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Commentary

Fighting fire with fire: oral antibiotics for the suppression of colonization with multidrug-resistant Enterobacterales

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As the world experiences wave after wave of COVID-19, it is difficult to remember that there are other pandemics besides those caused by respiratory viruses. Antibiotic resistance is one such "silent" pandemic whose consequences, though much more subtle and difficult to estimate, are just as dangerous to neglect.

Immunocompromised patients such as solid-organ transplant (SOT) recipients are a steadily increasing population worldwide. They are at particular risk of infections caused by multidrug-resistant organisms (MDROs) because of iatrogenic immunosuppression, altered anatomy, frequent use of invasive devices, high antibiotic exposure and frequent contact with the healthcare system [1,2]. Asymptomatic colonization with MDROs, e.g., of the intestinal tract in the case of multidrug-resistant Enterobacterales, usually precedes infection and tends to persist for prolonged periods [3,4]. This raises the question whether treatments can be administered that eradicate or at least suppress carriage of MDROs during periods when patients are especially vulnerable, such as the immediate post-transplantation period.

So far, the results of trials using oral non-absorbable antibiotics, or other microbiota-altering strategies such as probiotics or faecal-microbiota transplantation, for Gram-negative MDROs colonizing the gut, have been mostly disappointing, with short-term suppression of detectable carriage but rapid rebound after treatment cessation [5–7]. The 2019 ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers therefore do not recommend routine decolonization, but suggest that high-quality prospective clinical studies in immunocompromised patients should be undertaken, with the idea that even temporary suppression may be beneficial in this patient population [8].

Such a study has now been conducted in SOT recipients in five centres in Spain [9]. One hundred and three adult SOT recipients (almost exclusively liver and kidney transplants) with intestinal colonization by multidrug-resistant Enterobacterales (MDRE), detected either pre-transplant or within 2 weeks after transplantation, were randomized 1:1 to either oral colistin and neomycin for 14 days or no specific intervention; no placebo was used in the control arm. Most MDROs were extended-spectrum β-lactamase (ESBL) producers with about 20% of patients being colonized with carbapenemase-producing Enterobacterales. The primary outcome was any infection by MDRE within 30 days after randomization. No statistically significant difference in the primary outcome was detected, neither in the intention-to-treat population (five infections in 53 patients (9.4%) in the treated group versus 7/52 (13.5%) in the control group), nor in the *per protocol* population. Diarrhoea, a well-known side effect of orally administered colistin and neomycin, was more frequent in the intervention group, with about 10% (5/53) having treatment discontinued prematurely because of it. Furthermore, colistin-resistant strains were observed more frequently in the intervention group (3/49 tested patients versus 1/50 tested patients in the control group) but resistance was not due to the mcr-1 gene.

Some issues are worth considering. Firstly, this was a challenging study requiring prolonged recruitment over 4 years despite a high proportion of included-to-screened patients, and the authors should be congratulated for this effort. Nevertheless, the study has some major limitations, the most important being its lack of power to detect small but potentially clinically meaningful differences in the primary outcome. The sample size calculation was based on an assumed incidence of 30% of infections within 30 days after randomization in the control group; the observed incidence, however, was 13.5%. In addition to complicating the interpretation of the primary outcome, any meaningful subgroup analyses are also

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rendered futile (and it would probably have been preferable to more clearly state their highly exploratory nature). For comparison, similar studies examining decontamination strategies in ventilated patients have included thousands of patients [10].

There are also methodological caveats, such as the unblinded design, the suboptimal randomization sequence (fixed blocks), the lack of information regarding concomitant antibiotic treatment and the handling of missing data. Despite all these caveats, the results seem to have good face value. Indeed, the decolonization regimen used was identical to the one we used in a randomized controlled trial for decolonization of ESBL carriers [7]. In that study we could show that rebound of detectable intestinal ESBL colonization occurs very rapidly after end of treatment, potentially indicating the need for a longer treatment duration than the 14 days used, albeit with the risk of more side effects and unknown consequences with regard to the selection of resistant microorganisms.

