Insight into the Antibiotic Susceptibility Algorithm Procedures for Detecting Carbapenem-Resistant Enterobacter Cloacae

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Abstract
The sudden increase in the predominance and clinical impact of infection caused by carbapenem resistance Enterobacter cloacae (CR-ECL) is a global health concern. CR-ECL is notably problematic when identified in the clinical microbiology laboratory. Due to CR-ECL’s intrinsic resistance to most cephalosporin and carbapenem and their ability to spread and colonize patients in healthcare settings, identifying and preventing the transmission of these organisms is a significant public health initiative, and coordinated international efforts are needed. Following established antibiotic susceptibility algorithms ensures a systematic and comprehensive assessment of bacterial resistance patterns. This approach helps identify potential resistance mechanisms and guide effective treatment strategies. The algorithm approach considers clinical factors such as patient history, site of infection, and local resistance patterns, enhancing the relevance and applicability of susceptibility testing results to individual patient management. Importantly, continuously monitoring CR-ECL antibiotic resistance patterns and surveillance of emerging resistance mechanisms is essential to adapting and refining antibiotic susceptibility algorithms to evolving clinical needs. This review highlights our current understanding of CR-ECL, emphasizing their epidemiology, detection, treatment, and control.

Introduction
Bacterial antibiotic resistance is a risk to contemporary medicine. Most Gram-negative microbes have recently become resistant to carbapenems class antibiotics, including Doripenem, imipenem, Doripenem, and meropenem. These bacteria produce different enzymes to render carbapenems useless. One of those Gram-negative is Enterobacter cloacae, which, though intrinsically resistant to cephalosporins, is among the microbes known to produce carbapenemases to cause nosocomial antibiotic resistance infections [1]. The magnitude at which Enterobacter cloacae resist these carbapenems antibiotics has a different diversity and has increased tremendously to become a serious global health problem that affects hospital and community patients [2]. Enterobacter cloacae (ECL) is a species of bacteria commonly found in the environment, including soil, water, and human and other animal’s digestive tracts. It is a member of the Enterobacteriaceae family and can sometimes be associated with healthcare-associated infections because it can potentially cause various diseases in hospital settings [3]. Over time, it has developed resistance to multiple antibiotics, posing a significant challenge in healthcare settings. The magnitude at which the bacterium resists antibiotics has a different diversity and has increased tremendously, becoming a serious global health problem for hospital and community patients [4]. The resistance patterns of Enterobacter cloacae are influenced by several factors: The overuse and misuse of antibiotics in both human medicine and agriculture have contributed to the development of resistance [5]. Enterobacter cloacae can acquire resistance genes through horizontal gene transfer from other bacteria, such as Escherichia coli or Klebsiella pneumoniae [6]. These bacteria are often resistant to beta-lactam antibiotics, like penicillin and cephalosporins, due to the production of beta-lactamase enzymes [6]. Again, some Enterobacter cloacae strains have developed resistance to carbapenems, a last-resort class of antibiotics, often through the production of carbapenemases. The

