Challenges for the treatment of MDR infections

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Conflicts of interest

- None for this presentation

- Merck, unrestricted grant for University-accredited Expert degree course (paid to my University)
- Research funds, IMI (European Union and EFPIA)

Challenges in the treatment of MDRO

- As attending physician
  - How should I treat this patient
  - How will my decision impact the next patients
- As scientist
  - How can I produce evidence for decisions

Challenges in the treatment of MDRO

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

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

Other priority bacteria

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

Tacconelli et al, Lancet Infect Dis 2018

Treatment of CPE: dilemas

- Should I use second line, old drugs if active?
  - Colistin, fosfomycin, some aminoglycosides, tigecycline…
  - Efficacy, toxicity

OR

- Should I use a new drug
  - Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, eravacycline, plazomicin…
  - Cost, development of resistance

AND

- What can I do if there are simply no options…

Carbapenems for CPE?

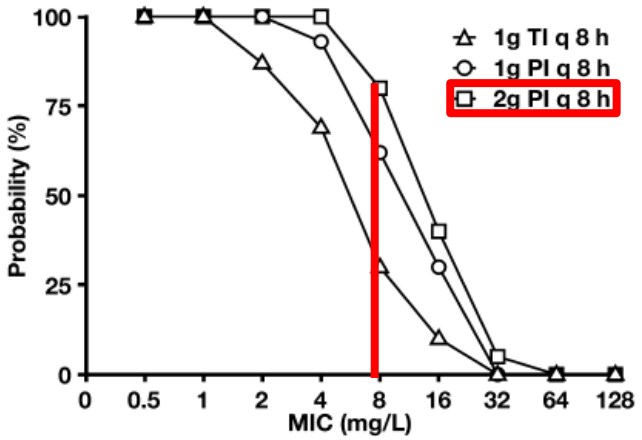


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% *T* > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

Daikos et al, Clin Microbiol Infect 2011

TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies[a]

MIC of carbapenem (μg/ml)	No. of patients	No. of successes	No. of failures	% Failure
≤1	17	12	5	29.4
2	12	9	3	25.0
4	7	5	2	28.6
8	6	4	2	33.3
Subtotal	42	30	12	28.6[b]
>8	8	2	6	75.0[b]
Total	50	32	18	36

Tzouvelekiset al, Clin Microbiol Revs 2012

Combination vs monotherapy for CRE - Cohort studies

- Combination not better
  - Capone, CMI 2013
  - De Oliveira, CMI 2015
  - Satlin, AAC 2015
  - Gomez-Simmonds, AAC 2016

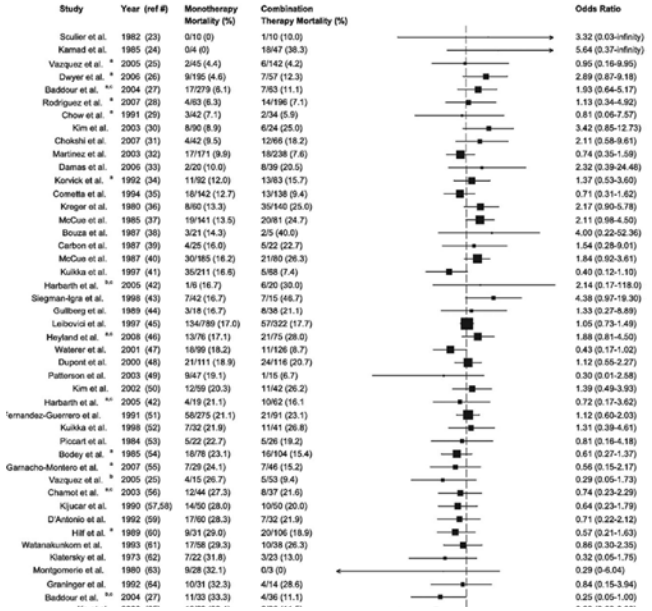
- Combination better
  - Qureshi, AAC 2012
  - Tumbarello, CID 2012
  - Daikos, AAC 2014
  - Tofas, IJAA 2016
  - Trecarichi, Am J Hematol 2016
  - Machuca, AAC 2017
  - Papadimitrou, EJCMID 2017

