Enterobacter Infections and Antimicrobial Drug Resistance

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Abstract

Recently, *Enterobacter* spp. are encountered as significant clinical pathogens. Most of them are naturally resistant to older and few newer antimicrobial agents. They have the inherent ability to develop antibiotic resistance to novel antibiotics.

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This genus is prevalent in nosocomial infections. Among the Enterobacteriaceae family, two well-known clinically important opportunistic pathogens emerged recently are *E. aerogenes* and *E. cloacae*. These are versatile pathogens known to cause nosocomial infections in intensive care unit patients. Recently, *Enterobacter* spp. are emerged in community other than the hospital settings causing life-threatening infections. This bacteria possesses intrinsic resistance to broad-spectrum beta-lactam drugs owing to the presence of beta lactamases. Majority of the *Enterobacter* resistance is due to the production of chromosomal AmpC beta-lactamases. AmpC is responsible for the resistance profiles of *Enterobacter* spp. toward first-, second-, and third-generation cephalosporins. Due to the acquisition of plasmids harboring genes that encode extended spectrum beta-lactamases and cephalosporinases, they often exhibit multiple drug resistance and are common in hospitalized patients. Emergence of plasmid-mediated quinolone resistance, aminoglycoside resistance, and carbapenem resistance appears to be rare cases. However, these resistant strains are troublesome during the antibiotic therapy as these drugs known as last line of treatment.

Keywords
Enterobacter spp. · Enterobacteriaceae · Multiple drug resistance · AmpC beta-lactamases

11.1 Introduction

Recently, *Enterobacter* spp. are rapidly establishing as deadly nosocomial pathogens. Hospital-acquired infections are one of the worse outcome associated with the multidrug-resistant *Enterobacter* spp. Recently, third-generation antibiotic, cephalosporin resistance among *Enterobacter* is important nosocomial pathogen associated with high mortality and infection morbidity (Ye et al. 2006). *Enterobacter* spp. causes several nosocomial infections such as bloodstream infections (BSIs), urinary tract infections (UTIs), ophthalmic infections, central nervous system infections, and skin and soft tissue infections. Among all, BSIs are the most invasive nosocomial infection caused by *Enterobacter* spp. These bacteria are ranked as the seventh most common infectious agent associated with nosocomial pneumonia and ninth most common pathogen causing nosocomial BSIs. The severity of this pathogen in hospital settings is high, where bloodstream infections are the second most invasive disease due to these bacteria (Kus 2014) (Fig. 11.1).

The genus *Enterobacter* was first suggested by Hormaeche and Edwards in 1960 (Grimont and Grimont 2006). *Enterobacter* spp. are having similar phenotypic and biochemical features of the genus *Klebsiella* but differ in their motility. Colonies of this genus are slightly mucoid in nature and less fermentative than *Klebsiella*. Clinically important and highly pathogenic one is known as *E. cloacae*. An anaerobic and yellow pigmented, *E. agglomerans* formerly called as *Erwinia herbicola* is

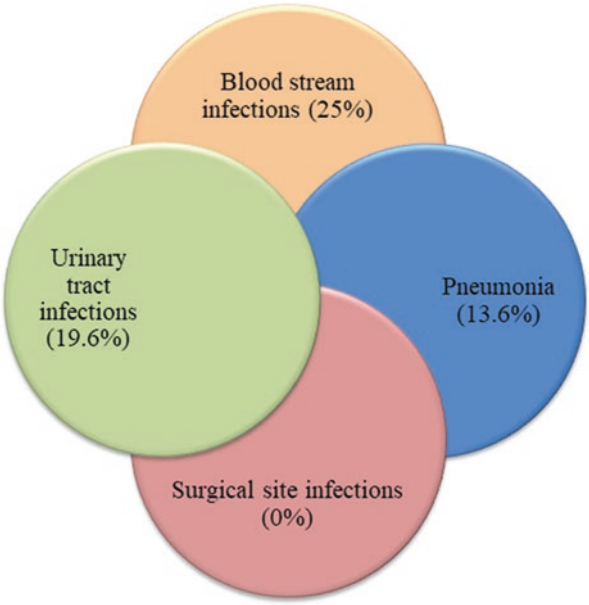

Fig. 11.1 Prevalence of *Enterobacter* species in different nosocomial infections

encountered occasionally in clinical settings (Greenwood 2012). This genus of bacteria is facultative anaerobes and straight Gram-negative bacilli having an approximate size of 0.6–1 mm × 1.2–3 mm. They are motile by peritrichous flagella and are nonspore formers. Bacteria are having capsules for protection from unfavorable conditions. *Enterobacter* colonies are pigmented or nonpigmented. Biochemical features of bacteria include mannitol fermenter, Voges-Proskauer test positive, methyl red test negative, ornithine positive, and citrate positive. They can grow on Moller's potassium cyanide medium at 30 °C and are lysine decarboxylase negative, gelatin test positive, indole negative, and oxidase test negative. Some of the species exhibit different biochemical properties. *E. agglomerans* do not deaminate phenylalanine and are ornithine decarboxylase negative. Also, they cannot produce hydrogen sulfide in triple sugar iron agar. Gelatin liquefaction test, indole test, oxidase test, and lysine decarboxylase test are some of the different tests for *E. aerogenes* and *E. gergoviae* (Kus 2014).

