

## *Enterobacter* spp.: Pathogens Poised To Flourish at the Turn of the Century

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### INTRODUCTION

*Enterobacter* spp. have been recognized as increasingly important pathogens in recent years. Most of these organisms are innately resistant to older antimicrobial agents and have the ability to rapidly develop resistance to newer agents. They have increased in incidence as causes of nosocomial infections in general, while multiply resistant strains have emerged in areas of high cephalosporin use within the hospital. More recently, it appears that *Enterobacter* spp., including multiply resistant strains, have spilled over into the community, occasionally infecting otherwise well individuals. These organisms have been implicated in an increasing number of clinical syndromes, occasionally mimicking those traditionally associated with other,

more easily treatable infectious agents, such as group A streptococci or *Staphylococcus aureus*. Other recent developments include recognition of relatively high rates of coinfection with other pathogens, predominance in liver and lung transplant infections, etiologic role in cotton fever, and increasing incidence in a variety of clinical syndromes.

Because of dramatic changes and expansion of the knowledge of *Enterobacter* spp., we initiated a review of the recent literature. The following databases were searched for the period 1990 to 1995: Medline, Excerpta Medica, Biosis, and Zeneca internal database. Approximately 1,300 citations were identified. Abstracts and summaries were obtained for each whenever possible. From this compilation, complete publications were selected for review on the basis of their relative contribution of new knowledge to the field or ability to provide access to the voluminous older literature. Herein, we have preferentially cited these publications. In addition, we have selectively cited older publications that provided necessary background to document recent trends, represented major

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TABLE 1. Differentiation between species of *Enterobacter* most commonly recovered from clinical material<sup>a</sup>

Test	Reaction of:			
	<i>E. aerogenes</i>	<i>E. cloacae</i>	<i>E. sakazakii</i>	<i>E. agglomerans</i>
Lysine decarboxylase	+	–	–	–
Arginine dihydrolase	–	+	+	–
Ornithine decarboxylase	+	+	+	–
Growth in KCN	+	+	+	Variable
Fermentation of D-sorbitol	+	+	–	Variable

<sup>a</sup> Data from references 58 to 60 and 136.

original contributions, or complemented the presentation of recent material. We review microbiology, epidemiology, antimicrobial susceptibility and resistance, clinical manifestations, and outcomes of therapy, and we conclude with a perspective on the future.

## MICROBIOLOGY

### The Organism

The genus *Enterobacter* belongs to the family *Enterobacteriaceae* and can be readily distinguished from the genus *Klebsiella* in that the former is motile, usually ornithine decarboxylase positive, and urease negative (58). Additionally, most *Enterobacter* spp. are resistant to cephalothin and cefoxitin whereas *Klebsiella* spp. are often susceptible to these agents. Although rare strains of *Enterobacter* may appear nonmotile and may decarboxylate ornithine slowly, care must be taken not to confuse these with strains of *Klebsiella* (55). The antibiotic susceptibility pattern of such strains can be most useful in heightening the suspicion that they belong to the genus *Enterobacter* (55).

There are 14 species or biogroups of *Enterobacter* listed in the most recent edition of *Manual of Clinical Microbiology* (58). Not all of these have been implicated as causes of diseases in humans. Among those that have, the most commonly encountered species include *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter agglomerans*, and *Enterobacter sakazakii* (7, 30, 37, 58, 60, 73, 77, 90, 94, 107, 186, 197, 207). *Enterobacter taylorae*, *Enterobacter gergoviae*, *Enterobacter asburiae*, and *Enterobacter amnigenus* are only rarely isolated from clinical specimens (30, 37, 60, 90). Several tests that can be used to differentiate the various species of *Enterobacter* that are more commonly recovered from clinical specimens are shown in Table 1.

*E. aerogenes* and *E. cloacae* are by far the most frequently encountered human pathogens among the genus *Enterobacter* (7, 30, 38, 90, 117, 236). These two species can be readily differentiated by tests for lysine decarboxylase and arginine dihydrolase (Table 1). *E. sakazakii* can be differentiated from *E. cloacae* by its inability to ferment D-sorbitol and its production of a yellow pigment (58–60, 94). *E. agglomerans* represents a heterogeneous group of diverse organisms that are often yellow pigmented, grow at 4°C, and are usually negative in decarboxylase/dihydrolase tests (58, 60, 136, 207). Although *E. agglomerans* has recently been renamed *Pantoea agglomerans* to reflect its genetic distance from the genus *Enterobacter* (27, 136), this organism will be referred to in this review as *E. agglomerans* since it has been included heretofore in the clinical literature on the genus *Enterobacter*.

Numerous approaches have been developed for identification of specific strains within each species of *Enterobacter* (18,

43, 77, 80, 91, 125, 126, 137, 140, 167, 204, 208, 229, 237, 238). Due to the metabolic diversity within certain species, biotyping has been a useful approach for strain identification in certain settings (125, 126). However, biotyping may not distinguish true strain differences in some instances (18, 80, 91, 137, 167, 237). The antimicrobial susceptibility pattern is generally unreliable for strain differentiation (18, 80, 91, 167). Different patterns can arise from the same strain before and after mutation of chromosomal genes affecting the expression of β-lactamase (see below). Conversely, similar antimicrobial susceptibility patterns can be seen among strains shown to be distinct by a variety of other methods. Typing by bacteriocin or bacteriophage pattern or serotyping based upon O or H antigens has also been developed (43, 77, 126, 137, 144, 238). However, all of these approaches require the use of highly specific reagents that may not be available outside a limited number of reference laboratories. Furthermore, the susceptibility to bacteriophages may change with the age of the culture, and some strains are not typeable by these methods. Therefore, a number of molecular approaches to strain identification have been developed. These include the determination of plasmid profiles with or without analysis of restriction endonuclease patterns, restriction endonuclease analysis of chromosomal DNA, pulsed-field gel electrophoresis of genomic DNA restriction fragments, random amplification of polymorphic DNA, amplification of short interspersed repetitive sequences, and ribotyping (18, 38, 80, 91, 107, 146, 167, 204, 208, 229, 237). Plasmid profiles, although the easiest to determine, may be of limited value, since many strains of *Enterobacter* may possess few, if any, plasmids. The utility of other molecular approaches appears to be maximal when used in concert with biotyping, serotyping, bacteriocin typing, or another molecular typing method (18, 80, 91, 167, 237). For epidemiological purposes, the most reliable approach to strain identification appears to be the use of multiple methods coupled with inclusion of control strains that consist of known related and unrelated strains.

### General Epidemiology

Species of *Enterobacter* are becoming increasingly important nosocomial pathogens (20, 57, 78, 105, 107, 174, 194, 236). In the preantibiotic era, they were not encountered in surveys of nosocomial bacteremia (153). By the 1970s, it was established that *Enterobacter* spp. could be nosocomial pathogens, although they were much less commonly encountered than *Escherichia coli* and *Klebsiella* strains (153). Data gathered in the National Nosocomial Infections Surveillance System (NNIS) have shown that *Enterobacter* spp. accounted for 5 to 7% of all nosocomial bacteremias in the United States from 1976 to 1989 (105, 106, 153, 194). However, the importance of *Enterobacter* spp. as nosocomial pathogens was highlighted in the most recent NNIS data published (105). These data showed that the increasing importance of *Enterobacter* spp. as nosocomial pathogens was most apparent when isolates from intensive care units (ICUs) were considered separately from the hospital at large. In hospital-wide data, *Enterobacter* spp. were not among the five most commonly isolated nosocomial pathogens from any body site except the respiratory tract, where they were the third most commonly isolated pathogens and accounted for 10.5% of all isolates (105). However, data from isolates recovered from the ICU revealed that *Enterobacter* spp. were not only the third most common pathogen recovered from the respiratory tract (11.1% of all isolates) but also the fourth most common pathogens recovered from surgical wounds (10.3%), the fifth most common pathogens recovered from the urinary tract (6.1%), and the fifth most common

pathogens recovered from blood (5.3%) (105). Since patients in special care units of the hospital appear to be at increased risk of acquisition of *Enterobacter* infections (see below), it is now obvious that data from these units must be analyzed separately from hospital-wide data to appreciate the increasing importance of this genus as a nosocomial pathogen.

Although community-acquired infections with *Enterobacter* spp. do occur, the majority of infections with this organism are nosocomial (107, 117). Patients at increased risk of acquiring an *Enterobacter* infection include those with a prolonged hospital stay, especially if a portion of it is spent in an ICU (1, 30, 65, 73, 80, 126, 151, 174). The presence of a serious underlying illness, especially malignancy, burns, and diabetes, also increases the risk of infection (6, 30, 37, 40, 71, 73, 78, 90, 107, 149, 227, 236). Immunosuppression from any cause, prematurity and low birth weight in neonates, and the presence of a foreign device (central venous catheters, endotracheal tubes, urinary catheters) are also associated with increased risk of acquisition of an *Enterobacter* infection (1, 7, 21, 38, 148, 151, 174, 236). The single most frequently cited risk factor for acquisition of an *Enterobacter* infection is the prior use of antimicrobial agents in the patient involved (1, 6, 7, 20, 30, 37, 38, 73, 80, 108, 151, 174, 236).

*Enterobacter* infections can be acquired from either endogenous or exogenous sources. This is not surprising, given the ubiquitous nature of the organism. Various species can be found in the feces of humans and animals and in water, plants and plant materials, insects, and dairy products (38, 57, 61, 77, 94, 107, 136, 137, 140, 151, 169, 200, 205). Single-source outbreaks have been traced to contaminated intravenous solutions, blood products, distilled water, endoscopes, hands of personnel, hydrotherapy water, stethoscopes, cotton swabs, cryopreserved pancreatic islet infusions, lipoidal solutions, and devices used for monitoring intraarterial pressure (17, 29, 38, 77, 94, 148, 149, 155, 157, 207–210, 228, 229). However, most nosocomial infections cannot be traced to a single common exogenous source or to any of a number of modes of nosocomial transmission (6, 57, 65, 77, 107, 126, 151). Most nosocomial *Enterobacter* infections appear to arise endogenously from a previously colonized site in the involved patient (57, 65, 77, 125, 126, 151). Colonization of the gastrointestinal tract and other body sites with *Enterobacter* spp. occurs frequently in the seriously ill patient, especially one who has received prior antibiotic therapy (24, 43, 62, 65, 67, 72, 96, 107, 116, 180). In fact, patients may be colonized with more than one strain at any given time (43, 65, 77). Thus, it appears that severe debility, coupled with the suppressive effects of antibiotics on the normal flora, provides an excellent opportunity for colonization by *Enterobacter* spp. This colonization most often precedes infection by the organism. Infection with *Enterobacter* spp. is more likely to ensue with longer hospital stays, more debilitating underlying illnesses, and more persistent and heavy colonization.

### Pathogenesis

Species of *Enterobacter* are clearly opportunistic pathogens and rarely cause disease in the otherwise healthy individual. As opportunistic pathogens that have only recently become important causes of nosocomial infections, very little is known about the factors impacting their pathogenicity and virulence. As gram-negative pathogens, they possess endotoxin and thus have all of the pathogenetic properties imparted to an organism by this virulence factor (22). Beyond endotoxin, however, very little is known about the pathogenetic potential of *Enterobacter* strains. Since *Enterobacter* infections often occur in

patients with foreign devices implanted (1, 7, 38, 236), it has been speculated that *Enterobacter* spp. have a greater affinity for such devices than do other organisms (236). However, a recent study of *E. cloacae* failed to show any specific serotype or biotype associated with infections involving foreign devices (237). The same study found that certain types were more frequently associated with bacteremia or urinary tract infection (237). Nevertheless, the authors concluded that these trends may have been more of a reflection of the type of patient involved (ICU versus non-ICU) than any intrinsic virulence of the organism itself.

