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Selective Digestive Decontamination in Hemato-Oncological Patients Colonized with Carbapenem-Resistant Enterobacterales

Descontaminação Digestiva Seletiva em Doentes Hemato-Oncológicos Colonizados por Enterobacterales Resistentes aos Carbapenemos

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ABSTRACT

Infections caused by multidrug-resistant Gram-negative bacteria, including carbapenem-resistant Enterobacterales, are a global threat and their gradual increase is alarming. They represent a major challenge to public health because of limited therapeutic options and high case-fatality rates. Hemato-oncological patients represent a high-risk subpopulation for these types of infections, more specifically in previous carbapenem-resistant Enterobacterales colonized patients, because of severe immunosuppression not only due to the disease itself but also due to treatment like intensive chemotherapy or allogeneic hematopoietic stem cell transplant. Selective digestive decontamination is a prophylactic intervention with the purpose of reducing or eliminating gut colonization by pathogenic agents, preserving beneficial endogenous flora but its application remains controversial due to great heterogeneity amongst studies. However, in this review we intend to examine the role of selective digestive decontamination in context of high-risk patients such as hemato-oncological carbapenem-resistant Enterobacterales carriers who will receive highly immunosuppressive treatments, as it appears to be an appealing short-term strategy for the prevention of difficult-to-treat infections.
Keywords: Carbapenems; Decontamination; Drug Resistance, Bacterial; Enterobacteriaceae; Enterobacteriaceae Infections; Gastrointestinal Tract; Hematologic Neoplasms

RESUMO

As infeções causadas por bactérias Gram-negativo multirresistentes, entre os quais se incluem Enterobacterales resistentes aos carbapenemos, são uma preocupação global e o seu aparecimento crescente tem sido alarmante. Representam, assim, um grande desafio em termos de saúde pública devido à limitação de opções terapêuticas e elevadas taxas de mortalidade. Os doentes hemato-oncológicos representam uma subpopulação de elevado risco para este tipo de infeções, mais especificamente em doentes previamente colonizados por Enterobacterales resistentes aos carbapenemos, uma vez que apresentam frequentemente imunossupressão grave, não só pela doença em si como também devido aos tratamentos a que são submetidos, como quimioterapia intensiva ou alotransplante de células estaminais hematopoiéticas. A descontaminação digestiva seletiva surge como uma intervenção profilática destinada a reduzir ou eliminar a colonização por agentes patogénicos ao nível do aparelho gastrointestinal, preservando a flora endógena benéfica, embora a sua aplicabilidade se mantenha controversa principalmente pela elevada heterogeneidade entre estudos. Contudo, pretende-se com esta revisão avaliar o papel de descontaminação digestiva seletiva no contexto de doentes de elevado risco, como doentes hemato-oncológicos colonizados por Enterobacterales resistentes aos carbapenemos e que vão ser submetidos a tratamentos associados a imunossupressão grave, uma vez que desperta interesse como uma estratégia a curto prazo para prevenir infeções por esses mesmos agentes.
Palavras-chave: Carbapenemos; Descontaminação; Enterobacteriaceae; Infecções por Enterobacteriaceae; Neoplasias Hematológicas; Resistência Bacteriana a Medicamentos; Trato Gastrointestinal

INTRODUCTION

The global rise of multidrug-resistant bacteria, such as carbapenem-resistant Enterobacterales (CRE), has been alarming and according to the 2024 World Health Organization priority list of pathogenic bacteria, CRE remain in the critical priority category, highlighting the urgent need for research and development of prevention, control, and treatment options in this field.[1] Amongst CRE colonized patients, there are high-risk populations such as hematological patients who are highly vulnerable to subsequent CRE infections due to their underlying disease and immune-suppressing treatments such as chemotherapy (with cytotoxic effects that lead to gastrointestinal mucositis and/or chemotherapy-induced neutropenia), immunotherapy, and hematopoietic stem cell transplantation (HSCT). Bloodstream infections are amongst the most common infectious complications in these patients, accounting for 20% - 30% of febrile neutropenia episodes in adult cancer patients, with mortality rates between 34% and 50%, which can rise to 80% in cases associated with CRE infections.[2-5]

Selective digestive decontamination (SDD) is a prophylactic intervention with the purpose of reducing or eliminating the CRE carriage state which in turn reduces the likelihood of infection by these multidrug resistant strains. Although SDD remains controversial as a strategy for the prevention of CRE infections, in this narrative review we aim to describe the current evidence of SDD in CRE carriers with a focus on the hemato-oncological population.

