

EUCIC MEDICAL GUIDELINES ON DECOLONISATION OF MULTIDRUG RESISTANT GRAM-NEGATIVE ORGANISMS

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Guidelines Committee

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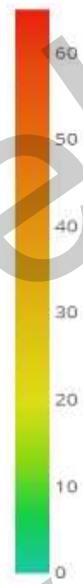
All members of the panel submitted COIs which were reviewed according to the ESCMID operational procedures for guidelines (available online before publication on www.escmid.org)

Personal COI: Financial support for research activities (last five years):

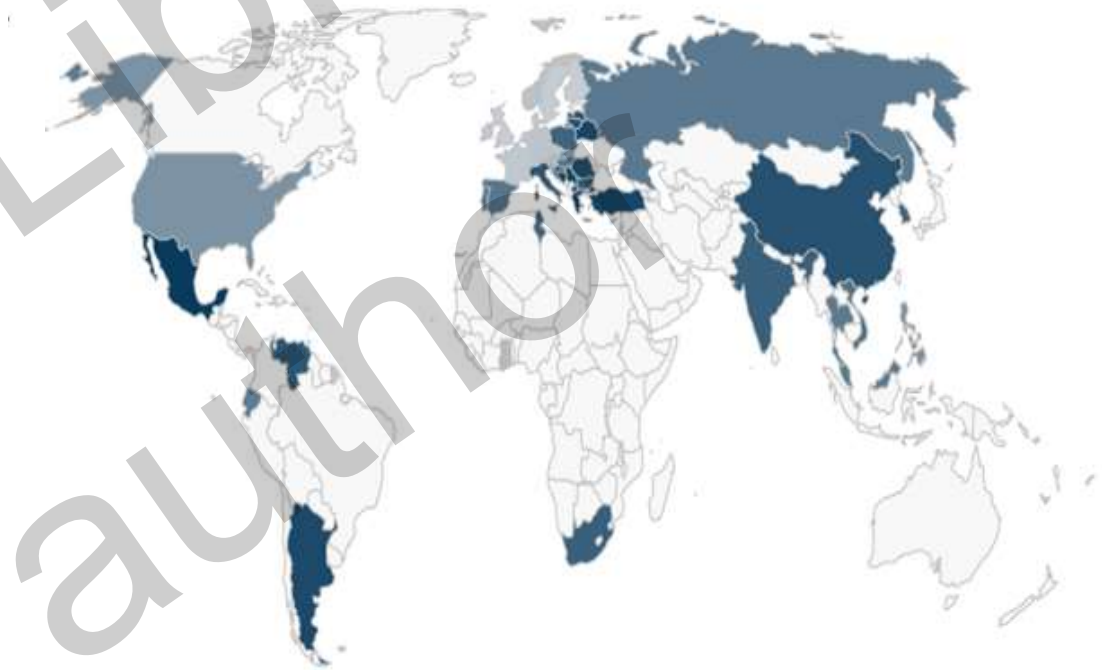
- German Center for Infectious Research;
- DG-Sanco;
- IMI;
- European Commission;
- WHO

Burden of MDR GN bacteria

Resistance of Acinetobacter to carbapenems (prevalence in invasive isolates)



Sample size < 1000 1000-10000 10000-100000 > 100000



<https://combacte/epi-net.eu>



<https://resistancemap.cddep.org>

Priority for R&D of new, effective antibiotics

Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*²⁵

Priority 1: critical

- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

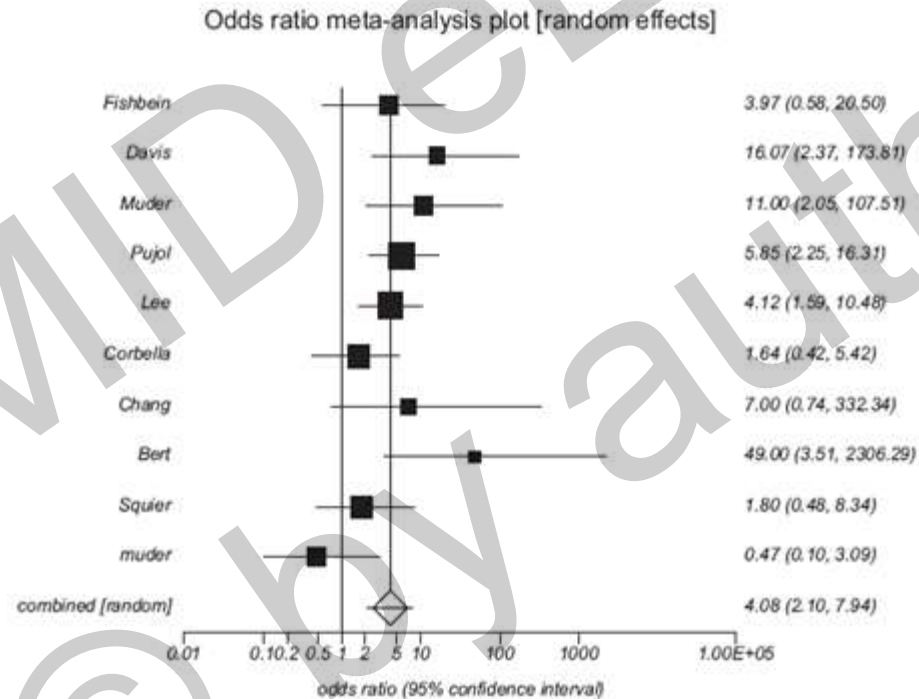
Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