Reviewed at Rodríguez-Baño et al, Clin Microbiol Rev 2018

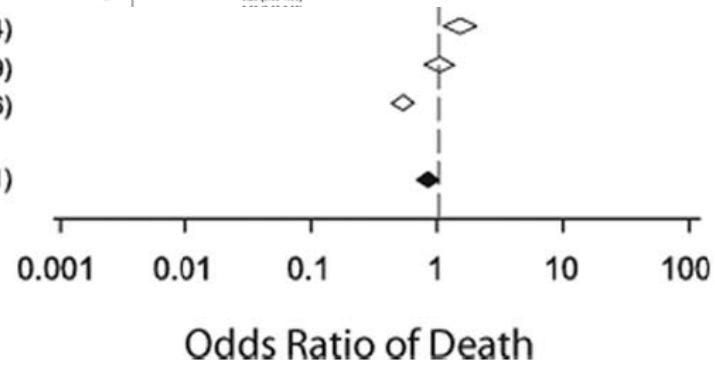
A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD

(Crit Care Med 2010; 38:1651–1664)



Monotherapy mortality <15%	125/1417 (8.8)	182/1363 (13.4)	1.53 (1.16-2.03)
Monotherapy mortality 15-25%	386/2123 (18.2)	247/1309 (18.9)	1.05 (0.81-1.34)
Monotherapy mortality >25%	414/1013 (40.9)	404/1279 (31.6)	0.54 (0.45-0.66)
Overall	925/4553 (20.3)	833/3951 (21.1)	0.86 (0.71-1.03)



A Predictive Model of Mortality in Patients With Bloodstream Infections due to Carbapenemase-Producing Enterobacteriaceae

Belén Gutiérrez-Gutiérrez, MD, PhD; Elena Salamanca, MD; Marina de Cueto, MD, PhD; Po-Ren Hsueh, MD; Pierluigi Viale, MD; José Ramón Paño-Pardo, MD, PhD; Mario Venditti, MD, PhD; Mario Tumbarello, MD; George Daikos, MD, PhD; Vicente Pintado, MD; Yohei Doi, MD, PhD; Felipe Francisco Tuon, MD, PhD; Ilias Karaiskos, MD, PhD; Isabel Machuca, MD; Mitchell J. Schwaber, MD; Özlem Kurt Azap, MD, PhD; Maria Souli, MD, PhD; Emmanuel Roilides, MD, PhD; Spyros Pournaras, MD; Murat Akova, MD; Federico Pérez, MD; Joaquín Bermejo, MD; Antonio Oliver, MD, PhD; Manel Almela, MD, PhD; Warren Lowman, MMed; Benito Almirante, MD, PhD; Robert A. Bonomo, MD; Yehuda Carmeli, MD, PhD; David L. Paterson, MD, PhD; Alvaro Pascual, MD, PhD; and Jesús Rodríguez-Baño, MD, PhD; Investigators from the REIPI/ESGBIS/INCREMENT Group

Mayo Clin Proc. 2016;91(10):1362-1371

TABLE 3. Assignment of Scores on the Basis of the Regression Coefficients Obtained for the Selected Variables Using Hierarchical Logistic Regression

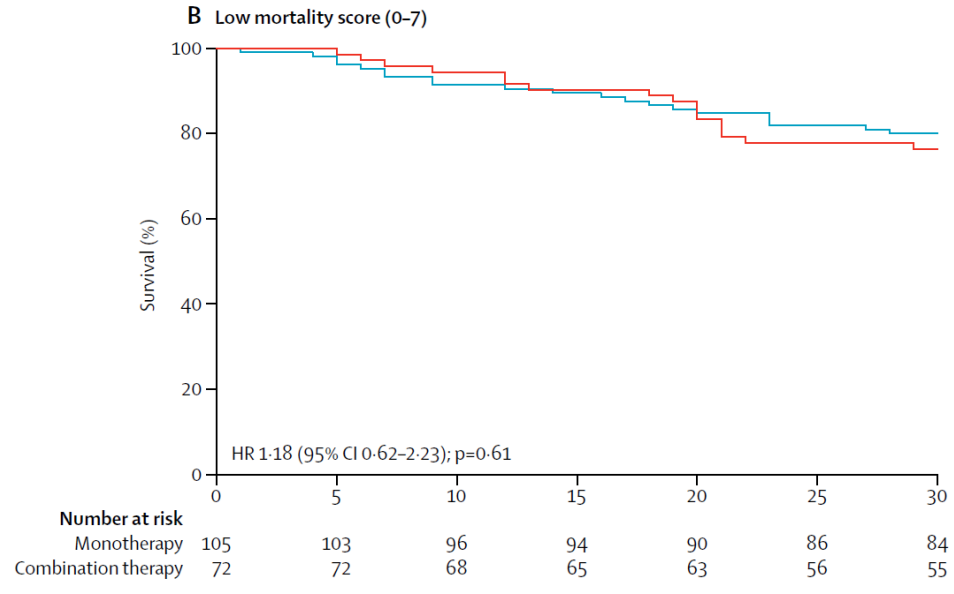
Variable	Regression coefficient (95% CI)	Score
Severe sepsis or septic shock	1.76 (1.01-2.50)	5
Pitt score ≥6	1.39 (0.54-2.25)	4
Charlson comorbidity index ≥2	0.93 (0.09-1.78)	3
Source of BSI other than urinary or biliary tract	0.92 (0-1.85)	3
Inappropriate early targeted therapy	0.69 (0.07-1.31)	2
Total points		*17*

