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Guidelines

ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers

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A B S T R A C T

Scope: The aim of these guidelines is to provide recommendations for decolonizing regimens targeting multidrug-resistant Gram-negative bacteria (MDR-GNB) carriers in all settings.
Methods: These evidence-based guidelines were produced after a systematic review of published studies on decolonization interventions targeting the following MDR-GNB: third-generation cephalosporin-resistant *Enterobacteriaceae* (3GCephRE), carbapenem-resistant *Enterobacteriaceae* (CRE), aminoglycoside-resistant *Enterobacteriaceae* (AGRE), fluoroquinolone-resistant *Enterobacteriaceae* (FQRE), extremely drug-resistant *Pseudomonas aeruginosa* (XDRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB), cotrimoxazole-resistant *Stenotrophomonas maltophilia* (CRSM), colistin-resistant Gram-negative organisms (CoRGNB), and pan-drug-resistant Gram-negative organisms (PDRGNB). The recommendations are grouped by MDR-GNB species. Faecal microbiota transplantation has been discussed separately. 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). The level of evidence for and strength of each recommendation were defined according to the GRADE approach. Consensus of a multidisciplinary expert panel was reached through a nominal-group technique for the final list of recommendations.

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Recommendations: The panel does not recommend routine decolonization of 3GCephRE and CRE carriers. Evidence is currently insufficient to provide recommendations for or against any intervention in patients colonized with AGRE, CoRGNB, CRAB, CRSM, FQRE, PDRGNB and XDRPA. On the basis of the limited evidence of increased risk of CRE infections in immunocompromised carriers, the panel 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. **E. Tacconelli, Clin Microbiol Infect 2019;25:807**

Introduction

Multidrug-resistant Gram-negative bacteria (MDR-GNB), including third-generation cephalosporin-resistant *Enterobacteriaceae* (3GCephRE), carbapenem-resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, are a critical priority for new antibiotic research and development according to the World Health Organization (WHO) [1]. One of the criteria weighed by WHO experts for prioritization of antibiotic-resistant bacteria was the availability of infection-control measures to reduce the spread of infection in community and healthcare settings. The most important criteria for prioritizing MDR-GNB were not only an empty pipeline and high attributable mortality in severe infections but also the dearth of effective infection control measures against these pathogens [2–5].

Decolonization has been an effective tool for reduction of morbidity and mortality from infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) [6]. The assumption underlying decolonization in individuals colonized by MRSA is that colonization increases the subsequent infection risk. A systematic review of the link between colonization and subsequent MRSA infection that included ten observational studies and 1170 patients showed a four-fold increase in infection risk associated with colonization [6]. Previous studies showed that colonization with MDR-GNB increases the risk of infections [7–16]. A prospective observational study in 497 haematological patients identified previous colonization with extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) as the most important risk factor for ESBL-E bloodstream infections [7]. Previous colonization with MDR-GNB also increases infection risk in transplant and intensive care unit (ICU) patients and those undergoing major abdominal surgery [8–16]. Several factors have been associated with carriage phenotype: species and susceptibility pattern [17], host features, antibiotic exposure duration and type, and the extent of contact with healthcare environments [18–22].

The most extensive experience in MDR-GNB decolonization is with selective digestive decontamination (SDD) in ICU patients, but studies have shown conflicting results [12,13,23–26]. In randomized controlled trials (RCTs) performed in ICUs with low MDR-GNB endemicity, SDD significantly reduced infections and mortality with limited impact on new resistance selection [26–31]. Recently a study performed in a high-endemicity ICU in Spain over 4 years showed that SDD reduced MDR-GNB infections with a non-significant increase in resistance to decolonizing agents [32]. Major limitations of these studies are heterogeneity in patient case mix, ward colonization pressure, and agents combined in the decolonization protocols.

The most recently developed guidelines on prevention of CRE spread in hospitalized patients, evaluating studies up to 2014, do not advise for or against decolonization because of a very low level of evidence [2–4]. The objective of these guidelines is to provide evidence-based recommendations for decolonization of MDR-GNB carriers, irrespective of age, co-morbidities and setting. Specifically, we address the following questions:

(a) What decolonization regimens have been evaluated for patients colonized with the target MDR-GNB?
(b) Do we recommend decolonization for patients colonized with the target MDR-GNB?
(c) What is the regimen of choice for patients colonized with the target MDR-GNB?

Expected users in hospital and community healthcare settings include infection control specialists, healthcare providers (clinical medical, nursing and paramedical staff) and policy-makers.

Methods

These guidelines 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 guidance documents. This expert panel reviewed the articles and discussed evidence-based tables, evidence certainty classification, and recommendation strength in two meetings at ECCMID 2017 and 2018, and by teleconference. Consensus of panel members for the final list of recommendations was reached through a nominal-group technique.

Literature search and data extraction

We began the guidelines development process with a systematic review of the published literature. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (https://doi.org/10.15124/CRD42017082729) and is available in full on the PROSPERO website (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=82729). The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33]. We included all studies evaluating any decolonization regimen targeting patients colonized with MDR-GNB. Articles were identified through computerized literature searches using PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and Web of Science. The search was restricted to full-text articles published in English without restriction of publication year. A combination of Medical Subject Headings and equivalent terms was used in the search strategy (see Supplementary material, Appendix S1). Literature searches for each target organism were performed between 9 and 16 August 2017.

Two independent reviewers performed a two-stage selection process. First, abstracts were screened against eligibility criteria and duplicate and irrelevant documents were excluded. We excluded studies involving universal decolonization (decolonization of all patients without previous screening), preoperative surgical prophylaxis, environmental decolonization, and *in vitro* and animal studies. Next, full-text articles were assessed, study data (design, population, target bacteria, intervention, comparison, treatment duration and outcomes) were extracted from eligible articles, and references were screened on title and abstract for further inclusion. At both stages each article was reviewed by two reviewers, and any discrepancies were resolved through discussion with a third reviewer (see flow charts in Supplementary material, Appendix S2).

