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Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis

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Background: ESBL-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) are rapidly spreading worldwide. Their natural reservoir is intestinal.

Methods: We carried out a systematic review and meta-analysis to estimate CRE and ESBL carriage duration and to evaluate the effect of decolonization therapy. We included cohort and comparative studies examining the natural history of CRE/ESBL colonization, examining rates of carriage following decolonization or comparing decolonization and no decolonization conducted in the healthcare setting or in the community. A comprehensive search was conducted until November 2015. We compiled carriage rates at 1, 3, 6 and 12 months with and without decolonization therapy and assessed the effect of decolonization.

Results: Thirty-seven studies fulfilled inclusion criteria. In healthcare settings, pooled ESBL/CRE colonization rates decreased without intervention from 76.7% (95% CI = 69.3%–82.8%) at 1 month to 35.2% (95% CI = 28.2%–42.9%) at 12 months of follow-up. Following decolonization, the rate was 37.1% (95% CI = 27.5%–47.7%) at end of therapy and 57.9% (95% CI = 43.1%–71.4%) at 1 month. In two randomized trials, carriage was significantly reduced at end of therapy (risk ratio = 0.42, 95% CI = 0.25–0.65), but the effect was not significant after 1 month (risk ratio = 0.72, 95% CI = 0.48–1.05), with no longer follow-up. Heterogeneity was explained by surveillance methodology, with no differences observed between ESBLs and CREs. Among community dwellers, ESBL colonization decreased from 52.3% (95% CI = 29.5%–74.2%) at 1 month to 19.2% (95% CI = 9.7%–34.4%) at 6 months.

Conclusions: A significant proportion of ESBL and CRE carriers remain colonized up to 1 year in the healthcare setting. While short-term decolonization therapy reduces carriage during therapy, its longer-term effects are unclear.

Introduction

ESBL-producing Enterobacteriaceae (ESBL-E) and carbapenem-resistant Enterobacteriaceae (CRE) pose a major clinical problem worldwide.[1,2] Carriage rates vary between different geographical regions and change over time; ESBL-E are prevalent worldwide nowadays and carriage has been reported in 8%–28.2% of ICU patients,[3–5] while CRE carriage rates range between 0.3% and 50% in different healthcare facilities.[6–11] Infections by these MDR Enterobacteriaceae (MDR-E) arise most commonly from gastrointestinal tract (GIT) carriage and carry high morbidity and mortality.[12,13] We have little information on the natural history of MDR-E carriage. Duration of carriage probably depends on antibiotic exposure, extent of contact with the healthcare system and possibly on continued use of catheters.[10,11,14,15]

Decolonization is an appealing measure to curtail the carriage state and possibly reduce infections. The major potential drawback of decolonization strategies is resistance induction or selection. Some experience on bowel decolonization has been gained with selective digestive tract decontamination (SDD), tested in many randomized controlled trials (RCTs) and shown to reduce infection rates and all-cause mortality.[16,17] Surprisingly, induction of antimicrobial resistance has been demonstrated in only few studies; rather, several studies suggested that SDD could reduce the emergence of resistant bacteria and lowered the incidence of the carrier state of these strains in ICUs.[16–20] However, most

