal and plasmid	*S aureus* Enterococci **P aeruginosa** Enterobacteriaceae
Fluoroquinolones			
Ciprofloxacin Ofloxacin	Altered DNA gyrase target	Chromosomal	**S. aureus** Enterobacteriaceae
Norfloxacin	Efflux or reduced permeability	Chromosomal	Enterobacteriaceae *P aeruginosa*
Aminoglycosides			
Amikacin Gentamicin Tobramycin	Modifying enzyme inactivation	Plasmid	Staphylococci Enterococci Streptococci
	Reduced permeability	Chromosomal	Enterobacteriaceae Pseudomonads
	Altered ribosomal target binding	Chromosomal	Streptococci
Macrolides and lincosamides	Methylation of rRNA target	Chromosomal and plasmid	*S. pneumoniae* Enterococci
Erythromycin Clindamycin	Efflux	Plasmid	Staphylococci Streptococci
Glycopeptides			
Vancomycin Teicoplanin	Altered target	Chromosomal and plasmid	Enterococci

Table modified from (26)

Enzymatic Inactivation or Modification of Antimicrobial Agents

β-lactamases, enzymes that hydrolyze the β-lactam ring of penicillins, cephalosporins, monobactams and/or carbapenems, are nearly universally present in Gram negative bacteria (GNB) (13, 14). More than 200 β-lactamases (both chromosomal and plasmid-associated) have been characterized (10, 14) β-lactamases can be categorized by the Ambler classification on the basis of DNA sequence homologies (15) or by the Bush-Jacoby-Medeiros system, which analyzes functional characteristics (e.g., substrate preferences and inhibition profiles) (13) .Virtually all GNB possess a chromosomal gene (*amp*C) which encodes β-lactamases (10, 14, 16). The primary target is cephalosporins but some activity against penicillins is retained; AmpC enzymes are not inhibited by ß–lactamase inhibitors (10, 14, 16). In some species (e.g. *Enterobacter, Serratia, Citrobacter* spp, *and P. aeruginosa*), additional genes regulate production of AmpC β–lactamase (10, 14). In the native state, these chromosomal β-lactamases are latent or repressed, but production is enhanced (induced) in the presence of antibiotics (e.g., cefoxitin or third generation cephalosporins (10, 14). Following removal of the antibiotic, *amp*C expression return to a latent state. Mutations in the regulatory regions of *amp*C lead to constitutive expression of large quantities of AmpC β-lactamases, sufficient to cause clinical resistance (10, 14). The use of ß-lactam antibiotics is the major factor selecting for derepressed mutants (10, 14).

Plasmids containing diverse β-lactamases are an important cause of antibiotic resistance in ICUs. In contrast to chromosomal enzymes, most plasmid-mediated enzymes are constitutively produced (10, 17). The most common plasmids in GNB are TEM-1 and SHV-1 but > 30 such plasmids have been identified (10, 14, 18). TEM-1 and SHV-1 are narrow spectrum enzymes that confer resistance to ampicillin, ticarcillin, and cephalothin, but do not affect broad-spectrum cephalosporins, cephamycins, or monobactams (10, 14). These β-lactamases are inactivated by sulbactam, clavulanic acid, or tazobactam (10, 14, 17). TEM-1 is found more commonly in *Escherichia coli, Hemophilus influenzae, Neisseria*, and *Vibrio* species; SHV-1 is most frequent in *Klebsiella pneumoniae* (10, 14, 19). PSE-1 is the most common plasmid in *P. aeruginosa* (10). These plasmids may cross species and genus lines (10, 14). For example, TEM-1 ß –lactamase, first discovered in the Enterobacteriaceae, subsequently moved to *P. aeruginosa* and later to *H. influenzae* and *N. gonorrhea* (14). Diverse mutations resulting from amino acid substitutions around the active site of TEM or SHV genes led to myriad plasmids capable of hydrolyzing third generation cephalosporins and

monobactams (10). These enzymes, termed extended spectrum ß-lactamases (ESBLs) were detected in Europe in the early 1980's (20). These "extended-spectrum" ß -lactamases (ESBLs), did not affect cephamycins (e.g., cefoxitin or cefotetan) or carbapenems (10). By 1988, similar plasmids were found in the USA, and spread rapidly since that time (particularly in ICUs) (12, 21). More recently, plasmids containing ESBLs related to AmpC β-lactamase (unrelated to either TEM or SHV) were found which conferred resistance to cephamycins, sulbactam, and clavulanate (10, 14, 21). These ESBLs do *not* affect the carbapenems (e.g., imipenem or meropenem) (10). However, plasmid-mediated metallo-β-lactamases, (e.g., Imp-1) confer resistance to carbapenems; these are not affected by β-lactamase inhibitors (9, 14).

β-lactamases represents only one mechanism for antibiotic inactivation. Diverse enzymes inactivate other antibiotic classes (e.g., aminoglycoside modifying enzymes; chloramphenicol acetyltransferase; ribosomal RNA methylase (confers resistance to clindamycin or erythromycin); alterations in dihydrofolate reductase (confers resistance to trimethoprim (10, 12, 17).

Alterations in the Antibiotic Site of Action

Target site modifications impair the activity of aminoglycosides, β-lactams, glycopeptides, macrolides, fluoroquinolones, sulfa drugs and other classes of antimicrobials (10, 12). Examples of target site modifications include: penicillin-binding protein (PBP) alterations (conferring resistance among *S. pneumoniae*) (22) or among *S. aureus* (e.g., *mec*A gene conferring methicillin resistance) (23); *vanA* plasmid conferring vancomycin resistance among Enterococci (24); *erm* genes in *S. pneumoniae* conferring resistance to macrolides, clindamycin, and streptogramins (25) mutations in *gyrA*, *parC,* and *parE* genes, leading to alterations in DNA gyrase and topoisomerase IV, conferring resistance to fluoroquinolones (FQs) (25, 26).

Impaired Antimicrobial Access

Antibiotic resistance may also result by limiting access of the antibiotic by reduced permeability of the bacterial cell wall or by active extrusion of the compound (i.e., efflux) (10, 27). Alterations in porin proteins on the outer membrane of GNB reduce permeability to β-lactam, carbapenem, or FQ antibiotics (10). High grade resistance results when high level β-

lactamase production *and* mutations in porins are present concomitantly (10). Not all antibiotics in a particular class use the same porin channel. Loss of the OmpD2 porin in *P. aeruginosa* confers resistance to imipenem but not meropenem (28).

Bacteria may acquire resistance by actively pumping antibiotics back into the extracellular environment. Energy-dependent efflux pumps encoded in plasmids or chromosomes are found in *Staphylococcus* spp, *S. pneumoniae*, *P. aeruginosa*, and *Enterobacteriaceae* (27), and can confer resistance to multiple classes of antibiotics (e.g., β- lactams, tetracyclines, FQs, chloramphenicol, macrolides quaternary ammonium compounds) (27). Efflux systems provide a pleuripotent system to dispel toxic compounds.

EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE IN NOSOCOMIAL PNEUMONIAS

The etiological agents of hospital acquired pneumonia (HAP) have been elucidated in numerous studies. Enteric gram negative bacteria are implicated in 55 to 85% of HAPs; Gram positive cocci (particularly *S. aureus*) account for 20 to 30%; 40 to 60% of HAPs are polymicrobial (7, 29, 30). Acuity and severity of illness, duration of hospitalization, and prior antibiotic exposure are major determinants of likely pathogens (6, 7, 30) In critically ill patients requiring prolonged mechanical ventilator support in ICUs, *P. aeruginosa* and *Acinetobacter* spp account for 30 to 50% of HAP; these pathogens are uncommon in non-ICU settings (31) (6, 7, 30, 32, 33). "Early-onset" HAP, (occurring in the first 4 days of hospitalization), is often due to community-acquired pathogens such as *H. influenzae*, *Streptococcus pneumoniae* and methicillin-susceptible *Staphylococcus aureus* (7, 30). In this context, pathogens with strong intrinsic or acquired antimicrobial resistances are rarely causative. In contrast, HAP developing 5 or more days after hospitalization ("late-onset") is often due to aerobic GNB (e.g., *P. aeruginosa*, *Enterobacteriaceae*, and *Acinetobacter* spp) or methicillin-resistant *S. aureus* (MRSA) (6, 7, 30). Surveillance cultures collected by the National Nosocomial Infections Surveillance System (NNIS), which incorporates community, university, and municipal hospitals, has elucidated the major pathogens responsible for HAP in the USA since the 1970's (34). Over the past two decades, MRSA and *Enterobacter* spp increased in prevalence as causes of HAP (34). NNIS data from 1981-1986 implicated *S. aureus* in 13% of cases of HAP compared to 16% from 1986-1989 and 19% from 1990-1996 (34-36) *Enterobacter* spp were implicated in 7%, 11%, and 11% of cases of HAP during these intervals, respectively. The prevalence of *K. pneumoniae* during these time periods was 12%, 7%, and 8%; *P. aeruginosa* remained constant at 17% during each of these time periods. Awareness of the relevant pathogens is critical to design empirical antibiotic

strategies for HAP. In addition, antimicrobial resistance continues to rise in nosocomial settings (particularly in ICUs) (2-7). Rates of antimicrobial resistance correlate with antibiotic usage patterns and increase in a stepwise fashion from the outpatient to the non-ICU inpatient to the ICU patient (4, 37). A survey of bloodstream isolates in North America (SENTRY surveillance program) noted that 31% of nosocomial strains of *S. aureus* were MRSA (compared to 25% in community-acquired strains). Rates of resistance to other pathogens included: ceftazidime resistance in 39% of nosocomial and 19% of community-acquired isolates of *Enterobacter cloacae*; imipenem-resistance in 14% of nosocomial isolates compared to 6% of community-acquired strains (38). Similarly, the ICARE project (Intensive Care Antimicrobial Resistance Epidemiology) showed statistically significant differences between MRSA, piperacillin-resistant *P. aeruginosa* and ceftazidime-resistant *P. aeruginosa* isolates from ICU and non-ICU inpatients (37). Antibiotic resistance in nosocomial settings continues to rise. A survey of NNIS hospitals in 1991 noted ceftazidime resistance in 3.6% of nosocomial isolates of *K. pneumoniae* and 39% of *Enterobacter* spp (39) By 1993, 12.8% of *K. pneumoniae* isolates from the NNIS survey were resistant to

Table 2. Selected antimicrobial resistances in isolates from inpatient setting.

Antimicrobial-resistant organism	**ICU's**	**Non-ICU inpatients**
Methicillin-resistant *staphylococcus aureus*	35.2%	31.9%
Vancomycin-resistant enterococci	13.0%	11.8%
Piperacillin-resistant *Pseudomonas aeruginosa*	12.2%	8.3%
Ceftazidime-resistant *Pseudomonas aeruginosa*	10.2%	7.2%
Third-generation cephalosporin-resistant Enterobacter species	25.0%	22.3%
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	3.7%	3.7%
Third-generation cephalosporin-resistant *Escherichia coli*	0.9%	0.8%
Ofloxacin or Ciprofloxacin-resistant *Escherichia coli*	1.3%	1.4%
Ofloxacin or Ciprofloxacin-resistant *Pseudomonas aeruginosa*	16.4%	17.6%

Penicillin-resistant *Streptococcus pneumoniae*	9.5%	10.4%

Table modified from (152)

ceftazidime, with rates > 40% in some hospitals (4). A study of ICUs in the USA documented a rise in ceftazidime resistance among *K. pneumoniae* from 3.3% in 1990 to 14.4% in 1993 (3). During that time, ceftazidime resistance in *Enterobacter* spp rose from 31% to 38% whereas rates of resistance among *P. aeruginosa* remained stable at 14%. Regional differences in antimicrobial resistance may be substantial. The SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) program monitored nosocomial bloodstream infections from 49 hospitals across the USA (40). Rates of MRSA varied from 14.5% in the Northwest to 38.5% in the Southeast; rates of vancomycin-resistant enterococci (VRE) ranged from 10% in the Northwest to 24% in the Northeast (40). Striking differences in rates of MRSA and VRE in bloodstream isolates were observed between Canada and the United States, (3% vs 26%, and 0% vs 18% respectively) (38). In Latin America, particularly high levels of antimicrobial resistance were noted, particularly among organisms implicated in HAP (38). Almost a quarter of all *P. aeruginosa* isolates was resistant to carbapenems, amikacin or piperacillin/tazobactam. *Acinetobacter* spp, the third most common cause of HAP in Latin America, was often susceptible *only* to carbapenems (41). The presence of antimicrobial resistance in patients with HAP increases mortality and morbidity. Mortality is especially high in patients with VAP due to *P. aeruginosa*, *Acinetobacter* spp, *S. maltophilia* or MRSA (6, 7, 42, 43). The dominant risk factors predisposing to VAP caused by antibiotic-resistant bacteria include: duration of mechanical ventilation, residence in the ICU, and prior use of antibiotics (particularly third-generation cephalosporins, FQs and imipenem) (6, 42). In the following sections, we discuss a few key pathogens responsible for VAP, detail the evolution of antimicrobial resistance, and outline approaches to therapy.

SPECIFIC PATHOGENS RESPONSIBLE FOR HOSPITAL ACQUIRED PNEUMONIA

Gram Positive cocci

Antibiotic resistance in Gram-positive pathogens has increased at an alarming rate over the past two decades (10, 44, 45). The problem is most apparent in hospitals, especially in ICUs (2, 4, 46) Methicillin-resistant staphylococci (both coagulase-positive and -negative) (23, 47), vancomycin-resistant *Enterococcus faecium* (24, 48), and penicillin- and macrolide- resistant

Streptococcus pneumoniae (22, 49) are endemic in many centers in the United States. Current therapeutic choices for infections caused by these organisms are limited. Restricted use of antibiotics (especially vancomycin) and infection control measures are essential to limit the spread of resistant Gram-positive organisms.