Evidence from Gram-positives

Colonisation precedes the infection: the case of MRSA

- MRSA infections develop in 11% to 33% of colonized patients
- Nasal carriage of MRSA increases risk of MRSA infections by 4 fold



Mest, Anesth Analg, 1994; Jernigan, ICHE, 1995; Sadfar, Am J Med 2008

ESBL colonisation precedes infections

Evidence

8 observational studies

High risk population: neutropenic patients (3 studies), those undergoing treatment in an ICU (3), recipients of solid organ transplantation (1), and mixed (1)

- **Meyer, 2009** (ICU population): 755 colonised patients; infections in **25%** colonised vs 5% in non-colonised
- **Bert, 2012** (transplant population): 29 patients (**OR 18.4**)
- **Reddy, 2017** (mixed population): 413 colonized - 35 (**8.5%**) developed a subsequent BSI
- **Gorrie, 2017** (ICU population): 498 colonised (rectal / throat carriage of *K. pneumoniae*, resistant and susceptible). Infection risk **16%** in colonised vs 3% in non-colonised / not screened (OR = 6.9, P < .001)

ESBL colonisation precedes infections

Haematological population

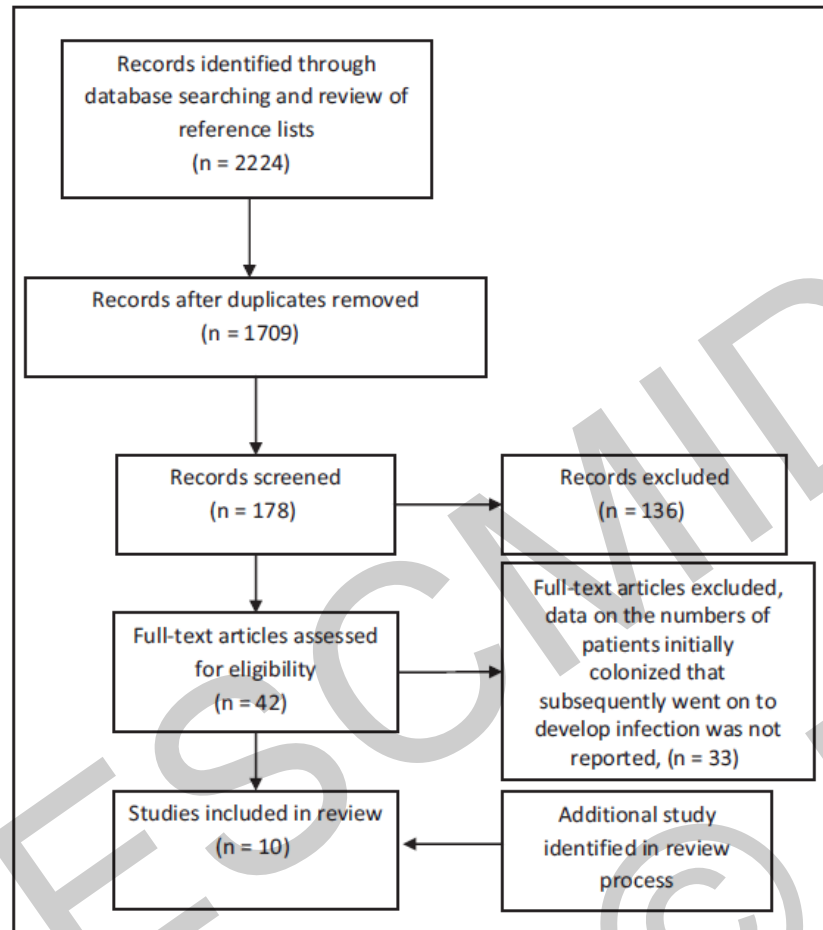
Table 3. Risk factors for BSI due to ESBL-E

Variable	Univariate P	Multivariate (only remaining variables)		
		P	OR	CI
Age	0.884			
AML/MDS	0.133			
Allogeneic SCT	0.134			
Autologous SCT	0.136			
Lymphoma	0.215			
ESBL-E colonization	<0.001	<0.001	52.00	5.71-473.89
ECOG score at first admission ^a	0.128			
Duration of hospitalization	0.010			

- Prospective, observational study at five German university-based haematology departments
- Screening for colonization within 72 h of admission, every 10 days thereafter, and before discharge
- 497 haematological high-risk patients
- 55 colonised patients
- 6 BSI (**10.9%**)

CRE colonisation precedes infections

Evidence



Systematic review (up to June 2015)

- 10 studies
- 1,806 patients
- Setting: mixed (5 studies); ICUs (4); transplant patients (1)
- All observational studies in adult inpatients
- Cumulative rate of infection **16.5%** ranging from no infection to 59% among colonised

Evidence after the SR 2014-2018

- **Giannella, 2014:** 143 carriers (all comorbidities)

Number of additional colonization sites (OR, 3.37 per site; 95% CI, 2.56–4.43; $p < .0001$) independent risk factor for infection (multivariate analysis)

- **Dickstein, 2016:** 146 carriers (ICU)

Colonization increases risk of infection [cause-specific hazard ratio (CSHR) 3.3; 1.3-8.4] (regression analysis)

- **McConnell, 2018:** 94 carriers (ICU)

Table 2. Predictors of CRE infection within 30 days of intensive care unit admission.