Enterobacter spp. belongs to the family Enterobacteriaceae. These are ubiquitous in the environment and are able to survive on dry and skin surfaces. This genus was recognized as pathogens after a nationwide septicemia outbreak at 25 hospitals in 1976 from unsterile intravenous solutions. These bacteria can cause sporadic outbreak owing to their ability to divide in the glucose-containing parental fluids (Maki et al. 1976). Several outbreaks of enterobacterial infections have been reported due to the use of unsterile humidifiers, respiratory therapy equipment, hydrotherapy water in burn unit, and enteral feedings. This genus causes a wide variety of nosocomial infections (infections of lung, urinary tract, abdominal cavity,

and intravascular devices). *E. sakazakii* is one of the bacteria that causes neonatal sepsis along with meningitis (Nazarowec-White and Farber 1997; Bar-Oz et al. 2007). Like other enteric Gram-negative bacilli, this genera is gifted with several factors such as siderophores, endotoxins, and adhesions capable of initiating pathogenesis. This genus can be readily separated from other members of Enterobacteriaceae family due to the ease in the isolation from the clinical specimens (Patel and Patel 2016).

11.2 *Enterobacter* Infections

These bacteria inhabit as commensal bacteria in the human gastrointestinal tract and in the environment including soil, water, sewage, and plants. Historically, this genus was categorized as mild pathogens causing low threat to humans. Now, *Enterobacter* spp. acquired attention as opportunistic pathogens causing infections in immunocompromised patients within the clinics. *E. cloacae* are responsible for most of the nosocomial infections in human beings and known as the most medically significant species (Davin-Regli and Pagès 2015). *Enterobacter* species are associated with a wide variety of clinical infections such as lower respiratory tract infections, urinary tract infections, bacteremia, skin and soft tissue infections, endocarditis, central nervous system infections, bone and joint infections, and gastrointestinal tract infections. In case of animals, these species are rarely linked with pneumonia, peritonitis, intravenous catheter infections, wound infections, dermatitis, otitis media infections, and urinary tract infections (Weese 2008). The arrival of antibiotic resistance profiles among this genus is of great threat in global health care system, which affects both humans and companion animals. The failure of antibiotic therapy emerges with new risks in humans and animals. This may further end up with several significant public health consequences. Hence, alternatives strategies for the elimination of antimicrobial-resistant strains among *Enterobacter* spp. are important from the view of veterinary medicine and public health care system (Harada et al. 2017; Weese 2008).

This genus has been associated with several clinical syndromes and occasionally some of the syndromes mimics with the disease patterns of easily treatable pathogens such as *Staphylococcus aureus* and group A *Streptococci*. In recent times, high rates of coinfections with other pathogens are detected in the liver and lung transplant areas with *Enterobacter* infections. This includes the growing dominance in a variety of clinical syndromes and their etiologic part in cotton fever (Sanders and Sanders 1997). Overall, infections by *Enterobacter* spp. are mostly similar to those by other facultative Gram-negative bacilli. A broad range of infections of this genus include bacteremia, infections of urinary tract, lower respiratory tract, central nervous system, skin, soft tissue, bone, gastrointestinal tract, and other organs (Fig. 11.2). Recently, an *Enterobacter* spp., *E. bugandensis* is isolated from neonates and immunocompromised patients with sepsis. This is known as one of the newly isolated and highly pathogenic species of *Enterobacter* (Pati et al. 2018).