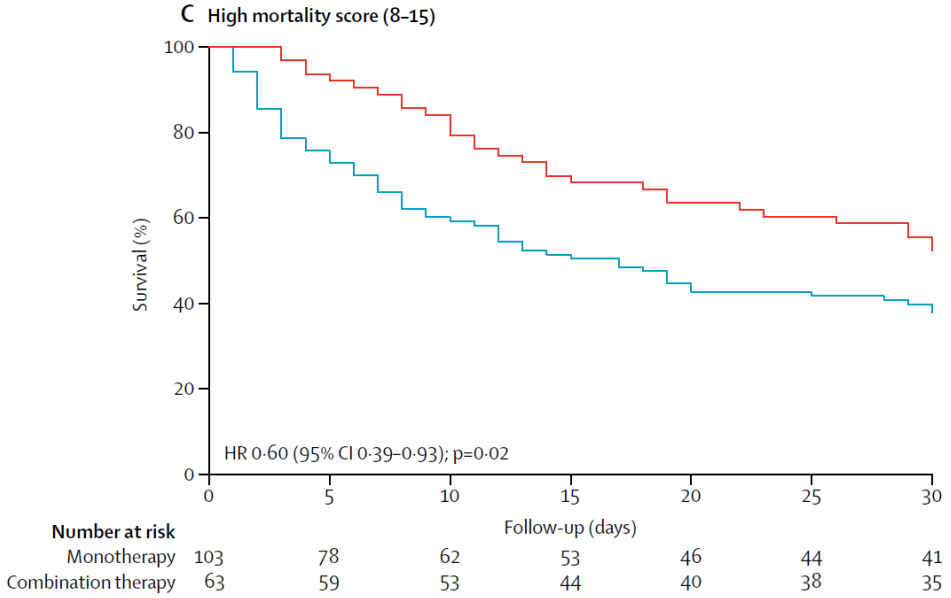
Score	Mortality
0-8	18%
9-13	50%
14-17	80%

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Belén Gutiérrez-Gutiérrez*, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†

Lancet Infect Dis 2017





Absolute difference -4%
aOR=1.21 (0.56-2.56) p=0.62

Absolute difference **14%**
aHR=**0.56** (0.34-0.91) p=0.02

Treatment of CPE with old drugs

- Carbapenems (optimized dosing) useful if MIC low enough
- Combination better in high-risk patients (pneumonia, shock)
  - Test combinations in vitro if needed
  - No evidence of which drug(s) or combination is better
- Optimization of dosing is critical
- Toxicity of colistin and aminoglycoside is an issue
- Some preferred drugs based on activity and source
  - UTI: aminoglycosides, fosfomycin
  - IAI: tigecycline

New drugs active against CPE

Drug	Clinical studies	Comparator	Results	Limitations
Ceftazidime-avibactam	Observationals (Van Duin, CID 2017; Tumbarello, CID 2019)	Colistin	Lower mortalidad	No randomization Resistance developement*
Meropenem-vaborbactam	TANGO-II (Wunderink, Infect Dis Ther 2018)	Best available therapy	Higher cure rate	Only 47 patients
Imipenem-relebactam	RESTORE-IMI 1 (Motsch, CID 2019)	IMI + COL	Superior in secondary outcomes	Most cases *P. aeruginosa*
Plazomicin	CARE (ECCMID 2017)	Best available therapy	Superior in secondary outcomes	Not published
Eravacicline	No studies in CPE	-	-	-