A population/participant, intervention, comparator/control, outcome, known as PICO, framework was developed. Population: any patient of any age in any community or healthcare setting with any screening sample yielding one of the following MDR-GNB were included: 3GCephRE, CRE, aminoglycoside-resistant *Enterobacteriaceae* (AGRE), fluoroquinolone-resistant *Enterobacteriaceae* (FQRE), extremely drug-resistant *Pseudomonas aeruginosa* (susceptibility maintained to up to two antibiotic classes: aminoglycosides, antipseudomonal carbapenem, antipseudomonal cephalosporin, antipseudomonal fluoroquinolone, antipseudomonal penicillin + β-lactamase inhibitor, monobactam, phosphonic acid, polymyxin [34]), carbapenem-resistant *Acinetobacter baumannii* (CRAB), co-trimoxazole-resistant *Stenotrophomonas maltophilia*, colistin-resistant Gram-negative organisms, pan-drug-resistant (non-susceptible to all tested agents) Gram-negative organisms [34]. Intervention: decolonization therapy, defined as any measure that leads to loss of detectable MDR-GNB carriage at any site. Decolonizing regimens included topical agents, systemic therapy, antibiotic inhaled therapy, natural compounds, bacteriophage therapy, alternative treatments, and novel regimens undergoing trials. Controls: patients receiving no intervention (spontaneous decolonization) or a second decolonization measure were included. Outcomes: four outcome types—microbiological, clinical, epidemiological and adverse events—were evaluated for each target organism. The microbiological outcomes of carriage rate or eradication rate were assessed at different time-points (at treatment end and at 7 days, 1 month, 6 months and 1 year after treatment). Clinical outcomes included attributable and all-cause mortality and infection incidence at the same time-points, and length of hospital stay. Epidemiological outcomes included acquisition incidence, transmission, and outbreaks in hospitals, healthcare settings or the community. Assessment of decolonization adverse events included the investigation of resistance development. Because of the expected paucity of RCTs and non-randomized controlled trials, uncontrolled studies were also reviewed.

Quality assessment

The quality assessment was performed using the Effective Practice and Organization of Care guidelines for RCTs [35] and the Newcastle–Ottawa Scale for non-randomized controlled trials [36]. Each article was assessed by two reviewers, and discrepancies were resolved by a third reviewer. Evidence certainty of controlled studies was classified as high, moderate, low or very low, and recommendation strength was classified as strong or conditional according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [37]. The panel also assessed recommendations for research and possible conditional use in restricted trials and good practice points. The Supplementary material (Appendix S3) gives a detailed description of the GRADE approach, grades of evidence and determinants of quality.

Results and recommendations

The guidelines are organized by target organism. Each section reports the main characteristics of controlled studies, a summary of the evidence, and a recommendation graded according to the available evidence. Flow charts of assessed studies are included in the Supplementary material (Appendix S2). No articles were found for extremely drug-resistant *Pseudomonas aeruginosa*, co-trimoxazole-resistant *Stenotrophomonas maltophilia*, colistin-resistant Gram-negative organisms or pan-drug-resistant Gram-negative organisms. Twelve studies were included for 3GCephRE, 18 for CRE, six for CRAB, one for FQRE and one for AGRE. Of these studies, two 3GCephRE studies and seven CRE studies focused on faecal microbiota transplantation (FMT) are discussed separately at the end of this section. Tables 1–3 provide details of study designs and results.

Third-generation cephalosporin-resistant Enterobacteriaceae

Study characteristics

The ten studies were performed in Europe (nine studies) and the USA (one study): two RCTs [38,39], two prospective cohort studies [40,41], one uncontrolled nested *post hoc* analysis of a cluster-randomized study with additional hospital data [42], and five case series without comparators [43–47]. Only one study had a multicentre design [42]. Two studies evaluated hospital patients [38,39]; five evaluated ICU patients [41–43,45,47]; one evaluated liver transplanted patients [46]; two studied outpatients [39,44], and two studies were conducted in paediatric wards [43,45]. Four studies were performed during a 3GCephRE outbreak [41,43,46,47], three studies were performed in healthcare centres reporting endemic 3GCephRE [40,44,45], and three studies did not specify local epidemiology [38–40]. All studies performed rectal screening [38–47], four included urine cultures [38,39,41,45], and two included respiratory tract cultures [43,45].

Huttner *et al.* conducted an RCT to assess the efficacy of oral non-absorbable antibiotics on rectal ESBL-E carriage in hospital patients [38]. Fifty-eight patients were allocated to either placebo or oral colistin sulphate (50 mg (salt) four times daily) and neomycin sulphate (250 mg (salt) four times daily) for 10 days (plus nitrofurantoin for 5 days in the event of urine detection) [38]. Jonsson *et al.* assessed the role of anti-ESBL immunoglobulin Y chicken antibodies in ESBL-E faecal carriage eradication, randomizing 24 outpatients to either active treatment or placebo [39]. The RCT was discontinued before completion because of high drop-out. In an 8-year prospective cohort study, Buehlmann *et al.* enrolled 35 asymptomatic ESBL-E carriers and treated with chlorhexidine mouth rinse for 4 days for throat colonization, oral paromomycin for 4 days for rectal colonization, or oral nitrofurantoin or fosfomycin (single dose) or ciprofloxacin or cotrimoxazole for 5 days for urinary colonization [40]. The course was repeated in patients with persistent ESBL-E carriage. Decré *et al.* performed a prospective cohort trial of 404 patients colonized or infected with ESBL-producing *Klebsiella pneumoniae* and compared universal with target SDD using oral erythromycin (1 g twice daily) and colistin sulphate (6 million units twice daily) [41]. Decolonization regimens in the six uncontrolled studies differed widely: the most common agent was oral colistin alone [44] or combined with either oral aminoglycosides (neomycin, amikacin, or tobramycin) [42,43,45,47], erythromycin [47], rifaximin [44], or norfloxacin [46]. Treatment duration, when reported, ranged from 5 to 28 days. Oostdijk *et al.* conducted a nested *post hoc* analysis without comparator of a cluster-randomized multicentre trial in 13 Dutch ICUs. Fifty patients received oropharyngeal application of a paste containing colistin, tobramycin and amphotericin B, each at a concentration of 2%, and a 10-mL suspension containing 100 mg of colistin, 80 mg of tobramycin, and 500 mg of amphotericin B via a nasogastric tube. Topical antibiotics were applied four times daily until discharge from ICU. In addition, intravenous cefotaxime (1000 mg, every 6 h) was administered for the first 4 days. Rectal carriage of 3GCephRE and AGRE was determined at admission and twice weekly during the ICU stay [42].

