Enterobacter spp.: - An emerging nosocomial infection

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Abstract

The taxonomic evolution of family Enterobacteriaceae has been a dynamic process and continued throughout the 1980s and 1990s. Today, there are more than 30 distinct genera and more than 100 species within the family. Enterobacter genus of family Enterobacteriaceae has gained in recent years the attention of taxonomists, microbiologists and clinicians alike. The members of genus Enterobacter are motile gram negative enteric bacilli belonging to the family Enterobacteriaceae. Enterobacter spp. are not considered to be the primary human pathogens; however like most Enterobacteriaceae they are capable of causing opportunistic infections in hospitalised or debilitated patients. A National Nosocomial Infection Surveillance System (NNIS) study found that Enterobacter accounts for 5 to 11% of all nosocomially transmitted blood, wound, and respiratory tract and urinary tract infections.

Until recently epidemiological studies on genus Enterobacter have been based essentially up on the study of phenotypic traits such as biochemical profiles, antibiotic resistance, serological, bacteriocin and phage typing although often very useful, there are some problems associated with them inability to demonstrate strain to strain variation, unavailability of specific reagents, poor sensitivity to phage, non-specific agglutination are some of the technical pitfalls inherent to the phenotypic studies.

The single most alarming trend regarding the genus Enterobacter is the increasing incidence of serious life threatening infections caused by strains resistant to multiple antibiotics. Some of the processes responsible for quick generation of resistance are plasmid β-lactamase and chromosomal cephalosporinase, variability of target of the antibiotic and modification of envelope permeability, including alteration of porins (OMPs) and expression of drug efflux.

Enterobacter spp. appears well adapted for survival and threats to cause immense mortality & morbidity by the proliferation of highly drug resistant strains both in the community and hospital environment.

Keywords: Enterobacter, nosocomial infection, national nosocomial infection surveillance system

Introduction

A taxonomically defined group of bacteria that has had a greater impact on infectious disease, medical and clinical microbiology and public health is Enterobacteriaceae. The family from its inception has been linked to the colonization of gastro-intestinal tract of humans and other vertebrates and to the pathologic processes that result from subsequent infection of the gut. The gastro-intestinal syndromes, caused by the enterobacteriaceae, pale in comparison to their role as nosocomial pathogens. Nosocomial data indicate that many genera of Enterobacteriaceae such as Escherichia, Enterobacter, Klebsiella and Serratia cause a significant proportion of hospital-acquired bacteraemia, urinary tract illness, respiratory tract disease and wound infections. Even more frightening has been the rapid rate at which they have developed antimicrobial resistance, particularly to extended-spectrum β-lactam compounds.

Enterobacter spp. have gained immense recognition as emerging pathogen in recent years. These organisms seem to have innate resistance to older anti-microbial agents and have the propensity to rapidly develop resistance to newer anti-microbial agents. It also appears that Enterobacter spp., including multiply resistant strains, have spilled over into the community, occasionally infecting otherwise well individuals. More recently, recognition of relatively high rate of co-infection with other pathogens, predominance in liver and lung transplants infection, etiologic role in cotton fever, and increasing incidence in a variety of clinical syndromes [1]. Dramatic changes and expansion of the knowledge of Enterobacter spp., we initiated a review of the recent literature on biology, typing clinico-pathogenicity and antibiogram of the genus.
General Epidemiology
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. However, the importance of Enterobacter spp. as nosocomial pathogens was highlighted in the National Nosocomial Infections Surveillance System (NNIS) data published [6]. Data form 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 pathogen recovered from surgical wound (10.3%), the fifth most common pathogen recovered from the urinary tract (6.1%), and the fifth most common pathogen recovered from the blood (5.3%) [6]. Although community–acquired infections with Enterobacter spp. do occur, the majority of infections with this organism are nosocomial [7, 8]. 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 [4, 9]. The presence of a serious underlying illness, especially malignancy, burns, and diabetes, also increases the risk of infection [4, 9]. Immunosuppression from any cause, prematurity and low birth weight in neonates, and the presence of a foreign device are also associated with increased risk of acquisition of an Enterobacter infection [3]. The single most frequently cited risk factor for acquisition of an Enterobacter infection is the prior use of anti-microbial agent in the patient involved [3, 4, 9]. Enterobacter infection can be acquired from either endogenous or exogenous sources. Given the ubiquitous nature of the organism, it is found in the feces of humans and animals and in water, plants and plant materials, insects, and dairy products [10-13]. Single-sources out-breaks have been traced to contamination of intravenous solution, blood products, distilled water, endoscopes, cotton swabs, hands of personnel, hydrotherapy water, stethoscope, cryopreserved pancreatic islet infusion, lipidal solutions, and devices used for monitoring intra-arterial pressure [10]. Colonization of the gastrointestinal tract and other body sites with Enterobacter spp. occurs frequently in the seriously ill patients may be colonized with more than one strain at any given time [12]. Thus, it appears that severe debility, coupled with the suppressive effects of antibiotics on the normal flora, provides an excellent opportunity for the colonization by Enterobacter spp.