METHODS

In terms of literature search strategy, the PubMed database was used to identify articles of interest. The search terms used were as follows: “decolonization”,

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"selective digestive decontamination", "carbapenem-resistant Enterobacterales", "CRE carriers", "hematology", "hemato-oncological patients" and "hematological patients". The search was restricted to full-text articles published in English without restriction of publication year. Literature search was carried out between October 2024 and January 2025. Articles that did not focus on CRE carriers or decolonization strategies with oral antibiotics were excluded. The main articles discussed in this study were organized and summarized in supplementary material [Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23139/15714)].

CARBAPENEM-RESISTANT ENTEROBACTERALES: A GLOBAL THREAT

Enterobacterales are an order of Gram-negative bacteria that include common microorganisms such as *Escherichia coli*, *Klebsiella* spp., *Serratia* spp., and *Enterobacter* spp. Although these bacteria are part of the normal intestinal microbiota of humans, under certain circumstances, can cause infections acquired both in the community and in healthcare settings.[6]

These microorganisms have the ability to easily acquire antimicrobial resistance genes and in the beginning posed as a public health threat due to the production of extended-spectrum β-lactamases, which conferred resistance to penicillins and cephalosporins.[6,7] Consequently, the medical community turned to carbapenems as the first-line empirical treatment in such situations, which subsequently led to the development of various resistance mechanisms against these antibiotics.[8]

Carbapenem-resistant Enterobacterales can be divided into two main groups according to their resistance mechanisms: carbapenemase-producing CRE, the most prevalent group, and non-carbapenemase-producing CRE, which include mechanisms such as efflux pumps and porin mutations.[8,9] A wide variety of carbapenemases have been identified (i.e., enzymes capable of hydrolyzing carbapenems) being *Klebsiella pneumoniae* carbapenemase the most prevalent and globally disseminated.[8,10]

In one study it was demonstrated that carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) represented the fastest-growing antibiotic resistance threat in Europe in terms of morbidity and mortality.[11] These bacteria cause severe infections such as bloodstream infections, pneumonia, urinary tract infections, and intra-abdominal infections. They pose a major public health challenge due to limited therapeutic options, requiring the use of reserve antibiotics (according to the WHO AWaRe classification[12]) and high mortality rates, resulting in a significant economic burden related to disinfection procedures and dissemination control.[8,13]

According to the European Centre for Disease Prevention and Control (ECDC) 2023 annual epidemiological report on antimicrobial resistance in the European Union, the incidence of bloodstream infections by CR-*Kp* was 57.5% higher than in 2019, far from the 5.0% reduction target set for 2030. In Portugal, the same report highlighted alarming CRE rates, with 13.1% of resistant isolates in 2023 (Fig. 1). Compared to 2019, there was a 43% increase in CR-*Kp* infection incidence and a staggering 700% increase in carbapenem-resistant *Escherichia coli*, the latter significantly contradicting the overall European trend.[14]

Additionally, according to the latest ECDC data, Portugal showed a 2.0% increase in total antibiotic consumption between 2019 and 2023, being the only country to demonstrate a statistically significant increase in hospital antibiotic consumption. Of these, 43.7% corresponded to broad-spectrum antibiotics, including carbapenems. Notably, the data from Portugal were exclusively derived from public hospitals in the mainland.[15]

To characterize the epidemiology of carbapenemase-producing CRE in Portugal, a retrospective study was conducted in 2012, based on data from the North Lisbon University Hospital Center. The study revealed carbapenemase-producing CRE dissemination across different wards,

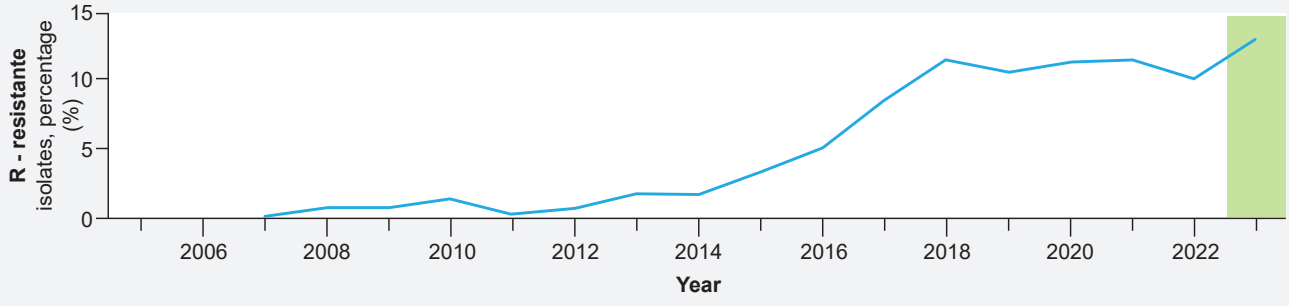

Figure 1 – Evolution of carbapenem resistance rates in *K. pneumoniae* in Portugal between 2007 and 2023 (public data from the ECDC Surveillance Atlas of Infectious Diseases)

with *Klebsiella pneumoniae* being the most frequently detected species (83%), and the Hematology department accounting for the highest number of cases (22%).[16]