Most epidemiologic aspects of *Enterobacter* infections reflect the opportunity for infection rather than the intrinsic virulence of the organism involved. For example, infections due to *E. sakazakii* and *E. agglomerans* are much less common than those caused by *E. cloacae* and *E. aerogenes* (1, 7, 30, 37, 65, 73, 77, 90, 107, 117). This difference probably reflects the special circumstances in which infections by the first two species but not the last two are usually seen. Infections by *E. sakazakii* are usually seen in neonates, and this organism has been recovered from powdered milk and infant formula (74, 94, 161, 169, 242). Whether this predilection for neonates reflects intrinsic virulence or the fact that the organism has the opportunity to be an early colonizer of the infants is unknown. Infections by *E. agglomerans* are usually associated with an identifiable exogenous source (17, 61, 148, 207, 228). This organism grows well at 4°C, is often associated with plants, and can be readily recovered from cotton (61, 136). Therefore, it is not surprising that it is often associated with outbreaks due to contaminated intravenous solutions and stored blood products as well as “cotton fever” in intravenous drug abusers (17, 61, 148, 207, 228). Although ubiquitous in nature, *E. agglomerans* is not as frequent a cause of endogenous nosocomial infections as *E. cloacae* or *E. aerogenes* (7, 30, 37, 73, 90, 117). This probably reflects the greater intrinsic susceptibility of *E. agglomerans* than other *Enterobacter* spp. to  $\beta$ -lactam antibiotics (see below).

Although *E. cloacae* and *E. aerogenes* are the two most common *Enterobacter* species causing nosocomial infections, little is known about their pathogenetic potential. A greater resistance to disinfectants and antimicrobial agents than that of other members of the *Enterobacteriaceae* is likely to play a role in their increasing prevalence as nosocomial pathogens (120, 226) (see also below). *E. cloacae* has also been shown to be capable of growth in 5% dextrose solution, which explains the early outbreaks reported with this organism (77, 148). A study of patients undergoing cardiac surgery suggested that *E. cloacae* may be more virulent than *E. aerogenes* (65). Of patients colonized with one or the other species, 26% of those colonized by *E. cloacae* went on to develop an infection while only 7% of those colonized by *E. aerogenes* subsequently developed infection (65). Another report suggesting greater virulence of *Enterobacter* spp. over other gram-negative nosocomial pathogens involved postoperative wound infections (218). In that study, specimens of the site were obtained intraoperatively for culture and patients were monitored for subsequent wound infection. Data showed that among patients from whom an *Enterobacter* sp. was recovered intraoperatively, 100% subsequently developed a wound infection with the organism (218). Intraoperative recovery of no other organism carried a 100% prediction of subsequent infection. Clearly, much more needs to be learned about the genus *Enterobacter* and its pathogenetic potential for the seriously ill patient.

TABLE 2. Antibiotic susceptibility of the four species of *Enterobacter* most commonly recovered from clinical material<sup>a</sup>

Antibiotic	MIC <sub>50</sub> /MIC <sub>90</sub> for following species (no. of strains tested) <sup>b</sup> :			
	<i>E. sakazakii</i> (195)	<i>E. agglomerans</i> (27)	<i>E. aerogenes</i> (25)	<i>E. cloacae</i> (29)
Ampicillin	2/4	32/>128	>128/>128	>128/>128
Piperacillin	2/2	4/32	4/>128	4/>128
Cephalothin	64/128	16/>128	>128/>128	>128/>128
Cefamandole	2/4	2/>128	4/>128	8/>128
Cefoxitin	8/16	8/>128	>128/>128	128/>128
Cefotaxime	0.12/0.12	0.25/32	0.12/0.5	0.25/8
Imipenem	0.12/0.25	0.5/0.5	1.0/2.0	0.5/1.0
Gentamicin	0.25/0.5	0.5/1.0	0.5/32	0.5/8.0
Ciprofloxacin	≤0.06/≤0.06	≤0.06/1.0	≤0.06/≤0.06	≤0.06/0.12

<sup>a</sup> Modified from reference 162 with permission of the publisher.<sup>b</sup> The MICs are given in micrograms per milliliter.

### ANTIMICROBIAL SUSCEPTIBILITY

Due to the diverse species within the genus *Enterobacter*, the antimicrobial susceptibility varies widely within the genus. One of the most complete analyses of differences in antimicrobial susceptibility between the various *Enterobacter* spp. was reported by Muytjens and van der Ros-van de Repe (162). These authors examined the activity of 29 antimicrobial agents against eight species of *Enterobacter*. As shown in Table 2, there are important differences in the antimicrobial susceptibility of the four species most often recovered from clinical specimens. Some strains of *E. sakazakii* and *E. agglomerans* may be susceptible to ampicillin, cephalothin, and cefoxitin, three β-lactam drugs to which *E. cloacae* and *E. aerogenes* are uniformly resistant (59, 61, 94, 135, 162, 214). This is due to the absence of the characteristic inducible Bush group 1 chromosomal β-lactamase in these strains (see below). Strains of *E. sakazakii* and *E. agglomerans* also tend to be susceptible to the aminoglycosides (Table 2). This reflects the fact that these species usually cause nosocomial infections from identifiable exogenous sources and are probably not part of the "stable" hospital flora. Thus, they have less opportunity than *E. cloacae* or *E. aerogenes* to acquire plasmids encoding for aminoglycoside-inactivating enzymes.

The in vitro activity of a variety of antimicrobial agents against *E. cloacae* and *E. aerogenes* has been examined by a number of investigators. Unfortunately, some investigators did not separate the results by species (3, 25, 84, 141, 215, 224, 233) and some examined *E. cloacae* only (34, 66, 71, 86, 99, 199). Nevertheless, the overall activity of a variety of agents becomes apparent from a composite of results from studies that examined each of these species specifically (Table 3) (15, 34, 66, 68–71, 92, 112–115, 118, 119, 135, 160, 162, 165, 166, 185, 196, 198, 199, 203, 206, 213, 225, 241, 244). Both *E. aerogenes* and *E. cloacae* are predictably resistant to ampicillin, cephalothin and other older cephalosporins, and cefoxitin (3, 34, 66, 71, 132, 160, 162, 214, 215, 232). Any laboratories showing 5% or more of strains of these species to be susceptible to these agents should examine their testing methods for possible sources of error (231). A low inoculum or short incubation period can lead to results falsely indicating susceptibility of strains of *E. aerogenes* or *E. cloacae* to these agents. Among the remaining β-lactam antibiotics, the in vitro activity varies widely (Table 3). In general, ureidopenicillins and carboxypenicillins are active against one-half or more of strains tested, and addition of a β-lactamase inhibitor does not improve the activity of these agents against *E. aerogenes* or *E. cloacae* (Table 3) (34, 68, 115, 160, 206, 213, 215). In fact, addition of clavulanate to ticarcillin may actually decrease the activity of the drug due to the ability of this inhibitor to induce the chromosomal β-lactamase that is characteristically present in these species (223) (see below). Cephalosporins like cefamandole and cefuroxime are not highly active against *E. aerogenes* or *E. cloacae* (Table 3) (34, 66, 71, 135, 141, 160, 162). The MICs at which 50% of isolates are inhibited (MIC<sub>50</sub>s) are often at or above the susceptible breakpoint for these agents. The activity of the expanded-spectrum cephalosporins and aztreonam exceeds that of the older cephalosporins (Table 3). However, MIC<sub>90</sub>s are often above the susceptible breakpoint for these agents. In recent studies, the new expanded-spectrum cephalosporins like ceftiprome and cefepime have been the most potent agents among the cephalosporin family, with MIC<sub>50</sub>s and MIC<sub>90</sub>s usually within the susceptible breakpoint for these drugs (Table 3). Among the β-lactam antibiotics, the carbapenems like imipenem and meropenem are most active against *E. aerogenes* and *E. cloacae* (Table 3). The MIC<sub>50</sub>s and MIC<sub>90</sub>s of these

TABLE 3. In vitro activity of various antibiotics against *E. aerogenes* and *E. cloacae*<sup>a</sup>

Antibiotic (breakpoint) <sup>b</sup>	<i>Enterobacter aerogenes</i>			<i>Enterobacter cloacae</i>		
	No. of strains	MIC <sub>50</sub> (μg/ml)	MIC <sub>90</sub> (μg/ml)	No. of strains	MIC <sub>50</sub> (μg/ml)	MIC <sub>90</sub> (μg/ml)
Ticarcillin (16)	259	2	64	550	2–8	>64
Piperacillin (16)	2,398	4–16	8–>64	3,361	2–32	64–>64
Ticarcillin-clavulanate (16)	1,401	2–8	4–>64	3,247	4–64	64–>64
Cefamandole (8)	66	2–4	>64	195	4–32	>64
Cefotaxime (8)	1,353	0.06–4	0.12–>64	3,423	0.25–32	2–>64
Ceftazidime (8)	1,575	0.1–4	0.25–>64	3,887	0.25–16	0.8–>64
Ceftiprome (8)	316	0.06–1	0.12–4	796	0.12–0.25	0.12–16
Cefepime (8)	219	0.03–0.5	0.06–8	896	0.03–0.5	0.5–4
Aztreonam (8)	1,117	0.06–1	0.25–>64	2,181	0.12–1	1–>64
Imipenem (4)	1,482	0.25–2	0.5–4	3,747	0.12–1	0.25–4
Meropenem (4)	113	0.03–0.06	0.06–0.25	267	0.03–0.12	0.03–0.5
Gentamicin (4)	182	0.25–2.0	0.5–32	1,150	0.25–4	0.5–>64
Amikacin (16)	60	2–4	4–16	425	1–4	2–16
Ciprofloxacin (1)	1,188	0.01–0.25	0.03–>16	3,085	0.01–0.12	0.03–4
Trimethoprim-sulfamethoxazole (2)	25	4	32	713	0.5–8	2.0–32

<sup>a</sup> Data for MICs from references 15, 34, 66, 68–71, 92, 112–115, 118, 119, 135, 160, 162, 165, 166, 185, 196, 198, 199, 203, 206, 213, 225, 241, and 244.<sup>b</sup> The breakpoint is the concentration (in micrograms per milliliter) at and below which strains are considered susceptible to the antibiotic. Data from references 52, 163, and 190.

agents are usually below the susceptible breakpoint, especially in tests with meropenem (15, 113, 119, 196, 241). Aminoglycosides and ciprofloxacin are active against the majority of strains of *E. aerogenes* and *E. cloacae*, while trimethoprim-sulfamethoxazole shows variable activity (Table 3).

## RESISTANCE

### Prevalence

Resistance of strains of *Enterobacter* to each of the major groups of antimicrobial agents varies widely among published reports. For the  $\beta$ -lactam antibiotics, the percentage of strains resistant to specific agents ranges from 9 to 50% for ticarcillin, 8 to 53% for mezlocillin, 6 to 54% for piperacillin, 5 to 63% for cefotaxime, 6 to 59% for ceftazidime, 6 to 44% for aztreonam, 0.2 to 9% for cefepime, and 0 to 4% for imipenem (25, 34, 71, 84, 85, 99, 127, 132, 141, 160, 176, 198, 206, 212, 215, 223–225, 232, 244). These percentages reflect, once again, the greater activity of the newer expanded-spectrum cephalosporins and carbapenems against *Enterobacter* spp. in general. For the aminoglycosides, the percentage of strains resistant to gentamicin ranges from 0 to 51%, the percentage resistant to tobramycin ranges from 0 to 43%, and the percentage resistant to amikacin ranges from 0 to 34% (25, 34, 71, 84, 85, 99, 127, 132, 141, 160, 176, 198, 206, 212, 215, 223–225, 232, 244). For ciprofloxacin, resistance varies from 0 to 36% of strains tested, and for trimethoprim-sulfamethoxazole, resistance varies from 0 to 60% of strains (34, 71, 85, 99, 127, 132, 141, 160, 198, 212, 213, 215, 216, 223, 224, 232, 244). These wide ranges suggest that numerous factors impact the occurrence of antimicrobial resistance among strains of *Enterobacter*.