Biology & Taxonomy
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 [2]. Additionally, most Enterobacter spp. are resistant to cephalothin and cefoxitin whereas, Klebsiella spp. are often s polymicrobial susceptible to these agents. There are 14 species or biogroups of Enterobacter listed in the most recent edition of Manual of Clinical Microbiology [2]. Not all of these have been implicated as causes of diseases in humans. Among those that have, the most commonly encountered species include Enterobacter cloacae, Enterobacter aerogenes, Enterobacter agglomerans, and Enterobacter sakazakii [3-5]. Enterobacter terrae, Enterobacter gergoviae, Enterobacter asburiae, and Enterobacter amnigenus are only rarely isolated from clinical specimens [4, 5].

E. aerogenes and E. cloacae are by the most frequently encountered human pathogen among the genus Enterobacter [1-5]. These two species can be readily differentiated by tests for lysine decarboxylase and arginine dihydrolase. E. sakazakii can be differentiated from E. cloacae by its inability to ferment D-sorbitol and its production of a yellow pigmented [2]. Enterobacter agglomerans represented a heterogeneous group of diverse organisms that are often yellow pigmented, grow at 4 °C, and are usually negative in decarboxylase/ dihydrolase tests [2].

Natural habitat
Enterobacter spp. are widely distributed in the environment and are found in soil, water and sewage. Enterobacter cloacae and Enterobacter aerogenes are part of the normal flora of the gastrointestinal tract and are found in a high proportion of sewage sample, at concentrations of up to 10^6organism g^-1. Environmental sources include rotting vegetable matter and dairy products.

Clinical Manifestation
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, gastro-intestinal 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.

a. Bacteremia: 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 their fold higher in specialized unites, such as cancer centers, and two- to threefold lowers in community hospitals. Although rate are lower in the community, the problem is significant and growing [13]. 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 bacteremia are acquired institutionally (range, 56 to100%) E. cloacae predominates in most series (range, 46 to91%) followed in order by E. aerogenes (range, 9 to43%) E. agglomerans, E. sakazakii and other from 14 to 53% of bacteremias appear to be randomly that involve Enterobacter spp. are polymicrobial [1].

Signs, symptoms, and laboratory findings: The incubation period of Enterobacter bacteremia estimated from common source outbreaks in which the organism was in fused directly into the bloodstream. The time for appearance of signs and symptoms has varied from as short as 2h to as long as 20 days, with most occurring in a few hours to 2 days.

Fever is the hallmark of bacteremia in both adults and children. Reported rates have ranged from 83 to 87 % in children and from 92to 98% in adults or mixed populations [5, 15, 16].
a) Hypotension or shock has been reported in 9 to 34% adults or mixed populations [15, 15, 16]. The frequency is similar in children (8 to 28 %) [3].
b) Altered mention is often (32 to 38%) noted concurrently in both adults and children.
c) Leukocytosis occurs in approximately two-third of patients with bacteremia. Leukopenia has been reported in 9to 17% of individuals of a broad range of ages.
d) Thrombocytopenia [10].
e) Jaundice, Hemorrhage have each been noted in a few series [15, 16].