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production of these enzymes is regarded as the primary resistance mechanism of this bacterium. The bacterium is not only resistant to penicillin, cephalosporins, and carbapenems but can also exhibit resistance to multiple classes of antibiotics, making treatment options limited [7]. Significantly, these bacteria are frequently associated with hospital-acquired infections and can be more resistant in healthcare environments due to selective pressure [8]. However, the resistance patterns can vary among different strains of Enterobacter cloacae, making it challenging to predict which antibiotics will be effective [9]. Coupled with the several resistance patterns, Carbapenem-Resistant Enterobacter Cloacae (CR-ECL) has recently emerged in the United States, Korea, China, and India; for example, [1,2] bacteria producing carbapenemase in China is attributed mainly to Metallo-β-lactamases (MBLs). Since the first case of CR-ECL harbouring blaNDM-1 was detected in Chongqing, blaNDM-1-producing Enterobacter cloacae strains have emerged in various regions nationwide. ECL has become China’s third most common carbapenem-resistant microorganism [3]. Surveillance of China Antimicrobial Surveillance Network (CHINET) reported that carbapenem resistance rates among ECL were < 1.0% in 2007, and by 2019, it accelerated to about 10% [3]. Conspicuously, genes encoding MBLs are most identified in Enterobacter cloacae and can be transmitted frequently through mobile genetic elements, leading to CR-ECL prevalence [1]. Previous studies have recognized that CR-ECL could increase the mortality rate, especially in vulnerable patients [10,11,12]. In this case, regular surveillance, judicious antibiotic use, and the development of new treatment strategies are essential to combat Enterobacter cloacae with evolving resistance patterns under these circumstances. Proper hygiene and infection control practices are crucial in preventing the spread of drug-resistant Enterobacter cloacae in healthcare settings. Further understanding of investigating CR-ECL, the most critical mechanism of transmission of resistance, is needed to prevent the spread of the organism. Therefore, exploring the general principles and algorithm detection of CR-ECL must be reviewed urgently. The review focused on the CR-ECL mechanism, identifying the Etiology of Enterobacter cloacae infections, evaluating Enterobacter cloacae sensitivity patterns, and outlining the general principles and algorithm detection of CR-ECL.

**General Features of Enterobacter Cloacae**

Enterobacter cloacae (ECL) is facultatively anaerobic, an elongated rod-shaped Gram-negative bacterium with a size that varies from 0.3-0.6 μm and 0.8 to 2.0 μm [10]. ECL was first described and identified as a distinct bacterial species in the scientific literature in the mid-20th century [11]. The bacterium was recognized as a separate species within the Enterobacter genus, a part of the Enterobacteriaceae family. The species was named “Enterobacter cloacae” to reflect its common association with wastewater and sewage (the term “cloaca” is derived from “cloaca,” a Latin word for sewer or drain) [12]. To help differentiate ECL from other Enterobacteriaceae, the bacterium biochemical test's reaction to catalase, citrate, and urease is positive, while indole, oxidase, and DNase reactions reacted negatively [10]. The bacterium is also positive for D-sorbitol, Beta-galactosidase, citrate utilization, arginine dihydrolase, nitrate reduction, ornithine decarboxylase, for the Voges-Proskauer reaction and ferments glucose. It is negative for dulcitol [10]. In addition, ECL is negative for dulcitol, phenylalanine deaminase, and pectate degradation. Among other features of this species is the mobile nature of the Enterobacter cloacae, which can form biofilms, which could cause colonization of different hospital devices [13]. This bacterium is intrinsically resistant to last-resort third-generation antibiotics because of the overproduction of AmpC β-lactamases by deciphering chromosomal genes and acquiring transferable AMP genes from plasmids. The essential AmpC β-lactamase enzyme contributed to more resistant Enterobacter pathogens [6]. ECL typically grows at 37°C, and the ColorexTM mSuperCARBA plate is used to incubate for 18-24h from inoculation as per the manufacturer’s instructions. **Etiology of Enterobacter Cloacae Infection**

The causes of ECL infections are typically multifactorial and involve a combination of host, environmental, and bacterial factors. Here are some key factors contributing to Enterobacter cloacae causes of infections: Patients with exhausted immune systems due to conditions such as cancer, HIV/AIDS, or immunosuppressive medications are at a higher risk of ECL infections [14]. People with underlying health conditions like chronic illnesses or diabetes, renal failure, or respiratory diseases may be more susceptible to this infection. Neonates, elderly patients, and individuals with immature or compromised immune systems are at increased risk [15]. In healthcare settings, ECL is often associated with healthcare-associated infections, such as hospital-acquired pneumonia, urinary tract infections, and bloodstream infections. Contaminated medical equipment and improper hygiene practices can contribute to infections in healthcare environments [16]. While in community settings, it is less common for ECL to cause community-acquired infections, such as urinary tract infections [16]. The bacterium possesses various virulence factors, including adhesins and toxins, which allow it to adhere to host tissues and evade the host immune response, producing enzyme resistance that can complicate treatment and lead to more severe infections [16]. On
the negative side, ECL can form biofilms on surfaces and medical devices, providing a protective environment for the bacteria and making them more challenging to eliminate [13]. In healthcare settings, transmission of this organism can occur from patient to patient via contaminated hands of healthcare workers or through contaminated medical devices. ECL can survive on surfaces and medical equipment, contributing to nosocomial (hospital-acquired) infections [17]. It is important to note that ECL is an opportunistic pathogen because it typically infects individuals with predisposing risk factors or in healthcare settings. Given these points, Preventing ECL should involve:

- Strict infection control measures.
- Proper hygiene.
- The prudent use of antibiotics to minimize the emergence of drug-resistant strains.