Fig. 11.2 Clinical manifestations of different *Enterobacter* infections

11.2.1 *Enterobacter bacteremia*

Often *Enterobacter* infections are complicated by their resistance to antibiotics of choice such as cephalosporins. In a study, 36% *Enterobacter* infections in intensive care units (ICUs) showed resistance to broad-spectrum cephalosporins. During the course of antibiotic therapy, these bacteria are adapted to the drugs through the increased production of beta-lactamase. Generally, cephalosporin-resistant *Enterobacter* bacteremia is significantly higher than those associated with the susceptible bacteremia. Species associated with *Enterobacter* bacteremia are *E. aerogenes*, *E. agglomerans*, *E. cloacae*, *E. asburiae*, *E. sakazakii*, *E. amnigenus*, *E. gergoviae*, and *E. hormaechei* (Kang et al. 2004). In all cases, bacteremia occurs in debilitated patients like those who had recently hospitalized, or received corticosteroid therapy, or previously received antibiotics or admitted to ICU. The mortality rate associated with *Enterobacter* bacteremia was 20 and 24% at 14 and 28 days after the diagnosis of bacteremia (Blot et al. 2003). Combination therapy is suggested for preventing the emergence of *Enterobacter* resistant strains. Combination

therapy includes the administration of beta-lactam drugs other than cephalosporins and aminoglycosides. Combination therapy is more effective than monotherapy as the organism will become resistant to only one of the two drugs given and remain susceptible to other drugs. Even, more sensible use of third-generation cephalosporins may reduce the prevalence of nosocomial multidrug-resistant bacteremia associated with *Enterobacter* spp. (Chow et al. 1991).

There are several risk factors involved in bacteremia such as malignancies, prematurity, gastrointestinal disease, life-threatening infections, use of a ventriculoperitoneal shunt catheter, parenteral nutrition, immunosuppressive therapy, use of ventriculostomy, and prolonged antibiotic therapy (Andresen et al. 1994). A survey in the USA reported that 3.9% of all nosocomial bloodstream infections are caused by *E. cloacae* (Wisplinghoff et al. 2004). Around 5–6% of bacteremia is contributed by *Enterobacter* bacteremia and also known for 8.7% of neonatal sepsis. This bacteremia is severe in children younger than 18 months. The predisposing factors of deaths associated with neonatal bacteremia are prematurity, respiratory problems, and leukocytosis (Chen et al. 2014). Generally, 56–100% of bacteremia is developed institutionally. The most common species associated with bacteremia in decreasing order are *E. cloacae* (46–91% of isolates), *E. aerogenes* (9–43%), *E. agglomerans*, *E. sakazakii*, and others. Some of the infections are contributed by *Enterobacter* spp. that are polymicrobial (14–53%) (Sanders and Sanders 1997).

11.2.2 Lower Respiratory Tract Infections

Like *Enterobacter* spp. are common cause of bacteremia, most of these species are implicated in lower respiratory tract infections. They involved in lung abscess, pneumonia, emphysema, asymptomatic colonization in respiratory secretions, and purulent bronchitis (John et al. 1982). These species surpassed *Klebsiella* spp. and known as the third most cause of nosocomial respiratory tract infections in the USA. It is recognized as a cause of community-acquired pneumonia (Pareja et al. 1992). In last decades, prevalence of lower respiratory tract infections by *Enterobacter* spp. increased continuously. Statistics suggested that only 2–9% cases of respiratory tract infections were reported in 1970s. This rate was increased from 9.5% in the 1980s to 11% in 1990 (Jarvis and Martone 1992). There was a prevalence of *Enterobacter* infections in lung transplant recipients. It is reported that around 40% of lung transplant patients developed acute bacterial pneumonia exactly following the transplantation. Manifestations of clinical pneumonia caused by other Gram-negative bacilli differ from those caused by *Enterobacter* spp. (Sanders and Sanders 1997).

11.2.3 Endocarditis

Infective endocarditis is usually caused by Gram-positive bacteria and accounts for high risk of mortality in renal failure patients. Occasionally Gram-negative bacteria

are encountered as one of the etiologic agents. *Enterobacter* is known to be a rare etiology of endocarditis. In a meta analyis of 2761 patients, two were confirmed with *Enterobacter* endocarditis (Karasahin et al. 2018). Another case series reviewed 37.7% mortality rate with *Enterobacter.* In a study, *Enterobacter* endocarditis was treated through monotherapy using carbapenem (Moon et al. 2012). Generally vancomycin along with meropenem is administered for critically ill patients and has risk factors for ESBL producing *Enterobacter* spp. (Gould et al. 2012). A case report showed that multidrug-resistant *E. cloacae* can be another possible pathogen of infective endocarditis and treated by continuous administration of beta-lactam drug and aminoglycoside (Yoshino et al. 2015).

