Colistin Resistant: Is it Preventable?

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OBJECTIVES

- Scenario
- Epidemiology of CR and CoRO GNB
- Evidence on control MDR-GNB
- Evidence on control of Colistin-resistant GNB

Case

A 72 year-old, Thai male, with DM, COPD, renal failure, and recurrent carbapenem-resistant *Acinetobacter buamnnii* treated with colistin for 4 episodes in the past year, presenting to ICU with pneumonia.

Patient was empirically treated with colistin + cefoperazone-sulbactam and was placed on isolation precaution.

His sputum culture grew colistin resistant *A. baumannii* with colistin MIC = 128 mcg/dL and IC team was notified.

Antimicrobial Susceptibility

In Vitro Susceptibility to Various Antibiotics of Colistin-Resistant Gram-Negative Bacterial Isolates in a General Tertiary Hospital in Crete, Greece

George Samones, Dimitrios K. Matthaiou. Diamantis Kofteridis, Sofia Maraki, and Matthew E. Falagas

Table 1. Results of In Vitro Susceptibility Testing of Colistin-Resistant Isolates against Various Antibiotics

Identifier	Isolate	Site of isolation	Sex	COL	IMI	CPFX	GM	CZID	CTAX	CFP	PIP-TAZ	TET	FM	TMP-SMZ	CHL
1	*Klebsiella pneumoniae*	Urine	M	R	R	R	R	R	R	R	R	R	S	R	R
2	*Pseudomonas aeruginosa*	Pus	F	R	S	S	S	S	R	S	S	R	S	R	R
3	*P. aeruginosa*	Bronchial	M	R	S	S	S	S	R	S	S	R	S	R	R
4	*Acinetobacter junii*	Pus	F	R	S	S	S	S	R	S	S	S	R	R	S
5	*A. junii*	Pus	M	R	S	S	S	S	S	S	S	S	S	S	S
6	*K. pneumoniae*	Urine	M	R	S	R	S	S	S	S	S	R	S	R	S
7	*K. pneumoniae*	Urine	M	R	S	R	S	S	S	S	S	R	S	S	S
8	*P. aeruginosa*	Pus	M	R	S	R	R	R	R	R	S	R	S	R	R
9	*P. aeruginosa*	Bronchial	F	R	R	S	S	R	R	R	R	R	S	R	R
10	*Acinetobacter baumannii*	Pus	M	R	S	R	R	R	R	R	S	R	S	R	R

NOTE. BAL, bronchoalveolar lavage; CFP, cefepime; CHL, chloramphenicol; COL, colistin; CPFX, ciprofloxacin; CTAX, cefotaxime; CZID, ceftazidime; F, female; FM, fosfomycin; GM, gentamicin; IMI, imipenem; M, male; PIP-TAZ, piperacillin-tazobactam; R, resistant; S, susceptible; TET, tetracycline; TMP-SMZ, trimethoprim-sulphamethoxazole.

In Vitro Susceptibility to Various Antibiotics of Colistin-Resistant Gram-Negative Bacterial Isolates in a General Tertiary Hospital in Crete, Greece

George Samones, Dimitrios K. Matthaiou. Diamantis Kofteridis, Sofia Maraki, and Matthew E. Falagas

CID 2010:50 (15 June) CORRESPONDENCE

[8], colistin-resistant isolates were found to be more susceptible to penicillins and carbapenems, as well as to cephalosporins, than were colistin-susceptible isolates. However, it is very interesting that these isolates were also susceptible to antibiotic classes that are normally not potent against gram-negative pathogens. In the other study [9], *Acinetobacter* isolates were identified after the determination of the partial *rpoB* gene sequence. According to the variability of the regions in the *rpoB* gene sequence, the susceptibility of *A. baumannii* isolates to other antimicrobial classes increased as their resistance to polymyxins increased.

This observed phenomenon of maintenance of susceptibility to various antimicrobial agents among colistin-resistant isolates in this study may be explained by assuming that the biological cost of antibiotic resistance to colistin led to suppression or loss of resistance genes to other antibiotic classes [10]. However, compensatory mutations may cause the accumulation of numerous drug resistance mechanisms in a pathogen without any reduction in its virulence [11].

Implementation of IC Measures

Enhanced contact isolations (e.g., strict adherence to HH and use of grow and gloves).

ASC from rectal and tracheal suction for all ICU patients on day 0 and 7 day later until discharged.

Twice daily environmental cleaning with detergent and phenolic agents for hi-touch items and site and site contaminated with blood.

Up-to-date real time education and real time feedback on IPC adherence to HCWs.

TABLE 1. Infection Prevention Control (IPC) Measures Monitored in an 8-Bed Intensive Care Unit over a 76-Day Study Period after Index Case Detection of Colistin-Resistant *Acinetobacter baumannii* Infection

Variable	Observation data
No. of patient-days monitored	540
Compliance with IPC measures, no. (%) of opportunities (n = 100)	
Hand hygiene	85 (85)
Contact isolation	74 (74)
Environmental cleaning	100 (100)
Active surveillance culture	81 (81)
Chlorhexidine bath	79 (79)
Chlorhexidine mouth care	100 (100)
New cases of colistin-resistant *A. baumannii* infection or colonization	0

Our findings suggest that intensified IPC measures after prompt case detection and isolation of the patient were associated with containment of colistin-resistant *A. baumannii* in a resource-limited setting. Additional studies to identify

Anucha Apisaranthanarak, MD;[1]
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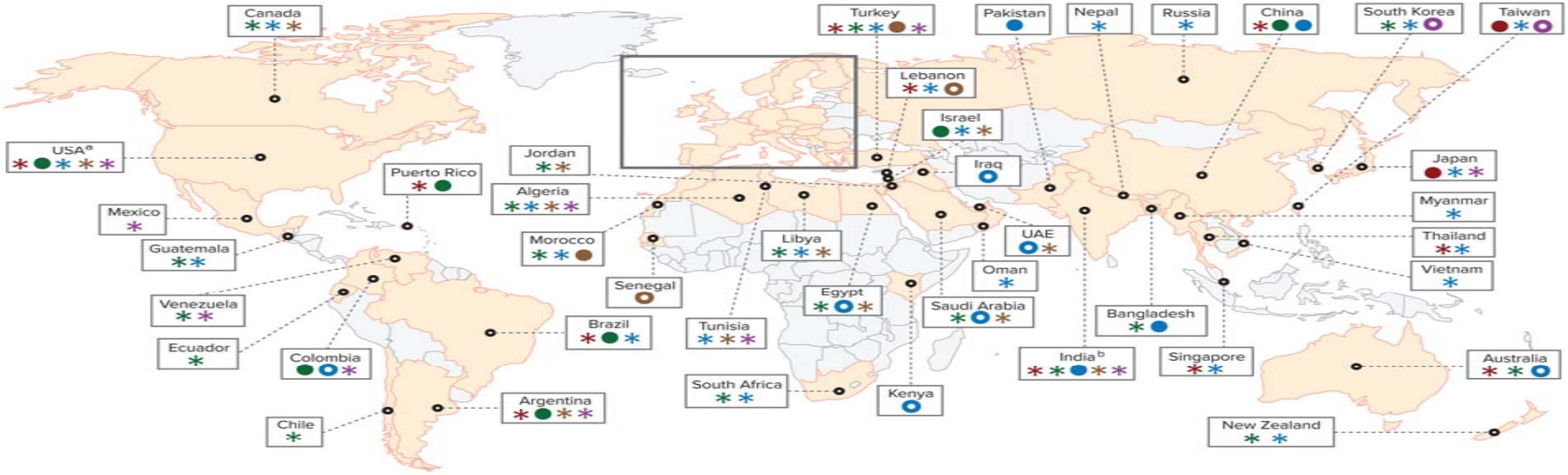
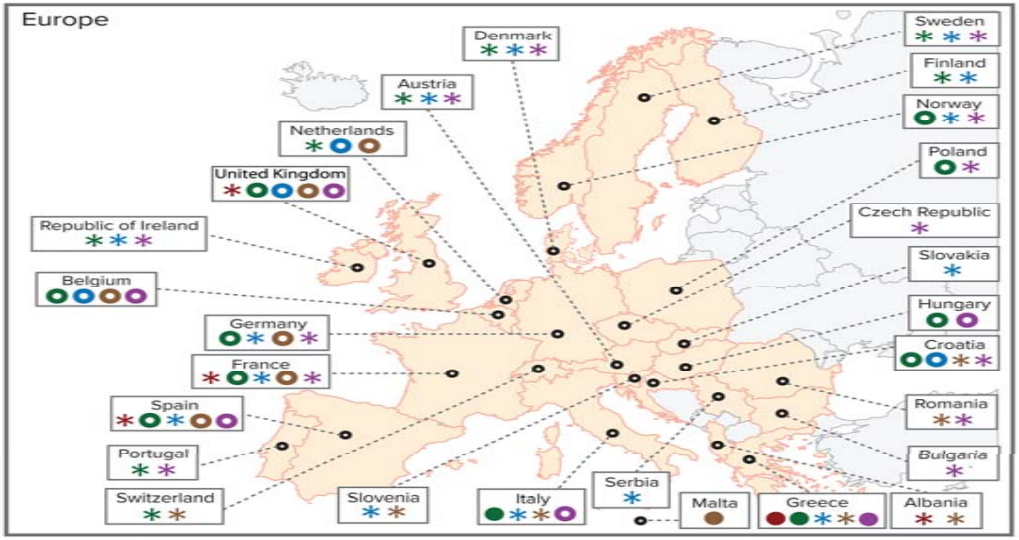
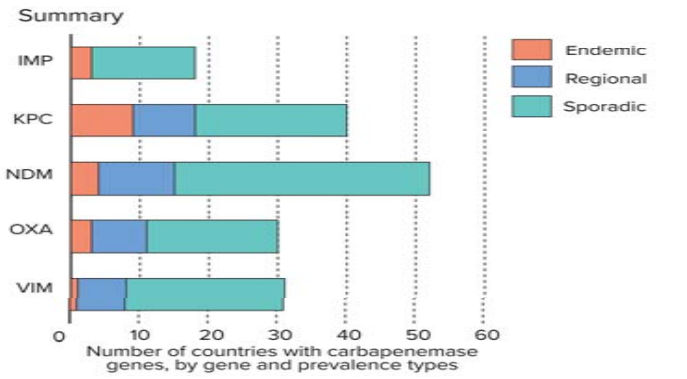
Linda M. Mundy, MD, PhD[2]