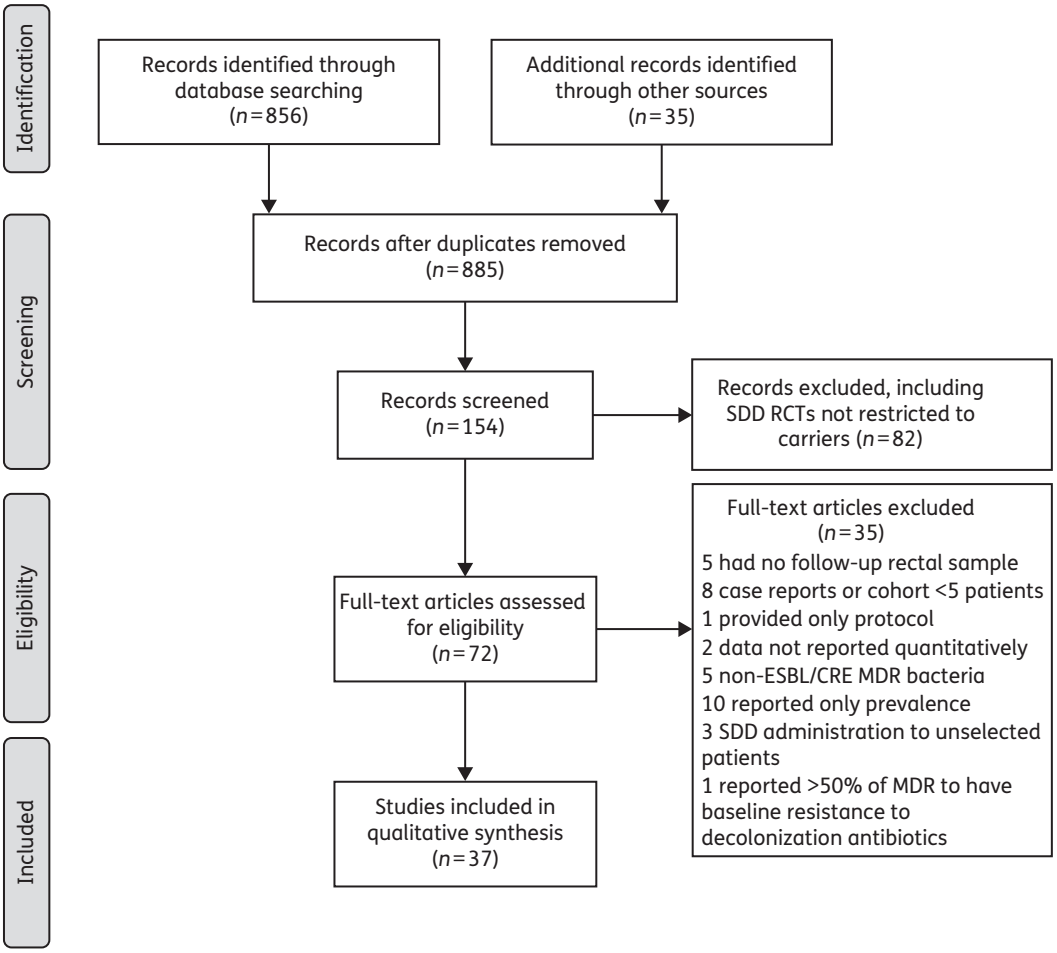

Figure 1. Inclusion/exclusion flow diagram.

of these studies were carried out in settings with low rates of ESBL carriage and no CRE endemicity.

In this systematic review and meta-analysis, we aimed to assess the natural duration of ESBL/CRE carriage in the GIT and the effect of decolonization therapy on the ESBL/CRE GIT carriage among carriers.

Methods

We included RCTs, prospective or retrospective cohort studies, case–control studies or case series of five patients or more examining the natural history of MDR-E colonization, examining rates of carriage following decolonization or comparing decolonization and no decolonization. Only studies performing at least one follow-up surveillance culture during follow-up or at end of decolonization treatment were included. We included adults and children as carriers of ESBL-E and/or CRE, diagnosed through rectal swabs, stool samples or clinical cultures, residing in the healthcare setting or in the community. We excluded studies assessing SDD in patients not selected by carriage.

In comparative studies, the intervention assessed was decolonization, defined as any single or combination regimen of non-absorbable antibiotics administered orally for any duration, with or without concomitant systemic antibiotics, versus placebo or no treatment. We documented rates of resistance of baseline ESBL/CRE isolates to decolonization therapy when reported and excluded interventional studies/study arms reporting >50% of isolates resistant to decolonization therapy.

The outcomes assessed in all studies were MDR-E carriage rates at 1, 3, 6 and 12 months. In studies using decolonization, we assessed also MDR-E carriage at the end of therapy. Eradication of carriage was optimally defined by three separate negative rectal swabs, at least one of which was performed using PCR methods. However, we accepted and documented the study definitions for eradication. Carriage rate at a defined time point was defined as the number of carriers out of all carriers that was evaluated at that time point. If the time points reported in the studies were different from ours, we used the time points closest to our definitions or estimated these from the duration of carriage. We converted medians into absolute number of patients using accepted methods.[21]

We searched the following electronic databases: PubMed, the Cochrane Library, EMBASE and Google Scholar. In addition, we searched the references of all included studies. We applied no limits by publication status, language or date of publication. The search in PubMed was the following and was tailored to the other databases: ((decolonization OR decolonisation OR eradication OR de-colonization OR de-colonisation OR decontamination OR de-contamination) OR ((carrier OR carriage) NEAR duration) OR ((carrier OR carriage) AND (Follow-Up Studies OR Time Factors)) OR ((carrier OR carriage) AND longitudinal study) OR ((carrier OR carriage) AND natural history)) AND (ESBL OR extended spectrum beta-lactamase OR CRE OR carbapenem-resistant OR Carbapenemase OR Carbapenamase OR KPC OR Klebsiella OR CRKP).