11.2.4 Urinary Tract Infections

E. cloacae are one of the chief pathogens involved in urinary tract infection. Extended-spectrum beta-lactamase (ESBL) producing *Enterobacter* spp. are major in hospital-acquired urinary tract pathogens. One of the effective antibiotics against ESBL producing strains were carbapenems but the expression of carbapenemase provided resistance to all beta-lactam drugs (Xu and He 2019). In a case report, New Delhi metallo-β-lactamase 1 (NDM-1) producing *E. aerogenes* was reported to cause UTI after the insertion of JJ ureteric stents in areas of Croatia and Europe. Urinary pathology and even urosepsis are the most common complications developed after JJ stent insertion due to the antibiotic resistance determinants of bacteria (Franolić et al. 2019). Pathogens enter the lower urinary tract, urethra, and then spread to upper urinary tract. Sometimes, nosocomial UTI is acquired through bloodstream infections. Incidence of UTI is 50 times higher in women than men (Lipsky et al. 1980). Another resistant UTI causing species that express *AmpC* beta-lactamase is *E. cloacae*. They confer resistance to a wide range of antibiotics such as cephalosporins, penicillins, clavulanic acid, and quinolones (Pallett and Hand 2010). The known risk factors associated with ESBL producing UTI are recent hospitalization, presence of comorbidities, bladder catheterization, and prolonged stay in health care facility (Vardi et al. 2012).

11.3 Versatile *Enterobacter* spp. Challenging Antibiotic Treatment

Vast majority of *Enterobacter* infections in humans are caused by four important versatile species such as *E. cloacae*, *E. aerogenes*, *E. agglomerans* (*P. agglomerans*), and *E. sakazakii.* These bacteria are lactose fermenters, motile, and form mucoid colonies. These strains arise from endogenous intestinal flora of hospitalized patients and occur as cause of common source outbreaks or transmit from patient to patient. Especially those patients who had undergone antibiotic therapy and those admitted in intensive care units encounters more infections. These species cause variety of nosocomial infections (UTIs, pneumonia, wound, and burn

infections, infections of intravascular devices, meningitis, and prosthetic devices) (Sanders and Sanders 1997). Among these, meningitis is primarily observed in neonates associated with contaminated powdered milk products (Bowen and Braden 2006).

E. aerogenes is isolated from clinical samples of urinary, blood, respiratory, or gastrointestinal tract. Epidemiology of these species was common in nosocomial infection outbreaks in Western Europe since 1993. *E. aerogenes* was regarded as a significant multidrug-resistant pathogen in intensive care units till 2003. International spread and transmission of extended-spectrum beta-lactam carrying epidemic plasmid in Europe resulted in *Enterobacter* infections in European hospitals and health care facilities. Also, antibiotic therapy using extended-spectrum cephalosporins and carbapenems caused an increase in infections caused by them in clinical wards. As a consequence of this therapy, pandrug-resistant *E. aerogenes* strains resistant to last line of drugs (colistin and carbapenems) are emerged. Identification of efflux pump mechanism in drug-resistant *E. aerogenes* highlighted the new methods in adaptive evolution of bacteria (Davin-Regli and Pagès 2015) (Fig. 11.3).

11.3.1 *Enterobacter cloacae*

E. cloacae are Gram-negative facultative bacteria widely found as saprophytes (sewage and soil) in nature. They are also found as commensals in human gastrointestinal tract. These are known as one of the important nosocomial pathogens causing UTIs, wound infections, sepsis in ICUs, and pneumonia with clinical significance (Wang et al. 2018). It is a known clinically significant species in *Enterobacter* genus owing to the presence of several antibiotic-resistant genes (Liu et al. 2013). This situation has become worse as there is a need for novel therapeutic drug discovery for broad-spectrum antibiotic-resistant *E. cloacae* (resistant to quinolones, carbapenems, and aztreonam). There are reports of combating *E. cloacae* ceftazidime-resistant and

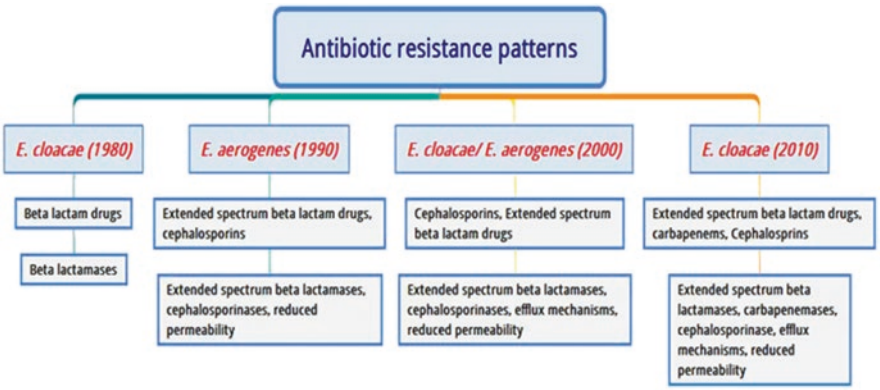

Fig. 11.3 Emergence of antibiotic resistance patterns in clinically important *Enterobacter* species with their mechanisms of antibiotic resistance

cefotaxime-susceptible strains with a triple combination of colistin with amikacin and cefepime (Lima et al. 2017). This bacterium has also been isolated from rice, meat, vegetables, and food processing plants. They lead to food spoilage and food safety problems due to the production of putrescine and cadaverine (Liu et al. 2018).