*Table 3. Evolution of antibiotic resistance in gram-positive organisms in the U.S.**

Year	Methicillin-Resistant Staphylococcus aureus %	Vancomycin-Resistant Enterococci %	Penicillin-Resistant S. pneumoniae %
1990	20-25	<1	4
1992	20-25	6	7
1994	--	8	16
1996	26	15	24-35
1997	25-45	18	31-45

Modified from references (103, 195).

Coagulase-Positive Staphylococcus (*Staphylococcus aureus*)

Staphylococcus aureus is the leading cause of nosocomial infections and HAP in the USA (34, 50, 51). In a nationwide survey in the USA from 1990-1996, *S. aureus* was implicated in 19% of HAP and 16% of Bacteremia (34). Analysis of nosocomial infections in 112 medical ICUs from 97 NNIS hospitals in the USA from 1992-1997 implicated *S. aureus* as the cause of 20% of pneumonias and 13% of blood stream infections (51). Liberal use of intravascular devices is major risk factor for bloodstream infections with Staphylococci (52-54). Risk factors for infection or pneumonia with *S. aureus* include: neurosurgery, head trauma, corticosteroids, human immunodeficiency virus (HIV) infection, burns, diabetes mellitus, prolonged ICU stay (42, 45, 54, 55). Nasal carriage is a strong risk factor for infections in immunocompetent patients (53, 56, 57) and in HIV-infected patients (58, 59).

Antimicrobial resistance has escalated dramatically among *S. aureus* (10, 45, 50). Currently, > 95% of Staphylococci produce ß-lactamase and are resistant to penicillin (50). Fortunately, this enzyme does not affect the semi-synthetic penicillins (e.g., methicillin, nafcillin, oxacillin) or cefazolin and is inhibited by the clinically available ß–lactamase inhibitors (50). Of greater concern is MRSA, which is now endemic in most hospitals in the USA (23, 45). Methicillin resistance is mediated by a chromosomal gene, *mec*A, which alters penicillin-binding protein-2a (PBP2a) and confers resistance to all β-lactam antibiotics, including cephalosporins and carbapenems (23, 60, 61). In 1975, only 2.4% of nosocomial isolates of *S. aureus* in the USA were MRSA; this rate had increased to 29% by 1991 (62). A survey of 8 USA hospitals in 1994-1995 noted that 33% of *S. aureus* isolates were MRSA (4). In a survey of 108 ICUs in the USA, 36% of 4,000 isolates of *S. aureus* were MRSA (46). The prevalence of MRSA is highest in large (> 500 bed) teaching hospitals (61). MRSA is endemic in many long-term care facilities (prevalence rates ranging from 8-53%) (45, 52, 57) and community sources of MRSA have recently been identified (4, 52, 63, 64).

The most consistent risk factor for carriage or infection with MRSA is prior use of β-lactam antibiotics (42, 54, 58, 65). Prior corticosteroid use, chronic obstructive lung disease, and prolonged (>6 days) of mechanical ventilatory support are risk factors for pneumonia due to MRSA (6, 42). Mortality rates are higher in pneumonia (42, 54, 66) or bacteremia (67, 68) caused by MRSA, compared to methicillin-susceptible strains. The higher mortality observed with MRSA likely reflects more serious co-morbidities rather than difference in the virulence of the organisms (67-69). Bacteremias due to MRSA significantly increase hospital costs compared to MSSA (70).

The antistaphylococcal penicillins remain the optimal treatment for infections caused by susceptible strains of *S. aureus* (50, 54). Vancomycin is less effective than ß -lactam antibiotics against MSSA (50, 54). In one study of bacteremic staphylococcal pneumonias, the use of vancomycin was an independent risk factor for mortality (54). The poor results with vancomycin may reflect low tissue levels of vancomycin or reduced bactericidal activity (54, 71). However, vancomycin is the *preferred* agent for serious infections due to MRSA (50, 72). For patients intolerant of vancomycin, trimethoprim/sulfamethoxazole (T/S), FQs, clindamycin, or minocycline can be used, but these agents are less effective (45, 50, 72). In the United States, many MRSA strains are resistant to multiple classes of antibiotics (e.g., FQs, gentamicin, macrolides, rifampin, and tetracycline) (23, 45, 55, 72, 73). Recent nationwide surveys in the USA detected ciprofloxacin resistance in > 35% of isolates of MRSA; some centers reported 100% resistance (11, 62, 74). Ciprofloxacin resistance confers cross-resistance to other FQs, but some newer FQs retain activity (74).

Development of vancomycin resistance in *S. aureus* is concerning (23, 75, 76). Recently, three strains of *S. aureus* with intermediate resistance to vancomycin (minimum inhibitory concentration > 4 ug/ml) were reported

in the USA (75, 76). All patients had comorbid illnesses and were receiving vancomycin for MRSA infections; in two patients, the courses were prolonged (> 18 weeks). The mechanism of reduced susceptibility to vancomycin in *S. aureus* represents an alteration in the bacterial cell wall (capsule) and is distinct from the vancomycin resistance gene found in enterococci (75, 76). However, there is a valid theoretical concern that the VRE gene will eventually be integrated into *S. aureus* (24, 48, 77). Quinupristin-dalfopristin and a new family of antimicrobials, the oxzolidinones, may be used, but data evaluating their efficacy for strains with reduced susceptibility to glycopeptides are lacking (50).

Guidelines to limit and control MRSA focus on preventing colonization and cross-transmission on the hands of hospital personnel (78, 79). Formulary restriction/control can reduce the prevalence of MRSA (60, 65). In one hospital, after restricting cephalosporins, imipenem, clindamycin, and vancomycin, the prevalence of MRSA decreased over a two-year period (65). Reducing risk factors may decrease MRSA infections (61, 78, 80). The use of antiseptic or antimicrobial impregnated catheters significantly decreases catheter-related infections (81-84).

Coagulase Negative Staphylococci

Coagulase-negative staphylococci (i.e., *S. epidermidis*, *S. saprophyticus*, *S. haemolyticus*) rarely cause VAP but are important causes of catheter-related infections, bacteremias, and skin and soft-tissue infections in the ICU (47, 51, 85-87). Coagulase-negative staphylococci (CNS) are the leading cause of nosocomial blood stream infections in the USA, implicated in 31% of cases (51) (34). In ICUs in the USA, CNS accounts for 36% of bacteremias (51). Patients with indwelling medical devices (e.g., central venous catheters, neurosurgical shunts, prosthetic heart valves; artificial joints) are at greatest risk for infections due to CNS (34, 45, 47, 51, 88).