Table 1. Characteristics of studies reviewed

Study	Country	Setting	Study years	Age (years), mean ± SD or median (range)	No. of patients included	% IM[a]	Study design
CRE							
Lübbert[25] 2014	Germany	tertiary hospital	2010–2013	62 (21–85)	86	25.6	prospective cohort, surveillance for spontaneous eradication
Lübbert[26] 2013	Germany	tertiary hospital	2010–2013	63 (41–82)	14	7.1	retrospective cohort, single arm, active decolonization therapy
Tascini[27] 2014	Italy	three tertiary hospitals	NS	63.7 ± NS	50	NS	prospective cohort, active decolonization therapy
Feldman[28] 2013	Israel	tertiary hospital and LTCF	2008–2011	67.5 ± NS	125	NS	retrospective and prospective cohort, surveillance for spontaneous eradication
Oren[29] 2013	Israel	tertiary hospital	2009–2011	53.4 (21–79)	41	52.3	controlled clinical trial, active decolonization therapy arm
Oren[29] 2013				65 (26–99)	47	26.4	controlled clinical trial, surveillance for spontaneous eradication arm
Zimmerman[15] 2013	Israel	primary hospital	2009–2012	78 (32–102)	97	NS	retrospective and prospective cohort, surveillance for spontaneous eradication
Saidel-Odes[30] 2012[b]	Israel	tertiary hospital	2008–2010	69 ± NS	40	30	RCT, double-blind, decolonization therapy versus placebo
Zuckerman[31] 2011	Israel	tertiary hospital	2008–2009	55 (32–80)	15	100	prospective cohort, active decolonization therapy
Ben-David[32] 2011	Israel	12 LTCF and rehabilitation centres	2008–2009	72.7 ± 16	123	NS	retrospective cohort, surveillance for spontaneous eradication
Schechner[33] 2011	Israel	tertiary hospital	2006–2008	72 ± 19	66	15.5	retrospective cohort, surveillance for spontaneous eradication
ESBL							
Rieg[34] 2015	Germany	tertiary hospital outpatient	2008–2012	57 (19–86)	45	33.3	prospective cohort, active decolonization therapy
Ruppé[35] 2015	France	community	2012–2013	36 ± 13	245	NS	prospective cohort, surveillance for spontaneous eradication
Papst[36] 2015	Slovenia	tertiary hospital	2009–2012	61 ± 16	114	7	prospective cohort, surveillance for spontaneous eradication
Jallad[37] 2015	Lebanon	LTCF	2012	84.3 ± 5.2	57	NS	prospective cohort, surveillance for spontaneous eradication
Lübbert[38] 2015	Germany	community	2013–2014	34 (32–80)	72	0	prospective cohort, surveillance for spontaneous eradication
Titelman[39] 2014	Sweden	tertiary hospital	2009	58.3 ± NS	61	NS	prospective cohort, surveillance for spontaneous eradication
Gutiérrez-Urbón[40] 2014	Spain	tertiary neonatal ICU	NS	preterm neonates	6	NS	prospective cohort, active decolonization therapy
Huttner[41] 2013[b]	Switzerland	tertiary hospital	2009–2012	54.5 (19–81)	58	10.3	RCT, double-blind, active decolonization therapy versus placebo
Birgand[42] 2013	France	tertiary hospital	1997–2010	62.8 (49–75)	448	NS	prospective cohort, surveillance for spontaneous eradication
Löhr[43] 2013	Norway	tertiary neonatal ICU	2008–2009	neonates and adults	62	NS	prospective cohort, surveillance for spontaneous eradication
Strenger[44] 2013	Austria	tertiary neonatal ICU	2007–2008	neonates	25	NS	prospective cohort, surveillance for spontaneous eradication
Paltansing[45] 2013	Netherlands	community	2011	33 (19–82)	133	NS	prospective cohort, surveillance for spontaneous eradication
Alsterlund[46] 2012	Sweden	community	2005–2010	40 (NS)	23	NS	prospective cohort, surveillance for spontaneous eradication
Tham[47] 2012	Sweden	community	2007–2010	38 (1–83)	58	NS	prospective cohort, surveillance for spontaneous eradication
Li[48] 2012	China	medical students	2011	21 (20–23)	41	NS	prospective cohort, surveillance for spontaneous eradication
Rogers[49] 2012	Australia	community	2008–2009	45.7 (NS)	20	NS	prospective cohort, surveillance for spontaneous eradication
Oostdijk[50] 2012	Netherlands	13 tertiary hospitals ICU	2004–2006	NS	77	NS	prospective cohort, active decolonization therapy
Abecasis[51] 2011	UK	tertiary paediatric ICU	2005–2006	paediatric	39	5.5	prospective cohort, active decolonization therapy

Continued

Table 1. *Continued*

Study	Country	Setting	Study years	Age (years), mean ± SD or median (range)	No. of patients included	% IM[a]	Study design
Buehlmann[52] 2011	Switzerland	tertiary hospital	2000–2008	67 (18–99)	100	18	prospective cohort, active decolonization therapy
Zahar[53] 2010	France	tertiary hospital	2006–2007	12.5 (NS)	62	46.8	prospective cohort, surveillance for spontaneous eradication
Tängdén[54] 2010	Sweden	community	2007–2009	47 (NS)	24	0	prospective cohort, surveillance for spontaneous eradication
Weintrob[55] 2010	USA	tertiary hospital	2008	29.1 ± 7.3	13	NS	prospective cohort, surveillance for spontaneous eradication
Tandé[56] 2010	France	community	2002–2005	neonates	31	NS	prospective, single arm, surveillance for spontaneous eradication
Apisarnthanarak[57] 2008	Thailand	tertiary hospital/community	2007	55 (21–65)	24	NS	prospective cohort, surveillance for spontaneous eradication
Reddy[58] 2007	USA	tertiary medical ICU	2000–2005	NS	40	NS	prospective cohort, surveillance for spontaneous eradication
Troché[59] 2005	France	tertiary surgical ICU	1995–2000	NS	37	NS	prospective cohort, active decolonization therapy
Paterson[60] 2001	USA	tertiary surgical ICU	1998	NS	5	100	prospective cohort, active decolonization therapy

NS, not specified.
[a]Immunosuppressive state (defined as concurrent immunosuppressive treatment or haematological malignancy).
[b]RCT.

Two reviewers independently applied inclusion criteria and extracted the data from included studies. Corresponding authors were contacted to retrieve missing data. We extracted data on the study settings (country, study years) and environment [hospital versus community versus long-term care facility (LTCF)]. We documented length of hospital stay as the measure of healthcare exposure, isolation precautions used in healthcare settings, antibiotic exposure and immunosuppressive state (defined as concurrent immunosuppressive treatment or haematological malignancy). As risk of bias assessment is not well-established for longitudinal studies that do not assess an intervention or exposure, we recorded study methods and variables we assumed related to the quality of colonization surveillance. The latter included the microbiological methods for MDR-E identification (strain and resistance mechanism) and whether these allowed for strict evaluation of persistence of initial strains at follow-up versus presence of a phenotypically similar MDR-E without proof of strain identity (presence versus persistence), the duration of follow-up, losses to follow-up and the eradication definition (see above). For RCTs and non-randomized comparative studies we assessed risk of bias using the domain-based approach recommended in the Cochrane Handbook[22] and the ROBINS-I tool,[23] respectively. Subsequently, the quality of evidence was rated according to GRADE recommendations.[24]

