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Review

Possibilities of Decolonization Targeting Carriers of Multidrug-Resistant Gram-Negative Bacteria (MDR-GNB) in the Gut

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Abstract

Intestinal carriage of extended spectrum β-lactamase *Enterobacteriaceae* (*ESBL-E*) and carbapenemase-producing *Enterobacteriaceae* (*CPE*) can persist for a long time (Huttner *et al*., 2019). Multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and their intestinal carriage is also a big problem, because studies in the last years have shown that the colonization with multidrug-resistant Gram-negative bacteria (MDR-GNB), especially in immunocompromised patients, increases the risk of infections (Tacconelli *et al.*, 2019). Therefore, the evaluation of decolonization regimens with oral antibiotics and faecal microbiota transplantation (FMT) used for eradication of MDR-GNB in the gut is of great importance in reducing morbidity and mortality in these patients.

Keywords: multidrug-resistant Gram-negative bacteria (MDR-GNB), faecal microbiota transplantation, immunocompromised patients

Резюме

Чревното носителство с продуциращи широко-спектърни бета-лактамази микроорганизми от сем. *Enterobacteriaceae* (*ESBL-E*), както и продуциращите карбапенемаза *Enterobacteriaceae* (*CPE*), може да персистира продължително време (Huttner *et al.*, 2019). Множествено-резистентните *Acinetobacter baumannii* и *Pseudomonas aeruginosa,* заедно с тяхното чревно носителство е също значителен проблем, тъй-като прочувания от последните години показват, че колонизацията с множествено-резистентни Грам-отрицателни бактерии (MDR-GNB), специално в имунокомпрометирани пациенти, води до риск от развитие на инфекции (Tacconelli *et al*., 2019). Ето защо, оценката на режимите за деколонизация след използването на орални антибиотици, както и трансплантация на фекална микробиота (FMT), използвани за ерадикация на MDR-GNB в червата, е от голяма значимост за редуциране заболеваемостта и смъртността при тези пациенти.

Introduction

The presence of MDR-GNB in the intestinal tract and the transition from colonization to infection is probably not so important for non-immunocompromised patients like those with urinary tract infections, but it is of greater importance in significantly immunocompromised patients, such as organ transplant and stem cell recipients (Kuijpe *et al.,* 2019). Prospective studies in haematological patients have identified previous colonization with extended-spectrum beta-lactamase-production *Enterobacteriaceae* (*ESBL-E*) as the most important factor for *ESBL-E* bloodstream infections and previous colonization with MDR-GNB also increases infection risk in intensive care unit (ICU) patients and those undergoing major abdominal surgery (Tacconelli *et al*., 2019). These patients are considered to be an important target for eradication strategies. For this purpose, different decolonization strategies based on oral antibiotics and faecal microbiota transplantation are used.

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The objective of this study is to provide data on the possibility of decolonization of MDR-GNB carriers on the basis of literature information.