**Evaluation of Enterobacter Cloacae Susceptibility Patterns to β-Lactamase Antimicrobial**

*Enterobacter cloacae* are intrinsically resistant to amoxicillin, cefoxitin, and first, second - and third-generation cephalosporins due to the production of essential AmpC β-lactamase [18]. The microbe displays a high magnitude of enzymatic resistance to broad-spectrum third-generation cephalosporins, and the overproduction of AmpC β-lactamases frequently causes this enzyme [18]. Moreover, its ability to form biofilms and survive in diverse environments contributes to its resilience [13]. It’s important to note that while intrinsic resistance exists, Enterobacter cloacae can also acquire additional resistance through genetic mutations or the acquisition of resistance genes from other bacteria [19]. Further complicating treatment strategies. This adaptability poses challenges in managing infections caused by *Enterobacter cloacae* in clinical settings. Therefore, the treatment with third-generation cephalosporins may be selected for AmpC-overproducing mutants. At this stage, Enterobacter cloacae only produce extended-spectrum beta-lactamase (ESBL) or AmpC beta-lactamase production combined with porin loss; this is usually commonly seen in Enterobacter spp. [19]. are not readily transferable between strains and do not pose the same infection prevention and control risk [20]. The carbapenem-resistant mechanisms in Enterobacter Cloacae (CR-ECL) mechanisms began when the microbe commenced gaining plasmid-encoded carbapenemase genes and the overexpression of efflux pumps and integral overexpression of AmpC and extended-spectrum β-lactamase (ESBL) production, combined with disrupted membrane outer membrane protein loss [21]. Furthermore, acquiring plasmid-mediated ESBL genes, including blaTEM, blaSHV, and blaCTX-M, can make *Enterobacter cloacae* resistant to most β-lactam drugs, thereby making the clinical treatment difficult [22]. Two significant groups of carbapenem enzymes are carbapenem-hydrolyzing serine β-lactamases and metallo-β-lactamases. These include OXA, NDM, KPC, NmcA, IMI, FRI, GES, VIM, IMP, and KPC, which have been noticed in carbapenem-resistant Enterobacteriaceae [22]. The most common description of KPC and NDM-1 was seen in Enterobacter cloacae isolates [23]. However, *Enterobacter cloacae* could be suspected to be carbapenemase using D72C in conjunction with D73C – MASTDISCS® Combi Carba Plus. This will differentiate carbapenemases from ESBLs and AmpCs and help facilitate the delivery of the appropriate targeted antibiotic therapy [23].

**Laboratory Algorithm Detection of Carbapenem-Resistant Enterobacter Cloacae**

**The Laboratory Algorithm Detection of Carbapenem in Resistant Enterobacter Cloacae** involved the traditional identification of ECL resistance solely on the phenotypic features of the isolate, as well as molecular methods. The emergence of various mechanisms for resistance underscores the need for a comprehensive approach. The detection of carbapenemase-resistance Enterobacter cloacae benefits a wide range of aspects, including infection control, public health measures, and patient management. The resistance to carbapenem can be mediated by AmpC expression and membrane permeability changes, making it challenging to detect carbapenemase production in clinical laboratory settings. Its examination should have a high suspicion indicator while examining the microbe for carbapenemase production. Because of these reasons, attention should be paid to two confounders to determine possible carbapenemase-producing *Enterobacter Cloacae* via its antimicrobial susceptibility patterns. Here’s a suggested minimum algorithm for detecting CR-ECL in clinical microbiology, considering phenotypic and molecular methods.