HEMATO-ONCOLOGICAL PATIENTS: A HIGH-RISK POPULATION

Hemato-oncological patients are considered a high-risk population for multidrug-resistant Enterobacterales infections, as they frequently present multiple risk factors for colonization, including prior antibiotic use and frequent and prolonged hospitalizations.[17,18] A recent systematic review and meta-analysis found an intestinal CRE colonization prevalence rate of 21.7% in hematological patients, which is comparable to other high-risk populations. Prior exposure to antibiotics (carbapenems, tigecycline, or penicillins), acute myeloid leukemia, neutropenia, and chemotherapy were identified as risk factors for CRE colonization in this population.[19]

Previous intestinal multidrug-resistant Enterobacterales colonization in hematological patients was found to be a risk factor for subsequent infections[20,21] and more than 30% of multidrug-resistant Enterobacterales colonized transplant recipients developed infections caused by the same colonizing agent.[22] A prospective multicenter study in Italy identified the following independent risk factors for CR-*Kp* bloodstream infections in carriers: intensive care unit admission, invasive abdominal procedures, undergoing chemotherapy/radiotherapy, and the number of additional colonized sites, besides rectal colonization.[23] Moreover, immunosuppression status was independently associated with mortality among CRE carriers in a prospective study by Bar-Yoseph *et al*,[24] where the majority of the study population consisted of hemato-oncological patients.

In 2013, European recommendations were developed for targeted antibiotic therapy against CRE in febrile neutropenic patients.[25] An appropriate CR-*Kp* targeted antibiotic therapy was defined as a combination including at least two among colistin/polymyxin B, tigecycline and gentamicin, preferably with the addition of meropenem, and eventually also fosfomycin. However, an Italian bone marrow transplant group (GITMO) study found that half of the patients who received a first line CR-*Kp* targeted antibiotic therapy still died due to the infection.[3,26] Similarly, Patel *et al*,[27] demonstrated that CR-*Kp* infections treated with combinations of susceptible non-β-lactam antibiotics were not associated with improved clinical outcomes. This led to the controversial questioning of whether HSCT, especially allo-HSCT, should be considered in CR-*Kp* carriers with prior infection, given the high associated mortality risk (64.4% in allo-HSCT *vs* 16% in autologous HSCT).[26]

Recently, new antibiotics have been developed, including β-lactam/β-lactamase inhibitor combinations (e.g., ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, aztreonam/avibactam), which have shown to be associated with improved clinical outcomes and reduced toxicity compared to regimens previously used, which, as was mentioned, were often polymyxin and aminoglycoside-based.[28] Nevertheless, in a more recent review, infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) remain a prevalent problem in high-risk hematological patients, with high mortality rates, especially when the initial empirical antibiotic treatment is inappropriate.[29] In a retrospective study, timely rectal swab screening, especially before the onset of carbapenem-resistant organism bloodstream infections, and preemptively adjusting an antibiotic regimen based on the results, significantly reduced 30-day mortality in hematological patients.[2]

SELECTIVE DIGESTIVE DECONTAMINATION: A PREVENTION STRATEGY

Given the previously outlined scenario, both regarding the alarming global situation of CRE and the susceptibility of hematologic patients to these hard-to-treat infections, it makes sense to explore options that anticipate the occurrence of infection, particularly through the identification of asymptomatic carriers to implement prevention and control measures. The eradication of intestinal CRE in asymptomatic carriers not only serves as a solution for infection prevention but also has the potential to limit bacterial dissemination to other patients.[18,30]

This introduces the concept of decolonization, which can be defined as a preventive infection method aimed at reducing or eliminating the burden of one or more pathogens through the administration or application of antimicrobial or antiseptic agents.[31] Various decolonization strategies exist, including selective digestive decontamination.[32]

According to the literature, the concept of SDD emerged in a study by Sleijfer *et al*[33] precisely from the understanding that antibiotic prophylaxis in patients susceptible to infections by intestinal Gram-negative bacteria should be performed selectively, as opposed to 'total intestinal sterilization'. The goal is to reduce or eliminate potentially pathogenic agents without affecting the anaerobic flora, which includes various species that naturally prevent colonization and overgrowth of those same contaminating agents.[33] This natural barrier concept was named colonization resistance, proposed by van der Waaij *et al*.[34] Thus, in general terms, the premise of the SDD strategy is, as the name suggests, to selectively decolonize the gastrointestinal tract, focusing on aerobic Gram-negative bacteria.