Variable n (%)	No infection (n = 312)	Infection (n = 26)	Univariable p-value	Adjusted OR (95% CI)	Multivariable p-value
Colonization Resistance Phenotype			<0.0001		0.0003*
Non-colonized	237 (76%)	7 (27%)		REF	
Ceph-R colonized	56 (18%)	2 (8%)		0.5 (0.1, 3.3)	0.5
CRE colonized	19 (6%)	17 (65%)		10.8 (2.8, 41.9)	0.0006

Guidelines methodology

- Systematic reviews process
- Systematic reviews, randomized controlled trials (RCTs), observational studies (cohort, 'before and after' studies, interrupted time series, cohorts, case-control studies)
- Two review authors independently screened all citations, identified abstracts, and screened full reports of potentially eligible studies
- Disagreements were resolved by discussion and rationales for exclusion of studies were documented
- Two/three authors independently performed quality assessment
 - EPOC Cochrane (RCT, semi RCT)
 - Newcastle Ottawa (cohort studies)
- GRADE system for the evaluation of evidence and definition of recommendation

Objectives and PICO

Aim: to review the current literature on multidrug resistant gram-negative (MDR-GN) bacteria decolonisation regimens in **healthcare and community settings** to allow evidence-based recommendations to be developed

- **Population:** any patient of any age in any community or healthcare setting with any sample yielding an MDR-GNO
- **Intervention:** all studies of all measures (iv/oral/topical; antibiotic/ antiseptic/natural compounds) applied to MDR-GNO decolonisation (defined as loss of detectable carriage by eradication or suppression to undetectable level) at all sites
- **Comparison:** spontaneous decolonisation or a second decolonisation measure
- **Outcome:** clinical, epidemiological, microbiological, and adverse effect outcomes

Outcomes

Microbiological outcomes

Carriage rate

- at the end of treatment
 - within 7 days
 - within 14 days
 - within one month
 - within 6 months
 - within 1 year
- after the end of treatment

Clinical outcomes

- incidence of infection (any-type)
 - at the end of treatment
 - within 7 days after the end of treatment
 - within 14 days after the end of treatment
 - within 1 month after the end of treatment
 - within 6 months after the end of treatment
 - within 1 year after the end of treatment
- mortality (all-cause and attributable)
 - at the end of therapy
 - 30 days after the end of treatment
 - 6 months after the end of treatment
 - one year after the end of treatment
- length of stay

Outcomes

Epidemiological outcomes

- incidence of colonisation
- incidence of transmission

Adverse events

- side effects of regimens
- detection of resistance to the decolonising agents

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Target bacteria

- Third generation cephalosporin-resistant *Enterobacteriaceae* (**3GCephRE**)
- Carbapenem-resistant *Enterobacteriaceae* (**CRE**)
- Aminoglycoside-resistant *Enterobacteriaceae* (**AGRE**)
- Fluoroquinolone-resistant *Enterobacteriaceae* (**FQRE**)
- XDR *Pseudomonas aeruginosa* (**XDRPA**)
- Carbapenem-resistant *Acinetobacter baumannii* (**CRAB**)
- Cotrimoxazole-resistant *Stenotrophomonas maltophilia* (**CRSM**)

9 main PICO questions and 183 subquestions

1. **What decolonisation regimens** have been evaluated for patients colonised with the target MDR-GN bacteria?
2. What is the **regimen of choice** for patients colonised with the target MDR-GN bacteria?
3. **Do we recommend** decolonisation for patients colonised with the target MDR-GN bacteria?

What this GL does not cover

- Universal decolonisation
- Methods to detect MDR-GN bacteria
- Performance measures
- Criteria for establishing carriage and for defining digestive clearance
- Animal studies

No evidence for:

- FQRE (721 articles screened)
- XDR-PA (47 articles screened)
- CR-*Stenotrophomonas maltophilia* (39 articles screened)

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Decolonisation protocols

Colistin	<ul style="list-style-type: none">• 3GCepha-RE• CRE
Gentamicin	<ul style="list-style-type: none">• CRE
Paromomycin	<ul style="list-style-type: none">• 3GCephaRE
Chlorhexidin	<ul style="list-style-type: none">• CRAB
Rifaximin	<ul style="list-style-type: none">• 3GCephaRE
Norfloxacin	<ul style="list-style-type: none">• 3GCephaRE