Eradication rates with and without decolonization therapy were compiled at the designated time points. From comparative studies, we also calculated and compiled risk ratios (RRs) for decolonization for intervention versus placebo/no treatment with 95% CIs. Meta-analysis of rates or RRs was conducted using a random effects model. Heterogeneity is reported using the I^2 measure of inconsistency, with values >50% denoting substantial heterogeneity.[22] Analysis was stratified by study settings [community versus healthcare (hospital and LTCF)]. In addition, sub-group analysis was performed according to the resistance type (ESBL or CRE), age group (paediatric versus adult patients), confirmed persistence of the same bacteria (presence or persistence of bacteria), eradication definition (only 1 negative sample versus >1 negative samples) and extra-intestinal MDR-E documentation [GIT alone or concomitant systemic infection/carriage at other sites (i.e. urine)]. Differences between subgroups and indirect comparisons between studies using decolonization or not was based on a χ^2 test of heterogeneity across subgroups. We planned meta-regression on other factors potentially underlying heterogeneity, including extra-intestinal MDR-E carriage, exposure to systemic antibiotics (both CRE-covering and non-CRE-covering), immunosuppression, presence of indwelling devices and exposure to the healthcare setting. For decolonization studies, we also assessed resistance to de-colonizing therapy. For analyses including more than 10 studies, we assessed the effects of small studies through visual inspection of funnel plot of the log event rate and standard error. Analyses were conducted using Comprehensive Meta-Analysis version 3 (NJ, USA) and Review Manager version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

The search, performed on 3 November 2015 resulted in 891 results. One hundred and sixty relevant abstracts were reviewed, of which 37 studies fulfilled inclusion criteria (Figure 1). Ten studies assessed patients colonized by CRE[15,25–33] and 27 assessed ESBL colonization,[34–60] of which 5[26,27,29–31] and 8[34,40,41,50–52,59,60] assessed decolonization strategies, respectively. There were two RCTs[30,41] and one[29] controlled clinical study assessing the efficacy of decolonization therapy, while the rest were retrospective or prospective non-comparative cohort studies. Both RCTs reported adequate randomization methods and were double-blinded, while the controlled clinical trial had serious risk of bias

Table 2. Surveillance protocol and eradication definition

Study	Molecular identification of MDR-E to strain level and resistance genotype	Surveillance protocol	Lost to follow-up[a], *n*/*N* (%)	Total duration of follow-up	Eradication definition (number of consecutive negative cultures ± PCR)
CRE					
Lübbert[25] 2014	no	1, 3, 6, 24, 48 months	2/86 (2.3)	2 years	3+PCR separated by 48 h
Lübbert[26] 2013	yes	weekly	0/14 (0)	9–154 days	
Tascini[27] 2014	yes	every 4 days during therapy and at 6 months	0/50 (0)	6 months	2
Feldman[28] 2013	no	0.5, 1, 2, 3 months	0/125 (0)	NS	2+PCR, not followed by any positive
Oren[29] 2013	no	weekly	10/52 (19.2)	1–76 days	3+PCR in at least 1 week
Oren[29] 2013	no	not routine	55/102 (53.9)	20–737 days	
Zimmerman[15] 2013	yes	not routine	0/97 (0)	1 year	1, not followed by any positive
Saidel-Odes[30] 2012	no	3, 7, 9, 14, 28, 42 days	1/40 (2.5)	7 weeks	1
Zuckerman[31] 2011	no	thrice weekly, once weekly post-discharge	0/15 (0)	NS	3+PCR in at least 1 week
Ben-David[32] 2011	no	once	0/128 (0)	NS	1
Schechner[33] 2011	no	re-admissions	0/66 (0)	1–658 days	1+PCR
ESBL					
Rieg[34] 2015	no	0, 0.5, 1 and 1.5 months	0/45 (0)	3 months	1
Ruppé[35] 2015	no	1, 2, 3, 6 and 12 months	47/292 (16)	1 year	1
Papst[36] 2015	no	every 3 months	15/114 (13.1)	2 years	NS
Jallad[37] 2015	no	1, 3 months	0/57 (0)	3 months	1
Lübbert[38] 2015	yes	6 months	23/49 (46.9)	6 months	1
Titelman[39] 2014	yes/no	1, 3, 6, 12 months	0/61 (0)	12 months	1, not followed by any positive
Gutiérrez-Urbón[40] 2014	no	2 days post-treatment	1/6 (16.6)	7 days	1
Huttner[41] 2013	no	1, 7, 28 days post-treatment	7/58 (12)	28 days	1
Birgand[42] 2013	no	re-admissions	0/448 (0)	NS	1
Löhr[43] 2013	yes	monthly in first year, quarterly thereafter	0/62 (0)	3 years	3
Strenger[44] 2013	yes	1, 2, 4, 6, 9, 12 months	7/25 (28)	1 year	1
Paltansing[45] 2013	yes/no	6 months	6/133 (4.5)	6 months	1
Alsterlund[46] 2012	yes	monthly to quarterly	0/23 (0)	4.5 years	1, not followed by any positive
Tham[47] 2012	yes/no	3 or 8 months and 3 years	0/54 (0)	3 years	1
Li[48] 2012	no	every 2 weeks	7/95 (7.3)	4 months	1
Rogers[49] 2012	yes	monthly	0/20 (0)	6 months	2
Oostdijk[50] 2012	no	bi-weekly	0/77 (0)	3–77 days	2
Abecasis[51] 2011	yes	bi-weekly	5/39 (12.8)	NS	1
Buehlmann[52] 2011	no	2 days post-treatment and re-admissions	4/39 (10.2)	2 years	1, not followed by any positive
Zahar[53] 2010	no	re-admissions	0/62 (0)	97–152 days	1
Tängdén[54] 2010	yes	6 months	3/24 (12.5)	6 months	1
Weintrob[55] 2010	yes	bi-weekly for 2 weeks then weekly	6/13 (46.1)	8 weeks	3, not followed by any positive
Tandé[56] 2010	yes	monthly	0/31 (0)	NS	3
Apisarnthanarak[57] 2008	no	every 2 weeks	0/24 (0)	6 months	NS
Reddy[58] 2007	no	re-admissions	0/40 (0)	1 year	1
Troché[59] 2005	no	weekly	0/37 (0)	NS	2
Paterson[60] 2001	yes	2, 14, 28 days post-treatment	1/5 (20)	28 days	1, not followed by any positive