GLOBAL DISTRIBUTION OF CARBAPENEMASES IN ENTEROBACTERIACEAE



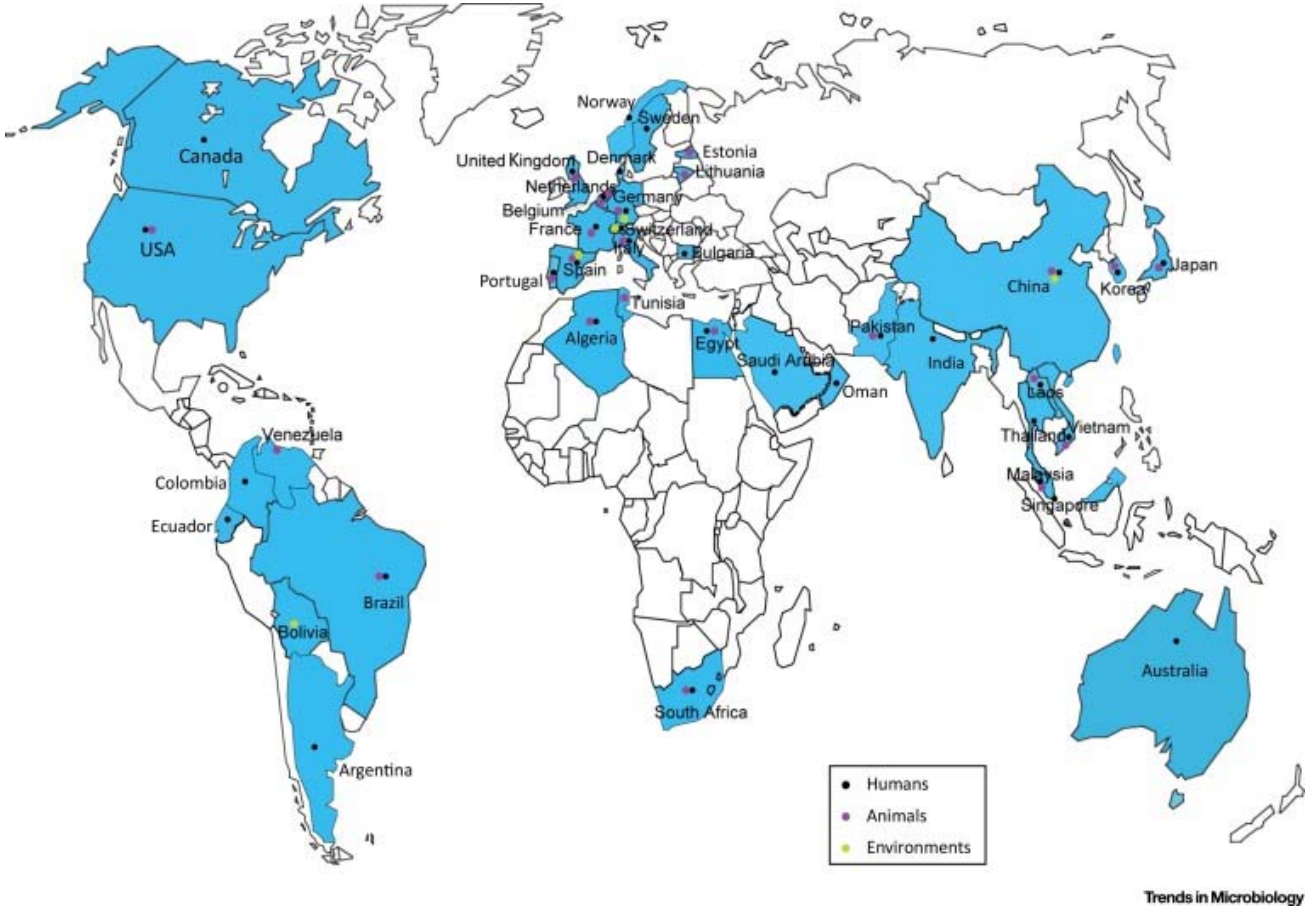


	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*



Logan LK, Weinstein RA. J Infect Dis 2017;215(S1):S28-36

Global Report of MCR-1 Like Colistin Resistant



Sun J, et al. Toward understanding of MDR-like colistin resistant. Trend in microbiology 2018

Colistin-Resistant *Acinetobacter baumannii*: Beyond Carbapenem Resistance

Clin Infect Dis. (2015)

Zubair A. Qureshi, Lauren E. Hittle, Jessica A. O'Hara, Jesabel I. Rivera, Alveena Syed, Ryan K. Shields, Anthony W. Pasculle, Robert K. Ernst, and Yohei Doi

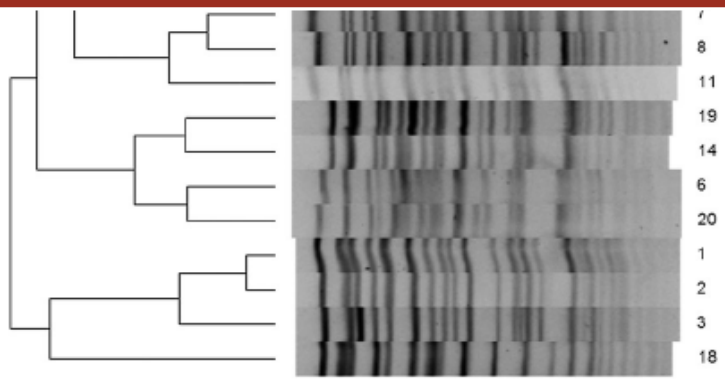
Genetic relatedness of colistin susceptibile and resistant AB

- Adequacy of colistin dosing to avoid suboptimal use
- Colistin should not be used to decolonize asymptomatic CRE carriage
- Empirical colistin should be subjected to tight restriction

from different pts were not.

By MLST, all isolates belong to International Clone 2

Modification of Lipid A was present in all Colistin-R isolates



RESEARCH ARTICLE

Risk factors for colistin-resistant Enterobacteriaceae in a low-endemicity setting for carbapenem resistance – a matched case–control study

Andrea C Büchler[1], Christian Gehringer[2,3], Andreas F Widmer[1], Adrian Egli[3,4], Sarah Tschudin-Sutter[1,5]

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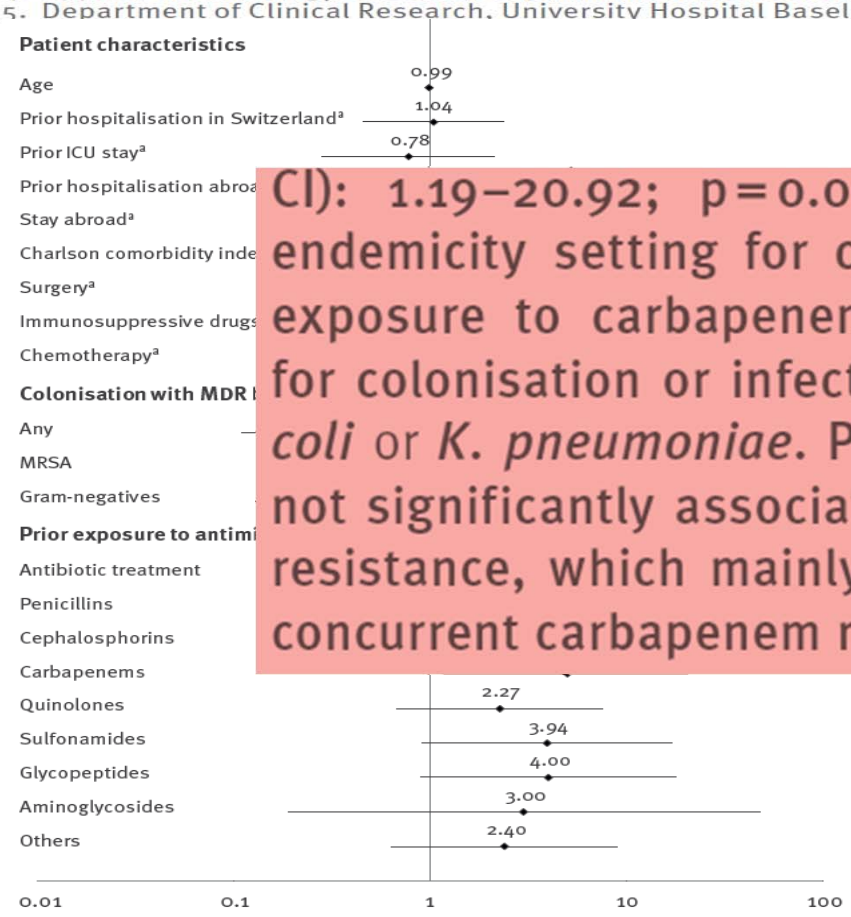
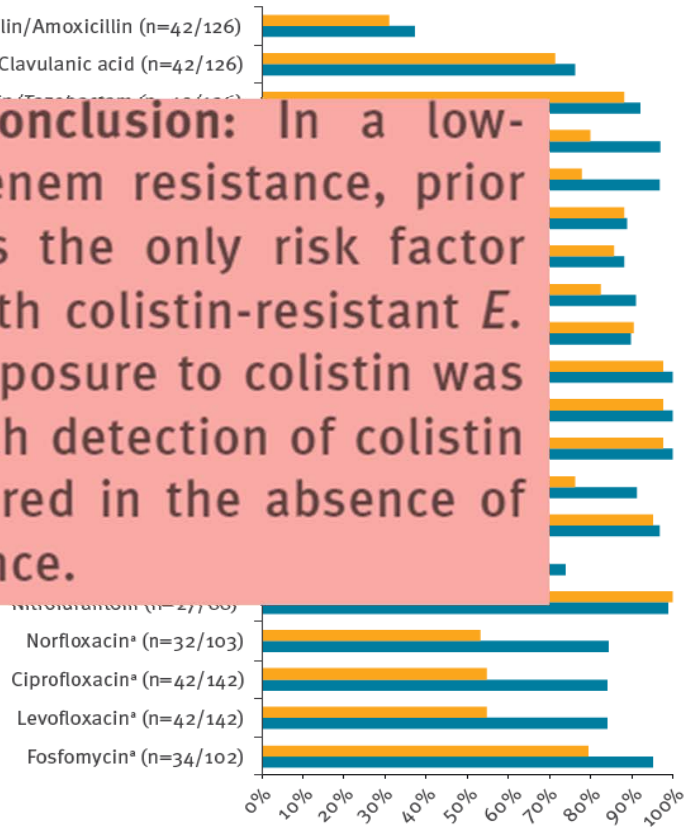
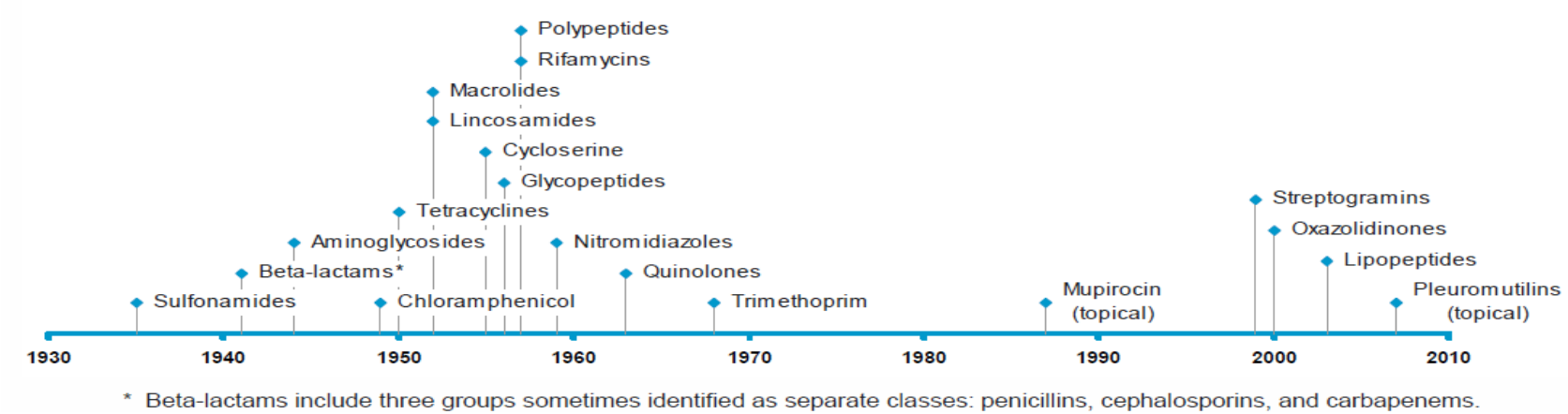