The issue of emergence of resistance to the decolonization regimen during or after treatment is important, especially since intravenous colistin remains among the last-resort antibiotics for the treatment of carbapenem-resistant Gram negatives. Furthermore, even if a decolonization regime is effective at preventing MDRE infections, emergence of resistance may make it less effective over time. Both polymyxins and aminoglycosides are and have been widely used in selective oral (SOD) and digestive (SDD) decontamination in intensive-care patients. At least in settings with a low prevalence of antimicrobial resistance, SOD/SDD do not seem to be associated with an increase in resistance to polymyxins or aminoglycosides in Gram negative organisms [11]. Nevertheless, this issue needs to be carefully monitored, especially in regions where carbapenem resistance is more prevalent.

What approach should physicians follow for patients colonized with MDR Enterobacterales undergoing SOT or other types of severe immunosuppression? First of all, COVID-19 has demonstrated once again that prevention is much more preferable to and less costly than treatment. While not all acquisition of MDR Enterobacterales can be avoided (especially that acquired in the community), carbapenemase-producing Enterobacterales are still mostly nosocomial pathogens in most high-income countries, and adequate infection-control procedures can limit their spread [12]. The main focus of transplant programs should therefore be to avoid MDRO acquisition in the first place by applying adequate infection control and antibiotic-stewardship measures. The relationship between the prevalence of MDRE and the potential benefit/cost-effectiveness of decolonization regimes is complex: while a higher prevalence of MDRE may also lead to benefits with regard to reducing transmission (although this is unproven) this is potentially offset by a higher risk of emergence/selection of strains resistant to the agents used for decolonization.

Further adequately powered studies assessing the feasibility of eradication or suppression strategies for MDRE using not only antibiotics but also alternative approaches such as phages, faecal-microbiota transplantation or antimicrobial peptides are certainly warranted. Using decolonization regimes in a “just-in-case-it-works” manner, as seems to be done for fecal microbiota transplantation (FMT) in some centres despite lack of good evidence, should be avoided and randomized trials should get the priority they merit.

For now, the available literature and the results of this new study support the idea that treating fire (antibiotic resistance partly driven by antibiotic use) with fire (more antibiotics) is rarely the wisest option, and should probably be considered outside clinical studies only in exceptional cases and prevention of MDRE acquisition should be the focus.

Transparency declaration

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References

[1] Bhatt PJ, Ali M, Rana M, Patel G, Sullivan T, Murphy J, et al. Infections due to multidrug-resistant organisms following heart transplantation: epidemiology, microbiology, and outcomes. Transpl Infect Dis 2020;22:e13215.
[2] Cervera C, van Delden C, Gavalda J, Welte T, Akova M, Carratala J, et al. Multidrug-resistant bacteria in solid organ transplant recipients. Clin Microbiol Infect 2014;20(Suppl 7):49–73.
[3] Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. J Antimicrob Chemother 2016;71:2729–39.
[4] Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: a systematic review. Am J Infect Contr 2016;44:539–43.
[5] Catho G, Huttner BD. Strategies for the eradication of extended-spectrum beta-lactamase or carbapenemase-producing Enterobacteriaceae intestinal carriage. Expert Rev Anti Infect Ther 2019;17:557–69.
[6] Huttner BD, de Lastours V, Wassenberg M, Maharshak N, Mauris A, Galperine T, et al. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. Clin Microbiol Infect 2019;25:830–8.
[7] Huttner B, Haustein T, Uckay I, Renzi G, Stewardson A, Schaerrer D, et al. Decolonization of intestinal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae with oral colistin and neomycin: a randomized, double-blind, placebo-controlled trial. J Antimicrob Chemother 2013;68:2375–82.
[8] Tacconelli E, Mazzaferri F, de Smet AM, Bragantini D, Eggimann P, Huttner BD, et al. ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. Clin Microbiol Infect 2019;25:807–17.
[9] Farinas MC, Gonzalez-Rico C, Fernandez-Martinez M, Fortun J, Escudero R, Moreno A, et al. Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant *Enterobacterales*: a multicentre, randomized, controlled, open-label, parallel-group clinical trial. Clin Microbiol Infect 2021;27:856–63.
[10] Wittekamp BH, Plantinga NL, Cooper BS, Lopez-Contreras J, Coll P, Mancebo J, et al. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a randomized clinical trial. JAMA 2018;320:2087–98.
[11] Wittekamp BH, Oostdijk EA, de Smet AM, Bonten MJ. Colistin and tobramycin resistance during long- term use of selective decontamination strategies in the intensive care unit: a post hoc analysis. Crit Care 2015;19:113.
[12] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20(Suppl 1):1–55.