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Carbapenem resistant *Enterobacteriaceae* – the basics for every medical specialty

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ABSTRACT

Enterobacteriaceae are ubiquitous gram-negative bacilli, part of the intestinal flora. The number of carbapenem resistance in this class has been increasing, and *K. pneumoniae* carbapenemase (KPC) is the most common carbapenemase. Although less frequent, New Delhi metallo--beta-lactamase (NDM-1) is an even more concerning carbapenemase, because of the extremely limited treatment options. The most important risk factor for colonization or infection with such pathogens is the use of broad spectrum cephalosporins and/or carbapenems. Strategies to treat carbapenemases-producing organisms depend not only on susceptibility tests, minimum inhibitory concentration (MIC) and severity of the infection, but also on the availability, costs and policies of antibiotics in each hospital/country. Hospitalized patients, infected or colonized with carbapenemase-producing bacteria, should be placed on contact precautions.

Keywords: antimicrobial therapy, carbapenem resistant *Enterobacteriaceae*, carbapenemases, KPC-producing *Klebsiella pneumonia*, multidrug resistance

INTRODUCTION

Antimicrobial resistance is reaching concerning numbers worldwide. If the rate of increase maintains constant, by 2050 10 million people will die every year due to antimicrobial resistance[1].

Carbapenems

Carbapenem are very broad-spectrum beta-lactam antibiotics. There are four drugs in this class: ertapenem, meropenem, imipenem and doripenem (the latter not marketed in Portugal). Ertapenem distinguishes itself from other carbapenems as it doesn't act on *Pseudomonas* spp, and is therefore appropriate to treat Gram-negative infections, where others antibiotic classes are not useful, because it doesn't create selective pressure on *Pseudomonas* spp.

Enterobacteriaceae

Enterobacteriaceae are ubiquitous gram-negative bacilli, part of the intestinal flora of most animals, including humans. They cause a variety of diseases in humans, including 25-33% of all bacteremia, over 70% of urinary tract infections (UTIs), and many intestinal/intra--abdominal infections[2].

Enterobacteriaceae include several bacterial species (namely *Escherichia coli*, *Klebsiella* spp, *Proteus* spp, *Citrobacter* spp, *Enterobacter cloacae*, *Morganella morganii*, *Serratia marcensces*), many with intrinsic antimicrobial resistance. Examples are the SPICE bacteria (*Serratia*, *Providencia*, "indole-positive" *Proteus* species, *Citrobacter*, *Enterobacter* species), that have inducible chromosomal AmpC beta-lactamase genes that may be derepressed during therapy, conferring *in vivo* beta-lactam resistance (except cefepime and carbapenems) despite apparent sensitivity *in vitro*[3].

In addition to intrinsic resistances, *Enterobacteriaceae* have the ability to acquire new genetic material by mobile genetic elements. This leads to the emergence of new strains with a distinct genetic repertoire, and the acquisition of new antimicrobial resistance mechanisms[2].

Carbapenemases

The number of extrinsic resistances has been emerging and increasing. Carbapenemases are carbapenem-hydrolysing beta-lactamases that confer resistance to a broad spectrum of beta-lactam substrates, including carbapenems, and they can arise from previously carbapenemase-negative strains.

Carbapenemases are rapidly spreading worldwide and fall into three main groups: KPC enzymes, belonging to Ambler class A; MBLs, belonging to molecular class B and including NDM, VIM, and IMP enzymes, among many others; and OXA enzymes, belonging to class D (in *Enterobacteriaceae*, OXA-48 is the most prevalent one) (Fig. 1)[4,5].