1) Not all carbapenem-resistant Enterobacter cloacae produce a carbapenemase. The combination of ESBL and AmpC can mediate its resistance [24].

2) Not all carbapenemase producers resist carbapenems because the enzymes are not the only mechanism of acquired resistance to carbapenems [24]. However, they are the most essential factor from a public health perspective. Other mechanisms like ESBL or AmpC enzymes associated with Enterobacter Cloacae may lose outer membrane porins through mutations or other disruptions in chromosomal genes) and reduce carbapenem uptake [20].

In contrast to carbapenemases, these combinatorial mechanisms of carbapenem resistance are not transferable between strains (though the contributing ESBL might be), and the porin-deficient mutants may have reduced fitness and be less likely to spread in healthcare settings [20]. This mechanism is often seen
in Enterobacter and a few other Enterobacteriaceae organisms, most markedly affecting ertapenem. The isolates may remain susceptible to other carbapenems at breakpoint concentrations but usually show some degree of reduced susceptibility or resistance, with the level contingent upon the amount of ESBL/AmpC activity and the precise nature of the porin lesion(s) (see Figure 1). The mechanism of acquired resistance to carbapenems must be considered before identifying Carbapenem-Resistant Enterobacter Cloacae from clinical and screening samples.

![Figure 1: The problem with spotting the carbapenemase producers in Enterobacter cloacae isolates](image)

*Note:* Courtesy of Professor Neil Woodford, Public Health England.

There is no universally applicable method to detect all carbapenem resistance mechanisms readily [25]. The ideal indicator carbapenem is one to which all carbapenemases confer resistance, even when production is insufficient. No carbapenem satisfies this criterion for all host species Enterobacteriales [26]. The most vital advice for laboratory staff is to have a high index of suspicion when screening clinical samples or preliminary detection of carbapenem resistance in cultured isolates for reduced carbapenem susceptibility or resistance (see Figure 1). All suspected isolates must be followed up with confirmatory tests locally and, if necessary, submitted to a referral laboratory following current European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Identification at the species level is highly desirable for interpreting resistance patterns. Identify at least to the genus level all isolates found resistant to any carbapenem to ensure reduced susceptibility or resistance, which is not an intrinsic trait. It must be identified at the species level if the genus is not known to produce intrinsic carbapenemases.

**Detection of CR-Enterobacter Cloacae in Screening & Clinical Samples**

Culture remains highly useful for isolating CR- *Enterobacter Cloacae* from stool samples, rectal swabs, or clinical samples as a stand-alone method or as a complement to molecular (PCR) methods. Culture is necessary to determine whether the gene is harboured by *Enterobacter Cloacae* rather than other species, such as *Pseudomonas* spp., *Acinetobacter* spp., or other glucose non-fermenters [27,28]. Several commercially available chromogenic media are designed to isolate CPE and carbapenem-resistant Enterobacterales (CRE), including those producing OXA-48-like enzymes. Chromogenic media for CPE incorporate antimicrobials to inhibit other microorganisms and two or more chromogenic substrates from differentiating key target species or groups of species into coloured colonies [29]. Their exact composition is often undisclosed and is subject to change over time. Providing firm recommendations for using a specific commercial chromogenic medium is impossible. However, reviewing the published literature can help laboratory staff make an informed choice. How can we suspect *Enterobacter cloacae* isolate on a chromogenic agar designed for Carbapenem-Resistant Enterobacter Cloacae (CR-ECL) before using maldi biomereux equipment? After 24 hours at 37°C incubation, the identification of the *Enterobacter cloacae* isolates from screening or clinical specimens using standard microbiological Colorex™ mSuperCARBA selective or chromogenic agar to interpret the isolated organism was established to detect Gram-negative and distinctive metallic blue colonies colouration from this chromogenic agar [29]. This unique metallic blue colour indicates Enterobacter species, and further identification of the organism using maldi biomereux equipment is needed to identify the organism to the genus level *Enterobacter cloacae*. Additional follow-up antimicrobial susceptible testing is required to determine if the ECL-producing carbapenemase enzyme is suspicious to be CPE positive before using PCR for confirmation; sets of antimicrobial susceptibilities testing are needed to give a preliminary result for the ECL-producing carbapenemase enzyme.
Antimicrobial susceptibilities indicators testing to provide an initial result for ECL-producing carbapenemase indicators include the antimicrobial combination disc system. A typical resistance mechanism encountered during ESBL investigations is AmpC; while still conferring multiple resistance in these isolates, the clinical and infection control significance of an AmpC producer is much less than that of an ESBL [30]. Another essential resistance is CPE, which can be suspected using this antimicrobial combination disc system [26].