Colistin +
Aminoglycosides

- CRE
- 3GCepha-RE
- ARE

Colistin +
Erythromycin

- 3GCepha-RE

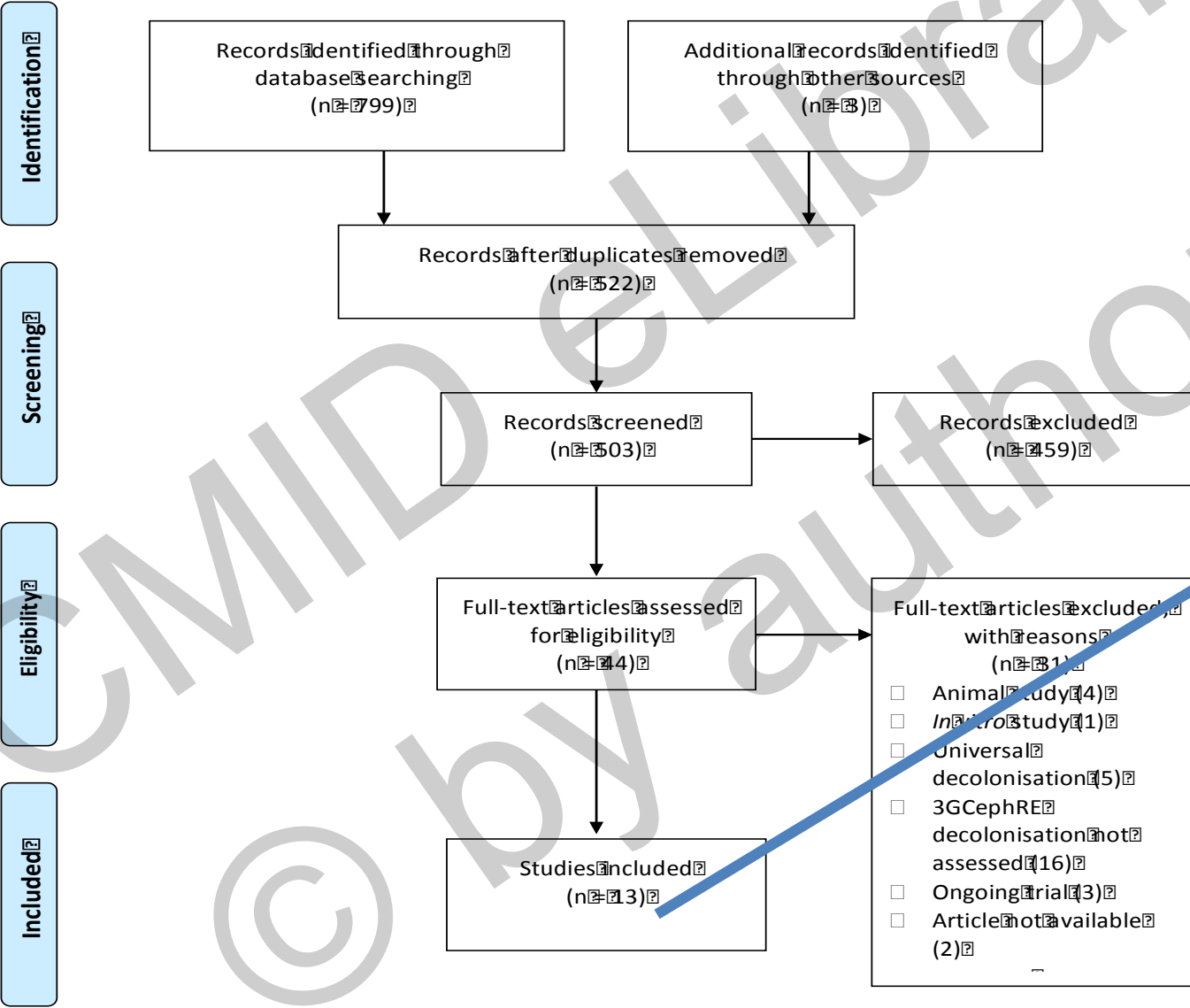
Neomycin +
Streptomycin

- CRE

High dose probiotics
+psyllium

- CRE

3GCephRE



2 RCTs
2 prospective cohort
7 case series
2 case reports

Oral colistin and neomycin

All hospitalised patients

Randomized, double-blind, placebo-controlled trial (Quality 7/8)

- Single-centre trial
- 58 patients
- Colistin sulphate (50 mg 4x/day) and neomycin sulphate (250 mg 4x/day) for 10 days plus nitrofurantoin (100 mg 3x/day) for 5 days in the presence of ESBL-Enterobacteriaceae (E) bacteriuria
- Primary outcome: detection of ESBL-E by rectal swab 28 days after the end of treatment; no difference among groups
- During treatment and shortly afterwards, there was significantly lower rectal ESBL-E carriage in the treatment group: 9/26 versus 19/22 on day 6 of treatment (P .001) and 8/25 versus 20/26 on day 1 post-treatment (P .001)

Prospective controlled cohort-study (404 patients), ICU (Quality: 3/7)

- Decolonisation: Erythromycin (1 g bid) and polymyxin E (6 million units bid)
- 3 phases: universal decolonisation (prophylactic); target decolonisation (curative); no decolonisation
- The number of infections in ESBL-producing *K. pneumoniae*-positive patients was reduced in period 1 and 2 (not significant)

Decolonisation of 3GCephaRE carriers

Summary of evidence

Microbiological outcomes

- The decolonisation with colistin and neomycin is temporary effective in reducing ESBL carriers rates at the end of treatment
 - Evidence level: Moderate (one trial, moderate risk of bias)
- The decolonisation is not effective in reducing ESBL carriers rates after end of treatment
 - Evidence level: Moderate (one trial, moderate risk of bias)



Routine decolonisation of 3GCephaRE carriers

Recommendation

- **Do not use routine decolonisation of 3GCephRE carriers**

Grading: **Conditional recommendation against routine use**



Decolonisation in high risk population

Recommendation

- **Consider a decolonisation treatment with oral colistin sulphate (50 mg four times daily) and neomycin sulphate (250 mg four times daily) to temporarily suppress the ESBL carriage in patients with severe neutropenia.** Ensure that the intervention, if chosen, is performed in the context of an IRB approval and appropriate quality controls and follow up.