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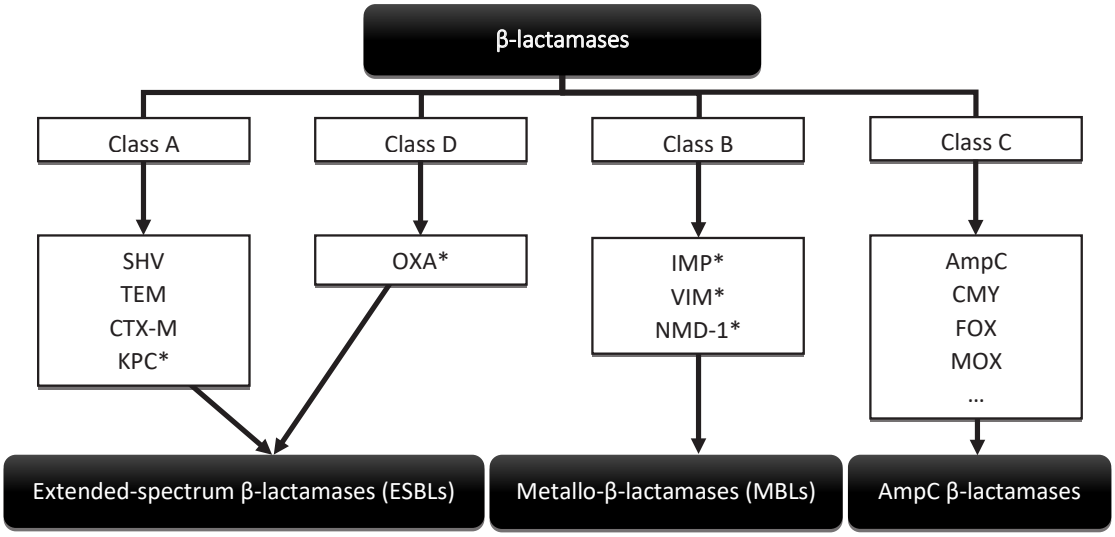
Figure 1

Ambler's molecular classification system[5]



*Also carbapenemases.

EPIDEMIOLOGY

K. pneumoniae carbapenemase (KPC) is the most common carbapenemase. Following the first description of KPC from a clinical isolate of *K. pneumoniae* in the late 1990s in North Carolina – USA[6,7], KPC-production has been identified in isolates almost all over the world. The CDC reported that the proportion of *Enterobacteriaceae* that were carbapenem resistant increased from 1 to 4 percent between 2001 and 2011; the proportion of carbapenem-resistant *Klebsiella* increased from 2 to 10 percent[8]. The proportion of carbapenem-resistant *Klebsiella pneumoniae* isolates in Portugal in 2017 was 8.6%[9].

The New Delhi metallo-beta-lactamase (NDM-1) was first described in December 2009 in a *K. pneumoniae* isolate from a Swedish patient who had been hospitalized in India[10]. Subsequent reports have included patients who have travelled and undergone procedures (so called "medical tourism") in India and Pakistan[11], as well as cases reported in Asia, Europe, North America, the Caribbean, and Australia[11-16].

RISK FACTORS

The most important risk factor for colonization or infection with these pathogens is the use of broad spectrum cephalosporins and/or carbapenems[17-20].

Other risk factors include advanced age, poor functional status, severe illness (trauma, malignancy), diabetes, healthcare-associated infection, extended hospitalization (less than three months ago), ICU hospitalization, mechanical ventilation, recurrent/obstructive UTI, genitourinary or biliary instrumentation, immunodepression, organ transplantation, surgical intervention or wound care[21-29]. Clinicians should be also aware of the possibility of NDM-1-producing *Enterobacteriaceae* in patients who have received medical care in India and Pakistan[12].

TREATMENT

Antibiotic options to treat infection due to carbapenemases-producing organisms are limited (Table I).

Table I

Typical resistances and sensibilities of carbapenemase-producing *Enterobacteriaceae*[4,30]

Usually resistant	Usually sensitive
Carbapenems	Colistin
Piperacillin/Tazobactam → 100%	Tigecycline
Ciprofloxacin → 98%	Aminoglycosides
Tobramycin → 94%	Fosfomycin
Cefepime → 60%	Ceftazidime/Avibactam
	Meropenem/Vaborbactam

Why not treat with a single antibiotic to which the carbapenemases-producing organisms are susceptible?

Data suggest that combination therapy may be beneficial for high-risk patients as it has a protective effect on mortality, and also suggest that monotherapy may be enough for lower-risk patients[31-34]. Thereby, low-risk infection (defined as having an INCREMENT mortality score less than eight points) can be treated with monotherapy according to susceptibility[4]. It is worth mentioning that ceftazidime/avibactam or meropenem/vaborbactam was not used in these studies.