### Table 1: Algorithm combination of Antibiotic Disc System

<table>
<thead>
<tr>
<th>MGN (Gram-negative Systemic) - panel</th>
<th>MGN+ (Gram-negative extra) – panel 1</th>
<th>MUGN+ (Urinary Gram-negative extra) – panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid 30</td>
<td>Ampicillin 10</td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Ciprofloxacin 5</td>
<td>Cefotaxime 5</td>
<td>Meropenem 10</td>
</tr>
<tr>
<td>Gentamicin 10</td>
<td>Ceftazidime 10</td>
<td>Temocillin 30</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam 36</td>
<td>Amikacin 30</td>
<td>Amikacin 30</td>
</tr>
<tr>
<td>Ertapenem 10</td>
<td>Aztreonam 30</td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime 10</td>
<td>Meropenem 10</td>
<td></td>
</tr>
</tbody>
</table>

Source: The Standards Unit, Public Health England

### Figure 2: Enterobacter cloacae Grow Distinctive Metallic Blue Colonies Colouration in a Chromogenic Agar

### Figure 3: The algorithm of measuring antibiotics susceptibilities to suspect CR-ECL. Carbapenemase-producing Enterobacter cloacae from Clinical samples.

**Source:** The Standards Unit, Public Health England

**Procedures**


If Ertapenem susceptible zone was = <25mm or Cefpodoxime <21mm.

Test for Extended MGN, & MUGN+, ESBL-AmpC CPE panel & inform the medics.
From above susceptibilities test: If Meropenem zone was <25mm OR Meropenem zone = 25 -27mm & (pip/tazo resistant zone <17mm) OR temocillin zone= <11mm) OR Meropenem zone = > 28mm & pip/tazo resistance & temocillin zone= < 11mm.

Test for: meropenem MIC, CPE-PCR & inform the medics to confirm CPE positive of negative. From this test, the following possible outcomes is received.

**PCR pos.**
- PCR neg & meropenem MIC >0.125
- PCR neg & meropenem MIC <0.125
- Meropenem > 28mm & temocillin zone >11 mm & ESBL/AmpC NOT detected.

Furthermore, isolated Enterobacter CPE by culture enables antimicrobial susceptibility testing and, when necessary, epidemiological typing. Molecular methods such as PCR can provide rapid results in as little as 1 hour, which can be a significant advantage, whereas culture typically requires at least 18 hours of incubation. When a PCR method indicates the presence of a carbapenemase gene(s), medics are informed immediately, releasing the isolate’s identity and antibiotic sensitivity reports. When PCR is negative, culture may be helpful to detect CPE with less common carbapenemase genes that may not be targeted by the PCR assay [31]. There is no ‘gold standard’ method for isolating CPE in stool samples or rectal swabs for screening and clinical samples for clinical treatment. Still, a wide range of different cultural media has been proposed [32,33].

**Difficulties around Reporting Carbapenem Susceptibility for CPE**

Opinion was divided about the reporting of carbapenem susceptibility for carbapenem-producing organisms. For several years, there has been an expert opinion that all carbapenemase producers should be reported to be resistant to all carbapenems, irrespective of susceptibility test results [34]. However, this approach has been superseded by EUCAST’s recommendation to report susceptibility testing by breakpoints [35]. EUCAST has adopted the view that low breakpoints and carbapenem susceptibility results can be taken at face value, and carbapenems can be used as therapy so long as carbapenemase producers appear susceptible in vitro. There is a need for more evidence of clinical success for carbapenems against carbapenemase producers with low MICs.