Table 1
Characteristics of 27 included studies (sorted by study design)

Author, year of publication [ref.]	Study design	Population	Target bacteria	Intervention	Comparison	Treatment duration
Saidel-Odes, 2012 [51]	RCT	Mixed population	CRE	Colistin (1 MIU) qid + gentamicin (80 mg) qid	Placebo	7 days
Nouvenne, 2015 [52]	RCT	Mixed population	CRE	High-dose probiotics + psyllium	Standard care	14 days
Huttner, 2013 [38]	RCT	Mixed population	3GCephRE ESBL producer	Colistin sulphate (1.26 MIU) qid + neomycin sulphate (80 mg) qid	Placebo	10 days
Jonsson, 2015 [39]	RCT	Mixed population	3GCephRE ESBL producer	Anti-ESBL IgG	Placebo	21 days
Tannock, 2011 [64]	RCT	Long-term care facility residents	FQRE	Probiotic strain *E. coli* Nissle 1917 (5×10^9 to 5×10^{10} bacteria daily, twice daily)	Placebo	5 weeks
Oren, 2013 [53]	Semi-randomized trial	Mixed population	CRE	Gentamicin (80 mg) qid or colistin (2 MIU) qid or gentamicin + colistin	Spontaneous decolonization	Up to eradication (maximum, 60 days)
Buehlmann, 2011 [40]	Prospective cohort	Mixed population	3GCephRE ESBL producer	Paromomycin (1 g) qid (intestinal colonization); chlorhexidine (oropharyngeal application, 0.2%) tid (throat colonization); nitrofurantoin (100 mg) tid or ciprofloxacin (750 mg) bid or cotrimoxazole (800/160 mg) bid or fosfomycin (3 g) single dose (urinary colonization)	Interrupted decolonization	4–5 days; repeated courses until achievement of eradication
Decré, 1998 [41]	Prospective cohort	ICU	3GCephRE ESBL producer	Erythromycin (1 g) bid + polymixin E (6 MIU) bid	Universal decolonization	Not reported
Borer, 2007 [65]	Prospective cohort	ICU	CRAB	Topical 4% chlorhexidine, one full body wash daily	Standard care	Not reported
Machuca, 2016 [55]	Retrospective cohort	Mixed population	Colistin-resistant CRE	Gentamicin (80 mg) qid or streptomycin (80 mg) tid + neomycin (40 mg) tid	Standard care	14 days
Lubbert, 2013 [54]	Retrospective cohort	ICU	CRE	Colistin sulphate (1 MIU) qid + gentamicin sulphate (80 mg) qid	Spontaneous decolonization	7 days
Agusti, 2002 [66]	Case–control	ICU	CRAB	Colistin (150 mg) qid + tobramycin (80 mg) qid	Standard care	Variable (mean, 35.8 days)
Chen, 2014 [67]	Case–control	Mixed population	CRAB	Inhaled colistin (2 MIU/160 mg) bid	Standard care	Not reported
Kuo, 2012 [68]	Case–control	Mixed population	CRAB	Inhaled colistin (2 MIU/160 mg) bid	Standard care	Variable (10.9 ± 3.6 days)
Oostdijk, 2012 [42]	Nested *post hoc* analysis	ICU	3GCephRE, AGRE	Colistin (2 MIU) qid + tobramycin (80 mg) qid + cefotaxime (1 g) qid	NA	Up to ICU discharge
Gutierrez-Urbon, 2015 [43]	Case series	Paediatric ICU	3GCephRE ESBL producer	Colistin (solution 1%, 1 mL/kg) qid + amikacin (solution 3.2%, 1 mL/kg) qid	NA	5 days
Rieg, 2015 [44]	Case series	Mixed population	3GCephRE ESBL producer	Colistin standard dose (1 MIU) or high dose (2 MIU) qid or rifaximin	NA	4 weeks
Abecasis, 2011 [45]	Case series	Paediatric ICU	3GCephRE ESBL producer	Colistin + tobramycin + cefotaxime (doses not specified)	NA	Not reported
Paterson, 2001 [46]	Case series	SOT	3GCephRE ESBL producer	Norfloxacin (400 mg) bid	NA	5 days
Troché, 2005 [47]	Case series	ICU	3GCephRE ESBL producer	2 among colistin sulphate (1.5 MIU) qid, neomycin (500 mg) qid or erythromycin (500 mg) qid	NA	Not reported
De Rosa, 2016 [56]	Case series	Haematological malignancy	CRE	Gentamicin (80 mg) qid	NA	Variable (mean, 5 days)
Tascini, 2014 [59]	Case series	Mixed population	CRE	Gentamicin (80 mg) qid	NA	>7 days, variable (mean, 16 days)
Zuckerman, 2011 [57]	Case series	Haematological malignancy	CRE	Gentamicin (80 mg) qid	NA	Up to eradication (mean, 27 days; range, 7–90 days)
Lambelet, 2017 [58]	Case series	Haematological malignancy	CRE	Gentamicin (80 mg) qid	NA	Up to eradication (range, 7–25 days)
Gray, 2016 [69]	Case series	Mixed population	CRAB	Chlorhexidine gluconate-impregnated wipes 2% daily	NA	Not reported
Hseih, 2014 [70]	Case series	Mixed population	CRAB	Colistin sulphate (2 MIU) bid	NA	Variable (range, 11–13.5 days)
Kronman, 2014 [61]	Case report	Haematological malignancy	CRE	Gentamicin + colistin (doses not specified)	NA	10 days
Brink, 2013 [60]	Case report	Mixed population	CRE	Colistin + tobramycin (doses not specified)	NA	Not reported