The syndrome of disseminated intravascular coagulopathy has been recognized in 0 to 6% of bacteremic episodes [15, 
[16]. most of the usual cutaneous manifestation associated with bacteremia have been noted occasionally. These include purpura fulminans, hemorrhagic bullae, and erythema gangrenosum. Cyanosis and motting has been encountered in two-thirds bacteremia children.

b. Lower Respiratory Tract Infection
Most of the species of Enterobacter have been implicated in a wide spectrum of lower respiratory infection including asymptomatic colonization of respiratory secretions, purulent bronchitis, lung abscesses, pneumonia, and empyema.

The incidence of lower respiratory tract infection due to Enterobacter spp. appears to have increased steadily over the last four decades. Estimates of the incidence of Enterobacter spp. in nosocomial respiratory infection in the 1970s ranged from less than 2to 9% [6]. The rates increased from 9.5% in the early1980s to11% in 1986 to 1990. Enterobacter spp. have recently surpassed Klebsiella spp. to become the third most common cause of nosocomial respiratory tract infections in the United States [6].

The recent recognition of an important role of Enterobacter spp. in community-acquired pneumonia in Spain is disquieting [17]. Enterobacter spp. have recently been recognized as major pathogens in lung transplant recipients. Approximately 40% of recipients will develop acute bacterial pneumonia in the 2 weeks immediately following transplantation [1]. The clinical and laboratory manifestations of Enterobacter pneumonia differ little from those observed for pneumonia due to gram-negative bacilli.

The widely accepted criteria for the diagnosis of pneumonia are new infiltrates and positive cultures of transtracheal aspirates or sputum plus blood, demonstration of tachypnea and tachycardia. Hemoptysis appears rarely. Leukocytosis with a shift to the left in differential cell count is usual (82 to 100%) [17].

c. Infection 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 infection [10].

Institutionally acquired infections of surgical wounds and burns: The proportion of nosocomial wound infections due to Enterobacter spp. has increased throughout recent decades. Result of the NNIS program for 1986 to 1990 indicated that Enterobacter spp. were the fourth most common cause of surgical wound infection in ICU and the most common gram-negative organism implicated [6].

d. Endocarditis: Endocarditis due to gram negative bacilli appears to be increasing in incidence. The risk appears highest in intra-venous drug abusers and individuals with prosthetics valves Enterobacter spp. have been implicated relatively infrequently. Prior to 1980, there were anecdotal reports Enterobacter endocarditis associated with penetrating foreign bodies, mechanical and porcine prosthetic valves, intravenous drug abuse, and cardiac surgery [7].

e. Intra-abdominal Infections: Enterobacter spp. have been implicated in Intra- abdominal Infections. This is consistent with their residence the colonic flora of many humans [7].

f. Urinary tract Infection: The clinical manifestations of Urinary tract Infection 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 [7]. Prior to 1980, Enterobacter spp. accounted for 0to 14%of infections reviewed by John et al [7]. More recently Enterobacter spp. have accounted for 2.4% of childhood Urinary tract Infection in Saudi Arabia (3) and 6to 7% of nosocomial infections in the incidence of Enterobacter spp. among nosocomial urinary pathogens is slowly increasing over the years [6]. Multiple drug resistance has been observed in nosocomial Enterobacter urinary isolates. The role of antecedent anti-microbial administration in selecting for resistance has been emphasized.

g. Central Nervous System Infection: Enterobacter spp. have been implicated as etiologic agent 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 [7].

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.

h. Ophthalmic Infection: Enterobacter spp. have been implicated in a variety of infectious processes involves the eyes and peri orbital tissues. Although Enterobacter spp. account for only small fraction of endophthalmitis, like pseudomonas spp. 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.

i. Septic-Arthritis and Osteomyelitis: Enterobacter spp. have been implicated in a variety of syndromes that involved the bones and joints, although relatively infrequent, severe septic arthritis, osteomyelitis, infection of multiple bones and joints in infants and children vertebral osteomyelitis hip infection have been reported over the past three decades [7].
**Pathogenicity**

**Pathogenicity:** Few studies have investigated potential virulence associated with the genus Enterobacter in human infections. The lack of significant research in this area is probably a reflection of the predominant role of these organisms as nosocomial pathogens.