Various virulence-associated genes are present in the pathogenic islands and codes for type IV or III secretion system that is acquired by horizontal gene transfer. Different antagonistic mechanisms present in *E. cloacae* allow them to endure in diverse environments (Liu et al. 2013). A case study reported these bacteria as unusual cause of necrosis of nasal mucosa. These species are intrinsically resistant to amoxicillin, ampicillin, and cephalosporins. Many studies revealed that the disproportionate use of broad-spectrum drugs (e.g., cephalosporins) developed *Enterobacter* sp. as significant nosocomial pathogens (Binar et al. 2015). Monotherapy or combination therapy using aminoglycosides was suggested for treatment of carbapenem or beta-lactam drug-resistant *E. cloacae*. Later, draft genome analysis showed that bacteria acquired high-level aminoglycoside resistance through *rmtD-2* gene (Martins et al. 2017). In an outbreak of bacteremia, *E. cloacae* were found to be the causative agent for 4.5% of all cases and remain endemic at medical center for 5 years (John et al. 1982). Infections caused by *E. cloacae* accounts for 5% hospital-acquired sepsis, 4% nosocomial pneumonia, 10% postsurgical peritonitis, and 4% nosocomial urinary tract pneumonia. Pathogenic mechanism in disease development includes the production of hemolysin, enterotoxins, and thiol activated pore-forming cytotoxins. Antibiotic-resistant biofilms are produced with the help of curli fimbriae. In general, these are widely found in nature but can also act as pathogens (Mezzatesta et al. 2012).

11.3.2 *Enterobacter aerogenes*

There is a greater concern associated with the nosocomial infections in immunocompromised individuals caused by *Enterobacter* sp. Among them, *E. aerogenes* and *E. cloacae* are the most important opportunistic pathogens, especially in patients on ventilation. *E. aerogenes* possess multiple resistance and virulence genes that contribute to increased pathogenesis. They produce extended-spectrum lactamases such as *AmpC* lactamase and have acquired resistance to cefoxitin, ampicillin, first-generation cephalosporins and amoxicillin (Azevedo et al. 2018). These bacteria were responsible for several outbreaks of nosocomial infections in Europe. Various redundant regulatory cascades present in bacteria efficiently allow the bacterial dissemination through control of membrane permeability during bacterial protection and expresses several detoxifying enzymes that codes for antibiotic resistance. Different factors involved in conferring antibiotic resistance include activation of OmpX porin membrane protein and other drug transporters such as AcrAB-TolC system, MacA, MdfA, OqxAB, Mar, Ram, Sox, and EmrE (Davin-Regli and Pagès 2015). The improved resistance toward broad-spectrum antibiotics was linked with the alterations in outer membrane that resulted in porin decrease and modification in the lipopolysaccharide components. To circumvent the emergence of

beta-lactam-resistant strains, combination therapy of imipenem and colistin are suggested (Thiolas et al. 2005). Another mechanism involved in multiple drug resistance (MDR) is the overexpression of efflux pumps. These efflux pumps exclude the antibiotics before they reach to their target. Two efflux pumps, such as ABC transporter- and proton motive force-dependent types, were reported as active in MDR strains of *E. aerogenes* (Martins et al. 2010). *E. aerogenes* is known as the fourth most regularly isolated bacteria from hospital. This is due to the emergence of extended-spectrum cephalosporins and carbapenems. After that, there was an emergence of pan drug-resistant *E. aerogenes* isolates, which are resistant to last line of drugs. It has been studied that around 40% of the MDR strains possess active efflux pump systems (McCusker et al. 2019).

11.3.3 *Enterobacter sakazakii*

E. sakazakii is a known food-borne pathogen causing necrotizing enterocolitis, bacteremia, and meningitis in preterm and full-term immunocompromised infants (Hu et al. 2013). Now, *E. sakazakii* is called as *Cronobacter sakazakii* and in 2002, International Commission on Microbiological Specification for Foods classified this species as a severe threat for restricted populations. It is associated with life-threatening food-borne disease in infants where powdered infant formula acts as source of infection (Akineden et al. 2017). This organism was first characterized as yellow-pigmented coliform causing septicemia in infants. Antibiotics effective against this pathogen are acyl ureidopenicillins, carbapenems, aminoglycosides, aztreonam, antifolates, cephalosporins, chloramphenicol, quinolones, nitrofurantoin, and tetracyclines. They show resistance to benzylpenicillin oxacillin, some macrolides, and clindamycin (Abdesselam and Pagotto 2014). Fatal rate of *E. sakazakii* infection in infants can range up to 80% (Shukla et al. 2018).