### Factors Associated with Resistance

The prevalence of resistance varies greatly among diverse geographic locations. Although not all geographic regions are equally represented in the published literature, certain trends can be seen. In general, resistance to  $\beta$ -lactam antibiotics, aminoglycosides, trimethoprim-sulfamethoxazole, and quinolones is most prevalent among *Enterobacter* strains recovered from patients in hospitals in southern Europe, Belgium, and Israel (8, 51, 54, 82, 85, 130, 132, 213, 216, 219, 223, 224). In various reports from Greece, resistance to cefotaxime, ceftazidime, ceftriaxone, and/or aminoglycosides has been found in as many as 60 to 70% of strains while resistance to fluoroquinolones has been found in over 10% in some surveys (82, 85, 130, 219). Although the prevalence of resistance to  $\beta$ -lactam antibiotics is highly variable elsewhere, the resistance of strains of *Enterobacter* to aminoglycosides and fluoroquinolones tends to be low in northern Europe, Scandinavia, the United States, and Canada (14, 34, 79, 97, 123, 127, 132, 141, 160, 198, 206, 212, 215, 225, 232, 244). A single report from a hospital in Taipei suggests that resistance to  $\beta$ -lactams, aminoglycosides, and trimethoprim-sulfamethoxazole is prevalent among *Enterobacter* spp. recovered from blood cultures (71).

One of the earliest studies that examined the antimicrobial susceptibility of a large number of *Enterobacter* spp. recovered from a single U.S. hospital was performed in 1969 to 1970, prior to the introduction of extended-spectrum cephalosporins (214). In that study, all 199 strains of *E. cloacae* and *E. aerogenes* studied were found to be uniformly resistant to ampicillin and cephalothin while one-half were susceptible to carbenicillin. Two-thirds of the strains were susceptible to nalidixic acid, while 98% were susceptible to gentamicin (214). Since that early report, susceptibility to all of the major groups of anti-

microbial agents has declined (8, 10, 26, 31, 47, 76, 77, 107, 111, 121, 122, 230). In general, the prevalence of resistance to the  $\beta$ -lactam antibiotics, aminoglycosides, trimethoprim-sulfamethoxazole, and quinolones has increased with time, and this is associated with increased use of the respective drugs in a given environment (1, 2, 6, 42, 81, 82, 109, 143). Increases in the prevalence of resistance to  $\beta$ -lactam antibiotics have been associated with increased use of the newer cephalosporins (11, 12, 37, 42, 48, 73, 109, 110, 158, 159, 164, 193, 234, 239). However, it should be noted that in some institutions, once the prevalence of resistance to older extended-spectrum cephalosporins reaches 25 to 35%, it tends to plateau at that level despite continued high use of these cephalosporins. This probably reflects the fact, noted above, that most *Enterobacter* infections arise from a patient's own endogenous flora rather than from the environment or a single nosocomial source. Therefore, the susceptibility or resistance of a particular *Enterobacter* strain will be more dependent upon antibiotic use in an individual than in the environment as a whole. This is reflected in the observation made by several investigators that multiple- $\beta$ -lactam-resistant *Enterobacter* infections are encountered significantly more often in patients who have received prior extended-spectrum cephalosporin therapy for any reason (37, 104, 234, 238). Moreover, a shift back to susceptible strains occurs when no cephalosporin is given (234). A recent study examined several different extended-spectrum cephalosporins and their association with the recovery of a resistant strain (104). Interestingly, the risk of recovery of a resistant strain increased linearly over approximately 1 week during therapy with ceftizoxime or cefotaxime, while with ceftazidime, even 1 day of therapy maximally increased risk of recovery of a resistant isolate.

Other factors that influence the prevalence of resistance of strains of *Enterobacter* to antimicrobial agents include the size and complexity of the hospital and the unit in the hospital (31, 54, 127, 201, 244). In general, the larger the hospital, the greater the prevalence of resistance to  $\beta$ -lactam antibiotics, trimethoprim-sulfamethoxazole, and quinolones (31, 127, 244). Interestingly, the size of the hospital did not affect the susceptibility of *Enterobacter* spp. to aminoglycosides in several studies (127, 244). Resistant *Enterobacter* spp. are also more likely to be recovered from patients in the ICU of the hospital than other areas (31, 54, 201). A recent NNIS survey involving 144 hospitals across the United States showed that ceftazidime resistance among *Enterobacter* spp. was associated more often with isolates recovered from (i) 1990 to 1991 than from those recovered from 1987 to 1989, (ii) patients in teaching hospitals or ICUs, and (iii) blood or urinary tract infections (31). In another study, multiple- $\beta$ -lactam resistant *Enterobacter* spp. were more frequently recovered from blood than from other sites (104).

### Mechanisms of Resistance

There are three major mechanisms whereby organisms can become resistant to an antimicrobial agent. These include the production of an inactivating enzyme, alteration of the target of the drug, and alteration of the ability of the drug to enter and/or accumulate in the cell. The first mechanism is most often involved in the resistance of *Enterobacter* spp. to  $\beta$ -lactam antibiotics and aminoglycosides, while the last two are most often involved in resistance to quinolones and trimethoprim-sulfamethoxazole (32, 41, 45, 46, 84, 100, 101, 107, 129, 130, 138, 141, 143, 175, 178, 183, 184, 187, 190, 192, 216).

All species of *Enterobacter* examined to date possess a chromosomally encoded Bush group 1  $\beta$ -lactamase (32, 178, 191,

192). In strains of *E. agglomerans* and *E. gergoviae* and some isolates of *E. sakazakii*, the enzyme is produced at very low, noninducible levels (178). This explains the greater susceptibility of these species to ampicillin, older cephalosporins, and cefoxitin (Table 2). The uniform resistance to these agents found among wild-type strains of *E. taylorae*, *E. cloacae*, *E. aerogenes*, and *E. asburiae* and most strains of *E. sakazakii* in general is due to the presence of an inducible Bush group 1  $\beta$ -lactamase (178). In wild-type strains of these species, this resistance arises either from the great lability of the drug to this particular enzyme or from the drug acting as an inducer of the enzyme, which hydrolyzes the drug more efficiently following induction. Resistance to extended-spectrum cephalosporins, broad-spectrum penicillins, and aztreonam emerges in these species of *Enterobacter* following mutation in a chromosomal gene, *ampD*, that normally prevents high-level expression of the enzyme (192). Once this mutation occurs, high levels of the chromosomal  $\beta$ -lactamase are expressed. Such *ampD* mutants have been referred to as stably derepressed mutants. Since the Bush group 1  $\beta$ -lactamase is intrinsically resistant to currently available  $\beta$ -lactamase inhibitors like clavulanic acid, these stably derepressed mutants are also resistant to  $\beta$ -lactamase inhibitor- $\beta$ -lactam drug combinations (192, 193). Among  $\beta$ -lactam agents, the only drugs maintaining activity include the carbapenems and newer expanded-spectrum cephalosporins like cefepime (23, 54, 193, 241). However, secondary mutations involving permeability through the outer envelope can lead to resistance to these agents as well among mutants already producing high levels of the chromosomal  $\beta$ -lactamase (55, 100, 128, 129, 134, 173, 177, 220).

Although the chromosomal  $\beta$ -lactamase of *Enterobacter* spp. is most commonly involved in  $\beta$ -lactam resistance encountered in this genus, other  $\beta$ -lactamases can also be found. Wild-type *Enterobacter* strains may become resistant to broad-spectrum penicillins like piperacillin via the acquisition of plasmids encoding the Bush group 2b TEM-1, TEM-2, or SHV-1  $\beta$ -lactamase or the Bush group 2d OXA-1  $\beta$ -lactamase (16, 138, 183, 187). These strains differ from mutants expressing high levels of their chromosomal  $\beta$ -lactamases in that they are susceptible to extended-spectrum cephalosporins and  $\beta$ -lactamase inhibitor- $\beta$ -lactam drug combinations. On occasion, wild-type strains of *Enterobacter* may become resistant to extended-spectrum cephalosporins via the acquisition of plasmids encoding the Bush group 2be  $\beta$ -lactamases, the extended-spectrum  $\beta$ -lactamases (ESBLs) (45, 46, 84, 98, 184). Although it may seem surprising that an organism with an inducible  $\beta$ -lactamase would ever acquire an ESBL, the resistance to other agents such as the aminoglycosides encoded on the same plasmid as the ESBL may often be the major factor driving the acquisition of these plasmids by *Enterobacter* spp. Most recently, there has been a report of carbapenem resistance in a clinical isolate of *E. cloacae* due to the presence of a chromosomally encoded carbapenemase (168). This enzyme, like the usual Bush group 1  $\beta$ -lactamase which was also present in the strain, was inducible by cefoxitin and carbapenems.

Mechanisms responsible for aminoglycoside resistance among clinical isolates of *Enterobacter* have been the subject of numerous investigations (101, 107, 130, 141, 143, 175). As with other members of the *Enterobacteriaceae*, resistance of strains of *Enterobacter* to aminoglycosides is due to the production of one or more aminoglycoside-inactivating enzymes. Acetylating enzymes, including AAC (3)-II, AAC (6'), AAC (3)-III, AAC (3)-I, and AAC (3)-V, appear to be the most commonly encountered. Nucleotidylating enzymes, ANT (2''), have also been encountered.

### Emergence of Resistance During Therapy

It is now well established that strains of *Enterobacter* may rapidly develop resistance to multiple  $\beta$ -lactam antibiotics during therapy with one of a number of  $\beta$ -lactam drugs (reviewed in references 37 and 193). The rate at which this occurs varies from less than 20% to over 70% depending upon the site of infection, the drug used in therapy, and the underlying condition of the patient (37, 104, 193, 201, 234). In a prospective study of *Enterobacter* bacteremia by Chow et al. (37), the emergence of resistance during therapy occurred significantly more often when an extended-spectrum cephalosporin was used than when an aminoglycoside or other  $\beta$ -lactam antibiotic was used. Furthermore, the use of an aminoglycoside in combination with the cephalosporin did not prevent the emergence of resistance (37). Emergence of resistance can be detected as early as 24 h after initiation of therapy or can require 2 to 3 weeks (37).

Emergence of resistance results from the selective pressure exerted by the drug used in therapy, which provides a survival advantage for the stably derepressed mutant over the wild type. Over the course of therapy, the wild-type cells, expressing their chromosomal  $\beta$ -lactamase inducibly, are killed by the drug while the mutant cells, producing high levels of chromosomal  $\beta$ -lactamase, are able to replicate. Unless the patient's normal defense mechanisms are sufficient to eliminate the mutant cells, which are present in very small numbers at the onset of infection (i.e. 1 in  $10^6$  to  $10^7$  wild-type cells), the multidrug-resistant mutant cells will become predominant. This scenario explains why the emergence of resistance is not seen in all patients infected with a wild-type *Enterobacter* strain who are treated with an extended-spectrum cephalosporin. In these patients, intrinsic defense mechanisms are capable of eliminating the mutant cells. It also explains why the emergence of resistance occurs more often in severely debilitated patients who are immunocompromised and why resistance can be detected in as little as 1 day or may require several weeks.

### CLINICAL MANIFESTATIONS

*Enterobacter* spp. have been implicated in a broad range of clinical syndromes. The literature is replete with descriptions of bacteremia and infections of skin and soft tissues, respiratory tract, urinary tract, bone and joints, central nervous system, gastrointestinal tract, and other organs. In general, the characteristics of infection due to *Enterobacter* spp. resemble those due to other facultative gram-negative bacilli. However, there are some distinctive features that may serve as guideposts to selection of therapy or to planning of institutional control measures.

#### Bacteremia

Of all clinical syndromes, bacteremia has been studied most often and in greatest depth. Fortunately, there has been general agreement among investigators upon the criteria for the diagnosis. As a result, data in individual reports tend to be reliable and comparisons between studies are facilitated.