CI): 1.19–20.92; p=0.028). **Conclusion:** In a low-endemicity setting for carbapenem resistance, prior exposure to carbapenems was the only risk factor for colonisation or infection with colistin-resistant *E. coli* or *K. pneumoniae*. Prior exposure to colistin was not significantly associated with detection of colistin resistance, which mainly occurred in the absence of concurrent carbapenem resistance.

Why we need to emphasize on infection control?



2009: Telavancin (complicated skin and skin structure infections)

2010: Ceftaroline fosamil (bacterial skin infections and pneumonia)

2011: Fidaxomicin (*Clostridium difficile*-associated diarrhea)

2012: Not available

2013: Talavancin (HAP, VAP)

2014: Ceftolozane/tazobactam (IAI, UTI), Oritavancin. tidizolid

2015: Ceftazidime/avibactam (G(-))

2016: Bezlotoxumab (C. diff)

2017: Delafloxacin tab (MRSA), meropenem/vaborbactam (KPC-UTIs)

2018: Omadacycline (MRSA), Plazomycin(CRE-UTIs),

http://www.centerwatch.com/drug-information/fda-approvals

Understanding the appropriate use of colistin to prevent colistin resistant

CPE: Carbapenemase-Producing *Enterobactereaceae*

Strains of *Enterobacterales* (mostly *K. pneumoniae* but also *E. coli*, *Enterbacter* spp., *Citrobacter* spp.,….) **producing carbapenemases**

	KPC-type	OXA-48like	Metallo-enzymes (NDM, VIM, IMP)
CARBAPENEM ACTIVITY	Strong	Weak	Strong
SPECTRUM	Extended (most ß-lactams)	Narrow (penicillins, narrow-spectrum Cephem)	Extended (most ß-lactams exc. Azteonam)
Clinically useful inhibitors	• Avibactam • Vaborbactam • Relebactam	• Avibactam	• None

Naas et al – Current Drug Targets 2016
Bush & Bradford – Cold Spring Harb Perspect Med 2016

Logan & Weinstein – JID 2017

Need for Molecular-directed Therapy!

TABLE 1 | The advantages and limitations of common detection methods.

Detection methods	Advantages	Limitations
Phenotypic detection assays		
Modified Hodge test (MHT)	1. Detecting KPC 2. Simple and inexpensive	1. False-positive and false-negative 2. Insufficient for MBLs 3. Time consuming
Colorimetric assay	1. Detecting KPC and most MBLs 2. Type carbapenemases 3. Simple and inexpensive	1. Insufficient for OXA-48 2. Specific reagents 3. Various infecting factors
Modified carbapenem inactivation method (mCIM)	1. Detecting all carbapanemeses 2. Clear criteria of judgment 3. Simple and cost-effectiveness	1. Time consuming
Spectrophotometric method	1. High sensitivity and specificity 2. Time saving 3. Simple and inexpensive	1. Specific instrument (spectrophotometer) 2. Various influencing factors 3. No standard equation and cut-off value 4. Small sample size
MALDI–TOF-based methods	1. Detecting KPC and NDM 2. Time saving 3. Easy to perform 4. Low measurement cost	1. Insufficient for OXA-48 2. No clear protocol and standard analysis 3. Expensive equipment
Molecular-based detection methods	1. Gold standards 2. Detecting all carbapanemeses genes 3. Type carbapenemase genes 4. Time saving	1. High technical requirements 2. Insufficient for expression of genes 3. High measurement cost

Combination Therapy for CRE

	Combination therapies	Advantages	Limitations	Mechanisms of resistance
Tigecycline-based combinations	1. +aminoglycosides[a] 2. +carbapenems[b] 3. +fosfomycin 4. +polymyxin	1. Effective for kinds of CRE (Sader et al., 2015) 2. Lower mortality rates	1. Unclear mechanism 2. Unclear optimal dose 3. Poor pharmacokinetic properties (Giamarellou and Poulakou, 2011) 4. Side effects were evident with increasing dose (Tasina et al., 2011; Ramirez et al., 2013) 5. Inducing resistance	1. Increasing expression of RND efflux pumps 2. Mobile resistance genes, *tet*(A), *tet*(K), *tet*(M), *tet*(X3), and *tet*(X4) (Linkevicius et al., 2016; He et al., 2019)
Polymyxin-based combinations	1. +carbapenems[b] 2. +tigecycline 3. +fosfomycin			1. Mobile colistin resistance genes
Other combinations	1. fosfomycin + aminoglycosides[a] 2. aztreonam + aminoglycosides[a] 3. Tigecycline + polymyxin + carbapenem[b]			1. Fosfomycin-modified genes and modification of MurA for fosfomycin resistance (Solomkin et al., 2014) 2. rmtB for aminoglycosides resistance

[a]*Aminoglycosides refer to amikacin and isepamicin.* [b]*Carbapenems refer to meropenem and imipenem.*

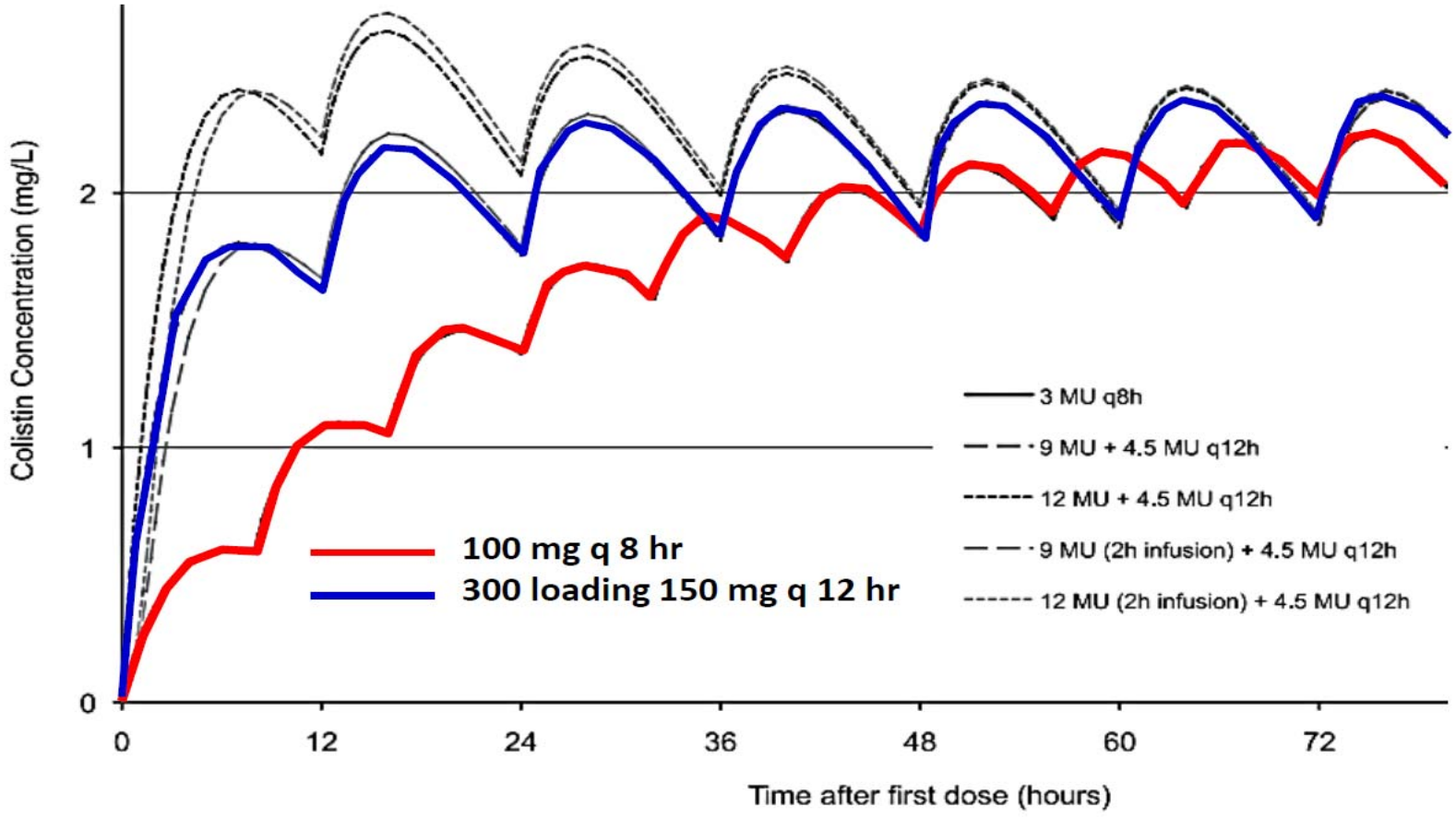
Xiaoyan Cui, Haifang Zhang and Hong Du*

Frontiers in Microbiology | www.frontiersin.org

NB: mechanisms for synergy has not yet been established for most commonly used regimens