Decolonization regimen with oral antibiotics

Gut colonization with MDR-GNB - *Enterobacteriaceae* and non-fermenters (*Pseudomonas aeruginosa and Acinetobacter spp.*) in hospitalized, immunocompromised patients is of great concern due to the persistence of intestinal carriage for months to years, exposing the carriers at risk of recurrent infections, and representing a reservoir for transmission (Feldman *et al*., 2013). Previous studies showed that colonization with MDR-GNB increases the risk of infections (Vehreschild *et al*., 2014; Tischendorf *et al*., 2016). One of the actions proposed by WHO experts with regard to MDR bacteria is the priority implementation of infection-control measures to reduce the spread of infections caused by these microorganisms in community and healthcare settings. Several decolonization strategies for *ESBL*-E and *CPE* carriers have been examined but studies were of low methodological quality or only showed moderate efficacy (Rieg *et al*., 2015). The most extensive experience in MDR-GNB decolonization has been achieved by selective digestive decontamination (SDD) in ICU patients, but studies have shown conflicting results (Debby *et al*., 2012). Major limitations of these studies are heterogeneity in the patient case mix, ward colonization pressure, and agents combined in the decolonization protocols (Tacconelli *et al*., 2019). In this sense, some researchers hypothesized that a decolonization regimen with oral antibiotics followed by a recolonization approach that restores intestinal microbiota for competition with MDR bacteria could be promising, hence faecal microbiota transplantation has been suggested for this purpose. (Manges *et al*., 2016; Huttner *et al*., 2019). In an extensive international study conducted in four academic centers in Switzerland, France, the Netherlands and Israel between February 2016 and November 2017 thirty-nine patients colonized with *ESBL-E,* who probably had at least one episode of symptomatic infection with *ESBL-E* requiring systemic antibiotic therapy within ≤180 days before inclusion, were investigated. Patients randomized to the intervention group were assigned to oral treatment with colistin sulphate (2 million international units 4×/day, and neomycin sulphate tablets (350 mg of neomycin base 4×/day), for 5 days followed by FMT. The results received in this international multi-centre randomized controlled trial, using oral non-absorbable antibiotics followed by FMT showed a lower proportion of intestinal colonization with ESBL-E/CPE during follow-up compared with the control (Huttner *et al.*, 2019). Decolonization regimens in other six uncontrolled studies differed widely: the most common agent was oral colistin alone (Rieg *et al.,* 2015) or combined with either oral aminoglycosides (neomycin, amikacin, or tobramycin) (Oostdijk *et al*., 2012), erythromycin (Troche *et al*., 2005), rifaximin (Rieg *et al.,* 2015), or norfloxacin (Paterson *et al*., 2001). Treatment duration ranged from 5 to 28 days. The studies reported decolonization rates at the end of the treatment, ranging from no effect to 100% (Paterson *et al.,* 2001, Troché *et al*., 2005; Abecasis *et al*., 2011; Oostdijk *et al*., 2012; Gutierrez-Urbon *et al*., 2015; Rieg *et al*., 2015). In this regard, guidelines have recently been developed on the prevention of CRE spread in hospitalized patients, evaluating studies up to 2014. They were developed by a multidisciplinary group of experts selected by the European Committee of Infection Control (EUCIC) according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations for developing guidelines. The aim of the guidelines was to present data and recommendations on decolonizing regimens targeting multidrug-resistant Gram-negative bacteria carriers in all settings. Four types of outcomes were evaluated for each target MDR-GNB: (a) microbiological outcomes (carriage and eradication rates) at treatment end and at specific post-treatment time-points; (b) clinical outcomes (attributable and all-cause mortality and infection incidence) at the same time-points and length of hospital stay; (c) epidemiological outcomes (acquisition incidence, transmission and outbreaks); and (d) adverse events of decolonization (including resistance development) (Tacconelli *et al*., 2019). The data obtained showed that evidence is currently insufficient to provide recommendations for or against any intervention in patients colonized with MDR Gram-negative bacteria. On the basis of limited evidence of increased risk of CRE infections in immunocompromised carriers, the group suggests designing high-quality prospective clinical studies to assess the risk of CRE infections in immunocompromised patients. These trials should include monitoring of development of resistance to decolonizing agents during treatment using stool cultures and antimicrobial susceptibility results according to the EUCAST clinical breakpoints (Tacconelli *et al*., 2019). The results from the systematic review of literature done by the group of experts show that the data presented are insufficient to provide solid

recommendations on decolonization. It is important to note the high heterogeneity found among the studies, which did not allow any meta-analytic approach but only a qualitative review. Some important gaps in the evaluated evidence were also additionally found, including inconsistent reporting, small sample size, wide heterogeneity between settings (outbreak, endemic), decolonization regimens and treatment duration. In summary, based on limited evidence of decolonization possibilities, the group of experts does not recommend routine decolonization of carriers of MDR bacteria (Tacconelli *et al.*, 2019).