Abbreviations: AGRE. aminoglycoside-resistant Enterobacteriaceae; bid, twice daily; CRAB, carbapenem-resistant Acinetobacter baumannii; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; FQRE, fluoroquinolone-resistant Enterobacteriaceae; ICU, intensive care unit; IgG, immunoglobulin G; NA, not applicable; qid, four times daily; RCT, randomized controlled trial; SOT, solid organ transplant; 3GcephRE, third-generation cephalosporin-resistant Enterobacteriaceae; tid, thrice daily.

Clinical outcomes

Two case series [43,45] and the nested *post hoc* analysis [42] included clinical outcomes (all-cause mortality at treatment end or length of stay)—Abecasis *et al.* reported a 20.5% (8/39) mortality rate [45] and Gutierrez-Urbon *et al.* reported no deaths [43]. Oostdijk *et al.* observed a median ICU stay of 12 days (range 3–77; interquartile range (IQR), 10) for 3GCephRE-colonized patients and 13 days (range 3–77; IQR, 11) for decolonized patients [42].

Microbiological outcomes

One RCT [38], one prospective cohort study [40] and all studies without comparator [42–47] included microbiological outcomes (carriage rate or eradication rate). Huttner *et al.* observed a significantly lower rectal carriage rate in the treatment group than in the placebo group at treatment end (32.0% (8/25) versus 76.9% (20/26); p 0.001), but the effect was lost at 7 days post-treatment (66.7% (18/27) versus 68% (17/25); p 0.92) and at 28 days post-treatment (51.9% (14/27) versus 37% (10/27); p 0.28) [38]. Buehlmann *et al.* showed that repeated decolonization significantly improved eradication rate at treatment end (88.9% (16/18) versus 41.1% (7/17); p 0.007) [40]. The studies without comparator reported decolonization rates at treatment end ranging from no effect to 100% [42–47].

Epidemiological outcomes

One prospective cohort study [41] evaluated the impact of decolonization regimen on epidemiological outcomes (incidence of acquired colonization and acquired infections). No significant difference from the historical control group was observed in the incidence of acquired 3GCephRE colonization in the digestive tract (10% versus 9.1%) or in the incidence of acquired infections (7.5% versus 3.6%).

Adverse events

Resistance development was assessed in one RCT and one uncontrolled study [38,42]. Huttner *et al.* observed no statistically significant changes in the colistin or neomycin MICs between baseline and final ESBL-E isolates in the treatment group [38]. Oostdijk *et al.* found no association with increased resistance over time when eradication failed [42]. Adverse events were evaluated in two RCTs [38,39] and one study without comparator [43]. In the Huttner *et al.* trial, 7/27 (25.9%) patients in the treatment group versus 2/29 (6.9%) patients in the placebo group (p 0.05) experienced liquid stool during follow up [38], whereas in the Jonsson study the proportion of participants who reported various adverse events was similar between the treatment and the placebo groups (58% versus 42%) [39].

Other relevant outcomes

A significantly lower rectal carriage rate was observed by Huttner *et al.* on day 6 of treatment (9/26 (34.6%) versus 19/22 (86.3%); $p < 0.001$) [38].

Evidence evaluation

Evidence was of moderate [38] and very low [40] certainty for microbiological eradication at treatment end, low for microbiological eradication at 7 days and 28 days post-treatment [38] and for resistance development [38], and very low for adverse events [38,39].

Recommendation

The panel does not recommend routine decolonization of 3GCephRE carriers.

Grading: conditional recommendation against the intervention.

Research and possibly conditional use in restricted trials

On the basis of the limited evidence of temporary effectiveness of decolonization [38,40] and the increased risk of developing ESBL-E bloodstream infections in neutropenic colonized patients [7,48,49], the panel suggests designing clinical trials of decolonization with oral colistin sulphate (50 mg (salt) four times daily) and neomycin sulphate (250 mg (salt) four times daily) to temporarily suppress 3GCephRE carriage in patients with severe neutropenia (absolute neutrophil count <500 μL). These trials should include careful monitoring for development of resistance to neomycin or colistin during decolonization using stool cultures and antimicrobial susceptibility results according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints [50].

Carbapenem-resistant Enterobacteriaceae

Study characteristics

The 11 studies were performed in Europe (6), Israel (3), South Africa (1) and the USA (1): two RCTs [51,52], one semi-randomized control trial [53], two retrospective cohort studies [54,55], and six case series and case reports without comparators [56–61]. Two studies had a multicentre design [55,59]. Six studies evaluated hospital inpatients [51–53,55,59,60], one assessed ICU patients [54], and four evaluated haematological patients [56,57,59,61]. Four studies were performed during a CRE outbreak [54,55,57,60]. Seven studies did not specify local epidemiology [51,53,55,56,58,59,61]. Rectal carriage testing was performed in all studies, and urinary carriage and respiratory tract colonization were assessed in one study each [51,54].