Severe reported outcomes of this bacterial infection are brain abscess, seizures, hydrocephalus, developmental delay, and death in 40–80% cases. People at greater risk rate are premature infants rather than mature infants, children, and adults (Bowen and Braden 2006). According to Center for Disease Control and Prevention in the USA, four to six infection cases related to these bacteria are reported per year. Furthermore, immunocompromised elderly patients have also been reported with infections (Lou et al. 2014). Virulence traits of bacteria were found through complete genome sequencing. These virulence factors associated with pathogenesis include hemolysin, plasminogen activator (cpa), and siderophore interacting protein. Other proteins found in bacteria such as outer membrane protein (Omp) A and X plays vital part in the adhesion and internalization to the cells. They are resistant to antibiotic treatment as *E. sakazakii* form biofilms (Holý et al. 2019).

11.3.4 *Enterobacter agglomerans*

E. agglomerans are now classified into a new taxon of Enterobacteriaceae family; Pantoea based numerical phonotypical analysis. These are isolated widely from humans (wounds, internal organs, urine, and blood), animals, plant parts, water, and seeds. Some of them cause stalk and leaf necrosis on onions and some develop galls on *Wisteria japonica*, *Gypsophila paniculata,* etc. (Gavini et al. 1989). *P. agglomerans* are known as obligate infectious agents of plants and opportunistic human pathogens. In humans, mostly, infection by *P. agglomerans* is acquired through wound infection by plant material or by nosocomial infection in immunocompromised individuals. Possible clinical outcomes of *P. agglomerans* infection include synovitis, septic arthritis, peritonitis, osteomyelitis, endophthalmitis, and endocarditis. Epidemics of nosocomial septicemia caused by *P. agglomerans* have been reported in both adult and pediatric patients. Generally, nosocomial infections were mild and proper antibiotic therapy led to complete recovery. Reports of infections by *P. agglomerans* in vertebrate animals are few compared to humans (Dutkiewicz et al. 2016). The pathogenic determinants of *P. agglomerans* are described as pathogenicity island containing plasmid (150 kb pPATH) (Barash and Manulis-Sasson 2009), large Pantoea Plasmid (De Maayer et al. 2012) and the type III secretion system (T3SS) (Nissan et al. 2006). These bacteria cause soft tissue or bone joint infections followed by the penetration of trauma by vegetation (Völksch et al. 2009).

E. agglomerans causes a variety of nosocomial infections such as UTIs, septic arthritis, intra-abdominal infections, ophthalmic infections, central nervous system (CNS) infections, bacteremia, endocarditis, lower respiratory tract infections, skin infections, and osteomyelitis in individuals associated with intravenous lines and immunocompromised patients. This bacterium is an unusual cause of spondylodiscitis, which is one of the manifestations of osteomyelitis. Only 31 suspected cases of *E. agglomerans* spondylodiscitis reported previously (Jayaweera et al. 2016). A report showed *P. agglomerans* as an infrequent cause of peritonitis in peritoneal dialysis patients (Sastre et al. 2017). It is also known to be an unknown cause of infections in children. Often, these bacteria in association with other conventional pathogens cause bacteremia with indwelling central access in children. *P. agglomerans* is suspected as an etiologic agent of penetrating trauma through vegetation or by soil coated objects that persist to be resistant to the conventional therapy (Cruz et al. 2007). The relative contribution of most common infections of *P. agglomerans* includes UTIs (21.4%), wound infections (35.7%), and pneumonia (21.4%). Infections by these bacteria may cause serious morbidity and mortality, especially in children with pneumonia. The drug-resistant patterns of community and hospital-acquired strains may vary with their different pathogenic and clinical features. Even though, 21.4% of the *P. agglomerans* isolates obtained from hospital setting showed resistance to carbapenem and caused infection (Büyükcam et al. 2018). One report showed nosocomial outbreaks of *P. agglomerans* in a tertiary care center associated with in-house prepared anticoagulant dextrose solution which was used for the priming of the plasmapheresis machine and for hemodialysis in acute care. Nosocomial outbreaks reported due to the contaminated parenteral nutrition,

transference tubes (used for intravenous purposes), blood and blood products (Boszczowski et al. 2012).

11.4 Antimicrobial Resistance Mechanisms and Associated Factors

Enterobacter spp. among Enterobacteriaceae family are documented as a foremost pathogen in hospital-acquired pathogen and continuously involved in several nosocomial outbreaks worldwide. The emergence of MDR strains is found to be responsible for the life threatening and more expensive outbreaks, which constitute a greater threat to the infection control teams. Increase in the number of carbapenemase and extended-spectrum beta-lactamase (ESBL) producing *Enterobacter* spp. remain as a concern for the physicians and scientists (Noël et al. 2019).