Furthermore, ‘susceptible’ MIC and zone test results for carbapenemase producers often have poor reproducibility, with discrepant results between methods. There is a need to improve the quality of laboratory testing and reporting [36]. The best advice is to apply utmost caution if carbapenems are used in severe infections due to known carbapenemase producers and to avoid using them as monotherapy [18]. New β-lactam and β-lactam/β-lactamase inhibitor combinations that have activity against some carbapenemases (principally KPC types, not MBLs) are under development or have been licensed by the European Medicines Directorate [37].

**Discussion**

CR-ECL isolates may be isolated by specific CPO screening tests using selective chromogenic media (29) or by clinical investigation of any sample submitted for clinical investigation. CR-ECL produces β-lactamase that hydrolyses Carbapenems (e.g., Doripenem, Ertapenem, Imipenem, and Meropenem). Carbapenems are antimicrobial drugs of last resort and are essential in preventing and treating life-threatening nosocomial infections [38]. Of clinical concern, CR-ECL confers resistance or reduced susceptibility to all or nearly all members of the β-lactam class, not just to Carbapenems. Extended and third-line susceptibility testing is often required for the isolates, especially on the first isolation. Some Carbapenemases are found naturally in some bacteria [39]. Still, the most dangerous ones are those acquired from other bacteria and are transmissible, and the spread of these enzymes needs to be reduced wherever possible. Rapid, effective treatment and isolation of the patient are very important. CR-ECL is confirmed by molecular testing in an in-house laboratory for common resistance enzymes or by referral for unusual, difficult-to-confirm isolates.

Identification of (CR-ECL) via genotypic characterization is a molecular testing technique like polymerase chain reaction (PCR) to identify resistance mechanisms (1). In the case of CR-ECL, this often involves detecting carbapenemase genes (e.g., KPC, NDM, IMP, VIM, OXA-48) that confer resistance. Whereas Whole Genome Sequencing (WGS) can provide detailed information on the genetic makeup of CR-ECL strains, helping to identify genetic determinants of resistance and trace their origins [40]. Potential sources of this infection or colonization must be identified, and their transmission within healthcare facilities or communities must be traced via epidemiological investigation. As a result, environmental sampling should be considered to evaluate the healthcare environment for possible reservoirs of CR-ECL, such as medical equipment or surfaces [41]. Infection control measures must be implemented, and infection control measures must be enhanced, including hand hygiene, isolation precautions, and proper disinfection of surfaces. Ensure healthcare workers are educated on appropriate practices to reduce transmission. Antibiotic stewardship programs must be implemented to help reduce the selection pressure for resistant strains. Patients infected or colonized with CR-ECL must be isolated to prevent further spread, and continuous monitoring of the prevalence and resistance patterns in healthcare facilities must be implemented. Data should be shared and collaborated regionally or nationally to...
understand the broader epidemiology of CR-ECL. Evaluate treatment options based on the specific resistance mechanisms identified in CR-ECL strains, which could lead to the combination of therapy or the use of last-resort antibiotics, which may be necessary. For successful surveillance and tracking, we must ensure CR-ECL infection or colonization cases are reported to public health authorities. Research and Development is an area in which we should support research into new antibiotics and alternative treatment strategies for CR-ECL infections and strategies to limit the spread of resistant strains. Addressing carbapenem-resistant Enterobacter cloacae patterns requires a multi-pronged approach involving clinical, laboratory, and public health efforts to prevent, control, and treat these infections effectively.

Conclusion
Upon detecting resistance to carbapenem antibiotics in Enterobacter cloacae strains, initiating a structured approach to determine antibiotic susceptibility is crucial. Adhering to antibiotic susceptibility algorithms is imperative for effectively addressing carbapenem resistance in Enterobacter cloacae. This approach ensures a standardized and comprehensive assessment of susceptibility patterns, facilitates informed treatment decisions, and contributes to the prudent use of antibiotics in clinical practice.

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