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[▽]

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

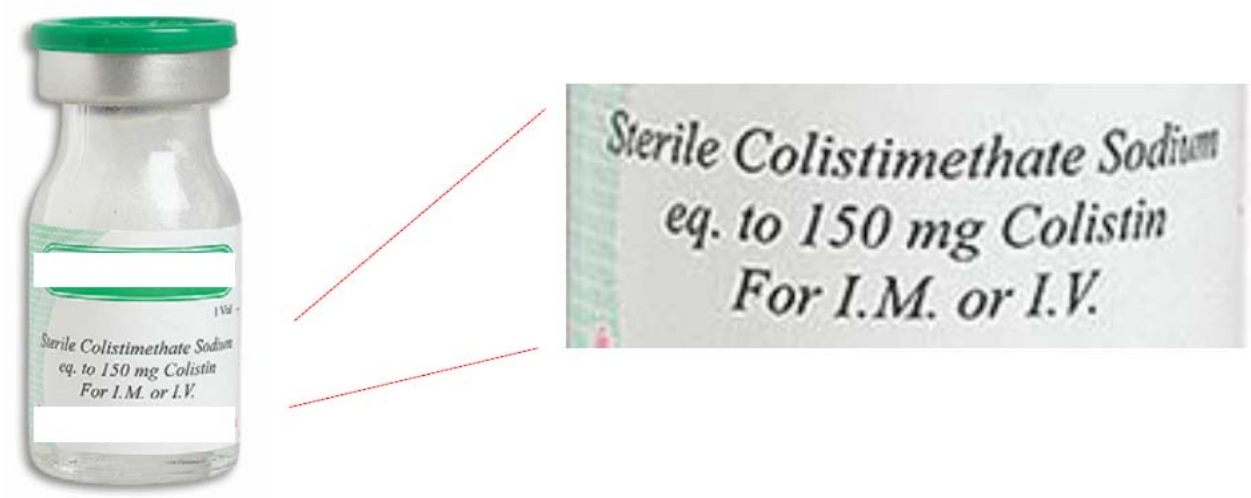


PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins:

We recommend initiating IV therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5–1 hours and to administer the first maintenance dose 12–24 hours later



Pharmacokinetic/Pharmacodynamic (PK/PD) Simulation for Dosage Optimization of Colistin Against Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli*

Kamonchanok Jitaree [1], Korbtham Sathirakul [1], Jantana Houngsaitong [1], Orarik Asuphon [2], Weerayuth Saelim [3], Visanu Thamlikitkul [4,*] and Preecha Montakantikul [5,*]

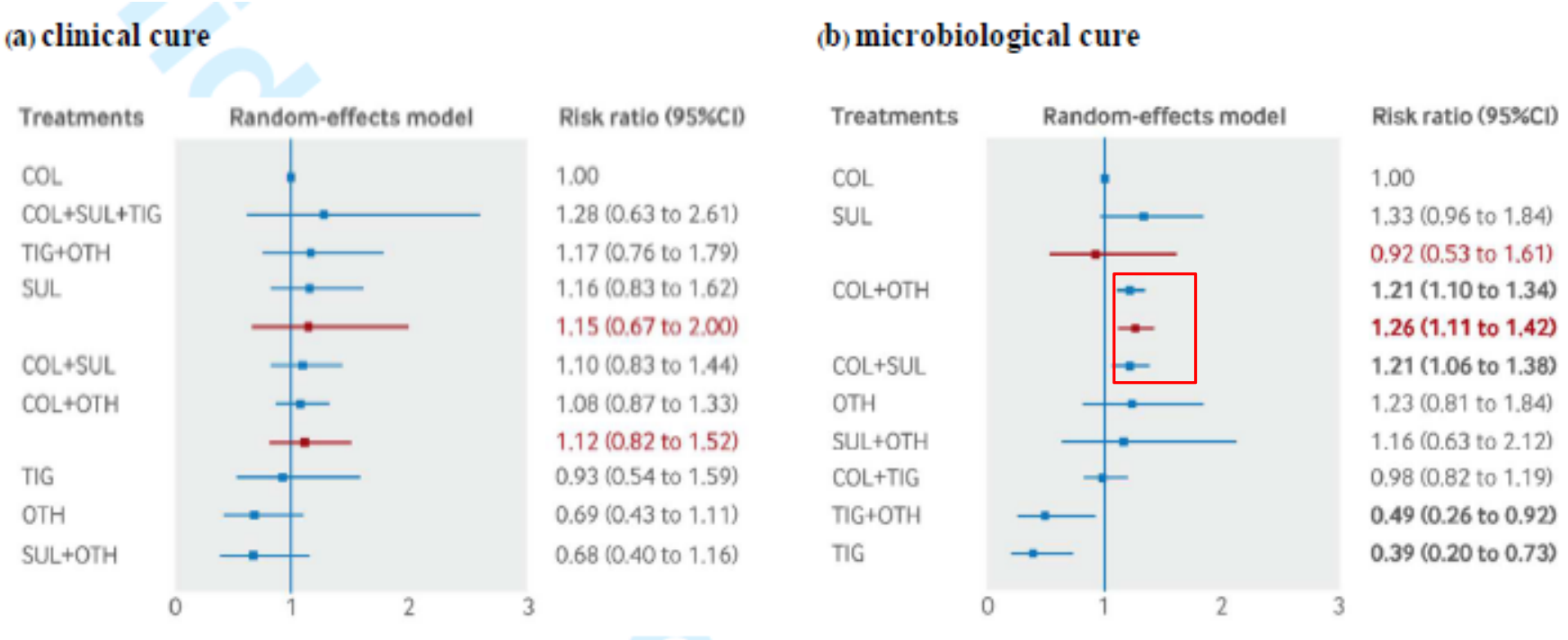
Table 5. The recommended dose based on the ability to achieve PTA target at various MICs.

Creatinine Clearance (mL/min)	MIC 0.5 mcg/mL Daily Dose (CBA)	MIC 2 mcg/mL Daily Dose (CBA)	MIC 8 mcg/mL Daily Dose (CBA)
≥80	150 mg every 12 h (EMA, FDA)	Not recommended	Not recommended
51–79	114 mg every 12 h (FDA)	180 mg every 8 h (our study)	Not recommended
30–50	150 mg every 24 h (FDA)	150 mg every 12 h (our study)	Not recommended
11–29	60 mg every 24 h (FDA)	150 mg every 12 h (our study)	150 mg every 8 h (our study)
≤10	60 mg every 24 h (FDA)	120 mg every 24 h (EMA)	180 mg every 12 h (our study)

Table 6. The recommended dose based on the ability to achieve PTA target at various MICs.

Creatinine Clearance (mL/min)	MIC 16 mcg/mL Daily Dose (CBA)	MIC 32 mcg/mL Daily Dose (CBA)
≥80	Not recommended	Not recommended
51–79	Not recommended	Not recommended
30–50	Not recommended	Not recommended
11–29	Not recommended	Not recommended
≤10	180 mg every 8 h (our study)	Not recommended

Impact of combination treatments on CR-*Acinetobacter baumannii*



Comparative efficacy and safety of treatment options for multidrug-resistant and extensively drug-resistant Acinetobacter baumannii infections: a systematic review and network meta-analysis.

Journal of Antimicrobial Chemotherapy

Kirati Kengkla[1], Khachen Kongpakwattana[2], Surasak Saokaew[1-5], Anucha Apisarnthanarak[4], Nathorn Chaiyakunapruk[2,3,5,6]*

Journal of Antimicrobial Chemotherapy

Which IC component work to control for different GNB?

Clinical Infectious Diseases

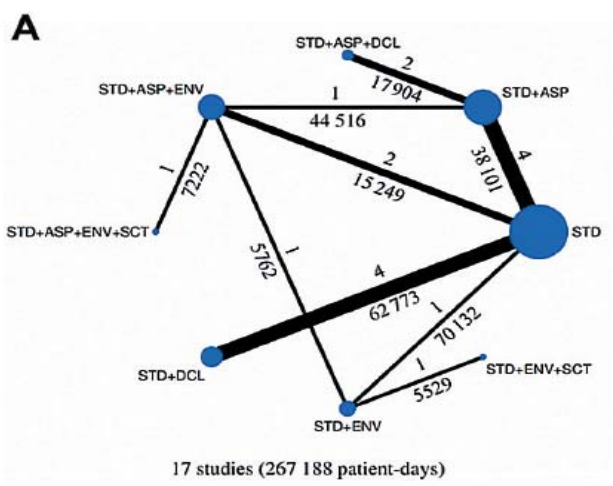
SUPPLEMENT ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

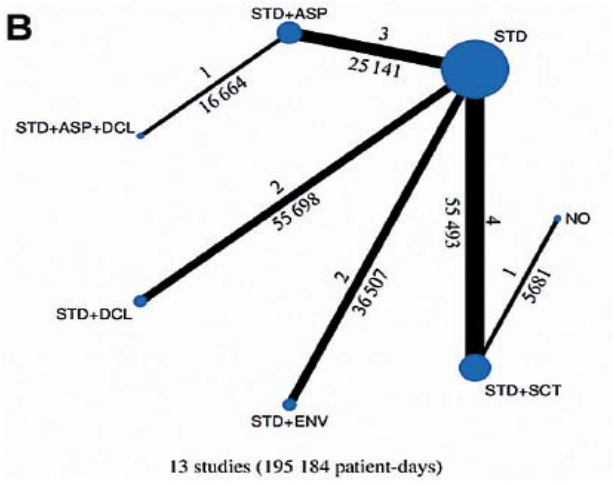
MDR Gram-Negative Bacteria in Adult ICUs • CID 2017:64 (Suppl 2)

Prevention and Control of Multidrug-Resistant Gram-Negative Bacteria in Adult Intensive Care Units: A Systematic Review and Network Meta-analysis