NS, not specified.
[a]Lost to follow-up/death at first time point of assessment (end of treatment for decolonization studies).

Table 3. Natural history of colonization without decolonization treatment among healthcare residents at the defined time points

Subgroup	No. of studies[a]	No. of patients[a]	Pooled rate of colonization (%)[b]	95% CI	I^2 (%)	*P* between subgroups
Total 1 months	12	429	76.7	69.3–82.8	52	
ESBL	6	190	80.2	67.7–88.7	56.9	0.383
CRE	6	239	73.9	64–81.8	47.9	
adult	10	360	74.8	67.7–80.7	39.7	0.306
children	2	69	92.1	46.5–99.4	81.0	
eradication defined as only 1 negative sample	5	86	69.4	59.7–77.7	0.0	0.068
eradication defined as >1 negative sample	7	274	81.5	71.4–88.6	64.7	
presence of MDR-E	9	362	75.0	67.7–81.1	46.5	0.315
persistence same MDR-E	4	128	83.9	65.5–93.5	54.7	
Total 3 months	10	431	75.2	64.6–83.4	74	
ESBL	6	268	76.5	61.1–87.1	76.9	0.852
CRE	4	163	74.6	56.6–86.9	72.7	
adult	8	359	72.5	61.6–81.2	68.9	0.017
children	1	51	96.1	80.7–99.3	0.0	
eradication defined as only 1 negative sample	5	210	69.2	52.3–82.1	62.4	0.168
eradication defined as >1 negative sample	5	221	82.9	67.8–91.8	80.7	
presence of MDR-E	7	294	70.7	56.2–82	65.7	0.496
persistence same MDR-E	4	198	78.0	59–89.7	87.3	
Total 6 months	10	408	55.3	43.7–66.4	76	
ESBL	5	223	56.1	38.7–72.1	83.7	0.945
CRE	5	185	55.2	37.3–71.9	67.3	
adult	7	322	53.0	38.8–66.8	55.6	0.659
children	2	67	67.6	38.4–87.5	95.5	
eradication defined as only 1 negative sample	4	141	43.1	26.9–60.9	4.7	0.079
eradication defined as >1 negative sample	6	267	63.9	48.9–76.5	82.2	
presence of MDR-E	8	302	47.6	35.6–59.8	43.2	0.065
persistence same MDR-E	3	167	68.3	49.9–82.4	90.7	
Total 12 months	12	861	35.2	28.2–42.9	67	
ESBL	7	689	35.7	26.3–46.2	76.9	0.899
CRE	5	172	34.6	22.9–48.5	46.0	
adult	9	782	33.5	26.4–41.5	53.9	0.555
children	2	65	39.4	21.1–61.1	88.0	
eradication defined as only 1 negative sample	6	620	30.9	22.7–40.6	54.1	0.208
eradication defined as >1 negative sample	6	241	39.8	29.9–50.7	62.9	
presence of MDR-E	10	787	32.6	25.8–40.3	60.4	0.328
persistence same MDR-E	3	135	40.0	17.7–53.8	63.3	

[a]For several outcomes and time points, the total number of patients does not fit the sum of both subgroups due to a variable number of patients evaluated for each.
[b]Pooled colonization rates from a random effects meta-analysis.

(Figure S1, available as Supplementary data at *JAC* Online) and, thus, we assessed its decolonization and control arms separately. The studies were performed between 1995 and 2014 and assessed mostly adults (28 studies). Immune-compromised patients were assessed in 16 studies (Table 1). Studies varied greatly in their surveillance protocols and eradication definition. Molecular techniques for specific strain and resistance genotype identification were used in 16 of 37 studies, ensuring that follow-up strains were identical to initial isolates and truly persistent. Eradication was based on a single negative rectal swab in 18 studies and on two or more consecutive samples (including a single negative sample with no further negative sample) in 16 studies (Table 2).