Many Enterobacter species cause the in vitro hemagglutination of erythrocytes obtained form a number of vertebrate species. These hemagglutinins are either mannose-sensitive (MSHA) or mannose-resistant (MRHA), and their phenotypic expression strongly correlates with production of type 1 or type 3 fimbriae, respectively [18].

Only E. gergoviae consistently expresses MRHA. Most E. cloacae isolates produce a hydroxyamate-type siderophore, aerobactin, which is commonly associated with microbial species causing invasive disease.

Several other pathogenic properties have been identified in random isolates of E. cloacae in the feces of an 11-month-old boy. *Bam HI* – digested DNA form this strain reacted with an E.coli α-hemolysin-specific probe. Paton and Paton described the isolation of a Shiga-like toxin (SLT) producing strain of *E. cloacae* from an infant with hemolytic–uremic syndrome [18].

Probably the most intriguing virulence factor identified so far in *E. cloacae* is the outer membrane protein, OmpX.155 This 17-kDa protein, encoded by a chromosomal gene, causes decreased porin production (OmpF, OmpC) in *E. coli* transformants, leading to increased antimicrobial resistance to several β-lactam compounds [19].

**Laboratory Diagnosis & Typing Methods**

**Laboratory Identification**

**Isolation** -Because their recovery from environmental sources and the gastrointestinal contents of humans has no apparent significance, development of enrichment techniques and selective media designed for the specific isolation of *Enterobacter* form such sample has not been attempted.

The majority of *Enterobacter* isolates are both sucrose-positive (with the exception of the *E. cancerogenus*) and lactose-positive (with the exception of the *E. cancerogenus* and *E. hormaechei*). Therefore most species, such as *E. cloacae* and *E. aerogenes* appear as pink (lactose-positive) or yellow (sucrose-positive) colonies on standard selective media containing these sugars (e.g., Mac Conkey agar, Hektoen enteric agar). On non-selective media such as trypticase soy or nutrient agars, *E. sakazakii* and many isolates of *E. agglomerans* produce a nondiffusible yellow pigment.

**Identification**

Commercial Systems- *Enterobacter* is one of the most difficult groups to correctly identify to species using commercial automated, semiautomated, or manual identification systems [20-22].

Commercial systems in general do not identify species accurately residing in the genus *Enterobacter* to a satisfactory degree (i.e., to >90% accuracy). Most manual systems (API 20E, API Bio Merieux, Hazelwood, MO; Crystal E/NF, Becton Dickinson, Cockeysville, MD; RapID OnE) appear to be better equipped to identify *Enterobacter* species accurately than fully automated panels such as the Micro Scan Walk Away and Vitek units.

Conventional Media - Because of the taxonomic uncertainties that exist within this group, it is currently impossible to construct accurate defining criteria for inclusion in the genus *Enterobacter*. Table-1 some of the major biochemical features that have traditionally been associated with inclusion in the genus *Enterobacter*. Most *Enterobacter* isolates are indole-negative and α-nitrophenyl-β-D-galactopyranoside (ONPG)-positive, reduces, trehalose, and cellobiose [23].

A majority of *Enterobacter* isolates can be identified to species with the use of a small number of additional biochemical characteristics including amino acid decarboxylases and sugar fermentation tests.

| Table 1: Present defining biochemical reactions for the genus *Enterobacter*<sup>a</sup> |
|--------------------------|---------------------------------|---------------------------------|
| **Test**                | **Phenotype<sup>b</sup>**       | **Exceptions<sup>c</sup>**      |
| Voges-Proskauer         | +                               | *E. asburiae, E. kobei*         |
| LDC                     | -                               | *E. aerogenes, E. gergoviae*    |
| ODC                     | +                               | *E. amnigenus biogroup 1*       |
| Citrate utilization     | +                               | *E. intermedium E. amnigenus biogroup 1* |
| Acid form               |                                  |                                 |
| L-Arabinose             | +                               | *E. asburiae, *E. aerogenes, E. gergoviae* |
| L-Rhamnose              | +                               | *E. asburiae, E. cancerogenus, E. hormaechei* |
| Raffinose               | +                               |                                 |
| D-Xylose                | +                               |                                 |
| Lipase                  | -                               |                                 |
| Gelatibase              | -                               |                                 |