Methicillin-resistance in CNS is mediated by the same *mec*A gene found in MRSA. Currently, most nosocomial isolates of CNS in the USA are resistant to methicillin. Recent NNIS data from 41 ICUs cited methicillin-resistance in 76% of 3,959 isolates of CNS (46). Prior receipt of ß-lactam antibiotics is a risk factor for colonization or infection with methicillin-resistant CNS (85). Vancomycin is the drug of choice for infections due to CNS, but judicious use is imperative. Alarmingly, some strains of *S. haemolyticus* and *S. epidermidis* have acquired high-level resistance to teicoplanin and vancomycin (45, 86). Prevention of infections due to CNS is essential to limit vancomycin use (37, 87).

Enterococci

Enterococci, primarily *E. faecalis* and *E. faecium*, have emerged as important nosocomial pathogens (particularly in the ICU) within the past decade. Currently in the USA, 10% of nosocomial infections (all sites) and 9% of nosocomial bacteremias are due to enterococci. (34) In medical ICUs, 16% of bloodstream infections are due to enterococci.(51) Enterococci rarely cause pneumonia, but frequently cause nosocomial urinary tract, pelvic, intraabdominal, skin, soft tissue, or wound infections (24, 34, 46, 48, 51, 89).

Enterococci are intrinsically resistant to a number of antibiotics, including all cephalosporins, clindamycin, and T/S (24). Bacterial growth is inhibited by penicillins, but bactericidal activity requires synergistic combinations of penicillin or vancomycin *plus* an aminoglycoside.(24) Within the past two decades, high-grade resistance to aminoglycosides, ampicillin, and vancomycin increased dramatically.(24, 48) Vancomycin-resistant *E. faecium* (VREF) are usually highly resistant to ampicillin and aminoglycosides.(55) Vancomycin resistance may be due to 3 major phenotypes: Van A, Van B, and Van C (24). The rapid spread of VRE in the USA is alarming (24, 48, 77). VRE were first reported in the USA in 1989; by 1993, 7.9% of nosocomial isolates of enterococci and 14% of enterococci in ICUs were VRE (77). A multicenter survey (SCOPE) between 1995 and 1996 noted that 14% of blood stream isolates of enterococci in the USA were VRE (90). By 1997, 23% of ICU isolates and 16% of non-ICU isolates were VRE (77). Risk factors for acquisition of VRE include: serious underlying disease; prolonged hospitalization or ICU stay; endemic VRE in a ward or unit; intra-hospital transfers; hyperalimentation; liver transplant recipients; prior use of cephalosporins, vancomycin, or multiple antimicrobials (24, 48, 77, 91-93). Recent reports cite emergence of VRE even in non-ICU nosocomial settings (46, 77). Surveys of outpatients in the USA *without* prior hospitalizations did not detect VRE (94) but community sources are likely to emerge in the future. Treatment options for VREF are limited. Chloramphenicol, minocycline, newer FQs, or quinupristin/dalfopristin may be used, with variable efficacy (24) (48, 95)

Surveillance and infection control measures are essential to control VRE (79). Once VRE is endemic, eradication is difficult, if not impossible (96). Screening high-risk patients for VRE colonization may reduce transmission in endemic areas. (97) Barrier precautions (gowns and gloves) with private rooms or cohorting may prevent transmission from patients colonized with VRE. (79, 97) Environmental contamination may foster spread. (91) Medical equipment such as thermometers, stethoscopes, and blood pressure cuffs should be dedicated to a single VRE-colonized patient or disinfected after each use. (79, 91) A multidisciplinary approach is optimal to control the spread of VRE. (79, 91, 98, 99) Aggressive infection control measures and contact precautions do not consistently reduce the rate of

colonization or infection with VRE. (96, 99) In some studies, decreasing antibiotic usage, particularly vancomycin and cephalosporins, led to decreases in colonization and infection with VRE. (24, 98, 99) Infection control efforts targeting MRSA and central-line-associated infections may reduce the need for vancomycin and may limit spread of VRE. (37)

Streptococcus pneumoniae

Streptococcus pneumoniae is an uncommon cause of VAP, but accounts for 4% to 20% of HAP developing in the first 4 days of hospitalization. (7, 100) Prior to 1992, fewer than 5% of pneumococci in the USA were penicillin resistant (PRSP) and < 2% were highly resistance to penicillin (Pc-R). (22, 101) Subsequent national surveillance studies from 1996-1998 noted PRSP in 34 to 44% of isolates (including Pc-R in 13.6% to 18%).(22, 49, 102) PRSP exhibit increased resistance to other β-lactam as well as non-β-lactam antibiotics (e.g., macrolides, tetracyclines, chloramphenicol, and T/S). (22, 49, 102) Over 99% of *S. pneumoniae* strains (both penicillin-sensitive and penicillin-resistant) are susceptible to the newer FQs. (22, 103-105) All strains are susceptible to vancomycin. (22, 49) Risk factors for colonization or infections with PRSP include: prior β-lactam use, (29) residence in nursing homes or recent hospitalization, (106) and immunosuppressive underlying disease. (29)

Although optimal therapy for pneumonia due to PRSP is controversial, the third generation cephalosporins (cefotaxime or ceftriaxone) appear to be efficacious for nonmeningeal infections.(29) The newer FQs are promising agents to treat infections due to penicillin- and macrolide-resistant pneumococci, but data are limited. (22, 104) For meningitis due to PRSP, vancomycin should be combined with cefotaxime or ceftriaxone.

Enterobacteriaceae

Bacteria within the family Enterobacteriaceae (which include *Enterobacter* spp, *K. pneumoniae, E. coli, Proteus spp, Serratia marcescens,* and *Citrobacter spp)* account for 30 to 40% of HAPs.(46) As was discussed earlier in this chapter, some organisms (e.g., *Enterobacter, Citrobacter* and *Serratia spp*) produce inducible chromosomal AmpC β-lactamases that inactivate cephalosporins, penicillins, and monobactams. (17, 107, 108) These inducible β-lactamases are uncommon among *E. coli, Proteus spp*, or *Klebsiella spp.* (17, 107, 108) Expression/production of AmpC ß–lactamases is induced (enhanced) following exposure to antibiotics (particularly