**Demographics.** The demographics of *Enterobacter* bacteremia are shown in Tables 4 through 6. The incidence of bacteremia parallels that of the total of *Enterobacter* infections reported over the past three decades (see above). Most institutions and services have experienced significant increases extending up to or into the present decade. The rates of bacteremia tend to cluster around 1 per 1,000 admissions for university hospitals or tertiary-care centers. These rates tend to be two- to threefold higher in specialized units, such as cancer

TABLE 4. Characteristics of bacteremia due to *Enterobacter* spp. encountered in general hospitals

Reference	Yr studied	Patient population	Total no. of episodes	Rate/1,000 admissions	Male/female ratio	Ages (yr)
Johnson and Ramphal (108)	1985–1989	Univ. teaching	51	ND <sup>a</sup>	ND	Adults
Chow et al. (37)	1.5 yr in late 1980s	Six teaching centers	129	ND	2.8 <sup>b</sup>	17–95
Haddy et al. (90)	1985–1987	Five community	75	0.3	1.4	10–98
Weischer (236)	1984–1989	Univ. teaching	53	ND	1.4	30–76
Al Ansari et al. (1)	1990–1992	Teaching hospital	22	ND	ND	ND
Peña et al. (174)	1984–1990	Univ. teaching	226	0.9–1.8	2.4	57 <sup>c</sup>
Vázquez et al. (224)	1981–1990	Univ. teaching	195	2.3–6.7	2.3	All
Bouza et al. (25)	1977–1983	General referral	50 <sup>f</sup>	1.3	1.3	All
Fung et al. (71)	1985	Veterans hospital	41	1.1	3.0	17–82
Watanakunakorn and Weber (232)	1980–1986	Community teaching	58	0.3	1.9	All
Andersen et al. (5)	1987–1988	Univ. teaching	10	ND	ND	ND

<sup>a</sup> ND, not determined.

<sup>b</sup> Two of the six hospitals were Veterans Administration Medical Centers with predominantly male populations.

<sup>c</sup> Patients had two *Enterobacter* spp. isolated.

<sup>d</sup> Rate at 14 days (the rate at 28 days was 24%).

<sup>e</sup> Mean age.

<sup>f</sup> Fifty cases randomly selected from a larger total for detailed analysis.

<sup>g</sup> Review restricted to *E. cloacae*.

<sup>h</sup> Attributable mortality.

centers, and two- to threefold lower in community hospitals. Although rates are lower in the community, the problem is significant and growing (64, 182).

In data gathered from institutions other than veterans' medical centers, *Enterobacter* bacteremia tends to occur more commonly in males in a ratio of 1.3 to 2.5:1.0. Males predominate among both infected adults and children. Bacteremia is more commonly encountered at the extremes of age, i.e., in neonates and the elderly. The majority of bacteremias are acquired institutionally (range, 56 to 100%). *E. cloacae* predominates in most series (range, 46 to 91% of isolates) followed in order by *E. aerogenes* (range, 9 to 43%), *E. agglomerans*, *E. sakazakii*, and others. From 14 to 53% of bacteremias that involve *Enterobacter* spp. are polymicrobial. The companion organisms in the polymicrobial bacteremias appear to be randomly distributed between gram-positive and gram-negative isolates. Anaerobes have been encountered in the presence of coincident gastrointestinal foci. Fungi and additional species of *Enterobacter* have been recognized occasionally. In comparative studies, the frequency of polymicrobial bacteremia has been significantly higher for *Enterobacter* spp. than for *Klebsiella* spp. (30 and 12%, respectively) (25) or *Escherichia coli* (53 and 6%, respectively) (236). The very high rate of polymicrobial bacteremia has profound implications for the selection of therapy when *Enterobacter* spp. are suspected or implicated.

Several investigators have detected seasonal variations in the occurrence of bacteremia due to *Enterobacter* spp. Clustering of cases in summer months has been recognized in children's hospitals in Michigan (7) and Texas (6) and in a survey of 18 hospitals in the United States (107). In none of these was the seasonal increase traced to a common source or mode of spread. Interestingly, a seasonal clustering in winter has been reported in a veterans' hospital in Taipei, China (71).

**Signs, symptoms, and laboratory findings.** The incubation period of *Enterobacter* bacteremia has been estimated from common-source outbreaks in which the organisms were infused directly into the bloodstream (148). The time for appearance of signs and symptoms has varied from as short as 2 h to as long as 20 days, with most occurring in a few hours to 2 days. In a pediatric outbreak, the incubation period was a mean of 6 days (148). Signs and symptoms are generally similar to those noted during bacteremia with other enteric bacilli in both adults and children. Two exceptions have been noted. First, *E. sakazakii*, unlike other enteric organisms, may cause a highly lethal syndrome of bacteremia with central nervous system involvement in neonates and young children (73). Second, bacteremia due to *Enterobacter* spp. has been notable for the relative infrequency of establishment of secondary metastatic foci (25, 71).

Fever is the hallmark of bacteremia in both adults and chil-

TABLE 5. Characteristics of bacteremia due to *Enterobacter* spp. encountered in pediatric hospitals

Reference	Yr studied	Patient population	Total no. of episodes	Rate/1,000 admissions	Male/female ratio	Ages	% Nosocomial
Gallagher (73)	1984–1988	Children's hospital	33	0.44	1.2	1 day–24 yr	67
Andresen et al. (7)	1989–1992	Children's hospital	32	0.3–1.1	2.3	6 mo–11 yr	56
Bonadio et al. (21)	1978–1990	Children's hospital	30	0.27	1.3	6 mo–<1 yr	57
Matsaniotis et al. (148)	1981	Children's hospital	63	ND	ND	10 days–17 yr	100 <sup>d</sup>

<sup>a</sup> Attributable mortality.

<sup>b</sup> ND, not determined.

<sup>c</sup> Review restricted to *E. cloacae*.

<sup>d</sup> Common-source outbreak within the hospital.

TABLE 4—Continued

Nosocomial	% of species					Polymicrobial	Crude mortality rate (%)	Special features
	<i>E. cloacae</i>	<i>E. aerogenes</i>	<i>E. agglomerans</i>	<i>E. sakazakii</i>	Other			
ND	ND	ND	ND	ND	ND	ND	25	One-third of the patients were neutropenic
84	72	27	1	1	2 <sup>c</sup>	ND	20 <sup>d</sup>	Analysis of emergence of resistance
80	57	36	4	0	1	ND	29	Growing importance in community
83	91	9	0	0	0	53	30	Contrasts to <i>E. coli</i> bacteremia
ND	68	14	0	9	9	ND	15	Most isolates multiply resistant de novo
81	46	27	9	ND	19	14	23	Increasing incidence over decade
ND	ND	ND	ND	ND	ND	16	ND	Slight decrease in incidence over decade
76	ND	ND	ND	ND	ND	30	42	Demographics compared to <i>Klebsiella</i> spp.
68	100 <sup>e</sup>	ND	ND	ND	ND	ND	46, 44 <sup>t</sup>	Sporadic cases, no clusters
72	50	43	7	0	0	34	69	High mortality, poor response to antimicrobial agents
70	100 <sup>e</sup>	ND	ND	ND	ND	ND	40	Multiple resistance curbed by restriction of cephalosporin use

dren. Reported rates have ranged from 83 to 87% in children (7, 21, 148) and from 92 to 98% in adults or mixed populations (20, 25, 37, 71). Lower rates have been observed in neonates (40%) (21) and among adults (61%), a high proportion of whom have normal or low leukocyte counts (90). The height of fever is usually substantial (20, 30, 148), and rigors occur in up to 75% of patients (148). Temperatures of 104°F or greater were observed in 28% of patients with cancer in one large series (148). No pattern of fever is predictive; intermittent, remittent, hectic, and sustained fevers have all been observed (148).

Hypotension or shock has been reported in 9 to 34% of adult or mixed populations (20, 25, 37, 71, 90). The frequency is similar in children (8 to 28%) (7, 21, 148). Altered mentation is often (32 to 38%) noted concurrently in both adults and children (37, 71, 148). Leukocytosis occurs in approximately two-thirds of patients with bacteremia (25, 71, 90). Leukopenia has also been reported in 9 to 17% of individuals of a broad range of ages (71, 90). Thrombocytopenia (25), hemorrhage (20), and jaundice (71) have each been noted in a few series. The syndrome of disseminated intravascular coagulopathy has been recognized in 0 to 6% of bacteremic episodes (20, 25, 71, 90). Most of the usual cutaneous manifestations associated with bacteremia have been noted occasionally. These include purpura fulminans (89), hemorrhagic bullae (140), and ecthyma gangrenosum (182). Cyanosis and mottling has been encountered in two-thirds of bacteremic children (148).

**Portals of entry.** The most commonly implicated portals of entry of *Enterobacter* spp. into the bloodstream are tabulated in Table 7. Most investigators relied upon a combination of presumptive evidence, clinical judgment, and cultures whenever

possible in establishing the portal of entry. Weischer and Kolmos (236) demanded microbiological confirmation to definitively establish an entry point. Despite the differing criteria, their results were near the median of those of all investigators for most portals. The extremes in percentages of portals of entry usually reflect the unique nature of the hospital or service in which the study was performed. For example, the highest percentage of "unknown" portals was found in a study performed in a cancer center, while the highest percentage of portals of gastrointestinal origin was reported from a study weighted with patients with hepatic transplantation. With a few such exceptions, there was a remarkable consistency of results regarding portals of entry in the series of bacteremias.

**Risk factors for development of bacteremia.** Nearly all studies of *Enterobacter* bacteremia have included an evaluation of potential risk factors. Many simply presented the percentage of bacteremic patients with a long list of putative risk factors. A few were controlled and subjected to a simple statistical analysis, such as a chi-square determination. A minority of investigators performed univariate or multivariate analyses. However, despite vast differences in methodology, the conclusions of the various studies have been remarkably consistent.

The sine qua non for development of bacteremia due to *Enterobacter* spp. is severe underlying illness. The few exceptions to this statement have generally occurred during outbreaks when the organism was directly inoculated into relatively healthy individuals. The most commonly cited factors associated with the acquisition of bacteremia due to *Enterobacter* spp. are listed in Table 8. In the absence of multivariate analyses, many of these factors, such as the various procedures and devices, may be mere surrogate markers for the severity

TABLE 5—Continued

<i>E. cloacae</i>	% of species				Polymicrobial	Crude mortality rate (%)	Special features
	<i>E. aerogenes</i>	<i>E. agglomerans</i>	<i>E. sakazakii</i>	Other			
70	15	12	3	0	18	24, 18 <sup>a</sup>	Prototypical for pediatrics
72	12	16	0	0	34	ND, <sup>b</sup> 6 <sup>a</sup>	Increasing incidence
100 <sup>c</sup>	ND	ND	ND	ND	20	10	Restricted to <i>E. cloacae</i>
65	35	0	0	0	ND	6	Common-source outbreak with spread to hands of personnel



TABLE 6. Characteristics of bacteremia due to *Enterobacter* spp. encountered in specialized units or populations

Reference	Yr studied	Patient population	Total no. of episodes	Rate/1,000 admissions	Male/female ratio	Ages (yr)	% Nosocomial
Burchard et al. (30)	1980–1984	Surgical service	63	ND <sup>a</sup>	2.9	Adults	Most
Wagener and Yu (227)	1987	Transplant recipients	19	ND	ND	16–67	95
John et al. (107)	1977–1980	Primarily burns	18	ND	ND	ND	Most
Mayhall et al. (149)	1976	Burn center	15	ND	ND	ND	Most
Bodey et al. (20)	1972–1986	Cancer hospital	296	1.8	1.3	1–83	74

<sup>a</sup> ND, not determined.

<sup>b</sup> Review restricted to *E. cloacae*.

<sup>c</sup> Attributable mortality.

<sup>d</sup> Polymicrobial infections excluded from analysis.

and extent of the underlying disease(s). The diseases most commonly identified as risk factors during the last three decades include those that impair systemic immunity, such as hematological malignancies, or alter natural barriers to invasion, such as gastrointestinal tract diseases and thermal injury. Procedures or devices that disrupt the integument also appear to favor access of the organism to the vasculature. The use of antibiotics has consistently been cited for providing a selective advantage for survival, colonization, and ultimately invasion by more naturally resistant organisms, such as *Enterobacter* spp. Recognition of the importance of prior infection or colonization as risk factors simply documents the second step in this selective process.