■ Antibiotics

Carbapenems

Carbapenemases-producing organisms are usually resistant to carbapenems, but can we treat *Enterobacteriaceae* KPC infections with these antibiotics when minimum inhibitory concentration (MIC) suggests susceptibility? The answer is yes: we can indeed treat *Enterobacteriaceae* KPC infections with carbapenems, depending of MIC. Low risk infection[4] can be treated with carbapenems in monotherapy if MIC is 4 mg/L or less. High risk infections (defined as having septic shock or, for bloodstream infections, an INCREMENT mortality score of eight or more points) should be treated with combined therapy between a carbapenem and another active antibiotic if the MIC is 8 mg/L or less; for superior MIC, avoid carbapenems.

Double carbapenem therapy can be prescribed when no other active antibiotic is available, using ertapenem as a "suicide substrate"[35] (in these cases, consider 2 g daily of ertapenem)[4].

The dose of meropenem should be the double of the usual dose: 2 g every 8 hours by extended infusion.

Carbapenems have been associated with central nervous system (CNS) adverse effects, including confusional states and lower seizure thresholds, so it should be used with caution with CNS disorders (e.g., brain lesions and history of seizures) and the dose should be adjusted in renal impairment to avoid drug accumulation.

Colistin

Colistin (polymyxin E) is part of the polymyxins antibiotics; polymyxin B is not available in Portugal. Polymyxins have bactericidal activity and renal excretion.

The recommended doses are listed in Table II.

Table II

Intravenous colistin (colistimethate sodium) dosing guideline for the treatment of multidrug resistant Gram-negative infections. eGFR = estimated glomerular filtration rate[36]

Dose	Patient category	Dosing suggestion
Loading	Critically ill or severe sepsis	9-12 MU
Maintenance	eGFR > 60mL/min	4.5 MU 12-hourly
	eGFR 30-60mL/min	3 MU 12-hourly
	eGFR 10-30mL/min	2 MU 12-hourly
	eGFR < 10mL/min	1 MU 12-hourly
	Intermittent haemodialysis	1 MU 12-hourly plus supplemental dose of 1 MU after each episode of dialysis
	Continuous renal replacement	4.5 MU 12-hourly

Because polymyxins are cationic polypeptides[37], they displace Mg^{2+} and Ca^{2+} out of cells, and ionogram vigilance should be regularly assessed during treatment.

Some adverse effects include nephrotoxicity and neurotoxicity (confusion, ataxia, vertigo, facial paralysis).

Tigecycline

Tigecycline have a bacteriostatic activity and should be avoided in monotherapy. Combined therapy is mostly recommended in intrabdominal infections when the MIC is less than 1mg/L, and the recommended dose is 100mg for loading dose and then 50 mg every 12 hours. When used in other kind of infections (pneumonia, UTI, bloodstream infections), the dose of tigecycline should be doubled: 200mg loading dose and then 100 mg every 12 hours[4].

Adverse effects include hepatotoxicity, with lower fibrinogen blood levels, and therefore this should be monitored.

Aminoglycosides

With bactericidal activity, they only should be used if MIC is less than 8mg/L.

It can be used in monotherapy only in UTI. Their use should be avoided when treating abscesses as it doesn't penetrate the pus, because of its low pH.

The usual dose for gentamicin is 5-7 mg/kg/day and for amikacin is 15-20 mg/kg/day. For hospital-acquired pneumonia or shock without other options, higher doses might be considered (gentamicin 10-15 mg/kg, amikacin 25-30 mg/kg), but the risk of toxicity is high. For both, therapeutic drug monitoring should be performed regularly[4].

Nephrotoxicity and ototoxicity are the major adverse effects.

Fosfomycin

Fosfomycin has a broad spectrum and a bactericidal activity. It is excreted unaltered by urine, and has a quick tissue distribution (it doesn't bind to proteins), so it is a good choice almost everywhere: soft tissue, kidney, lung, bone, central nervous system and cardiac valves.

The recommended dose is between 4 g every 6 hours and 8 g every 8 hours, intravenous. For intermittent hemodialysis, it could be administrated 2 to 4 g after each episode of dialysis. Of note, intravenous fosfomycin is not available in many countries.

It can induce hypokalemia, but this can be overcome through perfusions longer than two hours. It should be noted that it has a high sodium concentration (every gram of fosfomycin has 0.33mg of sodium).