*Mostly KPC, sometimes re-sensitization to carbapenems

Activity against beta-lactamase producers

Ambler class	Enzyme	Cefto/ TAZ	CAZ/ AVI	MER/ VAB	IMI/ REL
A	ESBLs	Yes	Yes	Yes	Yes
	KPC	No	Yes	Yes	Yes
B	MBL	No	No	No	No
C	AmpC	Yes	Yes	Yes	Yes
D	OXA-48	No	Yes	No	No

Clin Microbiol Rev 2018

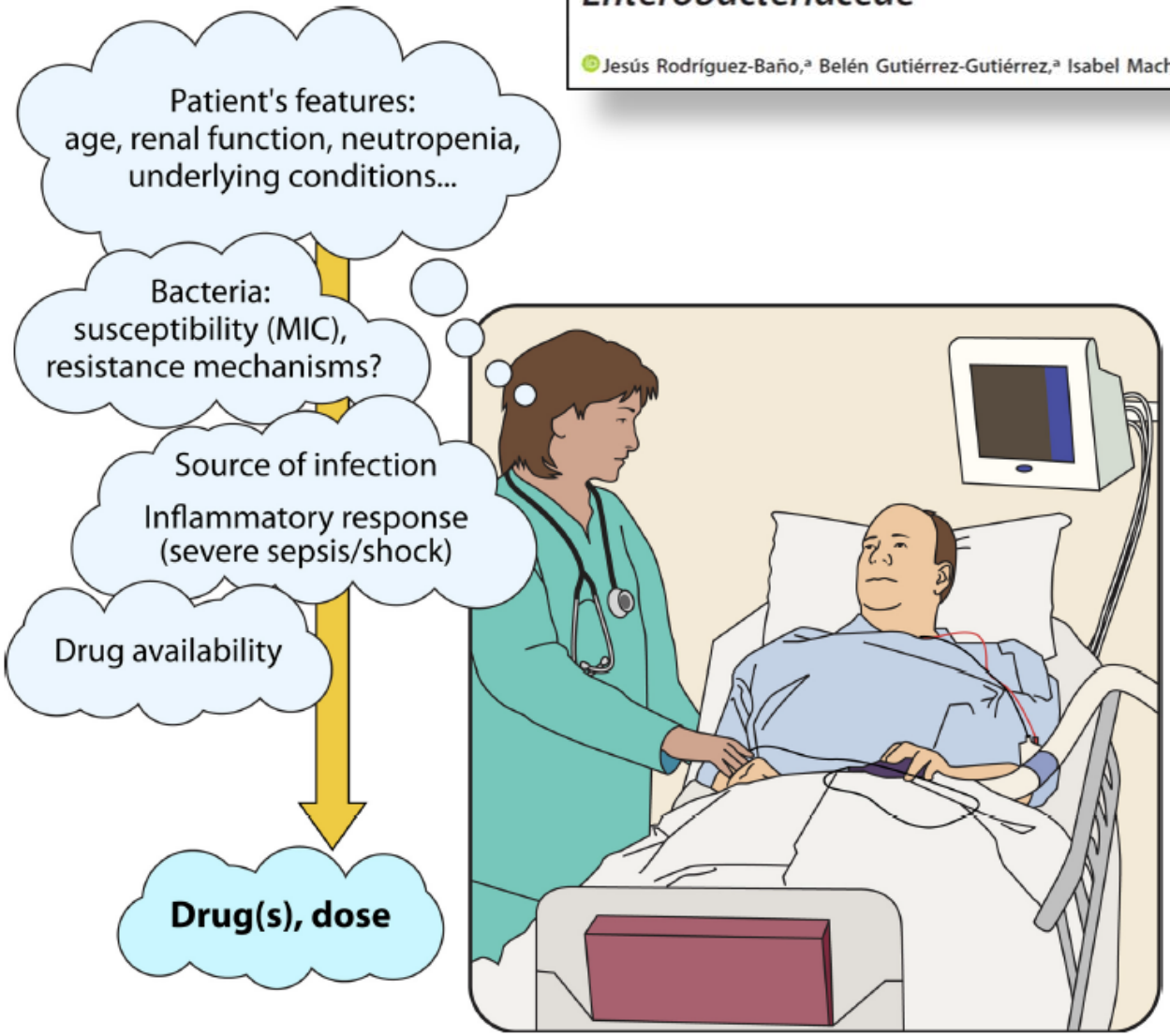
Isolate susceptibility	High risk: combination therapy
Susceptible to a β-lactam (use according to susceptibility)	**Backbone:** CAZ-AVI, MER-VAB **Alternatives:** MER (MIC ≤8 mg/L) or CAZ or ATM
	Accompanying drug: COL or TIG or AG or FOS* (CAZ-AVI or MER-VAB might not need combination)
Resistant to all β-lactams (MER >8 mg/L), susceptible COL and another drug	**Backbone:** COL
	Accompanying drug: TIG, AG (high risk of nephrotoxicity), FOS
Resistant to all β-lactams and colistin, susceptible to at least 2 drugs	**Backbone:** TIG or AG
	Accompanying drug: TIG, AG, FOS
Pandrug-resistant or susceptible only to one drug	(MER + ERT) or (CAZ-AVI + ATM) Consider: any active drug (CLO, RMP…), investigational drugs, in vitro testing for synergy
	Low risk: monotherapy
According to susceptibility and source	CAZ-AVI, MER-VAB, MER, CAZ, ATM, COL, TIG, AG