Saidel-Odes *et al.* conducted an RCT to test the efficacy of intestinal decontamination on CRE carriage. Forty patients were randomized to receive either placebo or colistin (1 MU four times daily) and gentamicin sulphate (80 mg four times daily) for 7 days [51]. Nouvenne *et al.* performed an RCT in 32 patients assessing the role of high-dose probiotics in CRE faecal carriage eradication. The patients were randomly assigned to either high-dose probiotics and psyllium for 14 days or standard care [52]. Oren *et al.* evaluated 50 patients treated with one of three regimens: colistin sulphate (2 MU four times daily), gentamicin sulphate (80 mg four times daily), or both [53]. The patients were assigned to antibiotic regimens either according to susceptibility or randomly (for carriers of strains susceptible to both colistin and gentamicin). Patients undergoing treatment were compared with controls (102 patients) for eradication and clinical outcomes. Machuca *et al.* analysed a retrospective cohort of 77 patients using two regimens: gentamicin solution (80 mg four times daily) or streptomycin sulphate (80 mg three times daily) and neomycin (40 mg three times daily) for 14 days [55]. Lubbert *et al.* analysed a retrospective cohort of 16 ICU patients treated for 7 days with colistin sulphate (1 MU four times daily) and gentamicin sulphate (80 mg four times daily) [54].

Clinical outcomes

All controlled studies [51–55] and four studies without comparator [56–60] included clinical outcomes (all-cause and attributable mortality, CRE-related infection incidence or length of hospital stay). Machuca *et al.* reported a significant reduction in all-cause mortality associated with the use of decolonization therapy at 6 months after treatment end (25% versus 54%; hazard ratio (HR) 0.18; 95% CI 0.06–0.55) [55]. Oren *et al.* observed a reduction in all-cause mortality without impact on attributable mortality during the follow-up period (timing not specified) (22% (11/50) versus 53% (54/102); $p < 0.001$) [53]. Nouvenne *et al.* and Lubbert *et al.* did not

Table 2
Microbiological outcomes

Author, year of publication [ref.]	Target bacteria	Sample size	Time-point	Eradication rate	95% CI	p value
Saidel-Odes, 2012 [51]	CRE	Intervention 20; control 20	7 days after EoT 28 days after EoT	OR, 0.13 58.5% vs. 33.3%	0.02–0.74 NA	0.0016 NS
Nouvenne, 2015 [52]	CRE	Intervention 18; control 14	NA	53% vs. 12%	NA	0.0094
Huttner, 2013 [38]	3GCephRE ESBL producer	Intervention 27; control 27	EoT 28 days after EoT	NA OR, 0.55	NA 0.18–1.62	0.001 NA
Tannock, 2011 [64]	FQRE	Intervention 36; control 33	5 weeks after EoT	23% vs. 42%	NA	NS
Oren, 2013 []53	CRE	Intervention 50; control 102	NA	44% vs. 7%	NA	<0.001
Buehlmann, 2011 [40]	3GCephRE ESBL producer	Intervention 18; control 17	EoT	OR, 11.42	1.6–102.6	NA
Machuca, 2016 [55]	CRE	Intervention 44; control 33	6 months after EoT	aHR, 4.06	1.06–15.6	0.04
Lubbert, 2013 [54]	CRE	Intervention 16; control 76	NA	57% vs. 83%	NA	NS
Agusti, 2002 [66]	CRAB	Intervention 33; control 21	EoT	52% vs. 9%	NA	<0.001
Chen, 2014 [67]	CRAB	Intervention 81; control 54	14 days after EoT 28 days after EoT	54% vs. 30% 67% vs. 52%	NA NA	0.005 NS
Kuo, 2012 [68]	AGRE	Intervention 39; control 39	14 days after EoT 28 days after EoT	85% vs. 10% 50% vs. 43%	NA NA	<0.001 NS
Oostdijk, 2012 [42]	3GCephRE	Intervention 77; control NA	NA	73%	NA	NA
Gutierrez-Urbon, 2015 [43]	3GCephRE ESBL producer	Intervention 6; control NA	EoT	0%	NA	NA
Rieg, 2015 [44]	3GCephRE ESBL producer	Intervention 45; control NA	14 days after EoT	Colistin SD 39%; colistin HD 25%; rifaximin 60%	NA	NA
Abecasis, 2011 [45]	3GCephRE ESBL producer	Intervention 39; control NA	EoT	77%	NA	NA
Paterson, 2001 [46]	3GCephRE ESBL producer	Intervention 9; control NA	EoT 14 days after EoT 28 days after EoT	100% 89% 44%	NA	NA
Troché, 2005 [47]	3GCephRE ESBL producer	Intervention 37; control NA	EoT	46%	NA	NA
De Rosa, 2016 [56]	CRE	Intervention 8; control NA	NA	25%	NA	NA
Tascini, 2014 [59]	CRE	Intervention 50; control NA	NA	68%	NA	NA
Zuckerman, 2011 [57]	CRE	Intervention 15; control NA	NA	66%	NA	NA
Lambelet, 2017 [58]	CRE	Intervention 14; control NA	NA	71%	NA	NA
Hseih, 2014 [70]	CRAB	Intervention: - Colonized group 61 - Pneumonia group 57 Control NA	NA	72% 79%	NA	NA
Kronman, 2014 [61]	CRE	Intervention 1; control NA	28 days after EoT	100%	NA	NA
Brink, 2013 [60]	CRE	Intervention 1; control NA	EoT	0%	NA	NA

Abbreviation: aHR, adjust hazard ratio; CRAB, carbapenem-resistant Acinetobacter baumannii; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; EoT, end of treatment; FQRE, fluoroquinolone-resistant Enterobacteriaceae; HD, high dose; NA, not applicable; NS, not significant; OR, odds ratio; SD, standard dose; 3GcephRE, third-generation cephalosporin-resistant Enterobacteriaceae.

find any significant effect of decolonization treatment on mortality during hospitalization [52,54].