Ceftazidime/Avibactam

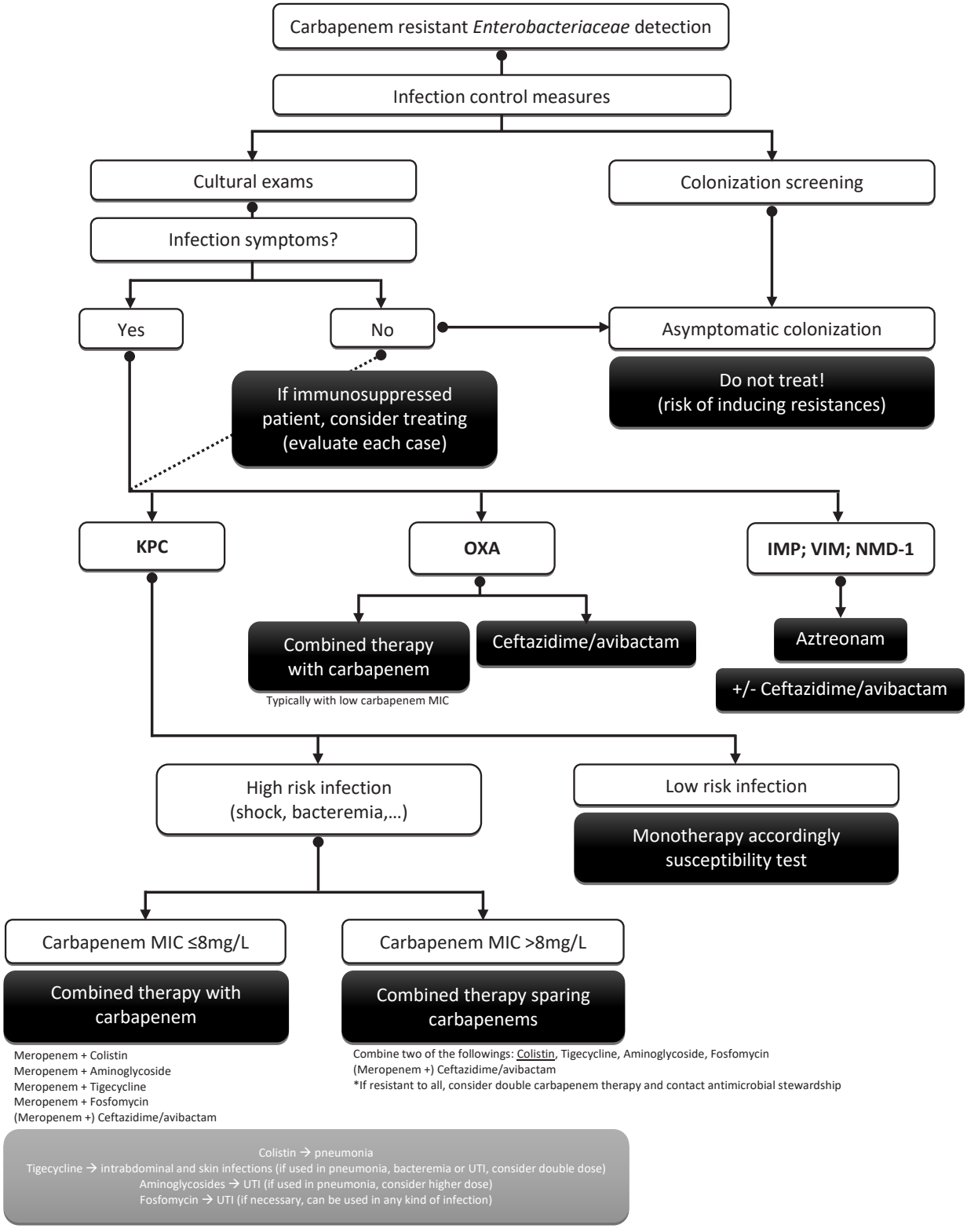
This also has a broad spectrum and a bactericidal activity. There are only a few studies into its use.