cefoxitin, clavulanic acid and imipenem). (10, 12, 107, 109) Upon removal of the antibiotic, expression decreases. Hyperproduction of AmpC β-lactamase confers high level resistance to most ß–lactam antibiotics (except carbapenems and fourth generation cephalosporins). (12, 17, 109) AmpC β-lactamases are resistant to the β-lactamase inhibitors, clavulanic acid and sulbactam.(12, 17, 109) A major risk factor for emergence of these de-repressed strains is the clinical use of extended-spectrum cephalosporins (ESCs) (particularly third generation cephalosporins).(17, 107-109) One prospective study at a single medical center assessed the prevalence of resistance to ESCs (via type 1 AmpC β-lactamases) among 366 isolates of *Enterobacter spp, P. aeruginosa, Citrobacter* spp and *S. marcescens*).(108) Rates of resistance to ESCs were: *C. freundii* (41%); *E.r cloacae* (31%); *E. aerogenes* (19%); *P. aeruginosa* (8%); *S. marcescens* (6%) (108) Resistance was associated with prior use of ceftazidime, cefotaxime, ceftizoxime, and piperacillin; other antibiotics were not associated with resistance. Resistance was less frequent in patients receiving ESCs plus an aminoglycoside. In a recent nationwide surveillance study in the USA, 35 to 50% of *Enterobacter* and *Citrobacter* isolates expressed an inducible (derepressed) ampC phenotype. (110) As a result of selection pressure from antibiotic use, *Enterobacter* spp have emerged as important nosocomial pathogens, and now account for 7 to 11% of HAPs in the USA. (34, 46) Given their propensity to facilitate resistance, cephalosporins should be avoided for serious infections due to *Enterobacter* spp (regardless of *in vitro* susceptibilities). Carbapenems are the most reliable therapy, but fourth generation cephalosporins (e.g., cefepime) may be efficacious. (17, 108, 111) Some strains of *Enterobacter* acquire additional mutations in a gene known as *ampD* that results in constitutive high-level expression of AmpC β-lactamase. (16) Carbapenem resistance, although rare among *Enterobacter* spp, results when both high-level AmpC expression and loss of outer membrane porin proteins are present. (17, 112, 113) Finally, in recent years, AmpC enzymes have appeared in plasmids within several species that do not normally express these ß–lactamases (e.g., *E. coli, K. pneumoniae* and *Salmonella* spp).(10, 12, 17) These resistant strains will present a major challenge for future therapy of serious HAP.

Extended Spectrum ß–lactamases (ESBLs)

The emergence of extended spectrum β-lactamases (ESBLs), initially among *K. pneumoniae*, but subsequently affecting other species, led to epidemics and endemic spread of serious nosocomial infections in ICUs.(10, 12, 17, 21, 114) Prior to the emergence of ESBLs, even nosocomial isolates of *K. pneumoniae* were highly susceptible to ceftazidime (as well as earlier generation cephalosporins). Wild type isolates of *K. pneumoniae* express *chromosomal* ß–lactamase only at low levels, owing to an inefficient

promoter.(12) Clinically, most cephalosporins and ß–lactam/ß-lactamase inhibitor combinations are efficacious against these strains. The change of a single base pair in the –10 region of this promoter result in dramatic increases in SHV-1 production. (12, 17) The combination of hyperproduction plus alterations in outer membrane proteins (porins) confers resistances to all cephalosporins and ß–lactam/ß-lactamase inhibitor combinations.(12, 17)

However, the most important mechanism by which *K. pneumoniae* acquire resistance to ceftazidime is via ESBLs.(12, 21) As we have indicated previously, ESBLs confer resistance to cephalosporins (including ceftazidime), but do not affect cephamycins or carbapenems.(10, 20) Most ESBLs remain susceptible to β-lactamase inhibitors (e.g., clavulanate, sulbactam, tazobactam).(17, 114-117) Extended spectrum cephalosporins (ESCs) promote the emergence of ESBLs, but ceftazidime is most often implicated. (12, 114, 118) Most ESBLs are derivatives of common TEM-, SHV-, or OXA-type β-lactamases. (12, 17, 18, 119) One or more point mutations alter active sites of the enzymes, allowing hydrolysis of ESCs. More than 36 ESBLs are derived from the TEM- family; at least 10, from SHV; 5, from OXA; in a few ESBLs, parentage has not been determined.(18) Most outbreaks of ESBLs in the USA were due to TEM-10, TEM-12, and TEM-26; TEM-6 was recently described; SHV-derived ESBLs are less common. (12, 14, 18, 120) In contrast, in France TEM-3 and TEM-5 are the most prevalent ESBLs; SHV is uncommon; TEM-26 is distinctly rare.(121) Since the initial detection of ESBLs among strains of *K. pneumoniae* in Western Europe in the early 1980's, ESBLs rapidly spread worldwide. (12, 18, 20, 120) By the late 1980's, ESBL-producing, ceftazidime-resistant strains of *K. pneumoniae* were endemic in some hospitals in the USA .(12, 21, 114) Transfer of ESBLs to other *Enterobacteriacea* has since occurred; these ceftazidime-resistant mutants are increasingly important as pathogens in ICUs. (12, 21, 118)

Although the prevalence of *K. pneumoniae* as a cause of HAP declined slightly over the past decade in the USA,(34-36, 46) antimicrobial resistance increased dramatically, in large part due to plasmids containing ESBLs (12, 21, 34, 36, 62, 118, 122) Recent surveys in the USA cite ceftazidime resistance in 9 to 14% of nosocomial isolates of *K. pneumoniae*;(3, 4, 39, 108) in some hospitals, > 40% of *K. pneumoniae* are resistant to ceftazidime.(21) Some ESBLs, encoded on large 80-300 kilobase plasmids, also carry resistance genes to aminoglycosides, tetracyclines and T/S. (17, 119) Multi-drug resistant ESBL plasmids from *Klebsiella pneumoniae* may spread to other Enterobacteriaceae (e.g. *E. coli*, *Serratia marcescens*, *Enterobacter cloacae*). (14, 17) Though less common, plasmid DNA may be exchanged from *P. aeruginosa* to Enterobacteriaceae. (14, 17)

Ceftazidime is particularly susceptible to these ESBLs. Ceftazidime is a highly charged, bulky molecule that enters the peri-plasmic space very slowly. *In vitro* resistance to ceftazidime may be obvious at conventional inocula whereas other cephalosporins (e.g., cefotaxime or ceftriaxone) *appear* active. (12, 123) At higher inocula, high-grade resistance (MIC > 256 ug/ml) to cefotaxime or ceftriaxone may be observed.(12) Animal models suggest that this inoculum effect is important, and failures of extended-spectrum cephalosporins may occur despite *in vitro* susceptibility at standard inocula. (12, 123) As a result, *K. pneumoniae* strains resistant to ceftazidime should be considered resistant to all cephalosporins. Some strains of ESBL-producing *K. pneumoniae* are susceptible to ß–lactam-ß-lactamase inhibitor combinations, FQs, T/S and aminoglycosides (12, 17, 114-116) Others carry multidrug- resistance determinants on the same plasmid which confer resistance to all of these antibiotic classes.(12, 17, 124) Carbapenems (e.g. imipenem, meropenem) are universally active against ESBL-producing *K. pneumoniae*, and are the preferred therapeutic agents (often combined with an aminoglycoside). (12, 17, 116)

Risk factors associated with infection or colonization with ESBL-producing *K. pneumoniae* include: increased severity of illness; prior use of antimicrobials; indwelling devices; residence in an ICU. (125, 126) In one study, (126) the risk for acquiring ESBL-producing *K. pneumoniae* in an ICU increased from 4 to 24% during the first month. In another ICU outbreak, 72 patients (38%) became colonized with ESBL-producing *K. pneumoniae*, (within the first week of admission in a majority of patients).(125) Risk factors for acquisition of ESBL were: the presence of arterial and urinary catheters; duration of urinary catheterization and mechanical ventilation.(125)