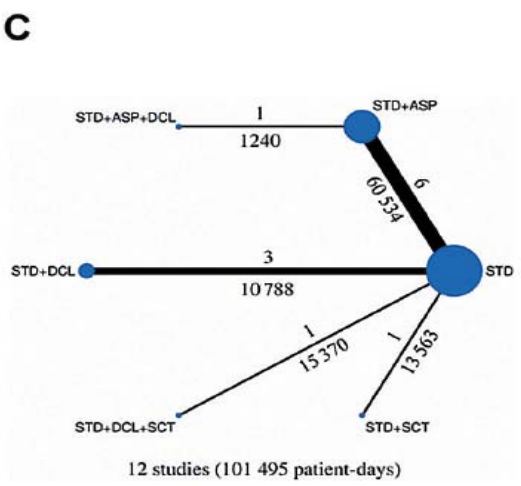
Nattawat Teerawattanapong,[1] Kirati Kengkla,[2] Piyameth Dilokthornsakul,[3] Surasak Saokaew,[2,3,4] Anucha Apisarnthanarak,[5] and Nathorn Chaiyakunapruk[3,4,6,7]



17 studies (267 188 patient-days)



13 studies (195 184 patient-days)



12 studies (101 495 patient-days)

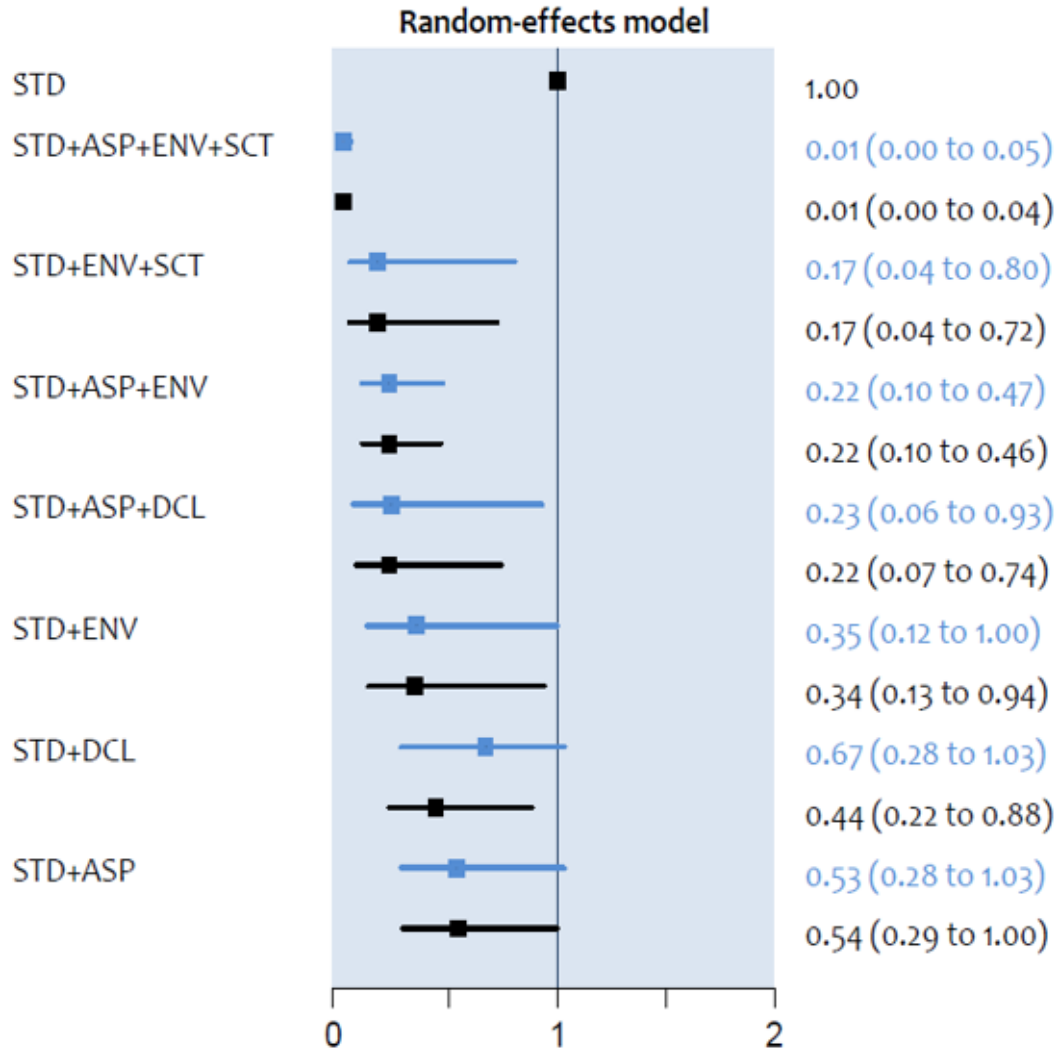
Rationale

To evaluate the existing evidence (RCT & observational studies) on the control of MDROs Gram negative

Interventions: standard of care (STD), antimicrobial stewardship (ASP), environmental cleaning (ENV), decolonization method (DCL), and source control (STC)

Outcomes: MDR-GNB acquisition as well as mortality

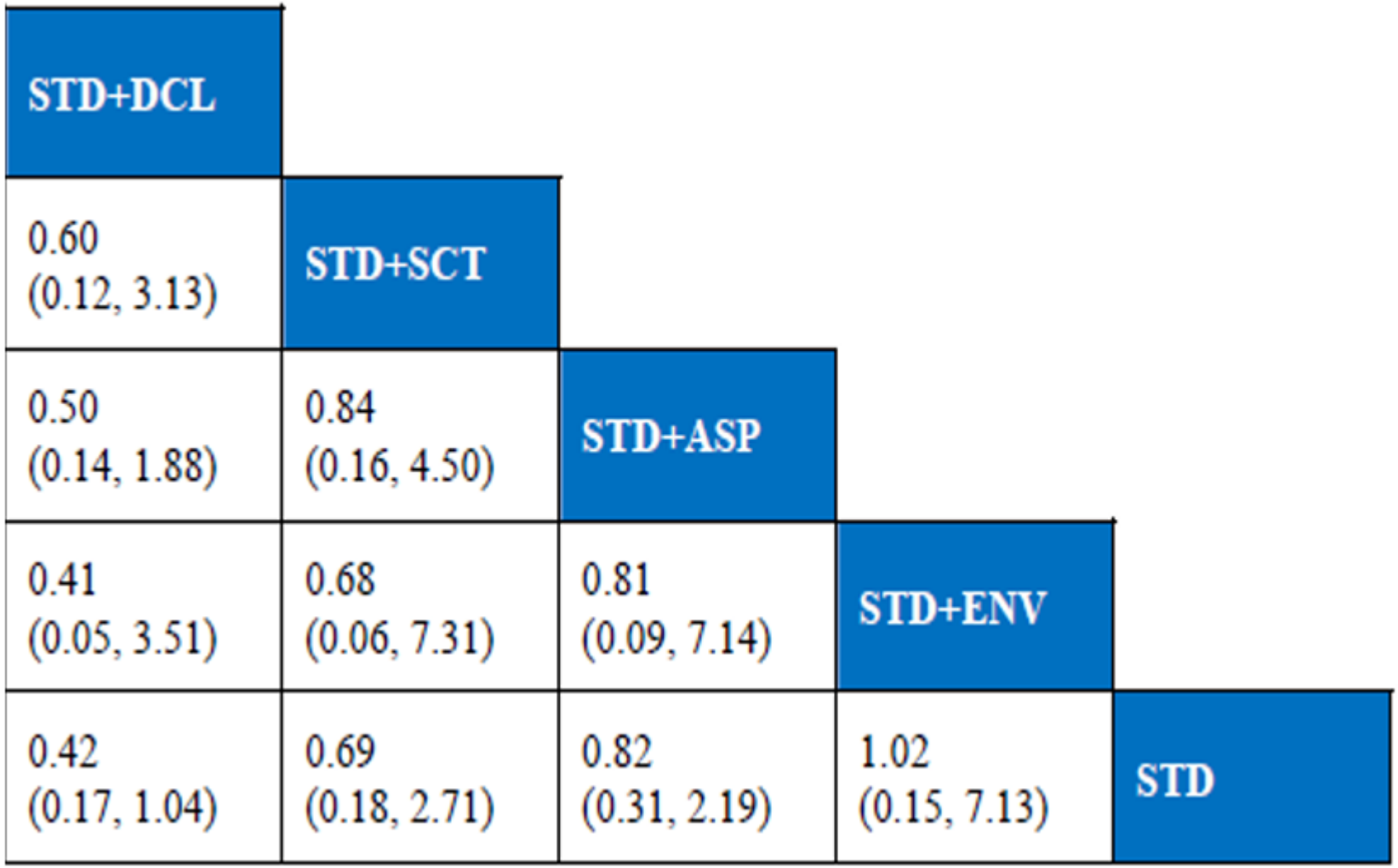
Figure 2 Summary of network meta-analyses results for MDR-GNB acquisition compared with standard care



eFigure 10.1 Network estimated rate ratios (95% confidence intervals) of IPC strategy for prevention of MDR- *Acinetobacter baumannii* acquisition.*

STD+ASP+ ENV+SCT						
0.08 (0.03, 0.24)	**STD+ASP+ ENV**					
0.02 (0.00, 0.39)	0.26 (0.01, 5.56)	**STD+ENV+ SCT**				
0.02 (0.00, 0.35)	0.18 (0.01, 4.95)	0.70 (0.18, 2.64)	**STD+DCL**			
0.02 (0.01, 0.07)	**0.28 (0.18, 0.43)**	1.07 (0.05, 23.55)	1.53 (0.05, 43.25)	**STD+ASP**		
0.01 (0.00, 0.18)	0.13 (0.01, 2.64)	**0.48 (0.35, 0.66)**	0.69 (0.19, 2.53)	0.45 (0.02, 9.83)	**STD+ENV**	
0.01 (0.00, 0.17)	0.09 (0.00, 2.37)	0.35 (0.11, 1.15)	**0.50 (0.28, 0.92)**	0.33 (0.01, 8.80)	0.73 (0.23, 2.29)	**STD**