The use of ceftazidime-avibactam alone or in combination should be evaluated. On the one hand, KPC-3-producing *Klebsiella* (the most common in Portugal) are vulnerable to mutations in the enzyme causing resistance[38]; on the other hand, two studies observed restoration of meropenem susceptibility among ceftazidime/avibactam resistant *Klebsiella pneumoniae*[39]. Therefore, it must be considered whether ceftazidime/avibactam should be used with a carbapenem to treat infections with KPC, especially in the KPC-3 producers[38].

The recommended dose is 2.5 g every 8 hours.

Figure 2

What to do after carbapenem resistant *Enterobacteriaceae* detection



*Also carbapenemases.

Severe neurological reactions have been reported with ceftazidime, including asterixis, coma, encephalopathy, myoclonus, neuromuscular excitability, seizures, and nonconvulsive status epilepticus.

Meropenem/Vaborbactam

This new antibiotic is already available in many countries, and soon will be available in Portugal.

Vaborbactam is a new-lactamase inhibitor which has been shown to restore the activity of meropenem against KPC producers.

A small phase 3 trial showed higher rates of clinical cure with meropenem/vaborbactam comparing with the best available therapy, as well as lower rates of nephrotoxicity[40].

Aztreonam

This antibiotic is particularly important in MBLs treatment, because MBLs confer resistance to all beta-lactam-type antibiotics except aztreonam[41].

The problem is that MBL-producing isolates often produce other extended-spectrum beta-lactamases that confer resistance to aztreonam. Although MBLs are not inhibited by any of the available beta--lactamase inhibitors, combining ceftazidime/avibactam and aztreonam can have a complementary effect, as the avibactam can inactivate the other beta-lactamases to render the aztreonam active[42-44].

How to treat?

Low risk infections

These infections (for example, acute simple cystitis) can often be successfully treated with a single active agent, such as an aminoglycoside[45], meropenem, or colistin[4]. Aminoglycosides can be given as a consolidated, extended-interval dose for 7 to 14 days, depending on response to therapy. Carbapenems can be given if MIC is 4 mg/L or less.Monotherapy fosfomycin is still the subject of research and trials. Dosage is still unestablished, with probably 3 g in one single dose insufficient, adding resistance acquisition risk[38].

High risk infections

For the most serious infections, the choice of therapy depends on the type of carbapenemase present and the susceptibility profile of the isolate.

For infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing organisms,

because of the antibiotics' availability, costs and policies, the first--line therapy can be different in each hospital. In Portugal, we still don't have meropenem/vaborbactam available and the cost of ceftazidime/avibactam is too high to give it as a first-line therapy. Thereby, if the carbapenem MIC is 8 mg/L or less, the first choice should be the combined therapy between a carbapenem and another active antibiotic. If the carbapenem MIC is higher than 8 mg/L, the combined therapy should be chosen accordingly with the susceptibility test, giving priority to colistin as long as the isolate is susceptible[4]. As said before, when the choice is ceftazidime/avibactam, one should consider adding a second agent, typically a carbapenem[38].

The source of infection can influence the second agent choice: for example, for gastrointestinal tract and skin, tigecycline should be considered; aminoglycosides should be avoided in abscesses, and in pneumonia other options (if available) should be tried, but it can be a good choice in urinary tract.

When beta-lactam agents are used for carbapenemase-producing isolates, prolonged infusion dosing can be considered.

For infections caused by isolates producing metallo-beta-lactamases (MBL), the combination of ceftazidime/avibactam plus aztreonam may be a possible option.

INFECTION CONTROL

Hospitalized patients, infected or colonized with carbapenemase--producing bacteria, should be placed on contact precautions[25,46-49].

After discharge, contact precautions should be continued (i.e., during future hospitalizations), given the prolonged colonization with such organisms and the limited treatment options. The period that these measures should be maintained is uncertain, and depending on guidelines that the hospital follows, they are maintained for at least six months (some hospitals maintained them indefinitely), or until there are three negative rectal colonization screenings in a row.

Other standard measures, such as hand hygiene, minimizing the use of invasive devices, and antimicrobial stewardship, are important to infection control in general and likely to limit spread of resistant organisms.

Screening high-risk patients to detect rectal colonization has been suggested as an important infection control modality[46,48,50,51]. Although the impact of surveillance itself is difficult to assess, it may be useful in the setting of outbreaks due to carbapenem-resistant organisms.

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