Grading: Recommendation for research and possibly conditional recommendation for use in neutropenic patients.

Based on the moderate evidence of temporary effectiveness of decolonisation and the increased risk of developing BSI due to ESBL-Enterobacteriaceae in colonised neutropenic patients (Arnan 2011, Liss 2012, Verheshild 2014).



Decolonisation in high risk population

Recommendation

- **Careful monitor for resistance to gentamicin and colistin during decolonization treatment using stool cultures**

Grading: Recommendation for research and possibly conditional recommendation for the intervention in neutropenic patients undergoing the decolonisation

Recommendation

- **Perform antimicrobial susceptibility testing according to the EUCAST clinical breakpoints**

Grading: Recommendation for research and possibly conditional recommendation for the intervention in neutropenic patients undergoing the decolonisation



Decolonisation in high risk population

Recommendation

- Evaluate risk of infection in high risk population including other type of resistance mechanisms than ESBL

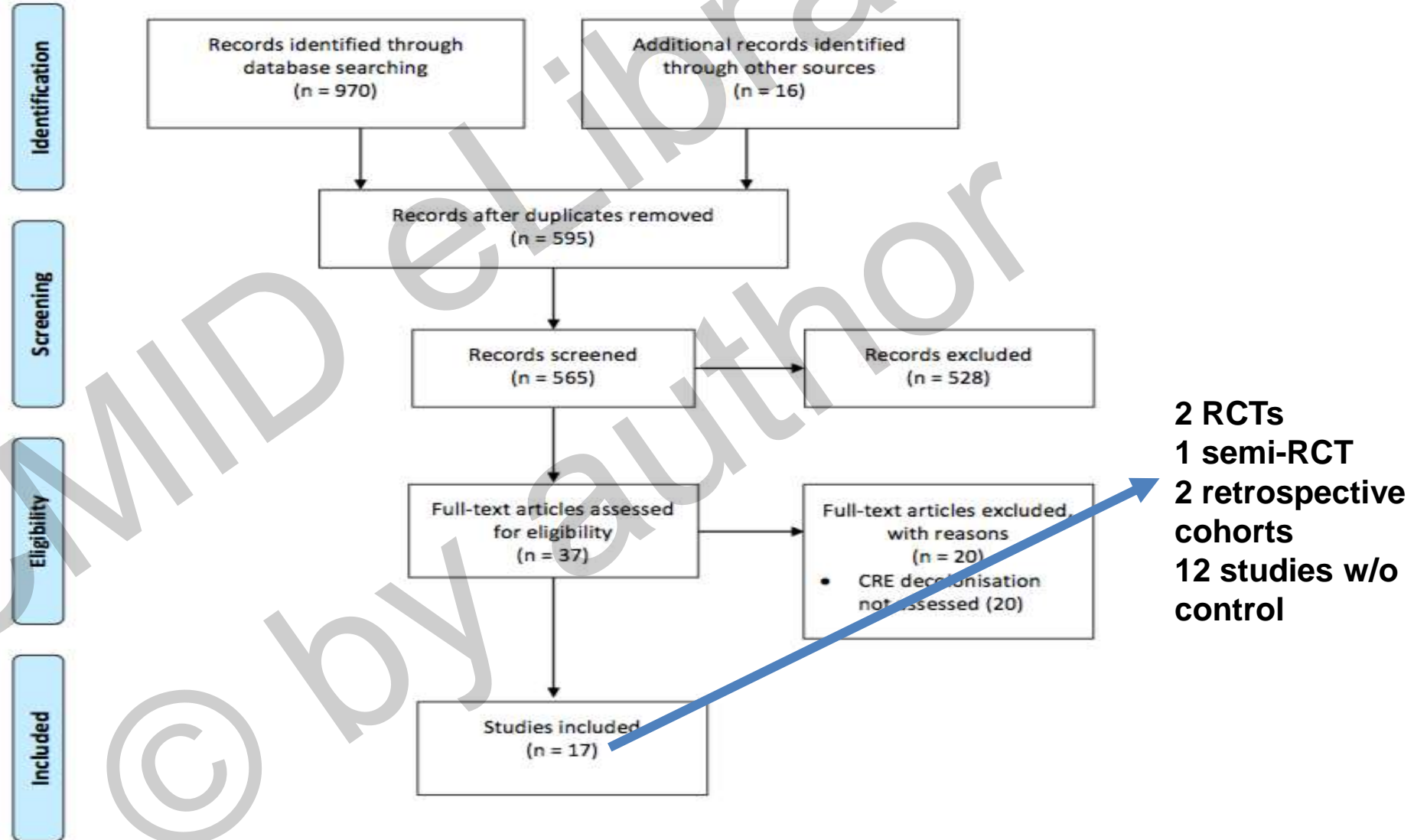
Grading: Recommendation for research

Recommendation

- Decolonisation of 3GCephaRE carriers in high population (ICU and transplants) needs clinical trial to define effectiveness and side effects