*TIG: mostly for cIAI; for HAP/VAP, consider double doce. AG: mostly for cUTI; for HAP/VAP, consider high doce and TDM. FOS: mostly for cUTI

Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

Jesús Rodríguez-Baño,[a] Belén Gutiérrez-Gutiérrez,[a] Isabel Machuca,[b] Alvaro Pascual[a]

Clin Microbiol Rev 2018



XDR *A. baumannii*

- Options:
  - Colistin, tigeycline, (sulbactam), (aminoglycosides), minocycline?
- Benefits of combination treatment nuclear/controversial
  - Meropenem + colistin not better than colistin
    - Paul et al, Lancet Infect Dis 2018
  - Other combinations
    - Colistin + sulbactam?? (network meta-analysis: Kengla et al, JAC 2018)
- Future – cefiderocol?

XDR *P. aeruginosa*

“Classic” options:

- Colistin, (aminoglycosides), (fosfomycin)

New drugs

- Ceftazidime-avibactam
  - Mendes et al, IJAA 2018; Stone et al, JAC 2018
- Ceftolozane-tazobactam: case series
  - Munita et al, CID 2017; Haidar et al CID 2017; Xipel et al, J Glob Antimicrob Resist 2018; Díaz-Cañestro et al, EJCMID 2018
- Imipenem-relebactam, meropenem-vaborbactam

Future

- Cefiderocol, murepavadine, cefepime-zidebactam

Horcajada et al, Clin Microbiol Rev 2019

Mechanisms leading to *in vivo* ceftolozane/tazobactam resistance development during the treatment of infections caused by MDR *Pseudomonas aeruginosa*

Pablo A. Fraile-Ribot[1], Gabriel Cabot[1], Xavier Mulet[1], Leonor Periañez[2], M. Luisa Martín-Pena[3], Carlos Juan[1], José L. Pérez[1] and Antonio Oliver[1]*

J Antimicrob Chemother 2018; **73**: 658–663

Ceftolozane/tazobactam for the treatment of multidrug resistant *Pseudomonas aeruginosa*: experience from the Balearic Islands

Manuel Díaz-Cañestro[1] · Leonor Periañez[2] · Xavier Mulet[3] · M. Luisa Martin-Pena[1] · Pablo A. Fraile-Ribot[3] · Ignacio Ayestarán[4] · Asunción Colomar[4] · Belén Nuñez[5] · Maria Maciá[5] · Andrés Novo[6] · Vicente Torres[7] · Javier Asensio[1] · Carla López-Causapé[3] · Olga Delgado[2] · José Luis Pérez[3] · Javier Murillas[1] · Melchor Riera[1] · Antonio Oliver[3]

European Journal of Clinical Microbiology & Infectious Diseases (2018) 37:2191–2200

8/58 (14%) developed R

- Mostly ST175 (OprD- and AmpC hyperproducer)
- AmpC structure mutation and acquisition of OXA-2, OXA-10