Several groups of investigators attempted to more fully characterize putative risk factors that were prominent in their institutions. Bodey et al. (20) calculated the relative risk posed by various types of malignancies at the M. D. Anderson Cancer Center for a 10-year interval. Rates of episodes of *Enterobacter* bacteremia per 1,000 new registrations were 17 for acute leukemias, 8 for hematological malignancies, and 1 for solid tumors. One may speculate that the observed differences in rate correlate with the degree of compromise of host defense associated with each class of malignancy.

Wagener and Yu attempted to dissect the risks associated with transplantation of various organs (227). They observed that kidney recipients had the lowest risk of bacteremia or fungemia (6%). The risk of bloodstream invasion was nearly twofold greater in heart recipients (11%) and fourfold greater in liver recipients (24%). *Enterobacter* spp. predominated as causes of nosocomial bacteremia acquired within 2 weeks of hepatic transplantation (10 of 32 episodes). They were encountered infrequently after 2 weeks or at any time in heart and kidney transplant recipients. Overall, *Enterobacter* spp. and *Pseudomonas* spp. were implicated with equal frequency (19 of 125 episodes of bacteremia/fungemia each) in the authors' experience (227).

Nearly all investigators have implicated previous antimicrobial therapy as a factor predisposing to bacteremia (Table 8). Among the various agents, the  $\beta$ -lactams and aminoglycosides have been cited most often but not exclusively (1, 37). In a study of bacteremia due to *Enterobacter* spp., Chow et al. (37) demonstrated significant associations of any antimicrobial agent (36 [35%] of 103) versus none (1 [4%] of 26;  $P = 0.002$ ) and third-generation cephalosporins (22 [69%] of 32) versus other agents (14 [20%] of 71;  $P = 0.001$ ) with the detection of multiple resistance in initial isolates. The importance of antibiotics in general and cephalosporins in particular was underscored by Burchard et al. (30). They identified previous antimicrobial agents as risk factors in two-thirds of their patients

on a surgical service. They then noted that the mean duration of administration prior to bacteremia was  $23.4 \pm 4.6$  days for all antimicrobial agents but only  $9.3 \pm 1.6$  days for cephalosporins (primarily first- and second-generation agents). Two groups of investigators have demonstrated that restriction of the use of cephalosporins (especially the newer drugs) reduces or eliminates the risk of bacteremia due to *Enterobacter* spp. (5, 28).

Bacteremia due to multiply  $\beta$ -lactam-resistant *Enterobacter* strains has been linked to prior use of ceftazidime versus use of penicillins and older cephalosporins (108), as well as use of cefotaxime and cefuroxime (73), cefotaxime (28), and newer cephalosporins in general (5, 37). The emergence of multiple resistance during therapy of bacteremia with newer cephalosporins has been documented (see above [37]). Multiple  $\beta$ -lactam resistance itself has been implicated as a risk factor for sepsis. Andersen et al. studied 69 patients with infections due to *E. cloacae* and found that 15 (22%) were infected by multiply resistant strains whereas 7 of 10 septic patients (70%) were infected by the resistant organisms (5).

**Determinants of the outcome of bacteremia.** The mortality rates for bacteremia due to *Enterobacter* spp. are shown in Tables 4 to 6. Crude mortality rates ranged from 15 to 87%, with two of the three highest rates noted in a burn center and a transplantation unit. Most rates clustered between 20 and 46%, with a median of 30%. Attributable mortality, when specified, ranged from 6 to 40%. The disparate rates in the various studies may have resulted from differences in (i) the population of patients studied (e.g., burn and cancer centers versus general hospitals), (ii) the prevalence of multiple resistance, and (iii) the time following diagnosis (days to months) at which mortality was assessed. In general, the mortality associated with bacteremia due to *Enterobacter* spp. was comparable to that for bacteremia due to other enteric bacilli, with mean and median crude rates most often 20 to 35% (20, 22, 53, 131, 222). Mortality rates for *Pseudomonas* species have been comparable (53, 228) or up to twofold greater (22, 53, 222) in various studies.

Factors associated with mortality in the series devoted to *Enterobacter* bacteremia are listed in Table 9. Most of these factors have been implicated as determinants of outcome in bacteremias due to other gram-negative bacilli (22, 53, 93, 222, 245). The single most important factor in determining the outcome of gram-negative bacteremia is the severity of the underlying disease—rapidly fatal versus ultimately fatal or nonfatal (22, 53, 93, 150, 222, 245). Most of the investigators who studied *Enterobacter* bacteremia acknowledged the importance of severity, but few stratified their analyses of risk factors accordingly. Those who did so reconfirmed the critical impor-

TABLE 6—Continued

<i>E. cloacae</i>	% of species				% Polymicrobial	Crude mortality rate (%)	Special features
	<i>E. aerogenes</i>	<i>E. agglomerans</i>	<i>E. sakazakii</i>	Other			
60	35	2	2	2	ND	35	Importance of antecedent colonization Predominance in liver recipients, early onset postoperatively
ND	ND	ND	ND	ND	21	63	
100 <sup>b</sup>	ND	ND	ND	ND	ND	ND	Reviews of early literature
100 <sup>b</sup>	ND	ND	ND	ND	ND	87–40 <sup>c</sup>	Cross-contamination implicated
75	17	7	1	1	ND <sup>d</sup>	21	Increasing incidence and survival during the last 5 years

tance of this factor (Table 9). Many of the factors identified in Table 9, such as the need for intensive care, parenteral nutrition, prolonged hospital stay, or various devices and procedures, may have been indicative of the severity of the underlying disease rather than direct contributors to mortality themselves. Multivariate regression analyses will be required to definitively assign a role to these factors. The extent of pathophysiologic changes (shock and associated complications) at diagnosis of bacteremia has been identified as an important determinant of outcome in series of patients with bacteremia due to *Enterobacter* spp. (Table 9) and other gram-negative bacilli (22, 53, 222, 245).

Some determinants related to antimicrobial therapy may set *Enterobacter* spp. apart from most other enteric bacilli. The results of analyses of the effect of the appropriateness of antimicrobial therapy on the outcome of *Enterobacter* bacteremia are shown in Table 10. There was wide variation in methods of analysis. For example, outcome was assessed after only 3 days in one study and up to 2 to 4 weeks in others. Most investigators based outcomes on crude mortality without stratification for severity, while one group used attributable mortality only. Most defined appropriate therapy as the use of any agent with activity demonstrable in vitro, while one group demanded the use of a bactericidal agent(s) to meet the criteria for appropriateness. Despite these variations in methodology, the weight of evidence indicates that appropriate therapy (defined as at least one active agent) may favorably influence the outcome. With stratification for severity, beneficial effects were observed in patients who did not have rapidly lethal underlying diseases. An additional factor that impinged upon outcome was de novo infection with a multiply resistant strain of *Enterobacter* or emergence of resistance during therapy. Johnson and Ramphal (108) noted a disproportionate percentage of deaths in patients infected with ceftazidime-resistant strains. Chow et al. (37) identified multiple resistance as a risk factor for mortality by univariate analysis and confirmed its role by multivariate regression analysis. Emergence of multiple resistance during therapy has often, but not invariably, resulted in unfavorable

therapeutic outcomes (37, 193). Survivors with emergence of resistance (although tabulated with "favorable" outcomes) may continue to shed the organism, posing a potential threat to themselves subsequently or to the environment (30, 37, 234). Finally, superinfection may occur during even appropriate and effective therapy of *Enterobacter* bacteremia. Bodey et al. documented superinfection in 57 (19%) of 296 episodes of *Enterobacter* bacteremia (20). The propensity for the development of resistance among *Enterobacter* spp. has had a profound impact upon survival and poses increasing challenges for selection of appropriate therapy.

At present, the weight of evidence suggests that currently available cephalosporins, with the possible exception of cefepime should be avoided in infections known or presumed to be due to *Enterobacter* spp. Serious infections due to relatively susceptible "wild-type" strains often respond to the combination of an expanded-spectrum penicillin and an aminoglycoside. Multiply resistant strains require the use of a carbapenem or a fluoroquinolone. Some physicians recommend combination with an aminoglycoside, at least initially. Some investigators prefer a carbapenem because of their greater experience with this class of agent and the relatively greater coverage of possible coinfecting gram-positive cocci and anaerobes.

#### Comparisons with bacteremias due to other enteric bacilli.

Two groups of investigators performed a controlled comparison of bacteremias due to *Enterobacter* spp. and another enteric bacillus. Weischer and Kolmos (236) compared *Enterobacter* spp. to *Escherichia coli*. During the period 1984 to 1989, *Enterobacter* spp. accounted for 1/10 as many bacteremias as *E. coli* (53 and 530, respectively). *Enterobacter* spp. were acquired significantly more often in the hospital (83% versus 44%;  $P < 0.0001$ ), and were more likely to be a component of a polymicrobial bacteremia (53% versus 6%;  $P < 0.0001$ ). The mean age of patients was lower with *Enterobacter* spp. (53 versus 67 years;  $P < 0.05$ ). Sources of the bacteremia differed markedly between these organisms. Microbiologically documented foci in burns ( $P = 0.006$ ), central venous catheters

TABLE 7. Portals of entry among patients with bacteremia due to *Enterobacter* spp.

Site	% of patients	Reference(s)
Unknown	12, 17, 19, 21, 21, 26, 30, 40, 47, 51, 72	20, 25, 30, 37, 71, 73, 90, 179, 224, 232, 236
Respiratory tract	8, 8, 9, 10, 11, 12, 18, 19, 34, 40, 50	20, 25, 37, 71, 73, 90, 179, 224, 232, 236
Genitourinary tract	7, 7, 11, 12, 13, 14, 14, 19, 26, 27	20, 25, 37, 71, 73, 90, 179, 224, 232, 236
Intravascular catheter	6, 10, 11, 11, 11, 15, 19	37, 71, 73, 90, 179, 224, 236
Wounds/surgery	7, 7, 11, 20, 20, 25	25, 37, 71, 90, 179, 224
Gastrointestinal tract/abdominal	5, 7, 9, 9, 12, 39	20, 37, 73, 90, 224, 232
Skin/soft tissue	5, 8, 12	20, 73, 90
Biliary tract	18, 19, 20	71, 73, 90
Burns	17	224

TABLE 8. Factors associated with the development of bacteremia due to *Enterobacter* spp.