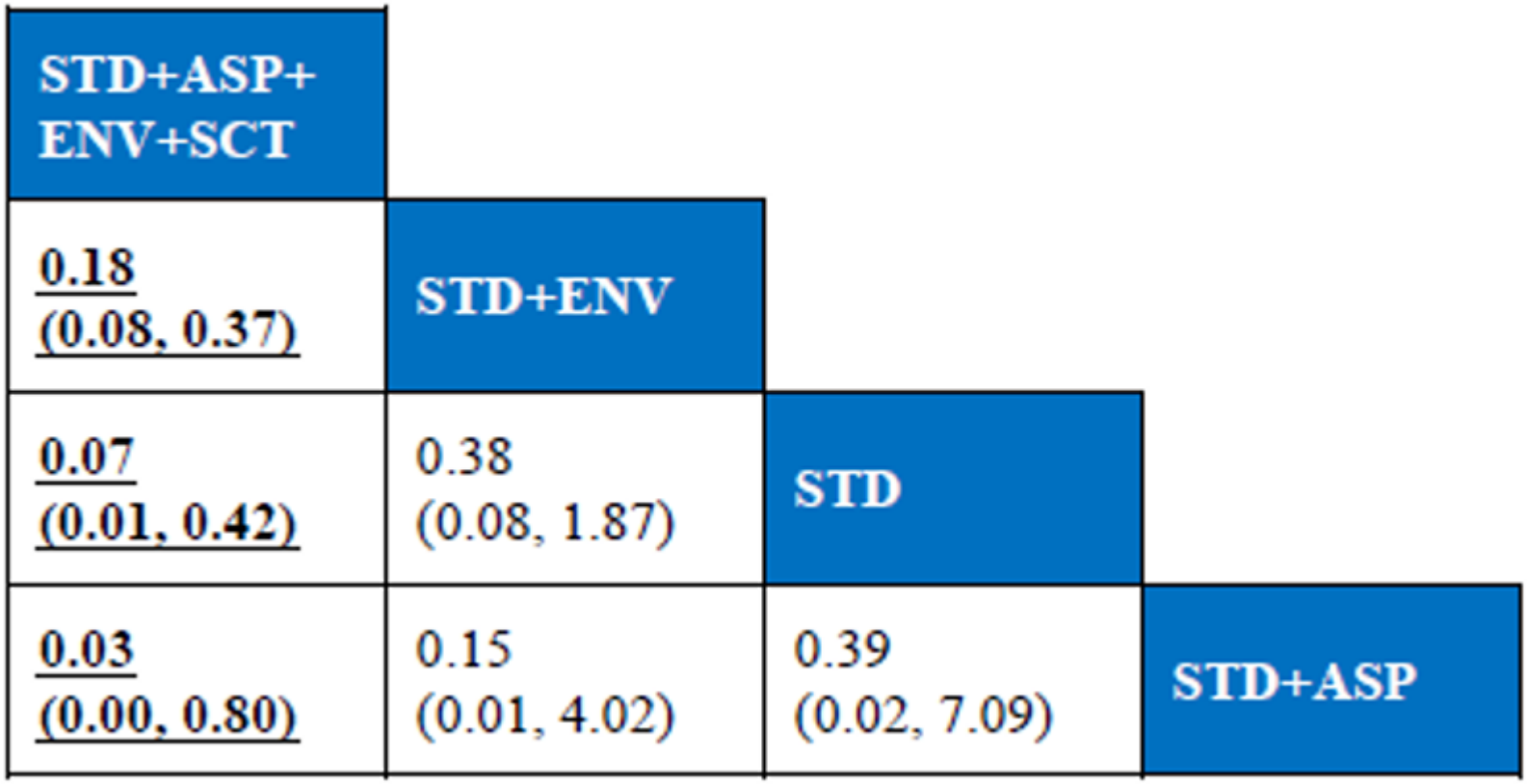
eFigure 10.2 Network estimated rate ratios (95% confidence intervals) of IPC strategy for prevention of MDR-*Pseduomonas aeruginosa* acquisition.*



eFigure 10.3 Network estimated rate ratios (95% confidence intervals) of IPC strategy for prevention of Extended-Spectrum Beta-Lactamases Enterobacteriaceae acquisition.*

STD+ASP+ ENV+SCT								
0.02 (0.00, 0.46)	**STD+ASP+ DCL**							
0.01 (0.00, 0.27)	0.84 (0.18, 3.87)	**STD+ASP+ ENV**						
0.01 (0.00, 0.21)	0.58 (0.11, 2.95)	0.69 (0.27, 1.76)	**STD+ENV**					
0.01 (0.00, 0.20)	0.49 (0.12, 2.09)	0.58 (0.18, 1.92)	0.85 (0.23, 3.12)	**STD+DCL**				
0.01 (0.00, 0.16)	0.41 (0.14, 1.16)	0.49 (0.16, 1.48)	0.71 (0.20, 2.45)	0.83 (0.31, 2.23)	**STD+ASP**			
0.00 (0.00, 0.09)	**0.23 (0.07, 0.80)**	**0.28 (0.11, 0.69)**	0.41 (0.14, 1.17)	0.48 (0.22, 1.01)	0.57 (0.30, 1.09)	**STD**		
0.00 (0.00, 0.02)	**0.03 (0.00, 0.31)**	**0.04 (0.01, 0.32)**	**0.06 (0.01, 0.49)**	**0.07 (0.01, 0.50)**	**0.09 (0.01, 0.58)**	**0.15 (0.02, 0.91)**	**STD+SCT**	
0.00 (0.00, 0.01)	**0.00 (0.00, 0.19)**	**0.00 (0.00, 0.20)**	**0.01 (0.00, 0.31)**	**0.01 (0.00, 0.33)**	**0.01 (0.00, 0.39)**	**0.02 (0.00, 0.65)**	0.12 (0.01, 2.67)	**NO**

eFigure 10.4 Network estimated rate ratios (95% confidence intervals) of IPC strategy for prevention of carbepenem resistant Enterobacteriaceae acquisition.*



Lessons Learnt

CRE: Practices all 4 core components

XDR-AB: ENV featuring measures

ESBL: ASP featuring measures

XDR-PA: None

Evidence on Control of Colistin-Resistant Gram Negative

PREVENTION AND CONTROL OF COLISTIN-RESISTANT GRAM-NEGATIVE BACTERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

ASUPON A, ET AL. (UNDER PREPARATION)

Study Design

Outbreak settings (n = 17 studies)

Non-outbreak settings (n = 11 studies)

Outbreak setting

- **Study design:** Observational (pre-post) 17 studies; no RCTs
- **Database searched:** only Pubmed

Pre-endemic intervention				Post-endemic intervention								Outcome	Number of studies	Difference between pre- and post-endemic intervention
HH+CP	HH+ENV	HH+CP+ENV	HH+CP+ASC	HH+CP	HH+CP+ASC	HH+CP+ENV	HH+ENV+ASC	HH+CP+ASP+ASC	HH+CP+ENV+ASC	HH+CP+SCT+ASC	HH+CP+ENV+ASP+ASC			
✓				✓								positive	4	enhanced
✓					✓							positive	1	add ASC
✓								✓				negative	1	add ASP and ASC
✓						✓						positive	1	add ENV
✓									✓			positive	2	add ENV and ASC
✓										✓		positive	1	add SCT and ASC
			✓						✓			positive	1	add ENV
		✓				✓						positive negative	1 1	enhanced enhanced
	✓								✓			positive	2	add CP and ASC
	✓										✓	positive	1	add CP, ASP and ASC
	✓						✓					negative	1	add ASC

Key Observations

IC interventions (work)

Enhanced HH + CP

Addition of ENV +/- ASC

Addition of SCT + ASC

Addition of CP + ASC +/-ASP

IC intervention (not work)

Addition of ASC +/- ASP

Do SDD/SOD work in Asia?

DOES IT WORK IN ENDEMIC REGIONS FOR MDR-GNB?

Two flavours

The strategy includes twice weekly surveillance sampling (rectum and respiratory tract)

SDD

- ✔ Oropharyngeal paste
- ✔ + Nasogastric suspension
  - 10 ml suspension
    * 100 mg colistin
    * 80 mg tobramycin
    * 500 mg amphotericin B
      (or: nystatin 2 ✖ 10^6 units)

SOD

- ✔ Oropharyngeal paste
  - 0.5 gram
    *2% colistin
    * 2% tobramycin
    * 2% amphotericin B
      (or: nystatin 1 ✖ 10^5 units)

=topical regimen, 4✖ daily, until extubation or ICU-discharge

- ✔ + day course of 3rd-generation cephalosporins IV

Expert Opinions (SDD)

AA: *"What kind of infrastructure do you need to start good SDD program?"*

MB: *"You really need to have a good team"*

AA: *"What do you mean by having a good team?"*

MB: *"It means you need to have good microbiology with quick turn around time. Regular meeting is needed to review the pattern of microbiology. If any MDR emerges, we will hold SDD program till it get back to the baseline rate."*

AA: *"Do you really think that SDD work in Europe?"*

MB: *"It works here in Netherland, but considered debatable in other parts of Europe"*

Expert Opinion (SOD)

AA: What is your suggestion on SOD?

SH: It has 2 caveats.

Logistical: Local production, ease of use, patient side effects and bad taste

Ecological: Selection of Col-R GNB

But I think that the benefit outweigh the risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Decontamination of the Digestive Tract and Oropharynx in ICU Patients

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Table 2. Primary and Secondary End Points.*

End Point	Study Group			Unadjusted Odds Ratio or Hazard Ratio (95% CI)†		Adjusted Odds Ratio or Hazard Ratio (95% CI)†		
	Standard Care (N=1990)	SDD (N=2045)	SOD (N=1904)	Standard Care	SDD	SOD	Standard Care	SDD	SOD
Death — no. (%)									
During the first 28 days	544 (27.5)	546 (26.9)	502 (26.6)	1.00	0.94 (0.82–1.08)	0.95 (0.82–1.10)	1.00	0.83 (0.72–0.97)	0.86 (0.74–0.99)
In the ICU	443 (22.3)	440 (21.5)	416 (21.8)	1.00	0.91 (0.79–1.06)	0.97 (0.83–1.13)	1.00	0.81 (0.69–0.94)	0.87 (0.74–1.02)
In the hospital	632 (31.8)	665 (32.6)	584 (30.7)	1.00	0.99 (0.86–1.13)	0.94 (0.82–1.08)	1.00	0.88 (0.76–1.01)	0.85 (0.74–0.98)
Time to outcome for survivors at day 28 — days									
Cessation of mechanical ventilation				1.00	1.06 (0.96–1.18)	1.01 (0.89–1.15)	1.00	1.10 (0.99–1.22)	1.03 (0.90–1.17)
Median	8	7	8						
Interquartile range	3–17	4–15	4–15						
Discharge from ICU				1.00	1.02 (0.92–1.12)	1.00 (0.89–1.11)	1.00	1.09 (0.99–1.21)	1.06 (0.94–1.19)
Median	9	9	9						
Interquartile range	6–19	6–18	6–17						
Discharge from hospital				1.00	1.04 (0.91–1.19)	1.05 (0.91–1.22)	1.00	1.13 (1.01–1.25)	1.13 (0.96–1.32)
Median	29	28	28						
Interquartile range	16–48	16–45	16–47						