Control of ESBL-producing *K. pneumoniae* outbreaks are best accomplished by reduction in the use of broad-spectrum cephalosporins (most often ceftazidime). (12, 21, 65) Switching to carbapenems or ß–lactam-ß-lactamase inhibitor combinations may curtail outbreaks. (12, 117, 118) A recent study from France suggested that the use of ß–lactam-ß-lactamase inhibitor combinations might protect against acquisition of ESBLs.(115) ESBL-producing *K. pneumoniae* may remain susceptible to ß-lactamase (12, 18, 114-116) Alterations in the active enzyme site in ESBLs facilitate entry of β-lactamase inhibitors through the cell wall, making ESBLs more susceptible to inhibition than the parent compounds. (12, 18, 116) However, in a recent study, increased use of piperacillin/tazobactam was associated with increased rates of *Acinetobacter* resistance to piperacillin/tazobactam and cefotaxime.(65) Further, overuse of imipenem/cilastatin for ceftazidime-resistant, ESBL-producing *K. pneumoniae* was associated with emergence of imipenem resistance in *P. aeruginosa* and *Acinetobacter baumanni*(21, 127) A recent study documented stepwise increases in resistance to imipenem in eight *K. pneumoniae* isolates *initially* susceptible to imipenem but resistant to all other β-lactams and aminoglycosides.(128) All patients were treated with imipenem (for 5 to 36 days). Three distinct clonal patterns were identified.

Resistance was due to a combination of hyperproduction of a plasmid-mediated ampC β-lactamase plus loss of a specific porin protein.(128) Thus, judicious and parsimonious use of antimicrobials must be the primary goal of antibiotic utilization strategies.

Non-Fermenting Gram-Negative Pathogens

Acinetobacter Species

Bacteria within the genus *Acinetobacter* are encapsulated, aerobic gram-negative coccobacilli that cause opportunistic infections in critically ill patients. (33, 129, 130) There are 19 recognized *Acinetobacter* genospecies, but *A. calcoaceticus-A. baumannii* complex accounts for the vast majority of infections. (33, 129) *Acinetobacter spp* rarely cause pneumonia in the community, but are implicated in 4 to 24 percent of VAPs in ICUs. (33, 51, 130) Less common sites of nosocomial *Acinetobacter* infections include: soft-tissue and wound infections, catheter-related infections, and urinary tract infections. (33, 129, 131) Mortality with bacteremias or pneumonias due to *Acinetobacter* spp is high (crude mortality rates of 30 to 75% percent). (33, 130)

Resistant *Acinetobacter* spp (principally *A. baumannii*) arise by selection pressure in debilitated ICU patients. (6, 33, 129, 132) Risk factors for acquisition of *Acinetobacter* species include: tracheostomy or endotracheal intubation, residence in an ICU, prolonged mechanical ventilatory support, invasive devices, and recent use of antibiotics (6, 33, 129-132) In critically ill patients, *Acinetobacter* spp may colonize the gastrointestinal tract, skin, and respiratory tract (133-135) and may be a precursor of infection. *Acinetobacter* species are ubiquitous in the environment, and may survive for prolonged periods in moist or dry surfaces.(136) Contaminated environmental sources may cause outbreaks of nosocomial infections.(130, 136-138) Dissemination of a limited number of clones may lead to epidemic or endemic spread within hospitals.(127, 129, 130, 138) Some nosocomial outbreaks have required temporary closure and decontamination of ICUs.

Nosocomial *Acinetobacter* species are usually resistant to cephalosporins, penicillins, and aminoglycosides. (33, 131) Resistance to β-lactams may develop by: β-lactamases (plasmid or chromosomal); alteration of PBPs; reduced permeability (33, 139) Plasmid-mediated TEM-1 and TEM-2 β-lactamases and carb 5 inactivate ampicillin and carbenicillin,

respectively, but do not affect cephalosporins.(139) However, chromosomal amp C β-lactamases confer resistance to cephalosporins. In one study, 98% of *Acinetobacter* isolates produced cephalosporinases. (33) High grade resistance to all β-lactams (except carbapenems) has been noted in the USA among mutants with hyperproduction of amp C β-lactamases *and* altered porin proteins. (122, 130) Recently, new ESBL-containing plasmids (PER-1) conferring resistance to ceftazidime were detected in Turkey and France (140, 141) These plasmids have not yet been found in North America. (122) Imipenem/cilastatin is the cornerstone of therapy of multi-drug resistant *Acinetobacter* spp. (122, 130) however, resistance to carbapenems may develop by selection pressure.(33, 118, 127, 131) Mechanisms include: plasmid-mediated carbapenemases;(142) decreased outer membrane permeability; altered PBPs. (122) Imipenem-resistant strains may be susceptible to sulbactam.(127, 131) The efficacy of ampicillin/sulbactam is entirely due to the antibacterial effect of sulbactam. (122) The activity of other classes of antimicrobials is variable. Thirty to 70 percent of isolates are susceptible to aminoglycosides (amikacin is the most active).(33) Resistance due to aminoglycoside-modifying enzymes correlates with increasing use of these agents.(33, 131, 143) The activity of the FQs against *Acinetobacter spp* is highly variable (3 to 70% susceptibility rates). (33, 131, 144) Resistance may develop by *gyr*A gene mutation, drug efflux, and/or decreased outer membrane permeability. (11, 145) Tetracyclines have variable activity against *Acinetobacter* spp; minocycline and doxycycline are the most active within this class. (122) The newer glycylglycines have promise. (122)

Empirical treatment of *Acinetobacter* pneumonia depends on susceptibility patterns within the institution or individual patients. We favor combining a β-lactam *plus* an aminoglycoside. Imipenem/cilastatin (combined with an aminoglycoside) is preferred for empirical therapy. Piperacillin-tazobactam is the most active of the β-lactam/ β-lactamase inhibitor combinations. (122)Activity of cephalosporins is inconsistent. Other therapeutic options include: ciprofloxacin,(144) ampicillin-sulbactam, (127, 146, 147) or polymyxins (127, 148) For multiresistant strains of *Acinetobacter*, combinations of two or more agents may be used to achieve synergy. Synergistic killing has been observed *in vitro* with the following combinations: polymyxin B or colistin plus rifampin (149, 150) polymyxin plus imipenem (122) polymyxin plus ampicillin/sulbactam;(150) ampicillin-sulbactam plus rifampin. (137, 150, 151)