Antecedent	% of patients	Reference(s)
<b>Diagnoses</b>		
Diabetes mellitus	8, 8, 10, 12, 40	25, 37, 71, 90, 232
Malignancy	16, 21, 22, 23, 32, 36	25, 37, 71, 90, 232, 236
Cardiovascular disease	18, 20, 29, 44	25, 30, 37, 232
Burns	3, 4, 9, 19	30, 37, 90, 236
Respiratory disease	5, 10, 14	25, 71, 232
<b>Gastrointestinal diseases</b>		
Any	16, 20, 37, 59	21, 25, 30, 232
Cirrhosis	10, 10	25, 71
Hepatic	14	232
Alcoholism	9	232
Biliary	4	90
Surgery	9, 24	90, 174
Renal disease	7, 10, 17	25, 71, 232
Genitourinary disease	16	232
<b>Previous infection</b>		
Non- <i>Enterobacter</i> bacteremia	15	236
<i>Enterobacter</i> spp. at any site	30, 40	1, 149
Surface colonization, <i>Enterobacter</i> spp.	16	90
Immunosuppressive states	5–26, 15, 57	21, 37, 236
<b>Drugs</b>		
<b>Antimicrobial agents</b>		
Any	36, 50, 54, 66, 67, 79, 80	7, 25, 30, 37, 73, 174, 236
β-Lactams	68	236
Penicillins	60	236
Cephalosporins	19, 33, 69	37, 73, 236
H <sub>2</sub> -receptor antagonist	70	1
Immunosuppressants	15, 23, 26	7, 37, 236
Total parenteral nutrition	23, 33	7, 30
<b>Devices, procedures, and locations</b>		
Hospitalized recently	28	37
Intensive care	30, 41	1, 174
Intravascular catheter	11, 50, 60, 73	1, 7, 30, 236
Surgery or trauma	13, 16, 20, 24, 36, 42, 50, 54	1, 7, 25, 30, 37, 90, 174, 236
Mechanical ventilation	20, 40	1, 37
Urinary catheter or procedure	46, 65, 66	1, 25, 37
Endotracheal tube	14	25
Nasogastric tube	35	1

( $P = 0.009$ ), and the respiratory tract ( $P = 0.08$ ) were more frequently infected with *Enterobacter* spp., while a urinary focus was most common for *E. coli* ( $P = 0.003$ ). Medical devices were more frequently associated with *Enterobacter* bacteremia: urinary catheter with a urinary focus ( $P = 0.003$ ), endotracheal tube ( $P = 0.0002$ ), central venous catheter ( $P = 0.02$ ), and peripheral venous catheter when no other focus was apparent ( $P = 0.02$ ). β-Lactam antibiotics, in particular the penicillins, were identified as a risk factor more often with *Enterobacter* spp. ( $P = 0.003$ ), while *E. coli* bacteremia was more likely to have occurred without prior antimicrobial exposure ( $P = 0.006$ ). The mortality associated with *Enterobacter* bacteremia (30%) was not significantly different from that associated with *E. coli* (24%).

Bouza et al. compared bacteremias due to *Enterobacter* spp. and *Klebsiella* spp. (25). Several potentially important differences were detected, but unfortunately statistical analyses were not performed. *Enterobacter* spp. were components of polymicrobial bacteremia (30%) more often than all gram-negative bacilli collectively (17%), *Klebsiella* spp. (12%), or *Serratia* spp. (9%). The two most common portals of entry were “unknown” surgical sites for *Enterobacter* spp. and urinary tract or “unknown” for *Klebsiella* spp. More patients developed bacteremia with *Enterobacter* spp. than *Klebsiella* spp. in an ICU (30%

versus 11%). The mortality rate was 42% for *Enterobacter* spp. and 25% for *Klebsiella* spp.

### Lower Respiratory Tract Infections

There is relatively little in the available literature concerning the clinical manifestations of lower respiratory tract infections due to *Enterobacter* spp. The few published series on *Enterobacter* spp. have been limited to less than 12 patients, while reviews of larger numbers of gram-negative bacillary pneumonias have seldom provided clinical details for *Enterobacter* spp. specifically. The following is thus a composite of largely fragmentary data from these sources.

Most of the species of *Enterobacter* have been implicated in a wide spectrum of lower respiratory infections, including asymptomatic colonization of respiratory secretions, purulent bronchitis, lung abscess, pneumonia, and empyema (40, 63, 107, 117, 133, 171). As with other gram-negative bacilli, there is still divergence of opinion regarding the validity of cultures of expectorated sputum and the optimal criteria for diagnosis of each of these clinical entities. As a consequence, data, especially regarding incidence, may vary widely from one study to another. Despite these variations, the incidence of lower respiratory tract infections due to *Enterobacter* spp. appears to

TABLE 9. Factors associated with unfavorable outcome of bacteremia due to *Enterobacter* spp.

Factor	Reference(s)
Severity of underlying disease.....	20, 25, 37, 90, 232
Inappropriate antimicrobial therapy <sup>a</sup> .....	7, 20, 25, 37, 71, 90, 108
Shock.....	20, 25, 71, 174, 222, 232
Thrombocytopenia, hemorrhage.....	20, 73
Nosocomial acquisition <sup>b</sup> .....	222, 232
Concurrent pulmonary focus of infection.....	20, 30, 232
Intensive care.....	25, 37
Renal insufficiency.....	30, 37
Intravascular catheter, urinary catheter, prior surgery, hepatic disease, coma, prior cardiac arrest, hemodialysis, multiple $\beta$ -lactam resistance.....	37
Prolonged hospital stay, prior focus of <i>Enterobacter</i> infection, prior bacteremia, total parenteral nutrition, respiratory failure.....	30
Entry site other than intravenous catheter, immunosuppressive therapy.....	174
Delay in diagnosis of bacteremia, delayed neutrophil response, low initial neutrophil count.....	20
Failure to remove intravascular catheters and other foreign bodies.....	7

<sup>a</sup> Two studies (30, 232) suggested that antimicrobial agents had little or no effect on the outcome.

<sup>b</sup> Two studies (25, 71) indicated that mortality was equivalent in community- and hospital-acquired bacteremia.

have increased steadily over the last four decades. These organisms were seldom linked to respiratory infections prior to 1970. Estimates of the incidence of *Enterobacter* spp. in nosocomial respiratory infections in the 1970s ranged from less than 2 to 9% (107). The rates increased from 9.5% in the early 1980s (117, 194) to 11% in 1986 to 1990 (105, 194). *Enterobacter* spp. have recently surpassed *Klebsiella* spp. to become the third most common cause of nosocomial respiratory tract infections in the United States (105, 194).

Pneumonia is perhaps the most important and well studied of lower respiratory infections due to *Enterobacter* spp. Until recently, it occurred almost exclusively in patients with severe underlying diseases and demonstrated a predilection for the elderly who were institutionalized. Chronic obstructive bronchopulmonary disease has been identified as a risk factor in

approximately one-half of patients (117). Patients with chronic obstructive bronchopulmonary disease also appear to be at a relatively greater risk of concomitant bacteremia, and this risk may be further enhanced by corticosteroid therapy (117). Other frequently cited risk factors include alcohol abuse, diabetes mellitus, malignancy, mechanical bronchial obstruction, and severe neurological diseases (40, 107, 117). Prior antimicrobial therapy appeared to be strongly associated with *Enterobacter* pneumonia in one study (40) and insignificantly so in another (117).

The recent recognition of an important role of *Enterobacter* spp. in community-acquired pneumonia in Spain is disquieting (171). By using relatively strict diagnostic criteria (acute illness, pulmonary infiltrates, positive blood cultures or pure cultures of respiratory secretions judged to be "adequate" microscopically or repeatedly positive cultures of respiratory secretions) and extensive bacteriologic and serologic evaluations, *Enterobacter* spp. were found to be the fourth most commonly encountered bacterial pathogens, comprising in excess of 10% of isolates (171). Although this trend may be confined to areas with high antimicrobial agent usage, it should be monitored rigorously.

*Enterobacter* spp. have recently been recognized as major pathogens in lung transplant recipients (49, 142). Approximately 40% of recipients will develop acute bacterial pneumonia in the 2 weeks immediately following transplantation. Mortality associated with pneumonia may be as high as 50%. *Enterobacter* spp. have been the second and fourth most common causes of pneumonia in two recent series (49, 142). In many instances, it appears that the etiologic agents in pneumonia in lung transplant recipients were present in the donor lungs at the time of transplantation. Two studies indicate that "donor" organisms vary in their ability to proliferate and induce pneumonia following their transplantation (49, 142). For example, *Staphylococcus aureus* is the pathogen most commonly encountered in donor lungs but pneumonia appears to result relatively infrequently in recipients (12 to 27% of transfers). On the other hand, *Enterobacter* spp. are highly efficient in producing disease following their transplantation; 60 to 67% of transfers resulted in pneumonia (49, 142). There is no obvious explanation for these apparent differences in "transfer efficiency."

The clinical and laboratory manifestations of *Enterobacter* pneumonia differ little from those observed for pneumonia due to other gram-negative bacilli. Symptoms may be subtle or

TABLE 10. Outcome of antimicrobial therapy in bacteremia due to *Enterobacter* spp.

Outcome of therapy		P	Reference	Comment
Appropriate favorable/total (%)	Inappropriate favorable/total (%)			
45/54 (83)	4/11 (36)	0.001	37	Monotherapy
54/64 (84)	4/11 (36)	0.001	37	Combination therapy
46/55 (84)	9/20 (45)	0.0008	90	Only bactericidal agents appropriate; effect demonstrable only in nonfatal or ultimately fatal underlying diseases
26/40 (65)	9/18 (50)	NS <sup>a</sup>	30	Only "active agent" administered for 3 days considered appropriate
195/250 (78)	6/14 (43)	ND <sup>b</sup>	20	Outcome compared to inappropriate therapy
195/250 (78)	6/20 (30)	ND	20	Compared to no therapy
22/31 (71)	3/15 (20)	$\leq 0.05$	25	
14/16 (88)	8/25 (36)	$< 0.01$	71	Outcome based on attributable mortality
15/33 (46)	4/9 (44)	NS	232	Outcome measured at 3 days of therapy

<sup>a</sup> NS, not significant.

<sup>b</sup> ND, not determined.

mented, especially in the elderly. For example, in a series of 11 predominantly elderly patients, Karnad et al. noted fever in 6 (55%) and cough in only 2 (18%) (117). However, these patients met relatively stringent criteria for the diagnosis of pneumonia (new infiltrates and positive cultures of transtracheal aspirates or sputum plus blood). Most patients demonstrate tachypnea and tachycardia. Hemoptysis appears rarely. Leukocytosis with a shift to the left in differential cell count is usual (82 to 100%) (117). Extrapulmonary sites of infection, such as the urinary tract, skin, or other tissues, are rarely detected. In the absence of extrapulmonary foci for possible hematogenous seeding of the lungs, it has been presumed that the infecting *Enterobacter* spp. arise from the normal flora and colonize the oropharyngeal secretions (117). Although bacteremia is relatively common in patients with *Enterobacter* pneumonia, shock is infrequent and metastatic foci of infection are seldom detected.

Roentgenographic features of *Enterobacter* pneumonia may vary widely (20, 40, 117). Chung et al. described 10 patients with nosocomial pneumonia over a 1-year period (40). Diagnostic criteria were relatively stringent (isolation from cultures of respiratory secretions as well as blood or pleural fluid). Infiltrates on chest roentgenograph were lobar (20%), bronchopneumonic (30%), interstitial (20%), and mixed (30%). Bodey et al. noted single-lobe involvement in 46% of 54 patients and multilobar or diffuse bilateral disease in 54% (20). Effusion, empyema, and cavitation have been reported, but they appear to be relatively infrequent in comparison with their occurrence in other gram-negative bacillary pneumonias (40, 63, 107, 117).

Pneumonias due to *Enterobacter* spp. are often lethal. Reported mortality rates range from 14 to 71% and tend to be higher than those for pneumonias due to many other gram-negative bacilli (20, 40, 117, 133, 142). The single most important determinant of outcome has been the severity of the underlying disease (20, 40, 117, 133). Additional risk factors for unfavorable outcome include implication of multiple pathogens (40, 117), antecedent corticosteroid therapy (117), and extent of disease on the chest roentgenograph (20, 117). Karnad et al. observed a trend toward a more favorable outcome with the use of two or more drugs, rather than one, to which the infecting *Enterobacter* spp. was susceptible (117). Unfortunately, the numbers of patients were too few to permit a meaningful statistical analysis.

### Infections of Skin and Soft Tissues

*Enterobacter* spp. have been implicated as causes of an array of clinical syndromes involving the skin and soft tissues: cellulitis, fasciitis, abscesses, emphysema, myositis, and wound infections (38, 56, 75, 95, 107, 124, 152, 170). The clinical and laboratory features of most of these syndromes differ little from those caused by other enteric bacilli, and approaches to management are comparable. However, two recent trends distinguish *Enterobacter* spp.: (i) an increasing role in institutionally acquired wound infections and (ii) the occurrence of skin and soft tissue infections in previously healthy individuals in the community, occasionally as a result of multiply resistant strains.