Table 3. Cumulative Incidence of ICU-Acquired Bacteremia and Candidemia.*

Type of Infection	Study Group			Crude Odds Ratio (95% CI)		
	Standard Care (N=1990)	SOD (N=1904)	SDD (N=2045)	SDD vs. Standard Care	SOD vs. Standard Care	SDD vs. SOD
		no. (%)				
Staphylococcus aureus	22 (1.1)	9 (0.5)	9 (0.4)	0.40 (0.18–0.86)	0.43 (0.20–0.93)	0.93 (0.37–2.40)
Streptococcus pneumoniae	3 (0.2)	1 (0.1)	1 (0.0)	0.32 (0.03–3.12)	0.35 (0.04–3.35)	0.93 (0.06–14.90)
GNF-GNR species†	36 (1.8)	17 (0.9)	16 (0.8)	0.43 (0.24–0.77)	0.49 (0.27–0.87)	0.88 (0.44–1.74)
Enterobacteriaceae	87 (4.4)	59 (3.1)	18 (0.9)	0.19 (0.12–0.32)	0.70 (0.50–0.98)	0.28 (0.16–0.47)
Enterococcus species	55 (2.8)	49 (2.6)	48 (2.3)	0.85 (0.57–1.25)	0.93 (0.63–1.37)	0.91 (0.61–1.36)
Candida species	16 (0.8)	14 (0.7)	8 (0.4)	0.49 (0.21–1.11)	0.91 (0.45–1.85)	0.53 (0.23–1.24)
Patients with at least one episode of bacteremia or candidemia — no. (%)	186 (9.3)	124 (6.5)	88 (4.3)	0.44 (0.34–0.57)	0.68 (0.53–0.86)	0.65 (0.49–0.85)

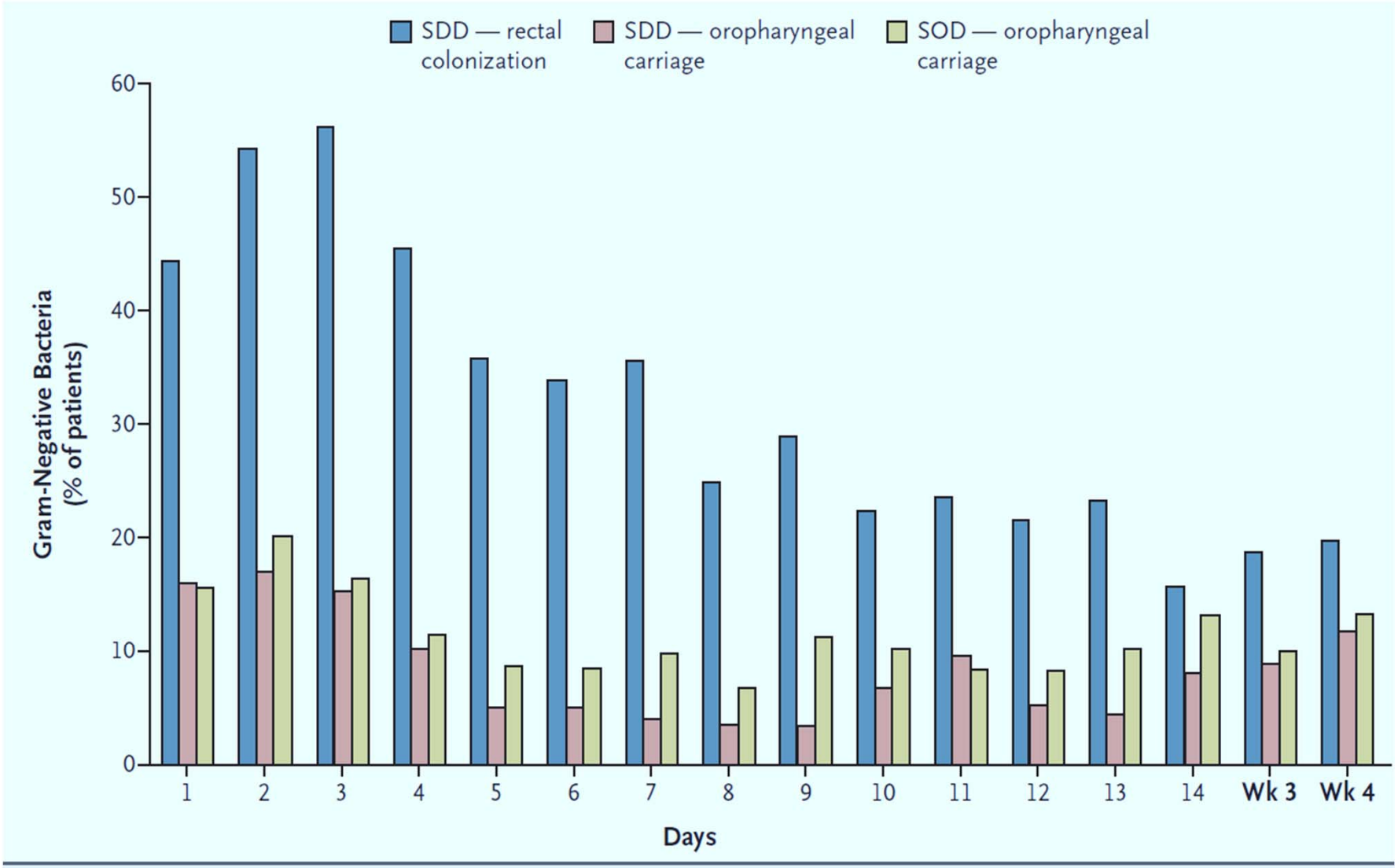

Figure 1. Detection of Gram-Negative Bacteria in Patients in the Intensive Care Unit Who Were Treated with Selective Digestive Tract Decontamination (SDD) or Selective Oropharyngeal Decontamination (SOD).

Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

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Interpretation

We report a novel study quantifying the effects of SDD, SOD, and standard care on occurrence of bacteraemia and respiratory tract colonisation with highly resistant microorganisms acquired in intensive-care units. SDD was associated with a 59% rate reduction of highly resistant bacteraemia compared with standard care in this setting, and a 63% rate reduction compared with SOD. SOD was associated with a rate reduction in acquired respiratory tract colonisation with highly resistant microorganisms of 32% compared with standard care, and SDD was associated with a 38% reduction compared with standard care.

	SDD vs SOD
Tobramycin resistanc	
Escherichia coli and *Kleb*	0·50 (0·23–1·11)
Other Enterobacteriace	0·38 (0·21–0·69)
Acinetobacter spp and *S*	1·18 (0·78–1·78)
Other glucose non-ferr	2·56 (1·51–4·35)
Gram-negative rods (t	1·11 (0·84–1·47)
Cefotaxime resistance	
E coli and *Klebsiella* spp	0·18 (0·04–0·79)
Other Enterobacteriace	0·45 (0·25–0·78)
Enterobacteriaceae (to	0·37 (0·22–0·62); ARR 4%; NNT 26
Colistin resistance	
Proteus spp and *Serratic*	0·49 (0·35–0·69); ARR 6%; NNT 17

Data are n (%) unless othe … e risk reduction.
NNT=number needed to t

Table 6: Respiratory tra

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Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients

A Randomized Clinical Trial

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Question

Is use of chlorhexidine 2% mouthwash, selective oropharyngeal decontamination (SOD), or selective digestive tract decontamination (SDD) associated with reduced risk of bloodstream infections due to multidrug-resistant gram-negative bacteria among ventilated patients in intensive care units (ICUs) with moderate to high prevalence of antibiotic resistance?

Design, Setting, and Participants

Randomized trial conducted from December 1, 2013, to May 31, 2017, in 13 European ICUs where at least 5% of bloodstream infections are caused by extended-spectrum β-lactamase–producing Enterobacteriaceae. Patients with anticipated mechanical ventilation of more than 24 hours were eligible. The final date of follow-up was September 20, 2017.

Interventions

Standard care was daily CHX 2% body washings and a hand hygiene improvement program. Following a baseline period from 6 to 14 months, each ICU was assigned in random order to 3 separate 6-month intervention periods with either CHX 2% mouthwash, SOD (mouthpaste with colistin, tobramycin, and nystatin), or SDD (the same mouthpaste and gastrointestinal suspension with the same antibiotics), all applied 4 times daily.

Main Outcomes and Measures

The occurrence of ICU-acquired bloodstream infection with MDRGNB (primary outcome) and 28-day mortality (secondary outcome) during each intervention period compared with the baseline period.

Prevalence of Unitwide Carriage of Antibiotic-Resistant Microorganisms in the Rectum and Respiratory Tract (Exploratory Outcome)

	Baseline	CHX		SOD		SDD	
Prevalence, %	Prevalence, %	aRR (95% CI)[a]	Prevalence, %	aRR (95% CI)[a]	Prevalence, %	aRR (95% CI)[a]	
Rectum							
HRMO enterobacteriaceae	16.1	21.7	1.07 (0.99-1.16)	19.7	1.04 (0.96-1.13)	13.9	1.05 (0.95-1.16)
Third-generation cephalosporin resistance	15.8	21.5	1.07 (0.99-1.16)	19.2	1.04 (0.96-1.13)	13.7	1.07 (0.97-1.18)
Carbapenem resistance	3.2	3.1	0.68 (0.54-0.86)	2.9	0.85 (0.71-1.03)	2.6	0.80 (0.64-1.01)
Resistance to ≥3 antibiotics (or classes)	10.8	15.5	1.07 (0.97-1.19)	14.2	1.06 (0.96-1.17)	10.0	1.10 (0.97-1.24)
Colistin resistance[b]	0.5	1.6	0.81 (0.54-1.21)	1.8	0.97 (0.65-1.45)	1.3	0.96 (0.60-1.54)

Conclusions and Relevance

Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream infections caused by MDRGNB compared with standard care.