Natural history

The natural history of MDR-E colonization without decolonization therapy in residents of a healthcare facility was reported in 26 studies, 25 of them in acute care hospitals. We included in this analysis studies assessing spontaneous eradication rates or placebo/no treatment arms of comparative studies comparing spontaneous eradication versus decolonization. Meta-analysis

Table 4. Decolonization regimens and resistance to decolonization antibiotics

Study	Decolonization regimen (route, type, dose and duration of antibiotic treatment)	Percentage of patients with bacteria resistant to eradication therapy
CRE		
Tascini[27] 2014	oral, 80 mg of gentamicin, 4 times daily for at least 8 days (median=16 days)	0%
Lübbert[26] 2013	oral solutions (1 MIU of colistin sulphate and 80 mg of gentamicin sulphate) and topical oropharyngeal application of a gel [gentamicin sulphate (1.6 mg/g) and colistin sulphate (1 MIU/g)], 4 times daily for 7 days	0% gentamicin and 45% colistin resistance
Oren[29] 2013	oral, 2 MIU of colistin sulphate OR 80 mg of gentamicin, 4 times daily OR both, up to eradication (median=33 days)	0% resistance by treatment groups
Saidel-Odes[30] 2012	oral, 80 mg of gentamicin sulphate and 1 MIU of colistin sulphate, 4 times daily and topical oropharyngeal application of 0.05 MIU of colistin sulphate and 0.8 mg of gentamicin sulphate, 4 times daily for 7 days	0%
Zuckerman[31] 2011	oral, 80 mg of gentamicin, 4 times daily for a median of 27 days	NS
ESBL		
Rieg[34] 2015	oral, 1 or 2 MIU of colistin 4 times daily for 4 weeks OR 400 mg of rifaximin twice daily for 2–3 weeks; for urinary colonization—3 g of fosfomycin (single dose) OR 100 mg of nitrofurantoin twice daily for 5 days OR 100 mg of cefpodoxime twice daily plus 875/125 mg of amoxicillin/clavulanic acid twice daily OR renal function adjusted dose carbapenem, for 3–7 days	10% colistin resistance
Gutiérrez-Urbón[40] 2014	oral solution [3.2% amikacin sulphate and 1% colistin sulphate (1 mL/kg)], 4 times daily for 5 days	0%
Huttner[41] 2013	oral, 1.26 MIU of colistin sulphate and 250 mg of neomycin sulphate, 4 times daily for 10 days; for urinary colonization—100 mg of nitrofurantoin, 3 times daily for 5 days	3.7% colistin resistance
Oostdijk[50] 2012	oral—10 mL (containing 100 mg of colistin, 80 mg of tobramycin and 500 mg of amphotericin B) oropharyngeal—paste (containing 2% colistin, 2% tobramycin and 2% amphotericin B) intravenous—1 g of cefotaxime; all given 4 times daily; all given continuously throughout stay during the first 4 days of study	32.5% had aminoglycoside resistance
Buehlmann[52] 2011	decontamination (DC) course—oral 1 g of paromomycin 4 times daily for 4 days, topical oropharyngeal application of 0.2% chlorhexidine 3 times daily for 5 days; for urinary colonization—100 mg of nitrofurantoin 3 times daily OR 750 mg of ciprofloxacin twice daily OR 800/160 mg of co-trimoxazole twice daily for 5 days OR 3 g of fosfomycin once; all patients received 1–3 DC courses	5% showed reduced susceptibility or resistance to aminoglycosides
Abecasis[51] 2011	parenteral cefotaxime and oral colistin/tobramycin, given continuously throughout stay	0% (resistant strains were excluded from meta-analysis)
Troché[59] 2005	oral combination of two of three antibiotics: 1.5 MIU of colistin sulphate, 500 mg of neomycin or 500 mg of erythromycin; 4 times daily, up to eradication	NS
Paterson[60] 2001	oral, 400 mg of norfloxacin, twice daily for 5 days	NS

NS, not specified.

of the studies at the different time points showed decreasing colonization rates from 76.7% (95% CI=69.3%–82.8%) at 1 month to 35.2% (95% CI=28.2%–42.9%) at 12 months of follow-up (Table 3). No difference between CRE and ESBL carriers in the duration of MDR-E carriage was observed at all time points (Table 3). Rates of eradication were higher when a single sample defined the end of carriage (versus multiple negative samples) and when isolates were only phenotypically identified [versus genotypically identified (documented persistence of the same bacteria)] at all time points, without statistically significant differences between subgroups. Further data presumed to underlie heterogeneity were inconsistently reported and data were insufficient to perform meta-regression analyses. Heterogeneity remained substantial in most analyses and the funnel plots for the overall analysis at each time point were symmetric.

Nine studies were performed in the community setting, mostly assessing rates and duration of ESBL carriage in returning travellers from endemic countries.[35,38,45–49,54,56] None assessed CRE. The pooled colonization rates at 1, 3, 6 and 12 months were 52.3% (95% CI=29.5%–74.2%, 401 persons, 6 studies), 52.5% (95% CI=24%–79.4%, 358 persons, 5 studies), 19.2% (95% CI=9.7%–34.4%, 544 persons, 9 studies) and 25.4% (95% CI=2.4%–82.7%, 271 patients, 3 studies), respectively. All