**Institutionally acquired infections of surgical wounds and burns.** The proportion of nosocomial wound infections due to *Enterobacter* spp. has increased throughout recent decades (57, 105, 107, 194). Results of the NNIS program for 1986 to 1990 indicated that *Enterobacter* spp. were the fourth most common cause (10.3% of total) of surgical wound infections in ICU and the most common gram-negative organisms implicated (105).

The importance of *Enterobacter* spp. as pathogens in this setting was first noted in thermal injury units in the late 1960s and early 1970s. The ascendancy of these organisms as agents of burn wound sepsis has been reviewed by John et al. (107). Although *Enterobacter* spp. have been implicated in surgical wound infection in almost every body site, two areas have been recently recognized as especially prone to involvement: sternum-mediastinum and posterior spinal tissues.

Infections of the sternal wound and mediastinum have been reported in 1 to 6% of cases following sternotomy for cardiac surgery. Historically, staphylococci have predominated, with cases occurring sporadically or in clusters (170). *Enterobacter* spp. were recognized as important pathogens subsequently. The experience of Palmer et al. has been typical (170). Distinguishing features in their hospital were (i) apparent clustering of cases with no demonstrable common source; (ii) involvement of *E. cloacae* or *E. aerogenes* or both; (iii) coinfection with staphylococci in 25% of patients; (iv) colonization of the sternum, groin, and wounds both before and after surgery; and (v) correlation of colonization with cephalosporin use. Diminution of the problem was achieved by (i) enforced barrier isolation, (ii) decreasing contacts in the immediate postoperative period, and (iii) reducing the duration of cephalosporin prophylaxis. Massie et al. have reviewed the literature and their experience with postoperative posterior spinal wound infections (147). Once again, *Enterobacter* spp. were noted to have emerged in an area previously dominated almost exclusively by *S. aureus*. *E. cloacae* accounted for 4 (18%) of 22 of their cases and was second only to species of staphylococci in frequency. The authors noted that over half of the infections were polymicrobial and that *Enterobacter* infection was closely associated with inferiorly placed drains left in place for greater than 48 h.

**Soft tissue infections in healthy individuals.** *Enterobacter* spp. have been increasingly recognized as causes of infection acquired in the community. More recent evidence indicates that these infections may occur in previously healthy individuals and occasionally involve multiply resistant strains. Four reports provide cases in point. Ganelin and Ellis described a 58-year-old physician who developed a subungual hematoma of his great toe while playing tennis in ill-fitting shoes (75). Within hours, the area developed signs and symptoms of infection. Culture of purulent exudate yielded *E. cloacae* that was resistant to all antibiotics tested except imipenem. The patient recovered uneventfully after a course of parenteral therapy. McCown described a deep infection of the hand in a previously well 11-year-old boy who had fallen at the edge of a pond, sustaining a laceration of his hand (152). Cultures of debrided material grew *E. cloacae* and a few colonies of *Citrobacter freundii*. The *E. cloacae* strain was susceptible only to extended-spectrum  $\beta$ -lactams and aminoglycosides, while the *C. freundii* strain was susceptible to all agents tested except cefazolin. The patient was treated with cefazolin and clindamycin. He responded definitively only after repeated debridements and removal of small pieces of wood from the palmar space on several occasions. Kronish and McLeish described the development of periorbital necrotizing fasciitis in a 26-year-old woman following trauma to her temple. *E. aerogenes* and *Citrobacter diversus* were recovered from debrided necrotic tissues (124). No gram-positive organisms were seen or cultured. Although the patient was originally given empirical treatment with penicillin and methicillin, she ultimately responded to debridement and gentamicin followed by oral ciprofloxacin. The authors noted that each of 15 previously reported cases of periorbital necrotizing fasciitis had been caused by a streptococcus, most often belonging to Lancefield's sero-

TABLE 11. Characteristics of endocarditis due to *Enterobacter* spp. in 18 patients<sup>a</sup>

Characteristic	No. (%)
Antecedent cardiac disease .....	12 (67)
Prosthetic valves.....	5 (28)
Rheumatic heart disease.....	4 (22)
Congenital.....	2 (11)
Trauma.....	1 (6)
Intravenous drug abuse.....	6 (33)
Valve involved	
Mitral.....	6 (33)
Mitral and aortic.....	4 (22)
Tricuspid.....	4 (22)
Polymicrobial etiology.....	2 (11)
Surgical therapy performed.....	3 (17)
Mortality	
Overall.....	8 (44)
Left-sided disease .....	7/14 (50)
Right-sided disease .....	1/4 (25)

<sup>a</sup> Modified from reference 217 with permission of the publisher.

group A. Finally, Helovuo et al. described oral infections due to "multiply resistant bacteria" including *Enterobacter* spp. and other gram-negative bacilli (95). Previous courses of antimicrobial agents for periodontal infections may have selected for these resistant strains (95).

### Endocarditis

Endocarditis due to gram-negative bacilli appears to be increasing in incidence. The risk appears highest in intravenous drug abusers and individuals with prosthetic valves (217). *Enterobacter* spp. have been implicated relatively infrequently. Prior to 1980, there were anecdotal reports of *Enterobacter* endocarditis associated with penetrating foreign bodies, mechanical and porcine prosthetic valves, intravenous drug abuse, and cardiac surgery (107).

Case reports in English from 1949 to 1990 have recently been reviewed by Tunkel et al. (217). The salient features of 18 cases are summarized in Table 11. Underlying heart disease and intravenous drug abuse were prominent risk factors. Left-sided cardiac involvement was most common except in intravenous drug abusers. Two (11%) of the cases were polymicrobial in etiology; additional organisms were *S. aureus*, *Candida albicans*, and *Paracolonobacterium aerogenes* in one and *E. faecalis* and a viridans streptococcus in another. Surgical therapy was performed in three patients (17%), two of whom survived. The overall mortality was 44%; the rate was twofold higher in patients with left-sided than in right-sided disease.

Tunkel et al. concluded that optimal treatment for *Enterobacter* endocarditis "remains unclear," but they have provided tentative guidelines for management (217). They suggest that antimicrobial therapy be selected on the basis of in vitro susceptibility test results plus "bactericidal synergy studies" with a  $\beta$ -lactam plus an aminoglycoside. They also recommend maintenance of trough bactericidal titers in serum of at least 1:8 with the combination. Although the appropriate duration of therapy remains controversial, the authors usually continue treatment for 4 to 6 weeks. Repeated culturing of blood is necessary to detect suboptimal responses or possible emergence of resistance. In instances of de novo multiple resistance

or emergence of resistance during therapy, the authors consider a carbapenem the "antimicrobial agent of choice," with fluoroquinolones as possible alternatives. Clinical experience has shown the likelihood of medical cure is greater for right-sided than left-sided endocarditis. Valvular surgery is appropriate for those failing medical management.

### Intra-abdominal Infections

*Enterobacter* spp. have often been implicated in intra-abdominal infections. This is consistent with their residence in the colonic flora of many humans. Traditionally, they have gained access to the peritoneum and other viscera by translocation or perforation to initiate a broad array of infectious syndromes. Their role in biliary sepsis was recognized prior to 1980 and continues prominently into this decade (4, 87, 107). More recent literature emphasizes the importance of *Enterobacter* spp. in bacteremia of gastrointestinal origin, especially in association with hepatic transplantation (see above). Newly recognized or better-defined syndromes include hepatic gas gangrene (172), fulminant emphysematous cholecystitis and bacteremias following endoscopic retrograde cholangiopancreatography (4, 208), acute suppurative cholangitis with intermittent obstruction due to biliary sludge (87), and secondary peritonitis following small bowel obstruction in the absence of perforation or known causes of ascites (195).

### Urinary Tract Infections

The clinical manifestations of urinary tract infections due to *Enterobacter* spp. differ little from those of infections due to other gram-negative bacilli. The spectrum of illness ranges from asymptomatic bacteriuria to pyelonephritis and urosepsis (107). Prior to 1980, *Enterobacter* spp. accounted for 0 to 14% of infections reviewed by John et al. (107). The highest rate was in North American women with bacteriuria detected on routine health examination. More recently, *Enterobacter* spp. have accounted for 2.4% of childhood urinary tract infections in Saudi Arabia (3) and 6 to 7% of nosocomial infections in the United States (105, 194). There is reason to believe that the incidence of *Enterobacter* spp. among nosocomial urinary pathogens is slowly increasing over the years (105, 194).

Multiple drug resistance has been observed in nosocomial *Enterobacter* urinary isolates (3, 88). The role of antecedent antimicrobial administration in selecting for resistance has been emphasized (88, 186). Unfortunately, the problem appears to have escaped the confines of the hospital setting. Mani and colleagues have described an instance of community-acquired urosepsis due to a multiply resistant *Enterobacter* sp. in a woman who had not received antimicrobial agents known to predispose to emergence of resistance (144). Continued surveillance of the susceptibility of community-acquired isolates now appears imperative.

### Central Nervous System Infections

*Enterobacter* spp. have been implicated as etiologic agents in a variety of central nervous system infections. Meningitis, ventriculitis, brain abscess, and infections proximate to foreign bodies have been reported episodically over the years (107). With few exceptions, the clinical manifestations of these infections did not differ from those of infections with other members of the *Enterobacteriaceae*. More recent reports have focused upon an overall increase in the incidence of meningitis due to enteric bacilli, emergence of resistance among strains of *Enterobacter*, use of novel regimens for treatment, and the special problems posed by *E. sakazakii*.

Unhanand et al. reviewed 21 years of experience with central nervous system infections due to gram-negative bacilli in neonates and infants (221). They found that the overall incidence was low (3.6%) but increasing, and they identified neural tube defects and urinary tract anomalies as major risk factors for all enteric bacilli. Antecedent surgery was also an important risk factor for *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. specifically. Wolff et al. reviewed the literature and their experience with *Enterobacter* meningitis in adults between 1983 and 1992 (243). They found an increase in incidence over the period of observation and noted that *Enterobacter* spp. were the second most common cause of meningitis due to gram-negative bacilli (17% of the total).

Almost all recent reports concerning central nervous system infections highlight the problem of emerging resistance of *Enterobacter* spp. to multiple drugs. Several anecdotal reports (44, 83, 97) and one systematic retrospective study (243) have been published. The overwhelming majority of instances of emergence of multiple  $\beta$ -lactam resistance have followed the use of extended-spectrum cephalosporins. Emergence of resistance to carbapenems and fluoroquinolones has been described rarely. Wolff et al. identified the emergence of multiple  $\beta$ -lactam resistance in 4 (40%) of 10 patients with *Enterobacter* meningitis who were given cephalosporins in their institution and in 8 (27%) of 30 similar patients described in the literature (243). The combined rate of emergence of resistance was 30% (12 of 40 patients). This exceeded the rate (19%) of emergence of resistance observed by Quinn et al. in patients with bacteremia (181).

There is no general agreement on the appropriate regimen(s) for treatment of central nervous system infections due to gram-negative bacilli in general and *Enterobacter* spp. in specific. This was underscored by Unhanand et al., who observed that 51 different antimicrobial regimens were administered to the 98 patients seen at their institution between 1969 and 1989 (221). The problem has been further compounded by emergence of multiple drug resistance, especially in the last decade. The early literature described occasional patients who were treated successfully with intrathecal or intracisternal plus parenteral aminoglycosides, most often gentamicin (107). More recent data suggest that in neonates at least, addition of local instillations of an aminoglycoside to nonaminoglycoside parenteral agents has little or no effect on the therapeutic outcome. Wolff et al. retrospectively compared outcomes of regimens containing extended-spectrum cephalosporins or trimethoprim-sulfamethoxazole (243). Cure was achieved with cephalosporin monotherapy in only 4 (50%) of 8 patients in their institution and 17 (71%) of 24 described in the literature. Although the numbers of patients were small (6), the addition of an aminoglycoside to the cephalosporin increased the cure rate to 83% overall. In contrast to the experience with cephalosporins, trimethoprim-sulfamethoxazole was successful as monotherapy in seven (100%) of seven patients and as part of a combination (two with a cephalosporin and one with an aminoglycoside) in three (100%) of three additional patients. Emergence of resistance was not observed during or after the use of trimethoprim-sulfamethoxazole. Recent anecdotal reports have described cures with fluoroquinolones in two (67%) of three adults with meningitis (243), high-dose imipenem (8 g/24 h) plus parenteral and intrathecal amikacin in an adult with meningitis (44), ciprofloxacin plus amikacin in an infant with ventriculitis (83), chloramphenicol plus trimethoprim-sulfamethoxazole in a neonate with meningitis and infected subdural effusion, and meropenem monotherapy in a child with a brain abscess (154). Many of the foregoing patients were in-

fectured with a multiply resistant strain or had failed to respond to cephalosporin-containing regimens.