Grading: Recommendation for research

CRE



Oral Gentamicin and Oral Polymyxin E

All hospitalised patients

Randomized, Double-Blind, Placebo-Controlled Trial (Quality: 4/8)

- 40 patients included
- Duration of treatment: 7 days
- All throat cultures became negative in the SDD arm after 3 days (P .0001)
- The percentages of rectal cultures that were positive for CRKP were significantly reduced at 2 weeks
- A difference between the percentages in the 2 arms was still maintained at 6 weeks

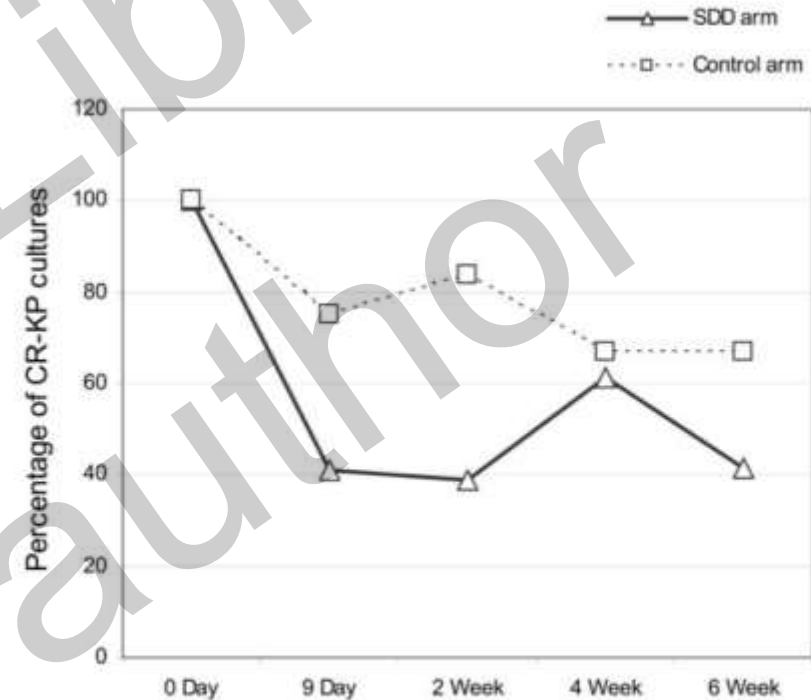


FIGURE 2. Frequency of rectal carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) colonization in the selective digestive decontamination (SDD) group and the control group.

Evidence

Microbiological outcome

- The decolonisation with gentamicin ± colistin is effective in reducing carriers rates at the end of the decolonisation treatment
 - **Evidence level: Low** (one RCT, moderate/high risk of bias)

Clinical outcome

- The decolonisation reduces crude mortality in high risk population (max follow up 6 months) after treatment in hospitalised patients
 - **Evidence level: Low** (one retrospective study)
- The decolonisation reduces infections after treatment (max follow up 6 months) in hospitalised patients
 - **Evidence level: Very Low** (one retrospective study)

Epidemiological outcome

- The treatment can increase the risk of colonisation with bacteria resistant to the decolonising agents
 - **Evidence level: Very Low** (one semi-randomised, high risk of bias; two retrospective cohort)



Decolonisation for CRE carriers

Recommendation

- **Do not use routine decolonisation of CRE carriers**

Grading: **Conditional recommendation against the routine use**



Decolonisation in high risk population

Recommendation

- **Consider a decolonisation treatment with oral colistin sulphate (50 mg four times daily) ± gentamicin (80 mg four times daily) to temporary suppress the CRE carriage in high risk population.** Ensure that the intervention, if chosen, is performed in the context of an IRB approval and appropriate quality controls and follow up.

Grading: Recommendation for research and possibly conditional recommendation for use in high risk patients

Based on the evidence of increased risk of developing CRE infections in **colonised ICU patients** (Chu 2014, Debby 2012, Pedramitou 2013, Pisney 2014, Latibeaudire 2015, McConville 2017) and the results of the effectiveness of decolonisation on CRE carriers (low quality evidence)



Decolonisation in high risk population

Recommendation

- **Careful monitor for resistance to gentamicin and colistin during decolonization treatment using stool cultures**

Grading: Recommendation for research and possibly conditional recommendation for the intervention in neutropenic patients undergoing the decolonisation

Recommendation

- **Perform antimicrobial susceptibility testing according to the EUCAST clinical breakpoints**

Grading: Recommendation for research and possibly conditional recommendation for the intervention in neutropenic patients undergoing the decolonisation



Decolonisation in high risk population

Recommendation

- **Evaluate risk of infection in high risk population including other type of resistance mechanisms than ESBL.** Current evidence in high risk populations is very limited and confounded by lack of adjustment for comorbidities in trials mainly performed in mixed ICU.