However, even after almost 40 years of studies in the field, particularly in intensive care units, the use of SDD remains highly controversial. This is mainly due to the heterogeneity of applied regimens – in terms of types and doses of

agents used, universal versus targeted strategy and target population – leading to the absence of robust scientific evidence on SDD efficacy.[35,36]

Focusing on SDD as a strategy for preventing CRE infections, in 2019, a multidisciplinary group of experts selected by the European Committee on Infection Control (EUCIC) conducted a systematic review[35] of existing studies on decolonization interventions specifically in carriers of MDR-GNB across all settings, with the aim of providing clinical recommendations on decolonization regimens for these cases. Unfortunately, due to several limitations, such as study heterogeneity, which precluded performing a meta-analysis, the panel considered the evidence insufficient to provide recommendations for any regimen and even did not recommend routine decolonization of MDR-GNB carriers. However, based on the results of SDD effects specifically in CRE carriers, the panel highlighted the need for high-quality research on the use of regimens with oral colistin sulfate, with or without oral gentamicin sulfate, in both hematologic and solid organ transplant patients, as they are a subpopulation at high risk of developing infections. It is noteworthy that, of the eleven studies with focus on CRE, only one was a randomized clinical trial and only three studies were on the hematological population, of which all were case series.

In the study by Saidel-Odes *et al*,[36] the application of both an oral gel and an oral solution formulated with a combination of gentamicin (80 mg) and colistin (1 million IU), given four times daily for seven days, was investigated in 20 CR-*Kp* carriers. They observed a significant reduction in CR-*Kp* colonization after two weeks compared to the placebo control group (61.1% *vs* 16.1%, respectively; $p < 0.0016$), but no significant difference at six weeks (58.5% *vs* 33.3%, respectively; $p \geq 0.05$). In another study, Oren *et al*[37] investigated three different SDD regimens (gentamicin 80 mg, colistin 100 mg, or both with same doses already mentioned), with the duration dependent on achieving eradication (defined as three consecutive negative cultures and a negative PCR in the last sample). The SDD application limit was 60 days, after which patients were considered persistent carriers. They observed a significantly higher eradication rate in the SDD group compared to the spontaneous eradication control group (44% *vs* 7%, respectively; $p < 0.001$). Additionally, they found a significantly lower mortality rate in the eradicated group compared to the persistently colonized group (17% *vs* 49%, respectively; $p = 0.002$). Machuca *et al*[38] evaluated the effects of two SDD regimens (gentamicin 80 mg or streptomycin 80 mg + neomycin 40 mg) applied for 14 days in high-risk patients carrying colistin-resistant CR-*Kp*. The results were compared to a control group after 180 days, and they found that the oral gentamicin regimen was associated with a lower risk of all-cause mortality, lower risk of CR-*Kp* infections, and greater microbiological response (i.e., at least two negative rectal swabs > 48 h after completing the SDD regimen).

More recently, a randomized clinical trial[39] specifically in hemato-oncological patients emerged, which was not included in the EUCIC systematic review. The aim of the study was to evaluate the efficacy of an SDD regimen with 2 million IU of colistin in the intestinal eradication of MDR-GNB carriers. They observed a significant positive effect at the end of the 14-day SDD period (61.3% vs. 32.3%; OR 3.32; 95% CI 1.17–9.44; p=0.0241), but the difference was not maintained at 21 days. Additionally, a lower incidence of bacteremia was observed 30 days after SDD.

Interestingly, despite the significant variability between applied regimens, the authors of the various described studies reached similar conclusions. Although no long-term benefits of SDD were observed, the primary interest of decolonization, more than eradication to contain bacterial transmission, is the hypothesis that SDD may be sufficient to reduce the pathogenic intestinal burden in the short term, representing a viable solution for preventing infection and death in high-risk patients.[36,37,39]

Another perspective to consider is the presence of concomitant systemic antibiotic treatment (CSAT). Tascini *et al*,[40] in an uncontrolled study of a SDD regimen with 80 mg of oral gentamicin in 50 patients colonized with CR-*Kp*, observed a significant difference in the decontamination rate between the group receiving only oral gentamicin compared to the group receiving CSAT (96% *vs* 44%, respectively; $p < 0.001$). Supported by other studies,[26,41-43] which reported systemic antibiotic exposure as a risk factor for CR-*Kp* acquisition and persistent colonization, they hypothesize that CSAT seems to favor the persistence of colonization through selective pressure on the intestinal microbiome, contributing to lower eradication rates compared to SDD alone. However, they do not exclude the possibility that CSAT could be a marker of more fragile patients with more severe disease. Lambelet *et al*,[44] in a small observational study, obtained similar results and reinforced the potential negative role that CSAT may have on the effect of SDD.