Faecal microbiota transplantation approach

Because of the largely disappointing results of 'conventional' decolonization regimens for MDR-GNB, the development of novel decolonization strategies through well-designed *in vitro* and *in vivo* studies is urgently needed. These strategies may include natural compounds (FMT, prebiotics, probiotics), alternative therapies (tea tree oil, photodynamic therapies, omiganan pentahydrochloride), and bacteriophage therapy (Tacconelli *et al*., 2017). Faecal microbiota transplantation is the administration of thoroughly screened, healthy-donor stool into a patient's gut, either into the colon (via enema or colonoscope) or into the upper small intestine (via nasojejunal tube or swallowed capsules) (Manges *et al*., 2016). Faecal microbiota transplantation (FMT), also known as gut flora transplant (GFT), is the process of implanting intestinal microbiota from a healthy donor into the gastrointestinal tract of the recipient. This process restores the recipient's intestinal flora and increases bacterial diversity, helping to achieve an optimal function of the intestinal system (IPPM, 2019). Unlike some other FMT providers, it is necessary to use whole, unprocessed stool taken from healthy donors. Instead, donated stool is filtered under special anaerobic conditions to remove all waste material such as digested food residues, mucus, dead cells, hormones etc., which significantly reduces the potential health risks and side effects of FMT (IPPM, 2019). In that sense, uncontrolled studies have been conducted on FMT for decolonization efficacy of intestinal MDR organisms (Dinh *et al*., 2018; Huttner *et al*., 2019). A study from France examined FMT for decolonization in eight carriers of carbapenem-resistant *Enterobacteriaceae* and nine carriers of vancomycin-resistant enterococci. One week after FMT, three out of eight with carbapenem-resistant *Enterobacteriaceae* and three out of nine with vancomycin-resistant *Enterobacteriaceae* had negative rectal swabs (Dinh *et al*., 2018). Additionally, the publication of the trial by van Nood and colleagues in 2013 reporting the outstanding efficacy of FMT for the treatment of recurrent *Clostridium difficile* infection has resulted in numerous reports examining FMT for various diseases (van Nood *et al*., 2013; Kakihana *et al*., 2016; Kang *et al*., 2017). Another uncontrolled study from Poland reported successful eradication of intestinal carriage in 15 out of 20 (75%) patients with haematological disease colonized by *CPE*, *ESBL-E* or other MDR organisms 1 month after FMT (Bilinski *et al*., 2017).

Conclusions

Infections caused by MDR- gram-negative bacteria are associated with significant morbidity, costs and mortality. Previous colonization with MDR-GNB also increases infection risk in transplant and intensive care unit (ICU) patients and those undergoing major abdominal surgery (Tacconelli *et al*., 2017). Controlling the spread of such problematic microorganisms is complicated by the persistence of intestinal carriage for months to years putting the carriers at risk of recurrent infections and representing a reservoir for transmission (Feldman *et al*., 2013). Decolonizing regimens used include topical agents, systemic therapy, antibiotic inhaled therapy, natural compounds, bacteriophage therapy, alternative treatments, and novel regimens undergoing trials. Major limitations in the studies in this area are heterogeneity in the patient case mix, ward colonization pressure, and agents combined in the decolonization protocols (Tacconelli *et al*., 2017). On the basis of the limited evidence of increased risk of developing MDR Gram-negative infections in the colonized ICU population and the results of the effectiveness of decolonization of carriers, the group of experts accepts and does not recommend routine decolonization of this type of carriers through the use of oral antibiotics (Tacconelli *et al*., 2017).

Clinical research on faecal transplantation has dramatically increased in the last few years and is still ongoing. The results of existing clinical studies show that FMT treatment can be beneficial for a wide range of acute and chronic diseases and new findings are continually published (IPPM, 2019). However, in the context of FMT for MDR organism decolonization, it should be kept in mind that antimicrobial resistance genes can also be acquired through FMT (Leung *et al*., 2018). Furthermore, the exact role of the donor microbiota composition on the impact of FMT on MDR organism carriage

needs further investigation (Huttner *et al*., 2019). The same opinion is shared by the multidisciplinary group of experts, who accept that the evidence is insufficient to provide a recommendation for or against FMT. Further studies are warranted to evaluate the effectiveness, applicability, and safety of FMT, and to confirm its role in intestinal decolonization of MDR-GNB (Tacconelli *et al*., 2019).

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