Pseudomonas aeruginosa

Pseudomonas aeruginosa accounts for 16 to 31 percent of HAPs (31, 34, 51, 152) and is responsible for an even higher proportion (20 to 43%) of VAPs in ICUs, (29, 51, 153) in patients with acute respiratory distress

syndrome (ARDS), (154-156) in hospitalized patients who recently received antimicrobials, (6, 7) or patients hospitalized for more than 4 days ("late onset" pneumonia). (6, 29, 155) In contrast, *P. aeruginosa* rarely causes "early onset" ($\leq$ 4 days) HAP in the absence of other risk factors. (30, 157) *P. aeruginosa* primarily colonizes or infects patients with specific or nonspecific impairments in host defenses. (158) Oropharyngeal or tracheal colonization with *P. aeruginosa* increases with increased length of hospitalization and severity of illness, and is an important risk factor for pseudomonas HAP (29, 159, 160) Prior use of non-pseudomonal antimicrobials increases the risk of colonization. (6, 29, 159) *P. aeruginosa* is ubiquitous in hospital environments. (159) Outbreaks of nosocomial *P. aeruginosa* infections have been linked to contaminated environmental sources or cross-infection from colonized patients or health care workers. (160) Mortality associated with *P. aeruginosa* HAP is high (> 40%), which partly reflects the debilitated state of patients infected with this organism. (7, 31, 32, 153) Clinical failure rates, persistence of the organisms, and relapse rates are high, even with therapy. (31, 32, 100)

P. aeruginosa is intrinsically resistant to most antibiotics. The most active agents (> 80% activity) are carbapenems, piperacillin, cefepime, ceftazidime, ciprofloxacin, amikacin and tobramycin. (3, 6, 51, 158, 161-163) Rates of resistance are higher in large, teaching hospitals and in ICUs and are strongly influenced by prior antibiotic use. (4, 158) Antimicrobial resistance develops rapidly under selection pressure.(31, 164, 165) Resistance may develop by: production of specific enzymes (e.g., β-lactamases, aminoglycoside-modifying enzymes; mutant DNA gyrase); alterations in outer membrane porin proteins; or active efflux. (9, 31, 158, 163-166) Inducible chromosomal β-lactamases are universally present in *P. aeruginosa* and confer resistance to cephalosporins. (3)These isolates remain susceptible to extended-spectrum penicillins or carbapenems.(8, 9) Hyperproduction of ampC β-lactamase, which has low intrinsic activity against *P. aeruginosa*, confers high grade resistance when *concomitant* porin proteins alterations are present. (167) Plasmid-mediated β-lactamases (typically PSE-1 and PSE-2) also confer resistance, but are less common than in *Enterobacteriaceae.*(8) Loss of D2 outer membrane porin (OprD2) confers resistance to carbapenems (158) Plasmid-mediated metallo-carbapenemases are less common.(8, 9) Selection pressure is a strong risk factor for emergence of imipenem-resistance.(4, 6, 21, 31, 163, 164, 168) Other factors predisposing to resistance include: respiratory source; residence in ICUs or large teaching hospitals; organ transplantation. (3, 4, 11, 163) Resistance to FQs may occur via mutations in DNA gyrase, decreased permeability, or active efflux of the antibiotic. (11) Factors associated with FQ resistance include: monotherapy

for pneumonia;(31) residence in ICUs;(5) prior use of FQs;(11) cystic fibrosis; sequestered sites. (44) Multidrug resistance may arise by combinations of impermeability and efflux, and production of inactivating enzymes. (8, 21, 158, 165) The risk of emergence of resistance varies with different antibiotics. (164, 165, 169) Resistance to ceftazidime remained relatively stable in the United States over the past decade whereas resistance to other antibiotic classes increased. (3, 162) A 1990-1993 survey of *P. aeruginosa* isolates from 396 ICUs from 45 states cited stable rates of resistance to ceftazidime (14-15%: resistance to carbapenems and FQs increased. (3)For some antibiotics (particularly imipenem), antimicrobial resistance develops rapidly by selection pressure. (21, 31, 163, 164, 168) In one study of 271 patients with infections due to *P. aeruginosa*, resistance developed while on antibiotic therapy in 10.2%. (164) The risk of developing resistance was lowest with ceftazidime; highest with imipenem; intermediate with piperacillin/tazobactam and ciprofloxacin. Ceftazidime-resistant *P. aeruginosa* often are resistant to multiple agents (including unrelated classes of antimicrobials). Even multiply-resistant strains of *P. aeruginosa* may be susceptible to polymyxins (e.g., colistimethate sodium). (148)

Optimal therapy for pseudomonas HAP is not well defined, as randomized therapeutic trials are lacking. However, given the high mortality rates with pseudomonas HAP, the high rate of relapses, and propensity to develop resistance, we advise combination therapy with two antibiotics with *in vitro* activity against *P. aeruginosa.* (32, 153) The incremental benefit (if any) from adding a second agent is not clear, as controlled studies comparing various therapeutic strategies have not been done. Historically, combination therapy with an antipseudomonal β-lactam and aminoglycoside has been used. (153, 158) The combination of a FQ (particularly ciprofloxacin) with an antipseudomonal β-lactam is an attractive therapeutic option, (158, 165) but data are lacking. Failure rates are high (30 to 70%) with monotherapy or combination therapies. (31, 32, 153, 165, 166, 168, 170, 171) Even with combination therapy, resistance may emerge. (32, 100) The influence of antibiotic regimen(s) on mortality is impossible to ascertain, as additional factors (e.g., residence in an ICU, severe comorbidities, multiorgan failure, etc.) independently affect mortality. (100) Further, the choice of optimal agents is not obvious. Recent studies suggest that piperacillin/tazobactam (4.5 gm q.i.d.) is at least as effective (and possibly more effective) than ceftazidime or imipenem/cilastatin for serious infections due to *P. aeruginosa.* (168, 170, 171) An aminoglycoside should be added to confer synergy. However, the value of aminoglycosides is controversial, as aminoglycosides penetrate poorly into bronchopulmonary secretions and have potential serious toxicities. (172) Optimization of aminoglycoside dosing and pharmacodynamics may be critical to optimize outcome for serious pseudomonas VAP, (173) but data are limited. The use of aerosolized aminoglycosides improved symptoms and reduced bacterial colony counts of *P. aeruginosa* in patients with cystic fibrosis (CF), (174) but has not been

studied in non-CF patients with pseudomonas HAP. Novel strategies combining FQs with β-lactam antibiotics are of interest, but have not been rigorously tested. In some *in vitro* studies, the combination of a FQ with a β-lactam achieves synergy, (175) but this is variable. Ciprofloxacin is the most active FQ against *P. aeruginosa in vitro* (176)although activity of levofloxacin (based upon concentration-time curve (AUC) may be adequate.(177-179) Additional studies are warranted to assess the role of FQ/β-lactam combinations for pseudomonas VAP. For multiresistant strains of *P. aeruginosa*, intravenous colistin is sometimes effective but toxicities are common (principally renal and neurotoxicities). (148)