11.4.1 Antibiotic Resistance and Mechanism

Major mechanisms involved in *Enterobacter* spp. antibiotic resistance are alteration in the target of drug, production of an inactivating enzyme and modulating the ability of the drug to enter the cells. *Enterobacter* spp. acquires resistance to beta-lactam antibiotics and aminoglycosides through the production of an inactivating enzyme, whereas resistance to quinolones and trimethoprim is acquired by altering drug targets and their ability to accumulate in the cell. Studies have shown that all species of *Enterobacter* possess chromosomally encoded Bush group type 1 beta-lactamases (Bush et al. 1995; Cohen et al. 1993; Conus and Francioli 1992). In certain strains of *E. gergoviae*, *E. aerogenes*, and *E. sakazakii*, lactamases are produced in very low and noninducible concentrations. These strains have greater sensitivity toward ampicillin, cefoxitin, and older cephalosporins. Mostly, uniform resistance pattern is observed in wild-type strains of *E. sakazakii*, *E. cloacae*, *E. taylorae*, *E. asburiae*, and *E. aerogenes* owing to the presence of Bush type 1 beta-lactamases (Pitout et al. 1997).

Resistance among wild-type strains arises mainly from great specificity of drug to this enzyme or from the drug that acting as inducer of enzyme. There is an ampD gene in *Enterobacter* spp. which on mutation causes the emergence of resistance to extended-spectrum cephalosporins, aztreonam, and broad-spectrum penicillins. Usually, this gene prevents high level expression of beta-lactamases. Hence, such a mutation to this gene has been referred as stable depression mutation. These stable depressant mutants are also resistant to beta-lactam inhibitor beta-lactam drug combinations. Among beta-lactam drugs, only carbapenems and newer expanded spectrum cephalosporins (cefepime) maintain their activity toward *Enterobacter* infections (Schaberg et al. 1991; Ehrhardt and Sanders 1993; Bonten et al. 1994). Wild-type strains may become resistant to broad-spectrum penicillins like piperacillin through the achievement of plasmids encoding Bush group 2 TEM1, TEM2 or SHV lactamases (Huovinen et al. 1989; Liu et al. 1992). Recently scientists reported

chromosomally encoded carbapenemases in *E. cloacae* which exhibited carbapenem resistance. Like Bush group 1 lactamases, this enzyme can also be induced by cefoxitin and carbapenems. *Enterobacter* spp. with aminoglycoside resistance are thought to produce one or multiple aminoglycoside inactivating enzymes. Acetylating enzymes such as AAC (6′), AAC (3) II, AAC (3) I, AAC (3) V and AAC (3) III, and nucleotidylating enzymes such as ANT (2″) have been investigated in *Enterobacter* spp. which exhibits aminoglycoside resistance (Huovinen et al. 1989; Maes and Vanhoof 1992) (Table 11.1).

11.4.2 Extended-Spectrum Beta-Lactamases (ESBL) and AmpC Beta-Lactamases

Beta-lactamases are bacterial enzymes produced to cleave beta-lactam antibiotics which results in the generation of inactive molecules. ESBLs have the ability to

Table 11.1 Different antibiotic resistance profiles exhibited by *Enterobacter* species

Enterobacter species	Antibiotics acquired resistance	References
Multidrug-resistant *Enterobacter* spp.	Tetracycline Amoxicillin Cephalosporins	Millar et al. (2008)
E. cloacae complex	Intrinsic resistance to penicillins, first- and second-generation cephalosporins Third-generation cephalosporins Aztreonam	Annavajhala et al. (2019)
E. cloacae	Extended-spectrum cephalosporins Plasmid-mediated quinolone Resistance	Harada et al. (2017)
E. aerogenes *E. cloacae* *E. cloacae* complex	Carbapenems	Khajuria et al. (2014)
E. bugandensis	Cefazolin Cefoxitin Oxacillin Penicillin Rifampin	Singh et al. (2018)
E. cloacae *E. aerogenes* *E. agglomerans*	Third-generation cephalosporins	Cosgrove et al. (2002)
Enterobacter spp.	Imipenem	Marchaim et al. (2008)
E. cloacae *E. aerogenes*	Sulfamethoxazole Cotrimoxazole Gentamicin Tobramycin Ampicillin Piperacillin Cefuroxime	Leverstein-van Hall et al. (2003)