* Clinically relevant species or biogroups (excluding *E. agglomerans* complex)  
<sup>b</sup> Reactions at 24-48 h.  
<sup>c</sup> >10% of strains deviating from the phenotype.  
LDC, lysine decarboxylase; ODC, ornithine decarboxylase.

**Typing:** Typing Method is important tool for establishing the source and modes of transmission for epidemic strains. Typing of genus *Enterobacter* can be done by a number of methods using.

- **Biotyping:** Schemes have been developed as a first approximation of strain relatedness in outbreak situations. The most common system used to assess strains identity has been the API 20E strip (Vitek Bio-Merieux, Hazelwood, MO) Gaston and associates analyzed API 20E profile for 790 isolates of *E. cloacae* not related to outbreaks. There-six profiles were found, with one bio-type (API profile 3305573) De Champs and colleagues used both the API 20E and API 50 CH Galleries to biotype 23 imipenem-resistant and imipenem-susceptible *E. aerogenes* strains [24].

Old proposed a biotyping system doe *E. Cloacae* using seven differential tests on conventional media. Off 110 isolated typed, 86 (78%) resided in biotype 4, again emphasizing the lack of discriminatory value that most phenotype typing schemes have [25].

- **Serotyping:** A serogrouping scheme based on the presence of somatic antigens was devised for *E. cloacae* in 1983. Twenty-eight serogroups were originally established after antigenic analysis of more than 300 *E. cloacae* isolates, with serogroups O: 3(21%) and O: 8(13%) predominating [26]. This scheme has since been expanded to include two additional serogroups, for a
Serogrouping has a greater discriminatory value than bio-typing in determining strain relatedness and at least 85% of all *E. cloacae* are typable [27]. Therefore, serogrouping has distinct advantages over biotyping but may not be able to stand alone as an epidemiologic typing system in outbreaks due to common serogroups (O: 3, O: 8, O: 13) or when isolates are not typable or spontaneously auto-agglutinate.

- **Phage typing:** A Phage typing scheme has been constructed for *E. cloacae*. Gaston developed a set of 25 bacteriophages that was able to type 76 (83%) of 92-field isolate [28]. Although this system is able to type serologically rough strains and those that fail to react in specific somatic antisera, it is less reproducible than biotyping.

- **Bacteriocin typing:** A 1982 German publication found that only 79% of more than 300 *E. cloacae* isolates were susceptible to 1 or more of 16 different bacteriocins; 52 provisional bacteriocin types were defined in this study [29]. Bacteriocin typing has also been applied to *E. aerogenes*; 70 (90%) of 76 isolates could be assigned to 1 of 15 sensitivity patterns based on bacteriocins secreted by one of five producer strains.

- **Plasmid Profile:** A number of molecular methods have been used as aids in determining strain relatedness among clusters of *Enterobacter* isolates associated with human infections. Of this group, plasmid analysis is by far the most widely employed technique. Most strains of *E. cloacae* harbor extrachromosomal elements ranging in molecular mass form 3 to 150 MDa. Because of the frequent plasmid carriage by *Enterobacter* species, plasmid analysis is an extremely useful fingerprinting tool [30]. Clark and associates because of plasmid instability, alternative method a may be necessary to confirm primary result [31].

- **Multilocus Enzyme Electrophoresis Testing:** Gaston and Warner used multilocus enzyme electrophoresis (MEE) mobility of 12 different cellular enzymes for 62 *E. cloacae* strains. Each enzyme generated between toward five different electromorphs. A subset of four enzymes (lactate dehydrogenase, 6-phosphogluconate dehydrogenase, glutamate dehydrogenase, and an unidentified enzyme band) were found useful in typing most *E. cloacae* strains that belonged to serogroups other than O: 3/0: 8 [32]. Although MEE is a valuable technique, it is relatively difficult to develop, technically demanding, and labor intensive.