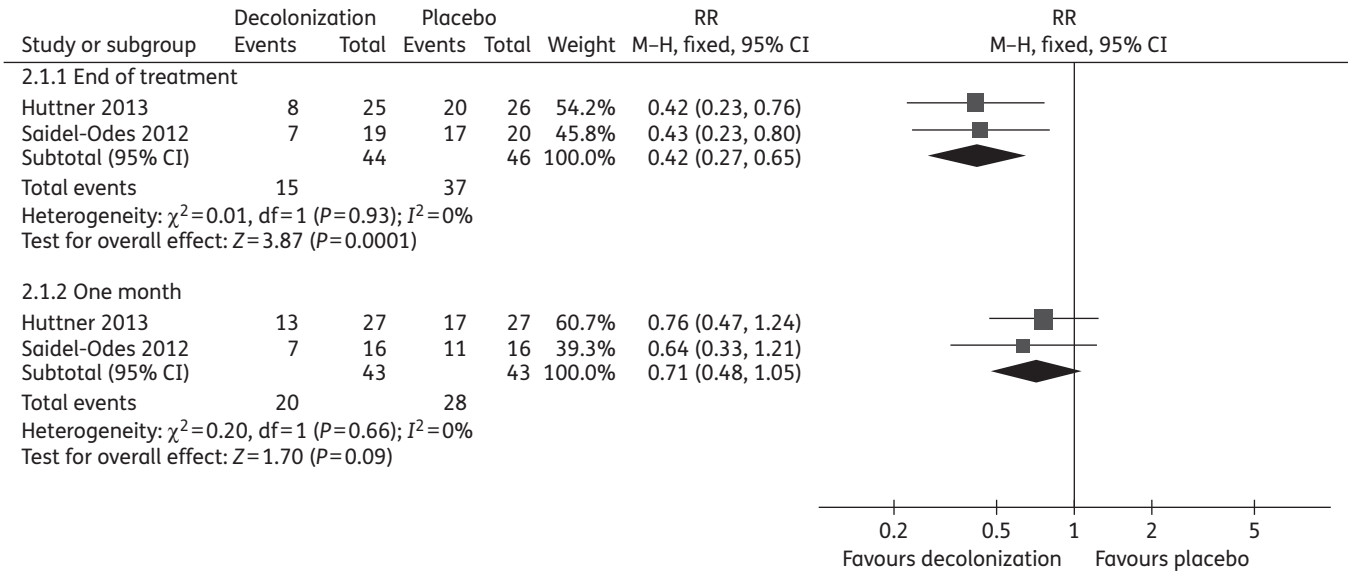

Figure 2. Effects of decolonization therapy in RCTs at end of therapy and 1 month after decolonization.

participants were adults, and most studies did not prove persistence of identical strains using molecular techniques. Subgroup analyses revealed that at all time points the number of negative cultures needed to define eradication influenced the colonization rate. In studies using a single negative sample,[35,38,45–48,54] 38.6%, 45.5%, 16.6% and 2.2% of the patients were colonized at 1, 3, 6 and 12 months, while 65.4%, 64.3%, 22.5% and 56.7% were colonized at these time points when more than one negative sample was required.[49,56]

Effect of decolonization therapy

Decolonization therapy was used in 13 studies (Table 4). Most decolonization strategies included oral aminoglycosides, colistin (polymyxin E) or a combination of both and some had extra oropharyngeal wash/urinary decolonization regimens. In studies that reported resistance to decolonization regimens at the start of treatment, most (10 of 13) reported low resistance rates or supplemented additional systemic MDR-E-covering antibiotics to carriers.

Across all 13 interventional trials, the colonization rate at the end of therapy was 36.6% (95% CI=27.0%–47.3%, I^2=67.15). At 1 month after the end of decolonization therapy, colonization rates were higher (57.9%, 95% CI=43.1%–71.4%, 5 studies, 87 patients, I^2=38%). Subgroup analyses for the duration of decolonization therapy (≤1 week versus until end of follow-up or eradication), ESBL versus CRE, age group, confirmed persistence of the same bacterial strain and eradication definition did not show significant impact on the colonization rate (data not shown). There was no significant difference in persistent colonization rates when patients had extra-intestinal isolation of the MDR-E or when only intestinal colonization was detected: 33.9% (95% CI=16.5%–57.0%, I^2=64.3%) versus 40.3% (95% CI=27.4%–54.6%, I^2=68.4%) at the end of therapy (P=0.388) and 54.2% (95% CI=32.5%–74.4%, I^2=77.3%) versus 62.1% (95% CI=38.9%–80.9%, I^2=0%) at 1 month (P=0.624), respectively. Heterogeneity remained in most analyses (0%–58%) and meta-regression analysis was not possible.

In the two randomized trials comparing decolonization therapy with placebo (one ESBL[41] and one CRE,[30] high-quality evidence), the RR for persistent colonization at the end of decolonization therapy was 0.42 (95% CI=0.25–0.65, I^2=0%). This effect was non-significant after 1 month (RR=0.72, 95% CI=0.48–1.05, I^2=0%) (Figure 2). In indirect comparisons, 1 month carriage rates were lower with decolonization (57.9%, 95% CI=43.1%–71.4%, I^2=38%) versus without (76.7%, 95% CI=69.3%–82.8%, I^2=52%), P=0.015. This trend was observed similarly for ESBLs and CREs.

The development of resistance to decolonization antibiotics was reported in four studies. Resistance to colistin developed in 2 of 6 patients and to gentamicin in 5 of 11 in one study.[26] In another CRE decolonization study, 1 of 13 developed resistance to colistin, 6 of 23 to gentamicin and 0 of 5 to both,[29] and in a third CRE decolonization study 4 of 50 developed resistance to gentamicin.[27] An ESBL decolonization study conducted in Switzerland reported that none of 29 patients developed resistance to decolonization treatment.[41]

Discussion

In this systematic review and meta-analysis, we present the natural history of MDR-E carriage and the effect of decolonization therapy. Overall, carriage rates remained significant up to 1 year of follow-up in the healthcare setting, with 76.7% of colonized patients still carrying the ESBL or CRE at 1 month, 75.2% at 3, 55.3% at 6 months and 35.2% at 12 months. These studies were mostly conducted in acute care hospitals and patients were followed in-hospital or in a recurrent admissions setting. Community residents seem to carry a lower risk for persistent colonization (52.3%, 52.5%, 19.2% and 25.4% at 1, 3, 6 and 12 months, respectively), but still a considerable number of patients carry MDR-E after a year of follow-up. The impact of decolonization therapy on ESBL and CRE carriers was assessed only for the short term. In two RCTs a significant reduction in carriage rates at the end of decolonization therapy (RR=0.42, 95%

CI = 0.25–0.65) was no longer significant and the effect was smaller at 1 month of follow-up. The same trend was observed in non-comparative studies with 36.6% patients colonized at end of decolonization and 57.9% at 1 month. In the few studies that reported on resistance development following decolonization, resistance was indeed documented with a total of 18 of 137 (13.1%) bacteria evaluated at the end of therapy developing resistance to decolonization therapy.