ST111 → AmpC mutation; re-sensitization to carbapenems and piptaz
Boulant et al, AAC 2019

Challenges in the treatment of MDRO

- As attending physician
  - How should I treat this patient
  - How will my decision impact the next patients
- As scientist
  - How can I produce evidence for decisions

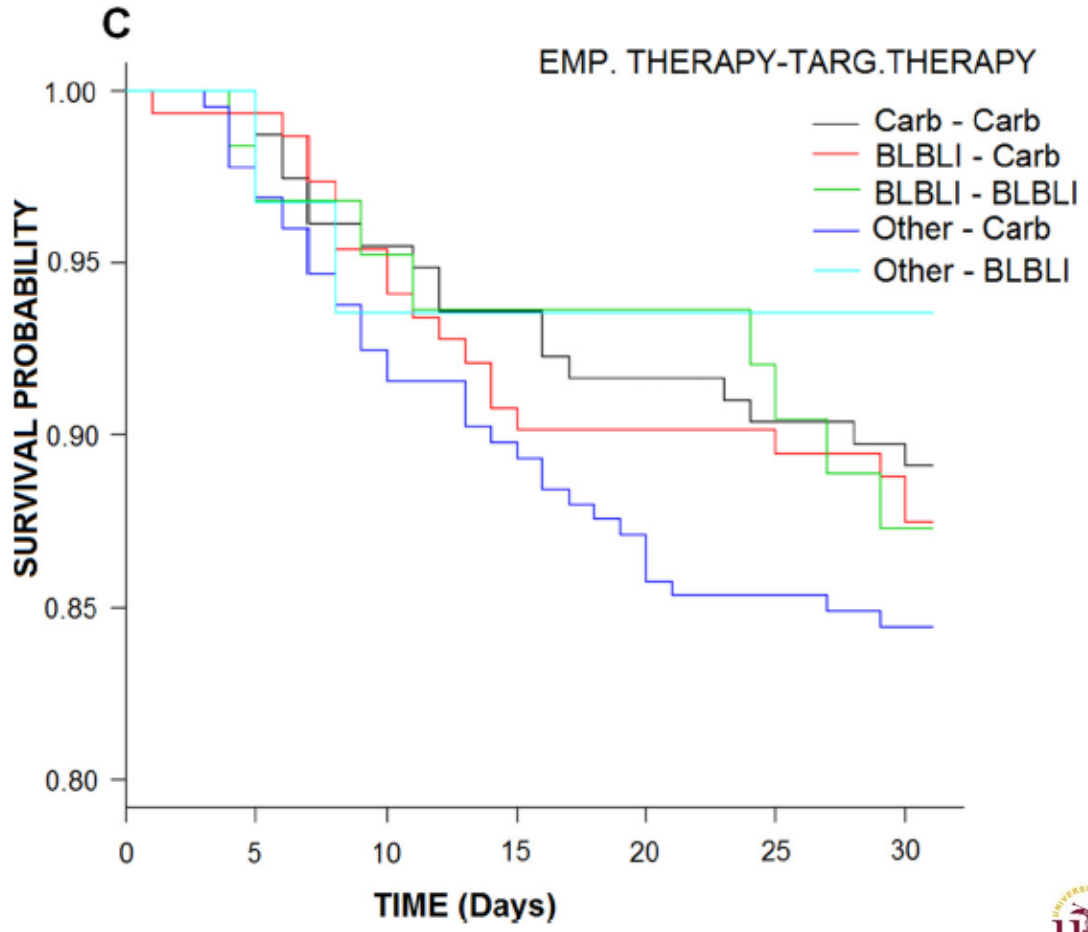
First example: can I avoid using carbapenems in some patients with Infections due to ESBL-producers?