Machuca *et al.* reported a significant reduction in the CRE-related infection incidence at 6 months follow up (4.5% (2/44) versus 39.4% (13/33); p < 0.001) [55]. Univariate analysis demonstrated a lower risk of carbapenemase-producing *K. pneumoniae* infections in the follow-up period associated with decolonization (HR 0.14; 95% CI 0.02–0.83). Only gentamicin was significantly associated with infection rate reduction in the analysis stratified by treatment (crude HR 0.86; 95% CI 0.008–0.94). Two studies analysing the effect of decolonization on length of hospital stay found no difference between treated and untreated patients [51,54].

Microbiological outcomes

All controlled studies [51–55] and all studies without comparator [56–61] included microbiological outcomes (carriage rate or eradication rate). In the RCT by Saidel-Odes *et al.*, significant carriage rate reduction was observed 7 days post-treatment (38.8% versus 83.9%; OR 0.13; 95% CI 0.02–0.74; p < 0.0016), but the effect was lost at 28 days, resulting in a non-significant difference between the two groups (41.5% versus 66.7%) [51]. In the RCT by Nouvenne *et al.*, significant reduction in carriage rate during hospitalization was associated with administration of high-dose probiotics (p 0.009) [52]. In the semi-randomized trial by Oren *et al.*, the eradication rate during follow up was significantly higher in the intervention group (56% (22/50) versus 7% (7/102); p < 0.001) [53]. The retrospective cohort study by Machuca *et al.* found a significant difference in decolonization rate between the control and treated groups (51.1% versus 9.1%; p < 0.001) at 180 days post-treatment (HR 4.06; 95% CI 1.06–15.6) [55]. When stratified by treatment regimen, gentamicin was associated with a significantly higher microbiological success rate (HR 5.67; 95% CI 1.33–24.1). The other regimen (streptomycin and neomycin combination) showed no significant association. The retrospective cohort study by Lubbert *et al.* showed no significant difference in the decolonization rate between the two groups [54].

Table 3
Clinical outcomes

Author, year of publication [ref.]	Target bacteria	Sample size	Clinical outcome	Time-point	Effect size	95% CI	p value
Nouvenne, 2015 [52]	CRE	Intervention 18; control 14	All-cause mortality	NA	31% vs. 12%	NA	NS
Oren, 2013 [53]	CRE	Intervention 50; control 102	All-cause mortality	NA	22% vs. 53%	NA	<0.001
			Attributable mortality		6% vs. 6%	NA	NS
Machuca, 2016 [55]	Colistin-resistant CRE	Intervention 44; control 33	All-cause mortality	6 months after EoT	aHR, 0.18	0.06-0.55	0.003
			Incidence of infection	6 months after EoT	aHR, 0.14	0.02-0.84	0.03
Lubbert, 2013 [54]	CRE	Intervention 16; control 76	All-cause mortality	NA	36% vs. 45%	NA	NS
			Incidence of infection		14% vs. 16%	NA	NS
Agusti, 2002 [66]	CRAB	Intervention 33; control 21	All-cause mortality	EoT	9% vs. 10%	NA	NS
			Incidence of infection	EoT	52% vs. 24%	NA	0.052
Chen, 2014 [67]	CRAB	Intervention 81; control 54	All-cause mortality	28 days after EoT	15% vs. 7%	NA	NS
Kuo, 2012 [68]	CRAB	Intervention 39; control 39	All-cause mortality	28 days after EoT	10% *vs* 13%	NA	NS
			Incidence of infection	EoT	31% *vs* 41%	NA	NS
Gutierrez-Urbon, 2015 [43]	3GCephRE ESBL producer	Intervention 6; control NA	All-cause mortality	EoT	0%	NA	NA
Abecasis, 2011 [45]	3GCephRE ESBL producer	Intervention 39; control NA	All-cause mortality	EoT	21%	NA	NA
De Rosa, 2016 [56]	CRE	Intervention 8; control NA	Incidence of infection	6 months after EoT	37%	NA	NA
Tascini, 2014 [59]	CRE	Intervention 50; control NA	Incidence of infection	NA	36%	NA	NA
Zuckerman, 2011 [57]	CRE	Intervention 15; control NA	All-cause mortality	NA	20%	NA	NA
			Attributable mortality		40%		
			Incidence of infection		53%		
Lambelet, 2017 [58]	CRE	Intervention 14; control NA	All-cause mortality	NA	7%	NA	NA
			Attributable mortality		7%		
			Incidence of infection		7%		
Gray, 2016 [69]	CRAB	Intervention 29; control NA	Attributable mortality	NA	21%	NA	NA
			Incidence of infection		17%		
Hseih, 2014 [70]	CRAB	Intervention: - colonized group 61 - pneumonia group 57 Control NA	All-cause mortality	28 days after EoT	28% 33%	NA	NA

Abbreviations: aHR, adjust hazard ratio; CRAB, carbapenem-resistant Acinetobacter baumannii; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; EoT, end of treatment; NA, not applicable; NS, not significant; 3GcephRE, third-generation cephalosporin-resistant Enterobacteriaceae.

Epidemiological outcomes

None of the studies evaluated epidemiological outcome.

Adverse events

Resistance development was assessed in one RCT [51], three controlled studies [53–55] and all studies without comparator [56–61]. Among controlled studies, an increase in secondary resistance to decolonizing agents was reported in three studies [53–55]. Machuca *et al.* found that a significantly higher proportion of patients undergoing decolonization had gentamicin-resistant isolates in follow-up cultures than those not treated (13% (6/44) versus 3% (1/33); p 0.008) [55]. In the Oren *et al.* and Lubbert *et al.* studies, 14% (7/50) and 28% (4/14) of patients, respectively, developed secondary resistance to decolonizing agents [53,54]. Saidel-Odes *et al.* did not observe increased resistance in their RCT [51]. None of the controlled studies reported a higher adverse event incidence in the intervention group.