Grading: Recommendation for research

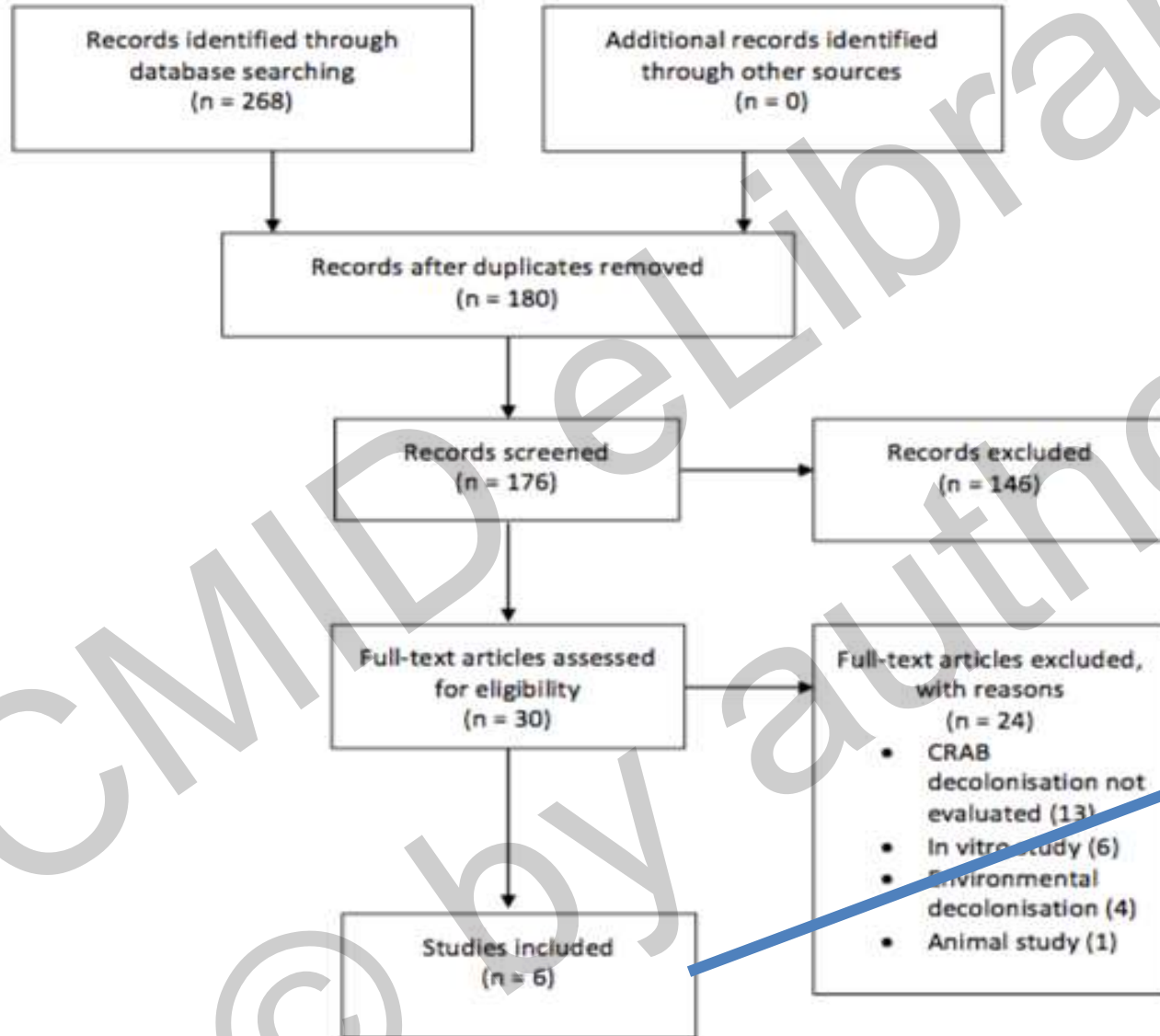
Recommendation

- **Decolonisation of CRE carriers in neutropenic and transplant population needs clinical trial to define effectiveness and side effects**

Grading: Recommendation for research



Identification
Screening
Eligibility
Included



1 cohort prospective
3 case-control
2 studies w/o control

4% chlorhexidine whole-body washing

Skin colonisation

Medical ICU (Quality: 4/7)

- Prospective cohort trial; 55 patients
- Disinfection was carried out on a daily basis until discharge
- 80% decolonised at 48 hours
- Prevalence of CRAB-BSIs decreased from 4.6% to 0.6% (P .001; OR: 7.6) and incidence decreased from 7.8 to 1.25 (85% reduction)