inactivate oxyimino aminothiazolyl cephalosporins such as monobactam, aztreonam, ceftazidime, cefepime, and cefotaxime (Pitout and Laupland 2008). As they are resistant to extended-spectrum cephalosporins, ESBL producers are difficult to detect through zone diameters or MICs. Also, detection of ESBL producers is difficult due to the presence of inducible *AmpC* chromosomal enzymes. It has been shown that clavulanate induces AmpC beta-lactamases and hydrolyze the cephalosporins. *Enterobacter* spp. are resistant to third-generation (cefepime) and fourth-generation cephalosporins that act as poor substrates for beta-lactamases (Crowley and Ratcliffe 2003). Mostly, resistance to beta-lactam drugs is mediated by the hyperproduction of chromosomal AmpC beta-lactamase which resulted by induction or by selection of depressed mutant strains (Barnaud 2001). It has been reported a plasmid-mediated ESBL production among resistant *Enterobacter* spp. Most common beta-lactamases found in *Enterobacter* spp. belong to SHV-, CTX-M-, and TEM-derived lactamases. There are several other lactamases reported in different geographical areas. IBC-1 is one of the recently reported enzymes in *E. cloacae* in Greece. Another VEB-1 was reported in clinical samples containing *E. cloacae* and *E. sakazakii* in Bangkok and Thailand. SFO-1 reported in Japan and associated with *E. cloacae* (Schlesinger et al. 2005).

There are different classes of beta-lactamases based on their substrate and inhibitor specificity. Group 1 describes cephalosporinases which are not inhibited well by clavulanate. Group 2 describes enzymes such as penicillinase, broad-spectrum beta-lactamase, and cephalosporinase activity inhibited by beta-lactamase. Group 3 are metallo beta-lactamase hydrolyzing penicillins, carbapenems, and cephalosporins poorly inhibited by most of the beta-lactamase inhibitors (Bush 2013). Ambler class C (Bush-Jacoby group 1) enzymes do not belong to the ESBL-type enzymes but hydrolyze third-generation cephalosporins. Several Gram-negative bacteria possess chromosomally located genes coding *AmpC* and have been recognized in 1960s. In some species *AmpC* gene is chromosomally located and is intrinsic, especially in *E. aerogenes* and *E. cloacae*. This is due to the inducible expression of *AmpC* gene controlled by transcription factors in those species (Corvec et al. 2007; Macdougall 2011; Harris and Ferguson 2012). Some species are found with *AmpC* gene located on plasmids which can transfer between species. Plasmid-mediated AmpC gene is found in clinical species associated with community onset, nosocomial and health care-related infections. There are ESBL producing strains with plasmid-mediated *AmpC* gene that are frequently resistant to quinolones or trimethoprim sulfamethoxazole. These plasmid-mediated *AmpC* genes are not inducible in nature but there are reports of plasmid-mediated inducible *AmpC* gene transmitting into new hosts (Alvarez et al. 2004).

Further, there are no reports describing the superior action of any antimicrobial agent over carbapenems to combat or treat infections by ESBL or AmpC producers. Overuse of carbapenem has raised a new alarming threat of carbapenem-resistant strains that developing on a global scale. Beta-lactam/beta-lactamase inhibitors (BLBIs) such as piperacillin and tazobactam can be suggested for treatment of ESBL producers. But theoretical studies limited the use of piperacillin against the *AmpC* producers. For urinary infections caused by ESBL producers,

amoxicillin–clavulanate is the choice of treatment. Some uncommon antibiotics such as temocillin, pivmecillinam, and fosfomycin are used to treat less critical infections (Harris 2015). A study reported intrinsic chromosomal resistance of *E. cloacae* to first-generation cephalosporins, penicillins, cephamycins, and beta-lactam or lactamase inhibitors due to the *AmpC* gene. One of the reasons for the resistance to cephalosporins by *Enterobacter* spp. is due to the overexpression of beta-lactamases. This class I beta-lactamases are encoded by chromosomal *AmpC* gene (Uzunović et al. 2018).

11.5 Conclusion and Future Perspectives

Recently, *Enterobacter* spp. are considered as significant clinical pathogens causing nosocomial infections. Most of the species associated with *Enterobacter* infections are innately resistant to older antibiotics. They have the ability to develop resistance to newer antibiotics also. Multiple drug-resistant strains are emerged in hospitals using beta-lactam drugs and cephalosporins. They have high prevalence of nosocomial infections in neonates and immunocompromised individuals. Among all isolates, *E. aerogenes* and *E. cloacae* are the most versatile opportunistic pathogens associated with nosocomial outbreaks. The saga of *Enterobacter* infections is associated with a logarithmic increase in the expression of beta-lactamases and extended-spectrum cephalosporinases. There are many fundamental questions to be answered for understanding the pathogenic mechanisms relevant to clinical infections caused by *Enterobacter* spp. that are different from other Gram-negative enteric bacilli. Strategies should be developed to suppress the expression of multiple drug-resistant strains and to minimize new emergence of resistance.

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