Evidence evaluation

Evidence was of low certainty for microbiological eradication at 1 week [51] and 6 months [55] post-treatment and CRE infection incidence at 6 months [55], and of very low certainty for microbiological eradication at 4 weeks [51] and all-cause mortality [55].

Recommendation

The panel does not recommend routine decolonization of CRE.

Grading: conditional recommendation against the intervention.

Research and possibly conditional use in restricted trials

On the basis of the limited evidence of increased risk of developing CRE infections in the colonized ICU population [12,13,62,63] and the results of the effectiveness of decolonization on CRE carriers [51,53], the panel suggests designing good-quality clinical studies to assess CRE infection risk in colonized haematological patients and solid organ transplant recipients. The panel further suggests using the results of these trials to design decolonization trials with oral colistin sulphate (50 mg (salt) four times daily) with or without gentamicin sulphate (80 mg (salt) four times daily) to temporarily suppress CRE carriage in high-risk patients. These trials should include careful monitoring of development of resistance to gentamicin and colistin during decolonization using stool cultures and antimicrobial susceptibility results according to the EUCAST clinical breakpoints [50].

Fluoroquinolone-resistant Enterobacteriaceae

Study characteristics

Tannock *et al.* conducted a multicentre RCT in New Zealand to evaluate the efficacy of the probiotic strain *Escherichia coli* Nissle 1917 on FQRE colonization [64]. Sixty-nine elderly residents in long-term care facilities excreting norfloxacin-resistant *E. coli* were randomized to receive either probiotic (5×10^9 to 5×10^{10} bacteria daily, one capsule twice daily) or placebo for 5 weeks. Rectal and urinary carriage testing were assessed in the trial.

Clinical outcomes

No clinical outcome was assessed.

Microbiological outcomes

No significant difference was found in decolonization rate between the control and treated groups at 5 weeks post-treatment.

Epidemiological outcomes

No epidemiological outcome was analysed.

Adverse events

No adverse event was evaluated.

Evidence evaluation

Evidence was of low certainty for microbiological eradication at 5 weeks post-treatment.

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

Aminoglycoside-resistant Enterobacteriaceae

Study characteristics

The Oostdijk *et al*. study [42] is described above in the 3GCephRE section.

Clinical outcomes

Median length of ICU stay was 11.5 days (range 4–82; IQR 9.5) for AGRE-colonized patients and 12 days (range, 4–82; IQR 8) for decolonized patients.

Microbiological outcomes

The eradication rate was 62% (31/50) after a median of 5.5 days (IQR 3–60 days) of decolonization.

Epidemiological outcomes

No epidemiological outcome was analysed.

Adverse events

No increased resistance overtime was seen when eradication failed.

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

Carbapenem-resistant Acinetobacter baumannii

Study characteristics

Three studies were performed in Taiwan and one each in Canada, Spain and Israel: one prospective cohort study [65], three case–control studies [66–68] and two case series without comparators [69,70]. All studies had a single-centre design. Four studies evaluated hospital patients [67–70] and two studied ICU patients [65,66]. Two studies were performed during a CRAB outbreak [66,69], one study was performed in a centre where CRAB was endemic [65], and three studies did not specify local epidemiology [67,68,70]. Respiratory tract cultures were performed in three studies [67,68,70], skin cultures in three studies [65,66,69], and rectal screening in two studies [66,69].

Borer *et al*. prospectively evaluated the impact of daily 4% chlorhexidine body wash in a cohort of 320 ICU patients [65]. Two controlled [67,68] studies and one case series [70] compared inhaled colistin (160 mg twice daily) with variable duration (7.3–13.5 days) to standard care in hospital patients. One controlled study [65] and one uncontrolled study [69] evaluated topical chlorhexidine during hospitalization. In one case–control study 21 ICU patients receiving an SDD regimen of colistin sulphate (50 mg (salt) four times daily) and tobramycin (80 mg four times daily) were compared to 33 ICU patients receiving standard care until discharge [66]. Gray *et al*. described the management of a CRAB ICU outbreak involving 29 patients using a multimodal intervention including 2% chlorhexidine washes; in this case series none of the outcomes evaluated in this systematic review were assessed [69].

Clinical outcomes

Three case–control studies [66–68], one prospective cohort study [65], and one uncontrolled study [70] assessed clinical outcomes (all-cause mortality and infection rate). No significant difference in all-cause mortality during ICU stay was observed after oral decolonization [66]. All-cause mortality was assessed in two case-control studies comparing inhaled colistin with standard care, and no significant differences in mortality was observed [67,68]. Only Borer *et al*. observed a significant reduction in CRAB bloodstream infections after the intervention (0.6% versus 4.65%; $p < 0.001$) [65].

Microbiological outcomes

Three studies evaluated eradication rate [66–68]. Persistent CRAB carriage 14 days after treatment was assessed in two controlled studies. Chen *et al*. observed 14-day eradication in 54.3% of patients receiving decolonization versus 29.6% of controls (p 0.005), although a significant association was not observed for 28-day eradication rates (66.7% versus 51.9%; p 0.084) [67]. Kuo *et al*. observed a significant 14-day eradication rate (84.6% versus 10.3%; $p < 0.001$) [68]. Agusti *et al*. found significant reduction in faecal (48% versus 91%; p 0.001) and pharyngeal (38% versus 78%; p 0.03) carriage at discharge in patients who received SDD compared with controls. SDD did not affect cutaneous carriage [66].

Epidemiological outcomes

No epidemiological outcome was analysed.

Adverse events

Kuo *et al*. assessed colistin resistance development, specifically changes in colistin MIC (one-fold to two-fold) between isolates cultured from the same patients. No significant difference between case and control groups was observed (8/28 (28.6%) versus 4/30 (13.3%); p 0.15) [68].