The methodology of screening and documenting persistent carriage affected results. In one of the studies that assessed different screening sites, perirectal screening alone was 80% sensitive for identification of *Escherichia coli* and 67% for *Klebsiella pneumoniae* colonization, while combined use of groin and perirectal cultures had a 100% sensitivity and specificity for both strains.[55] Studies with longer follow-up reported that negative screening samples were frequently followed by positive samples, arguing against the use of a single negative screening sample to declare eradication. Oren *et al.*[29] reported that 45% of CRE carriers who had a negative sample had further positive samples later on. In other studies, between 47% and 88% of carriers had at least one negative sample followed by a positive one.[28,34,55] Some studies suggest the need for urinary screening and supplementation of decolonization regimens with urinary secreted antibiotics if the MDR-E is isolated in the urine.[34,41,52] Most studies in our review did not perform molecular identification of MDR-E to the strain level and resistance genotype, and without these methods some of the persistent isolates might be due to new acquisition of a similar MDR-E, particularly in the healthcare setting. Overall, in our analysis, we observed an effect of the number of negative samples required to define eradication and the use of molecular methods to establish persistence on results.

We analysed jointly the ESBLs and CREs in the primary analyses, since the types of bacteria and their colonization niche are similar. We believe we can learn from the natural history of ESBLs for CRE, as ESBLs have been recognized prior to CRE and more studies addressed ESBLs. Studies examining the natural history of MDR-E colonization varied in the denominator used for reporting of carriage during follow-up, some using all carriers and some excluding those declared as negative at previous time points. We standardized the analyses by evaluating all carriers at all time points (except those lost to follow-up) and analysed the effects of the 'negative' definitions. We evaluated carriage at defined time points rather than compiling the duration of carriage, since durations of carriage were variously reported and non-normally distributed. Furthermore, the former analysis results in information that is easier to implement in clinical practice.

There are limitations to this review. Data on clinical variables affecting the persistence of colonization were limited. Residual heterogeneity in most meta-analyses attests to the probable importance of such predictors. These include systemic antibiotic use, immunosuppressive therapy, catheters and devices, extra-intestinal isolation of the MDR-E and variables associated with possible re-acquisition of MDR-E such as stay in hospital and isolation precautions when hospitalized. Data on these factors were sparse and we could not show the effect of all clinical variables assessed on the duration of colonization or effect of decolonization therapy. Geographical differences in antibiotic usage and infection control practices might underlie heterogeneity. Since actual persistence proven molecularly was rarely assessed, different rates of MDR-E re-acquisition in the healthcare setting is another factor.[61] The analysis on the effect of decolonization therapy was limited by heterogeneity of decolonization regimens used in different studies, mainly the length of decolonization. Part of the effect observed at the end of therapy is artificial, since some studies defined the duration of decolonization by the duration of colonization, continuing decolonization until proof of eradication. Carriage rates observed at 1 month of follow-up after decolonization might better reflect the true effect of decolonization, which was statistically non-significant. The main limitation of evidence in the decolonization effect is the lack of long-term follow-up data. Finally, only two high-quality RCTs assessed the effects of decolonization and all other data rely on non-comparative cohort studies.

Our results have implications for clinical practice and infection control in hospitals. Carriage of MDR-E is significantly associated with clinical infections caused by these organisms.[62,63] Rates of >50% persistent colonization up to 6 months after the detection of carriage mandate attention when prescribing empirical antibiotic treatment for severe infections among carriers. Between 6 and 12 months, colonization rates of ~20% are more difficult to address. Regarding isolation precautions in hospitals, a preventive intervention and without significant adverse events, probably all rates of carriage up to 1 year mandate attention. Our results also point at the need for more than a single negative screening sample before declaring the patient a non-carrier; the precise number of samples and methods (culture versus PCR) is yet unclear. Guidelines do not give clear recommendations on the duration of contact isolation for carriers and number of negative samples needed to declare eradication of the carrier state. Of note, in most parts of the world, single rooms are not available for contact isolation and carriers are cohorted. Cohorting of known carriers on the assumption of continued carriage carries a risk of MDR-E re-acquisition. Given the non-negligible long-term carriage rates, rapid point of care tests for the detection of carriage might be needed to assist judicious care of MDR-E carriers in hospitals. The data on the duration of ESBL carriage in the community shed light on the epidemiology of resistance in the population at large.

Further studies are needed to examine duration of carriage in hospitals in specific patient subgroups and the modifiers of the duration. Decolonization is an appealing strategy to curtail the duration of MDR-E, particularly CRE, thus preventing spread of resistant isolates and reducing clinical infections. However, RCTs are needed to examine the long-term effects of decolonization and its clinical impact. Such trials should separate persistence from re-acquisition of MDR-E and address resistance development. The data to date raise doubt as to the efficacy of decolonization for MDR-E carriers.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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