Respiratory Tract							
HRMO Enterobacteriaceae	6.6	7.6	0.94 (0.81-1.09)	4.2	0.93 (0.80-1.09)	4.7	0.94 (0.78-1.13)
Third-generation cephalosporin resistance	6.4	7.4	0.95 (0.82-1.10)	4.2	0.93 (0.80-1.09)	4.5	0.94 (0.78-1.13)
Carbapenem resistance	1.4	1.1	0.71 (0.47-1.07)	0.9	0.68 (0.48-0.94)	0.5	0.59 (0.37-0.97)
Resistance to ≥3 antibiotics (or classes)	4.0	5.2	1.02 (0.84-1.23)	3.3	0.92 (0.76-1.12)	3.5	1.04 (0.83-1.31)
Colistin resistance[b]	0.1	0.8	0.57 (0.29-1.14)	0.9	0.66 (0.36-1.21)	0.3	0.61 (0.30-1.22)
HRMO glucose nonfermenting GNB	3.4	2.9	0.80 (0.64-1.00)	3.8	0.84 (0.70-1.00)	2.7	0.75 (0.58-0.96)
MDRGNB, regardless of antibiotic susceptibility	3.8	5.2	1.16 (0.94-1.44)	3.2	0.97 (0.77-1.22)	3.6	1.04 (0.83-1.31)
Any MDRGNB (aggregate)	12.9	15.2	0.98 (0.88-1.08)	10.3	0.93 (0.84-1.04)	10.2	0.94 (0.83-1.06)
MRSA	1.7	1.1	0.95 (0.66-1.36)	1.3	0.77 (0.59-1.00)	1.7	0.73 (0.54-0.97)

Evaluation of SDD/SOD on Col-R GNB Colonization

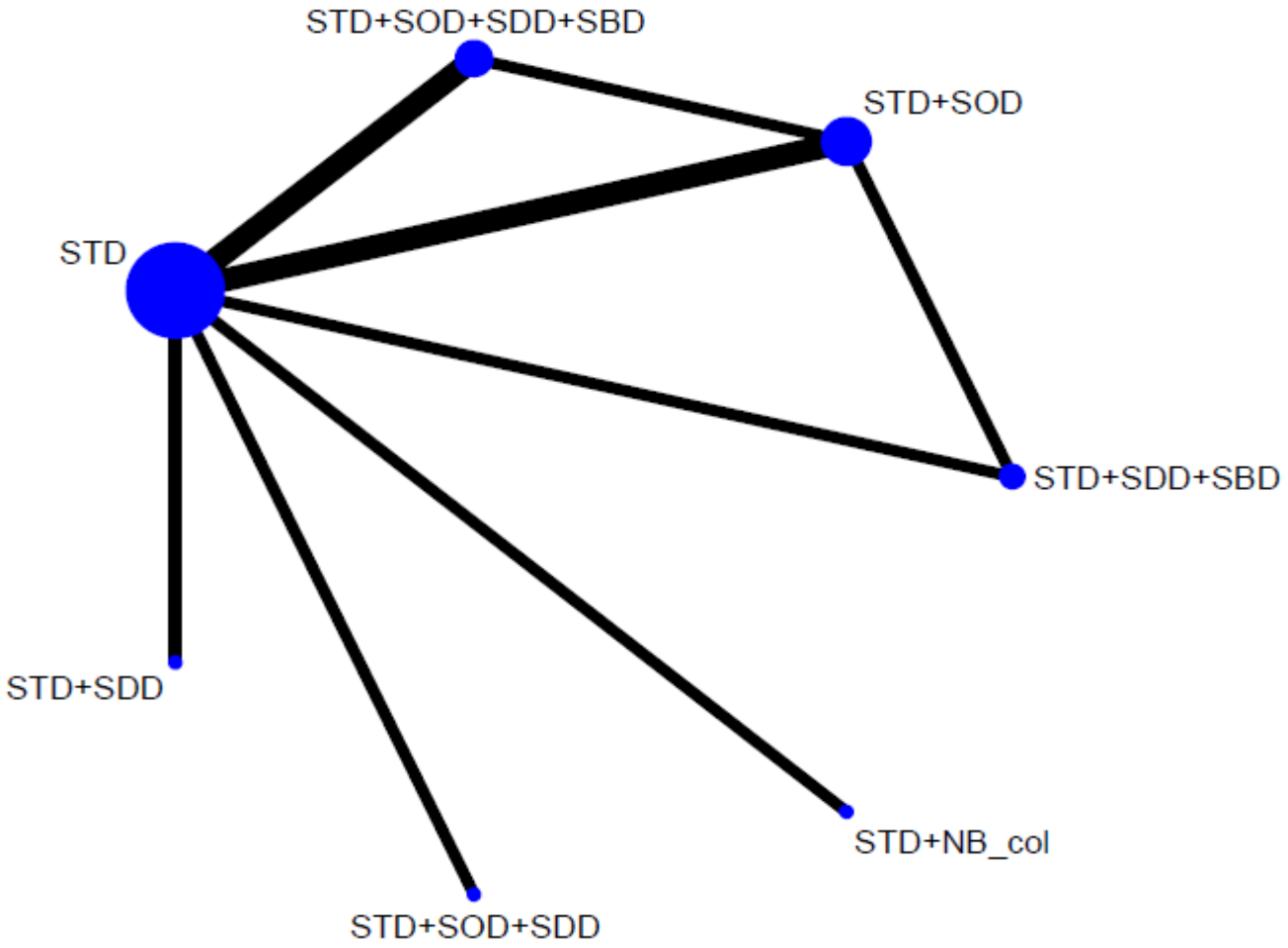
	id	author	year	t	n	r	design	outcome
1.	1	Arnow PM	1996	STD	33	0	RCT	colonization
2.	1	Arnow PM	1996	STD+SOD+SDD+SBD	36	2	RCT	colonization
3.	2	de Jonge E	2003	STD	395	2	RCT	colonization
4.	2	de Jonge E	2003	STD+SDD+SBD	378	4	RCT	colonization
5.	3	de Smet	2011	STD	881	130	RCT	colonization
6.	3	de Smet	2011	STD+SOD	886	112	RCT	colonization
7.	3	de Smet	2011	STD+SOD+SDD+SBD	828	55	RCT	colonization
8.	4	Karvouniaris M	2015	STD	84	3	RCT	colonization
9.	4	Karvouniaris M	2015	STD+NB_col	84	7	RCT	colonization
10.	6	Oostdijk EA	2014	STD+SOD	5881	18	RCT	colonization
11.	6	Oostdijk EA	2014	STD+SDD+SBD	6116	35	RCT	colonization
12.	11	Abele-Horn M	1997	STD	30	4	RCT	colonization
13.	11	Abele-Horn M	1997	STD+SOD	58	0	RCT	colonization
14.	12	Agusti C	2002	STD	33	0	RCT	colonization
15.	12	Agusti C	2002	STD+SDD	21	0	RCT	colonization
16.	16	Unertl	1986	STD	20	1	RCT	colonization
17.	16	Unertl	1986	STD+SOD+SDD	19	1	RCT	colonization

Prevention and Control of colistin-resistant Gram-negative bacteria: A Systematic Review and Meta-analysis

Asupon A, et al. (under preparation)

ID	Author	Year	Intervention	Decolonization regimens
16	Unertl K	1987	STD	–
			STD+SOD+SDD	SOD = Polymyxin, gentamicin, amphotericin B SDD = Polymyxin, gentamicin
15	Flaherty J	1990	STD	–
			STD+SDD	SDD = Polymyxin, gentamicin, nystatin
17	Wiener J	1995	STD	–
			STD+SOD+SDD	SOD & SDD = Polymyxin, gentamicin, nystatin
1	Arnow PM	1996	STD	–
			STD+SOD+SDD+SBD	SOD & SDD = Colistin (polymyxin E), gentamicin, nystatin SBD = IV Cefotaxime and ampicillin
11	Abele-Horn M	1997	STD	–
			STD+SOD	SOD = Colistin (polymyxin E), tobramycin, amphotericin B
12	Agusti C	2002	STD	–
			STD+SDD	SDD = Polymyxin, tobramycin
5	Krueger WA	2002	STD	–
			STD+SDD+SBD	SOD = Polymyxin, gentamicin SBD = IV Ciprofloxacin
2	de Jonge E	2003	STD	–
			STD+SDD+SBD	SDD = Colistin (polymyxin E), tobramycin, amphotericin B SBD = IV Cefotaxime
14	Camus C	2005	STD	–
			STD+SCT	SCT = Chlorhexidine body washing
			STD+SDD	SDD = Polymyxin, tobramycin
			STD+SDD+SCT	SDD = Polymyxin, tobramycin SCT = Chlorhexidine body washing
3	de Smet AM	2011	STD	–
			STD+SOD+SDD+SBD	SOD & SDD = Colistin (polymyxin E), tobramycin, amphotericin B SBD = IV Cefotaxime
4	Karvouniaris M	2015	STD	–
			STD+NB_col	NB_col = Nebulized colistin
6	Oostdijk EA	2014	STD+SOD	SOD = Colistin (polymyxin E), tobramycin, amphotericin B
			STD+SDD+SBD	SDD = Colistin (polymyxin E), tobramycin, amphotericin B SBD = IV Cefotaxime or IV ceftriaxone

1. Colonization of CoRO



Evidence of Harm

STD+NB-Col					
1.51 (0.03,91.17)	STD+SDD				
1.43 (0.34,6.01)	0.94 (0.02,47.89)	STD+SDD+SBD			
2.74 (0.72,10.45)	1.82 (0.04,88.81)	**1.92 (1.12,3.29)**	STD+SOD		
2.22 (0.11,44.72)	1.47 (0.01,166.23)	1.55 (0.10,24.57)	0.81 (0.05,12.15)	STD+SOD+SDD	
5.09 (1.32,19.69)	3.37 (0.07,165.80)	**3.57 (1.93,6.61)**	**1.86 (1.37,2.53)**	2.30 (0.15,34.76)	STD

STD +SDD and STD + SDD + SOD lead to more Col-R colonization > STD + SOD

All decolonization regimens tend to have more Col-R colonization > STD

Conclusions

Colistin resistant GNB is preventable by infection control

Caveats: detect it early enough, need to enhance effort of IPC, avoid unnecessary use of colistin as decolonization agents

Colistin should be used in combination with other antibiotics for ecological purposes (reduce transmission of CR-GNB and Colistin resistant GNB)

It is very likely that combination approaches inclusive of STD + ASP + ENV + SCT will be the core component for control of Colistin resistant GNB

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ขอบคุณครับ