*E. sakazakii* has been recognized for over three decades as the cause of a distinctive syndrome of meningitis in neonates. Willis and Robinson described 2 cases of their own and reviewed an additional 15 cases from the literature in 1988 (242). Although the presenting symptoms were no different from those due to other gram-negative bacilli, complications were more common and the ultimate outcome was dismal. Cysts or abscesses or both were described in 7 (41%) of 17 patients, although they were not specifically sought in several instances. Willis and Robinson reported a case/fatality rate of 50% (242), which contrasts sharply to the 17% rate noted for meningitis due to all enteric bacilli (221). Similarly, the rate of severe sequelae among survivors (94%) was higher with *E. sakazakii* (53) than that (61%) for other enteric bacilli (221).

Recent evidence has shed some light on the pathogenesis of the cerebral damage initiated by *E. sakazakii*. Initially, many of the lesions were interpreted as abscesses. Subsequently, it was recognized that others were noninfected cysts (242), and it was suggested that these were in fact liquefied infarcts (74, 242). Using enhanced computed tomography, Gallagher and Ball have confirmed that the initial event is infarction that, because of ring enhancement, may mimic abscess formation (74). The subsequent course of events appears to be liquefaction and usually sterile cyst formation. However, only aspiration and culture may definitively exclude an infectious process. This distinctive clinical syndrome has also been observed during the course of meningitis due to *C. diversus*, an organism that shares a 50% relationship to *E. sakazakii* by DNA-DNA hybridization techniques (74).

### Ophthalmic Infections

*Enterobacter* spp. have been implicated in a variety of infectious processes involving the eyes and periorbital tissues (39, 124, 156). Most reports, which span the last three decades, have been anecdotal. The most important recent development is recognition of the etiologic role of gram-negative bacilli in endophthalmitis, especially that occurring postoperatively or following trauma (103). Cataract extraction with placement of intraocular lenses is the ophthalmic surgical procedure most commonly performed today (156). Postoperative endophthalmitis is a devastating consequence that often results in loss of vision or of the eye itself. Historically, the overwhelming majority of these infections have been due to gram-positive organisms. Recent series indicate that up to 30% of cases may be due to gram-negative bacilli (103, 156). The prognosis is best for infection due to coagulase-negative staphylococci and worst for infection due to gram-negative bacilli, especially *Pseudomonas* spp. and *Enterobacter* spp. (103, 156, 157). Although *Enterobacter* spp. account for only a small fraction of cases of endophthalmitis, they are among the most aggressive pathogens, may be multiply resistant de novo or become resistant during therapy, and may cause outbreaks arising from environmental contamination (103, 156, 157).

Milewski and Klevjer-Anderson recently described a patient who was prototypical for *Enterobacter* ophthalmitis (156). An 81-year-old woman with polymyalgia rheumatica receiving corticosteroid therapy underwent cataract extraction and intraocular lens placement. Three days postoperatively, she developed a relentlessly progressive infection due to *E. cloacae*. Despite in vitro susceptibility of the *E. cloacae*, administration of ticarcillin-clavulanate and then ceftazidime, both supplemented by parenteral and intraocular aminoglycosides, failed to alter the course of the infection. Current recommendations for therapy

TABLE 12. Mimicry by *Enterobacter* spp. of syndromes commonly attributed to other organisms

Syndrome (reference[s])	Usual pathogen(s)	Traditional empiric antimicrobial therapy
Acute purpura fulminans (89)	Meningococci, viruses	A penicillin
Ecthyma gangrenosum (182)	<i>Pseudomonas aeruginosa</i>	Antipseudomonal $\beta$ -lactam and aminoglycoside
Necrotizing fasciitis, especially periorbital (124)	Group A streptococci	A penicillin
Posterior spinal wound infection (147)	<i>Staphylococcus aureus</i>	Penicillinase-resistant $\beta$ -lactam
Postoperative mediastinitis (170)	Staphylococci	Penicillinase-resistant $\beta$ -lactam or vancomycin
Emphysematous cholecystitis (4)	<i>Clostridium</i> spp., other enteric bacteria	A penicillin or other $\beta$ -lactam
Lobar pneumonia in the elderly (20, 40, 117)	<i>Streptococcus pneumoniae</i>	A penicillin or vancomycin
Neonatal bacteremia, meningitis, cerebral infarction, and cyst formation (74, 242)	<i>Citrobacter diversus</i>	Older penicillins or cephalosporins, aminoglycosides
Postoperative endophthalmitis (103, 156)	Staphylococci, rare enteric bacteria	Penicillinase-resistant $\beta$ -lactam, aminoglycoside

and prophylaxis of endophthalmitis include ceftriaxone (157) or ceftazidime (103), especially if the presence of a gram-negative bacillus is known or suspected. Given the relatively high rates of de novo resistance and emergence of resistance during therapy, consideration of alternative agents such as carbapenems or fluoroquinolones may be prudent.

#### Septic Arthritis and Osteomyelitis

*Enterobacter* spp. have been implicated in a variety of syndromes that involve the bones and joints. Although relatively infrequent, severe septic arthritis (19, 102, 107, 240), osteomyelitis (102, 107, 240), infections of multiple bones and joints in infants and children (107), vertebral osteomyelitis (107, 145, 202), bilateral hip infections (107), and prosthetic hip infections (107) have been reported over the past three decades. Recent literature concerning these entities is scant. However, two developments are noteworthy. The first is the implication of *Enterobacter* spp. as a cause of septic arthritis following arthroscopy, although these organisms are a distant third in frequency after *S. aureus* and coagulase-negative staphylococci (9). The second is a spate of recent case reports of vertebral spondylodiscitis due to *E. cloacae* (35, 145, 202). This syndrome has been seen in elderly individuals and in an intravenous drug abuser. The diagnosis has been made by culture of blood, puncture biopsy, or both. Successful treatment has been observed with pefloxacin plus amikacin parenterally followed by pefloxacin plus cefixime orally (145), trimethoprim-sulfamethoxazole parenterally for 10 days followed by 6 months orally (202), and cefixime orally (35).

#### Cotton Fever

Cotton fever is a "street term" for an acute febrile reaction experienced after intravenous injection of heroin that has been filtered through cotton (61). Thompson introduced the term into medical jargon in 1975 to describe a syndrome in intravenous drug abusers of fever and leukocytosis in the apparent absence of bacterial infection (211). Since that time, cotton fever has been thought to be a usually benign, self-limiting syndrome that mimics sepsis. A variety of theories have been advanced to explain the pathogenesis of cotton fever. These include the presence of pyrogenic chemicals in cotton, hypersensitivity to components of cotton extracts, and endotoxin reactivity (61, 188, 189). Ferguson et al. have recently implicated *E. agglomerans* as the most probable cause of cotton fever (61). They described a 28-year-old patient who experienced typical signs and symptoms 10 min after intravenous injection of a heroin-tap water mixture that he had filtered through cotton. Cultures of his blood contained *E. agglomerans*. The patient ultimately responded to a course of tri-

methoprim-sulfamethoxazole. Two strains of *E. agglomerans* were isolated from the cotton used for filtration; one had an antimicrobial susceptibility pattern that was identical to that of the bloodstream isolate. Two other observations support the proposed role of *E. agglomerans*. First, cotton and cotton plants are commonly heavily colonized by gram-negative bacilli, especially *E. agglomerans* (189). Second, *E. agglomerans* endotoxin has been shown to recruit neutrophils and activate pulmonary macrophages, resulting in fever, chest tightness, and bronchoconstriction in workers exposed to cotton dust (188). As a result of these observations, it may be prudent to assume that patients with cotton fever are infected with *E. agglomerans* until proven otherwise.

#### Mimicry of Syndromes Commonly Attributed to Other Organisms

As *Enterobacter* spp. have been implicated in the causation of an increasing number of clinical entities, it has become apparent that in many instances they may closely mimic pathogens that cause syndromes heretofore commonly or even exclusively associated with other organisms. Since the antimicrobial susceptibilities of the *Enterobacter* spp. may differ markedly from those of the pathogen mimicked, traditional regimens for empiric therapy of these syndromes may need to be modified accordingly. Some of the more common syndromes that may be mimicked and their usual etiologies are shown in Table 12. The literature reviewed gives the impression that mimicry in most of the entities listed is distinctly more common with *Enterobacter* spp. than with other opportunistic gram-negative bacilli. The need for reevaluation of traditional empiric regimens is apparent.

#### PERSPECTIVE ON THE FUTURE

*Enterobacter* spp. appear well adapted for survival and proliferation as the turn of the century approaches. Options for control of these organisms are quite limited. Rigid infection control procedures and meticulous attention to principles of antisepsis may reduce the occurrence of the relatively infrequent outbreaks that are traceable to human vectors or environmental contamination. However, the usual infection control procedures are unlikely to affect the overall incidence of nosocomial *Enterobacter* infections, because the overwhelming majority arise endogenously from the flora of the patient who has become chronically colonized. Studies to determine fundamental biological factors that favor colonization are clearly warranted. Selective decontamination of the gastrointestinal tract and avoidance of the use of agents that lower the gastric pH to reduce oropharyngeal colonization are rational, but unproven, approaches that should be subject to controlled clinical



trials (50, 116, 235). Evidence, summarized above, is mounting that extended-spectrum cephalosporins play an important, if not major, role in favoring colonization and subsequent infection by *Enterobacter* spp. In fact, these agents may be equally important in selecting multiply resistant strains of enterococci in the hospital (36, 246) and pneumococci in the community (13, 33). Severe restriction of the use of these cephalosporins could reduce or eliminate the selective advantages afforded to *Enterobacter* spp. in general and several other multiply resistant organisms as well.

The evidence that *Enterobacter* spp., including multiply resistant strains, are increasingly important etiologic agents in community-acquired pneumonia in Spain and are anecdotally responsible for soft tissue and urinary tract infections in otherwise well individuals in North America is indeed disquieting. Rigorous surveillance is necessary to confirm and monitor this trend. Epidemiologic studies should be designed to identify risk factors for the acquisition of *Enterobacter* spp. in the community. The potential role, if any, of new extended-spectrum oral cephalosporins in providing a selective pressure favoring *Enterobacter* spp. should be assessed promptly. This is especially important given the known association between the use of parenteral cephalosporins and *Enterobacter* infections in the hospital and the temporal concordance of marketing of the new oral agents and appearance of *Enterobacter* spp. in the community.

Many other fundamental questions remain unanswered. What pathogenetic mechanism(s) sets *Enterobacter* spp. apart clinically from other gram-negative enteric bacilli? What favors the survival and transmissibility of the organisms in solutions and on surfaces of catheters or medical devices? What accounts for the extremely high efficiency of *Enterobacter* spp. relative to other organisms in producing disease following infusion or transplantation into uninfected recipients? What are the implications of the recently recognized high rate of coinfection by other pathogens for the diagnostic laboratory and for selection of empiric therapy? What are the mechanisms and factors favoring the emergence of resistance to "fourth-generation" cephalosporins, carbapenems, and fluoroquinolones? Can further emergence of resistance be minimized? What controls the expression of the inducible  $\beta$ -lactamases in *Enterobacter* spp.? Is it possible to suppress the induction process or expression, thus restoring susceptibility to multiply resistant strains? Only with additional basic research may innovative approaches be designed for therapy and ultimately for prevention.

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