Stenotrophomonas (Xanthomonas) maltophilia

Stenotrophomonas maltophilia, a non-fermenting gram-negative rod, causes opportunistic infections in critically ill, debilitated patients who have received broad-spectrum antibiotics (particularly imipenem/cilastatin).(180) The commonest sites are catheter-related infections and pneumonia.(181) Crude mortality rates of *S. maltophilia* infections range from 10 to 60%. (180, 181) Predisposing factors for colonization or infection include: residence in an ICU, tracheotomies; invasive devices; serious comorbidities; hematologic malignancies; neutropenia; organ transplantation; cytotoxic chemotherapy or systemic corticosteroids; central venous catheters; mechanical ventilation; prior antibiotic therapy.(180-182) *S. maltophilia* can be isolated from environmental sources (particularly in the ICU) including: water sources;(183) ventilator tubing and suction equipment;(184) disinfectant solutions; hospital sinks; nebullizers, and spirometers. (180)

Stenotrophomonas maltophilia is intrinsically resistant to most β-lactam antibiotics.(185, 186) Ticarcillin/clavulanate is the most active β-lactam but fewer than 50 percent of isolates are susceptible. (185, 186) Imipenem/cilastatin and aminoglycosides have poor activity. (180, 185) Fifteen to 40% of strains are susceptible to FQs. (185, 187) Multi-drug resistant *S. maltophilia* may emerge via selection pressure.(188) Resistance may reflect constitutive impermeability of the outer membrane and/or various inducible β-lactamases or aminoglycoside-modifying enzymes.(185, 189) The most active antibiotics against *S. maltophilia* are T/S and minocycline (69 to 97 percent susceptibility *in vitro*); however, these agents are bacteriostatic. (185) Nonetheless, T/S is the preferred agent. (180, 185) For serious or refractory infections, T/S can be combined with other antibiotics to which the organism is susceptible in order to achieve synergy. (180, 185) *In vitro* synergy between ciprofloxacin and cefoperazone has been noted.(190)

Burkholderia (Pseudomonas) cepacia

Burkholderia (*Pseudomonas*) *cepacia*, an aerobic gram-negative rod, is a rare cause of nosocomial pneumonia in patients with specific risk factors e.g., cystic fibrosis, mechanical ventilation, multiple course of antimicrobials (particularly imipenem), debilitation, intravenous drug abuse, or impaired immune defenses.(180, 191) Sporadic outbreaks of infection or colonization with *B. cepacia* have been noted in ICUs or burn units. (191) Contaminated irrigation or disinfection solutions, topical anesthestics, or nebullizers have been linked to epidemics of nosocomial pneumonia. (180, 191) A nosocomial outbreak of *B. cepacia* infections due to a single dominant clone was described in 90 non-CF patients; 86% were in the ICU at time of first isolation of the organisms; 85% had previously required mechanical ventilation; 92% had received prior antibiotics. (191) Severity of illness score was a significant risk factor for acquisition. (191)

Burkholderia cepacia is intrinsically resistant to penicillin, ampicillin, first and second-generation cephalosporins, imipenem, and aminoglycosides. (180) Activity of antipseudomonal penicillins is variable. (180) Trimethoprim/sulfamethoxazole, ceftazidime, minocycline, and FQs are the most active agents. (180) Choice of therapy depends upon *in vitro* susceptibility testing. Combinations of agents, which confer synergy, may be optimal, but data are lacking.

PREVENTION OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is well characterized from biochemical, genetic and, to some extent, epidemiological perspectives. As we have shown, the most important factors predisposing to antibiotic resistance in hospitals include: prior use of antimicrobials; prolonged hospitalization or residence in ICUs; prolonged mechanical ventilation; need for invasive devices; severity and acuity of illness. (6) Unfortunately, there is a paucity of data describing interventions to *prevent* emergence and dissemination of resistance. No one will argue that the prudent use of antimicrobial agents is an important step in controlling resistance. Strategies aimed to minimize resistance have been advocated. (192-194) Strategies include: optimizing preoperative antimicrobial prophylaxis; judicious use of appropriate antimicrobial agent(s) and duration of empiric therapy; pathogen-specific prescribing practices; computer-assisted antibiotic management. (192-194) In one center, a computer-assisted antibiotic management program resulted in reduced excess drug dosages, fewer antibiotic-susceptibility mismatches and fewer adverse drug events. (194) Several hospitals developed treatment algorithms and antibiotic guidelines or selectively controlled or restricted particular

antimicrobial agents (or antibiotic classes).(12, 21, 65, 118, 125) However, randomized, controlled trials assessing optimal approaches to curtailing resistance have not been done. Antibiotic control has not proven as effective as hoped. In many cases, restricting a particular drug (or class) reduces the level of resistance to that agent(s), but results in escalation of resistance to substituted or alternative agents.(21, 65, 118, 127) Resistance rates rarely return to baseline and when restrictions are rescinded, the problem recurs. Increased use of broad-spectrum agents can lead to colonization and superinfection with new highly resistant opportunists such as *Acinetobacter* or *S. maltophilia.* (21, 65, 118, 127, 180) Surveillance of hospital susceptibility and drug use patterns should not be limited to single drug relationships.(169) Restricting single agents may fail to prevent or reverse antimicrobial resistance.(169) Some investigators advocated combination antimicrobial therapy in an attempt to reduce resistance.(172) This is a common practice in many ICUs, but studies have not yet shown that this strategy affects hospital resistance rates. Drug rotation ("crop rotation") provides a way to vary selective pressures placed on bacteria and theoretically may reduce resistance. A truncated trial of drug rotation in a coronary care unit was recently described. (152) Six hundred eighty consecutive patients undergoing cardiac surgery were prospectively evaluated. Historically, ceftazidime had been used as empirical therapy for suspected gram-negative bacterial infections. This practice was changed to ciprofloxacin for a 6-month period. Rates of infections were compared among the cohort during the FQ period ("after period") and the preceding 6-month time frame when ceftazidime was used ("before period"). The incidence of VAP decreased in the after-period compared to the before-period (6.7% versus 11.6%); this was primarily due to a reduction in VAP attributed to antibiotic-resistant GNB (0.8% versus 4.0%). The incidence of bacteremias due to antibiotic resistant GNB was also reduced with ciprofloxacin (0.9% versus 1.7%). (152) Although such an approach is promising, this study analyzed a single drug switch from a previously heavily used agent to a new class of antibiotic that had been used sparingly in this hospital setting. Large cooperative trials are required to address more fully the role (and efficacy) of "crop rotation" strategies. Many studies have shown the clonal spread of highly resistant organisms within and between hospital units and nearby hospitals. A strong antimicrobial surveillance system within each hospital is critical. Systems that effectively and rapidly recognize and report changes in antimicrobial resistance are essential in hospitals. The efficacy of surveillance systems depends on the prompt delivery of information back to the caretakers. Basic hospital infection control practices, particularly hand washing, isolation and environmental hygiene, are recommended to limit the dissemination of

resistant strains in hospitals.

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