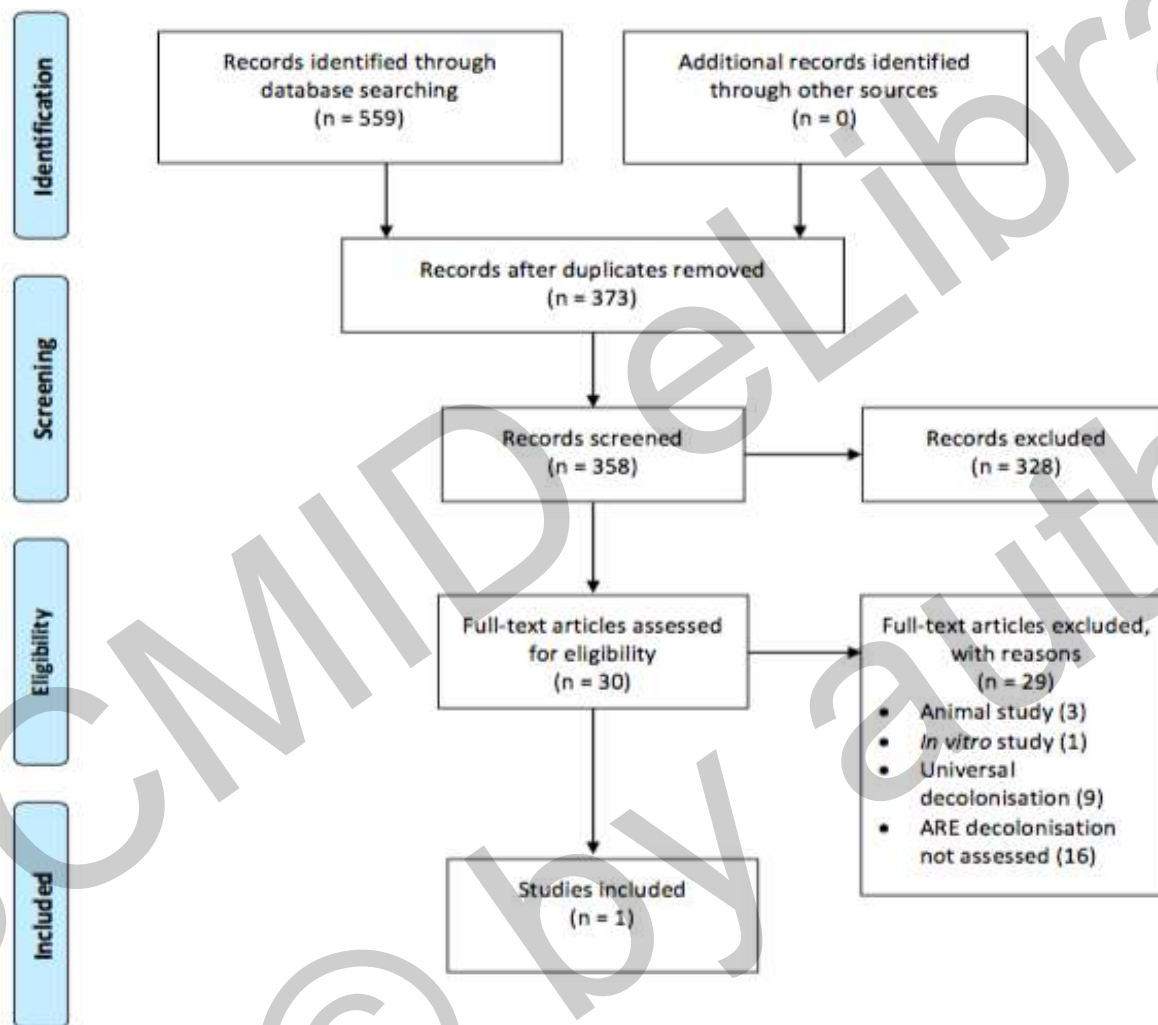
Decolonisation of CRAB carriers

Recommendation

- **Do not use decolonisation of CRAB carriers**

Grading: **Conditional recommendation against the use**

AGRE



Nested post-doc analysis of a cluster RCT without comparator

Oral decontamination

13 ICUs (Quality: 5/7)

- Oropharyngeal application of a paste containing colistin, tobramycin, amphotericin B (2% concentration) plus 10 mL of a suspension containing 100 mg of colistin, 80 mg of tobramycin, 500 mg of amphotericin B via a nasogastric tube, 4 times daily until ICU discharge. Cefotaxime (1000 mg, every 6 h) i.v. 4 days.
- Decontamination rate of 62% (31/50) after a median of 5.5 days (IQR, 3-60 days) of decolonizing treatment.
- If eradication failed, no associations were found with increased resistance in time.



Decolonisation of AGRE carriers

Recommendation

There is not enough evidence to provide recommendations for, or against, any intervention

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Decolonisation and fecal transplantation

FECAL MICROBIOTA TRANSPLANTATION STUDIES			
CRE			
Author	Year	Design	Number of patients
Bilinski	2017	Case Series	20
Bilinski	2016	Case report	1
Davido	2017	Case Series	6
Garcia-Fernandez	2016	Case report	1
Lagier	2015	Case report	1
Freedman	2014	Case report	1
Ponte	2017	Case report	1
3GCephRE			
Author	Year	Design	Number of patients
Singh	2014	Case report	1
Bilinski	2017	Case Series	13
Bilinski	2016	Case report	1

Recommendation

There is not enough evidence to provide recommendations for, or against, the intervention

Conclusions

- There is low quality evidence of increased risk of severe infections in ESBL-Enterobacteriaceae and CRE carriers in high risk settings (haematology, ICU and transplant).
- Based on the evidence at the time of this guidelines the panel does not recommend routine decolonisation for MDR-GNO of hospitalised patients.
- The panel suggests to consider decolonisation treatment with colistin with or without gentamicin to temporary suppress ESBL-Enterobacteriaceae and CRE colonisation in high risk population under controlled intervention and monitoring of resistance and side effects.

Conclusions

- There is a strong recommendation for research to define most effective drugs, dosages, and duration.
- R&D should consider targeting research on selective agents for decolonisation and topical disinfectants effective against MDR-GN bacteria.
- Based on the available evidence and the current antibiotic pipeline the panel strongly suggest enhanced infection control and antimicrobial stewardship programme in high risk population.
- The panel consider this ESCMID guidelines as 'living' project and will constantly monitor evidence to update the recommendation when new evidence will be available
- The panel will also be working on developing clear indications on studies to be performed to improve available evidence.

Guidelines Committee

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