Evidence evaluation

Evidence was of very low certainty for all the assessed outcomes.

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

Faecal microbiota transplantation

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) [71]. The potential benefit of FMT as an MDR-GNB decolonization strategy has been tested in nine uncontrolled studies with a high level of heterogeneity [72–80].

A single-centre study by Bilinski *et al*. investigated the use of FMT for MDR-GNB eradication in patients with haematological disorders [72]. Twenty-five FMTs were performed in 20 patients with intestinal MDR-GNB colonization, mainly carbapenemase- or ESBL-producing *Enterobacteriaceae*. Complete decolonization was achieved in 60% (15/25) of the cases at 1 month and in 13/14 (93%) of cases at 6 months post-treatment. Antibiotic use within 7 days post-treatment hampered the effectiveness of the intervention.

Davido *et al*. reported the results of a series of eight FMTs, of which six were performed in patients colonized with carbapenemase-producing *Enterobacteriaceae* [73]. Eradication was obtained in two patients at 1 month post-treatment. No relapse of

Table 4
Characteristics and results of nine studies on faecal microbiota transplantation

Author, year [ref.]	Population	Target bacteria	Study design	Time-point after EoT	Successful eradication
Bilinski, 2017 [72]	Haematological malignancy	3GCephRE	Case series	1 week	12/13
				1 month	12/13
Bilinski, 2017 [72]	Haematological malignancy	CRE	Case series	1 week	12/20
				1 month	12/16
Bilinski, 2016 [74]	Haematological malignancy	3GCephRE	Case report	1 week	1/1
				1 month	1/1
Bilinski, 2016 [74]	Haematological malignancy	CRE	Case report	1 week	1/1
				1 month	1/1
Davido, 2017 [73]	Mixed population	CRE	Case series	1 month	2/6
				3 months	2/6
Friedman-Moraco, 2014 [78]	Haematological malignancy	CRE	Case report	EoT	1/1
Garcia-Fernandez, 2016 [75]	Mixed population	CRE	Case report	EoT	1/1
				6 months	1/1
Lagier, 2013 [77]	Mixed population	CRE	Case report	1 week	1/1
Ponte, 2017 [76]	Mixed population	CRE	Case report	1 month	1/1

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; EoT, end of treatment; 3GcephRE, third-generation cephalosporin-resistant Enterobacteriaceae.

colonization was detected through 3 months of follow up. Table 4 provides details of study design and results.

Recommendation

Evidence is insufficient to provide a recommendation for or against FMT. Further studies are warranted to evaluate the effectiveness, applicability, and safety of FMT to confirm its role in intestinal decolonization of MDR-GNB.

Limitations of the evidence and future research

Our systematic review has identified important gaps in the literature on targeted decolonization strategies in MDR-GNB carriers. Studies have been evaluated for only a few clinically relevant MDR-GNB in specific settings, and, of those assessed, data are insufficient to provide robust recommendations on decolonization. High heterogeneity was detected among studies and did not allow any meta-analytic approach but only a qualitative review. The panel identified the following major flaws in the evaluated evidence: inconsistent reporting, small sample size, key outcomes not assessed, inconsistent effectiveness definition, colistin susceptibility testing not in accordance with current recommendations, and wide heterogeneity between settings (outbreak, endemic), decolonization regimens and treatment duration. The assessment typically evaluated a single intervention although multiple infection control measures are often implemented together as a bundle in clinical practice.

Because of the lack of effective drugs for MDR-GNB, the development of novel decolonization strategies through well-designed *in vitro* and *in vivo* studies is urgently needed [81]. These strategies may include natural compounds (FMT, prebiotics, probiotics), alternative therapies (tea tree oil, photodynamic therapies, omiganan pentahydrochloride), and bacteriophage therapy. Well-designed multicentre RCTs are required to determine the impact of decolonization strategies on microbiological, epidemiological and clinical outcomes and development of resistance. Furthermore, the studies should evaluate the optimal dosing, duration, target populations and setting (endemic versus outbreak), and cost-effectiveness. Sequential interventions (e.g. oral SDD followed by FMT) should be explored. Evaluation of the efficacy of multimodal decolonization methods in stepped-wedge cluster RCTs should also be considered. Metagenomic studies assessing the effect of decolonizing agents on the microbiota composition and dynamics could provide valuable evidence for designing RCTs and drive choices of old and new drugs to be tested. Although it is understandable that research to date has focused on organisms with current significant clinical impact (3GCephRE, CRE, CRAB), we should not neglect other MDR-GNB (e.g. extremely drug-resistant *Pseudomonas aeruginosa*, pan-drug-resistant Gram-negative organisms) for which current experience is low but is likely to increase in the future.

Key points

- The panel does not recommend routine decolonization of MDR-GNB carriers.
- The effectiveness and long-term side effects of decolonization of 3GCephRE and CRE in high-risk populations (e.g. ICU, neutropenic and transplant populations) needs to be evaluated with RCTs with proper design and sample size calculation.

Transparency declaration

ET, FM, AMD, DB, BDH, EJK, JCL, NTM, MJS, Maria Souli, JTC, JRP declared no conflicts of interest. PE has witnessed advisory and consultancy roles at Abionic, 3M, Pfizer, Aridis and received research support from 3M. Maurizio Sanguinetti received research support from Recordatai, Pfizer and Menarini s.p.a. JRB participated in accredited educational activities supported by Merck through unrestricted grants and was coordinator of a drug-unrelated research project funded by AstraZeneca.

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Updating

Evelina Tacconelli and the current expert group are responsible for updating these guidelines with a time frame of 2 years between publishing and commencing the next updating process. If high-quality evidence is published within the 2-year time frame, the group will analyse the data and report to the scientific community in a timely manner.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.01.005.

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