- **Analysis by Pulse Field Gel Electrophoresis (PFGE):** These studies have indicated considerable DNA polymorphism in the clinically important *Enterobacter* genus and good correlation between isolates from single patients. So they seen to provide extremely discriminatory result and highly useful epidemiology information.

- **Ribotyping:** Ribotyping is a common epidemiologic technique used with other gram negative bacteria, has also been found to be highly discriminatory in distinguishing strain relatedness in *Enterobacter*- associated outbreaks or incidents [33]. It can offer advantage over other molecular strategic (e.g. Restriction enzyme analysis) in both specificity and ease of gel interpretation.

- **PCR Based methods:** PCR and Rep PCR are rapid and useful methods for tracing epidemic strains during outbreaks on a day today basis. A comparative study of biotyping, antibiogram susceptibility, whole cell protein gel electrophoresis of chromosomal DNA and PCR with arbitrary primer of *Enterobacter* Spp. isolates can be performed to determine the best markers for epidemiology purposes. Biotyping whole cell protein and plasmid analysis was the least discriminatory method where as anti-microbial susceptibility and PCR with arbitrary primer showed moderate discriminatory power. Typing based on pulse field gel electrophoresis of chromosomal DNA appeared to be best discriminatory method.

### Anti-microbial Susceptibility

The single most alarming trend regarding the genus *Enterobacter* is the increasing incidence of serious, life-threatening infections caused by strains resistant OT multiple antibiotics. In the latest NNIS report, *Enterobacter* spp. was the third most common cause of gram-negative nosocomial infections. This distressing fact is exacerbated by the increasing tendency of *E. cloacae* and *E. aerogenes* to gain resistance to many commonly administered antibiotics, including third-generation cephaplospirins. Such resistance often arises de novo in-patients receiving empiric therapy for systemic infections. Later, these drug-resistant enterobacters, primarily residing in the gut, may emerge to produce severe or fulminate illnesses in debilitated persons [34].

Cephaplospirin resistance in *Enterobacter* spp. is caused by constitutive expression of a chromosomal β-lactamase or similar activity carried on a plasmid [1]. Plasmid-mediated β-lactamase activity most commonly involves extra-chromosomal and Plasmid-mediated extended-spectrum β-lactamase (ESBL) activity imparts general resistance to most β-lactam antibiotics except imipenem [1]. While rare, resistance to imipenem in *Enterobacter* has been documented in most instances, imipenem resistance to *Enterobacter cloacae* has been associated with elevated expression of chromosomal β-lactamase and permeability changes in the outer membrane [1].

Introduction of a plasmid carrying a wild-type amp D allele into this imipenem-resistant isolate restored full susceptibility to β-lactamase antibiotics.

### Conclusion

*Enterobacter* spp. appears well adapted for survival and proliferation as the turn of the century approaches. Options for control off these organism are meticulous attention to principles of antisepsis may reduce the occurrence of the relatively infrequent outbreaks that are traceable to human vectors or environmental contamination. 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.
The evidence that *Enterobacter* spp., including multiply resistant strain, are increasingly important etiologic agents in community-acquired pneumonia in Spain and are responsible for soft tissue and urinary tract infections in otherwise well individuals in North America is indeed disquieting. Many other fundamental questions remain unanswered. What pathogenic mechanism(s) sets *Enterobacter* spp. apart clinically from other gram-negative enteric bacilli? What favors the survival and transmissibility of the organism in solutions and on surfaces of caterers or medical devices? What are the mechanism and factors favoring the emergence of resistance to “fourth generation” cephalosporins, carbapenems, and fluoroquinolones? Can further emergence of resistance be minimized? What control the expression of the inducible β-lactamase in *Enterobacter* spp.? Only with additional basic research may innovative approaches be designed for therapy and ultimately for prevention.

**References**