On the contrary, in a retrospective cohort[45] of 14 ICU CP-*Kp* carriers treated for seven days, four times daily, with colistin sulphate (1 million IU) and gentamicin sulphate (80 mg), no significant difference in the decolonization rate was found in comparison to non-decolonized patients. Also, there was no significant effect of decolonization treatment on mortality during hospitalization or on length of hospital stay between the two groups. The authors considered that the unsuccessful SDD treatment could be explained by the relatively short course applied, in addition to the low dosage of colistin, as other SDD protocols used up to 3 million IU. Additionally, a more recent study in Spain,[46] in a population of CR-*Kp* carriers, applying a regimen four times daily of

colistin (100 mg), amikacin (80 mg), and nystatin (300 mg) for 10 days, compared to a non-intervention group, did not show significant differences in eradication rates after one month of follow-up, nor did they observe any effect on clinical infection rates. However, the authors considered that the clinical infection risk of the study population was not high, which may explain why it was not significantly influenced by the intervention. This supports the recommendation that decolonization strategies should only be considered in patients with a well-defined high infectious risk.

One of the main concerns regarding SDD is the subsequent development of resistance to the antimicrobials used, especially since colistin and gentamicin are currently last-resort antibiotics for treating CR-*Kp*. According to a recent review[30] on SDD, the authors considered that the results, particularly in intensive care units, provided some reassurance on this matter. However, they emphasized that many of the studies were conducted in low multidrug resistance pressure environments and have limited follow-up times. In fact, based on the studies analyzed in this article, there were divergent results on this issue. However, among the studies reporting the emergence of resistance,[37,38,45] it is noted that two of them applied SDD regimes in monotherapy rather than combination therapy. Lubbert *et al*[45] observed rapid emergence of resistance, even with a double combination SDD protocol but it is important to highlight, with respect to colistin, that 45% of the isolates in SDD treated patients were initially resistant. As Lubbert *et al*[45] had mentioned, the use of suboptimal doses regarding colistin, Oren *et al*[37] also mentioned this possibility, particularly concerning gentamicin. However, other studies using a monotherapy regimen with gentamicin at the same dosage (80 mg, 4 x/day), with follow-up ranging from three to nine months, did not observe the emergence of resistance to this agent.[44,47] Moreover, these studies were conducted in areas considered endemic for CR-*Kp*. Finally, considering the two randomized clinical trials mentioned earlier, they did not observe the occurrence of resistance to the agents used in the SDD regimens.[36,39]

CONCLUSION

In the 2019 systematic review,[35] a lack of robust scientific evidence was identified regarding the various decolonization strategies directed at MDR-GNB carriers, mainly due to the significant heterogeneity between studies. However, given the major threat these pathogens currently represent, it is imperative to continue research to identify the best possible strategy for infection control, prevention, and treatment.

Although there are no solid recommendations and the general stance is against the routine use of decolonization in carriers, the literature reviewed in this work suggests that SDD can be a very promising measure, particularly in preventing infections during critical high-risk periods, such as those that occur in CRE colonized hemato-oncological patients undergoing immunosuppressive treatments like intensive chemotherapy or allogeneic hematopoietic stem cell transplantation. Selective digestive decontamination could be considered more as a short-term strategy aimed at temporarily reducing colonization burden, rather than achieving long-term total eradication.

It is important to note that several other types of decolonization strategies not relying on antibiotics are being studied. Some involve natural components such as fecal microbiota transplantation (FMT), prebiotics and probiotics, while others explore alternative therapies like tea tree oil, photodynamic therapy, *omiganan pentahydrochloride*, and the use of bacteriophages. Focusing on combined treatments, such as SDD followed by FMT or probiotics, should also be taken into account as an effort to develop well-defined and effective strategies against the multidrug resistance phenomenon.

AUTHOR CONTRIBUTIONS

SAL: Study conception and design, data collection and analysis, writing and critical review of the manuscript.

CMS: Study design, data analysis, critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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