A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*

Belén Gutiérrez-Gutiérrez,[a] Salvador Pérez-Galera,[a] Elena Salamanca,[a] Marina de Cueto,[a] Esther Calbo,[b] Benito Almirante,[c] Pierluigi Viale,[d] Antonio Oliver,[e] Vicente Pintado,[f] Oriol Gasch,[g] Luis Martínez-Martínez,[h] Johann Pitout,[i] Murat Akova,[j] Carmen Peña,[k] José Molina,[a] Alicia Hernández,[l] Mario Venditti,[m] Nuria Prim,[n] Julia Origüen,[o] German Bou,[p] Evelina Tacconelli,[q] Mario Tumbarello,[r] Axel Hamprecht,[s] Helen Giamarellou,[t] Manel Almela,[u] Federico Pérez,[v] Mitchell J. Schwaber,[w] Joaquín Bermejo,[x] Warren Lowman,[y] Po-Ren Hsueh,[z] Marta Mora-Rillo,[aa] Clara Natera,[bb] Maria Souli,[cc] Robert A. Bonomo,[v,dd] Yehuda Carmeli,[w] David L. Paterson,[ee] Alvaro Pascual,[a,ff] Jesús Rodríguez-Baño,[a,gg] the REIPI/ESGBIS/INCREMENT Group

Antimicrob Agents Chemother 2016

N=627



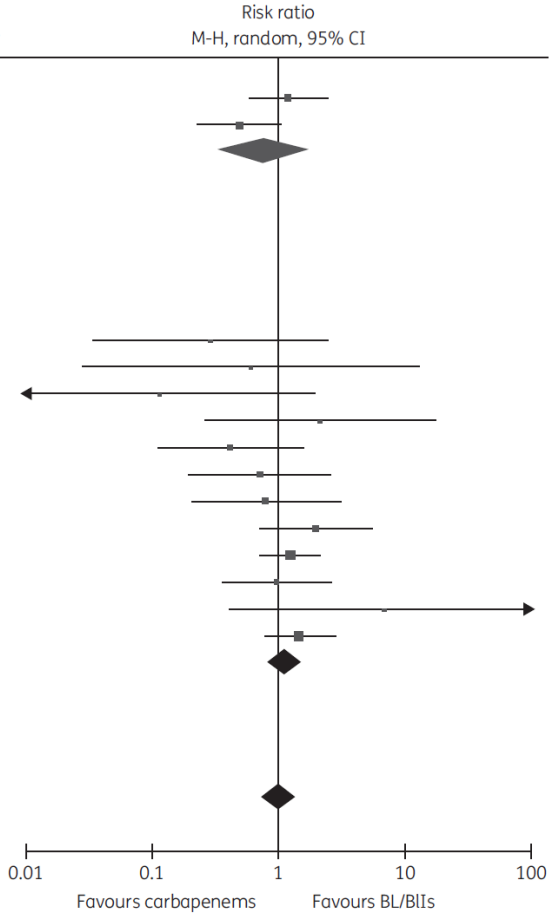
Clinical effectiveness of carbapenems versus alternative antibiotics for treating ESBL-producing Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Soo Kyung Son[1,2], Na Rae Lee[1,2], Jae-Hoon Ko[3], Jae Ki Choi[4], Soo-Youn Moon[5], Eun Jeong Joo[6], Kyong Ran Peck[3]† and Dong Ah Park[1]*†

J Antimicrob Chemother 2018; **73**: 2631–2642

(a)

Study or subgroup	Carbapenems events	Carbapenems total	BL/BLIs events	BL/BLIs total	Weight	Risk ratio M-H, random, 95% CI	Year
2.1.1 Comparative studies							
Kang 2012	21	78	8	36	13.5%	1.21 [0.59, 2.47]	2012
Tamma 2015	9	110	17	103	12.2%	0.50 [0.23, 1.06]	2015
Subtotal (95% CI)		188		139	25.7%	0.78 [0.33, 1.89]	
Total events	30		25				
Heterogeneity: Tau^2 = 0.26; χ^2 = 2.84, df = 1 (P = 0.09); I^2 = 65%							
Test for overall effect: Z = 0.55 (P = 0.59)							
2.1.2 Others							
Bin 2006	0	3	0	7		not estimable	2006
Tumbarello 2007	1	28	4	33	2.0%	0.29 [0.03, 2.49]	2007
Apisarnthanarak 2008	0	5	1	10	1.0%	0.61 [0.03, 12.80]	2008
Chaubey 2010	0	10	6	16	1.2%	0.12 [0.01, 1.91]	2010
Lee 2010	4	24	1	13	2.1%	2.17 [0.27, 17.43]	2010
De Rosa 2011	8	57	2	6	5.0%	0.42 [0.11, 1.55]	2011
Quirante 2011	2	6	6	13	5.2%	0.72 [0.20, 2.58]	2011
Gudiol 2011	2	5	3	6	4.8%	0.80 [0.21, 3.05]	2011
Rodriguez-Baño 2012	6	31	7	72	7.9%	1.99 [0.73, 5.44]	2012
Peralta 2012	18	70	24	117	19.7%	1.25 [0.73, 2.14]	2012
Ha 2013	7	27	5	19	8.1%	0.99 [0.37, 2.64]	2013
Kang 2013	3	9	0	9	1.2%	7.00 [0.41, 118.69]	2013
To 2013	14	47	15	74	16.0%	1.47 [0.78, 2.76]	2013
Subtotal (95% CI)		322		395	74.3%	1.14 [0.83, 1.56]	
Total events	65		74				
Heterogeneity: Tau^2 = 0.01; χ^2 = 11.24, df = 11 (P = 0.42); I^2 = 2%							
Test for overall effect: Z = 0.79 (P = 0.43)							
Total (95% CI)		510		534	100.0%	1.01 [0.74, 1.38]	
Total events	95		99				
Heterogeneity: Tau^2 = 0.05; χ^2 = 15.44, df = 13 (P = 0.28); I^2 = 16%							
Test for overall effect: Z = 0.07 (P = 0.94)							
Test for subgroup differences: χ^2 = 0.61, df = 1 (P = 0.44); I^2 = 0%							



JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

JAMA. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

- Randomised, multinational trial
- Pip-tazo (4,5 g/8h, 30 min) vs meropenem (1 g/8h, 30 min)
- Bacteremia due to ceftriaxone non-susceptible *E. coli* o *Klebsiella* spp and susceptible to pip-tazo and meropenem
- Primary outcime: 30-day mortality
- Recruitment stopped because of higher mortality with pip-tazo
- Conclusion: pip-tazo did not demonstrate to be non-inferior

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

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JAMA. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

- Comments - limitations
  - Disbalance in confounders (not controlled in multivariate análisis)
  - Mortality unrelated to infection
  - Isolates not susceptible to pip-tazo!!
  - Site effect
  - Piptaz administered in 30 minutos

Rodríguez-Baño et al, JAMA 2019

Mortality in patiens with Charlson <2:

pip-tazo 2/69 (2.9%), meropenem (2/76 (2.6%)

(data kindly provided by P. Harris and D. Paterson)

Association with 30-day mortality and MIC in patients treated with piperacillin/tazobactam for Escherichia coli and Klebsiella pneumoniae bloodstream infections that are non-susceptible to ceftriaxone from patients enrolled in the MERINO trial

Henderson A[1,2], Tan E[1], Cottrell K[1], Bauer M[1], Tambyah PA[3], Lye DC[4,5,6], Yilmaz M[7], Alenazi TH[8], Bassetti M[9], Righi E[9], Rogers BA[10,11], Kanj S[12], Bhally H[13], Iredell J[14,15], Mendelson M[16], Looke D[1,17], Miyakis S[18,19,20], Walls G[21], Crowe A[22], Ingram P[23,24,25], Daneman N[26], Griffin P[17,27,28], Athan E[29], Roberts L[30], Beatson S[30], Peleg AY[31,32], Harris-Brown T[1], Paterson DL[1,33], Harris PNA[1,34]
For the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

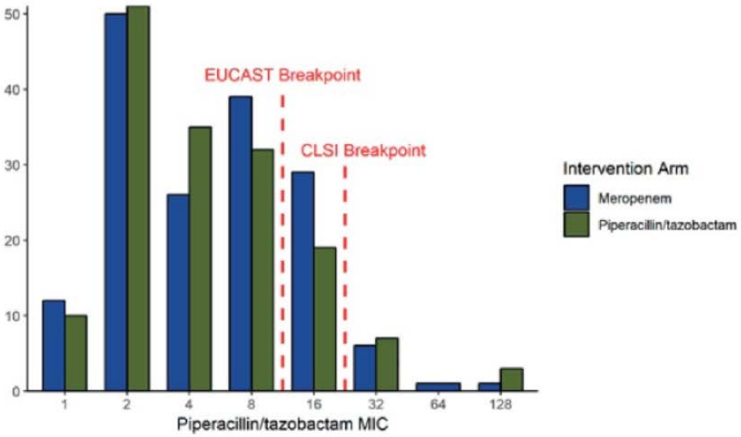

Figure 1. Distribution of piperacillin/tazobactam MIC stratified by intervention arm.

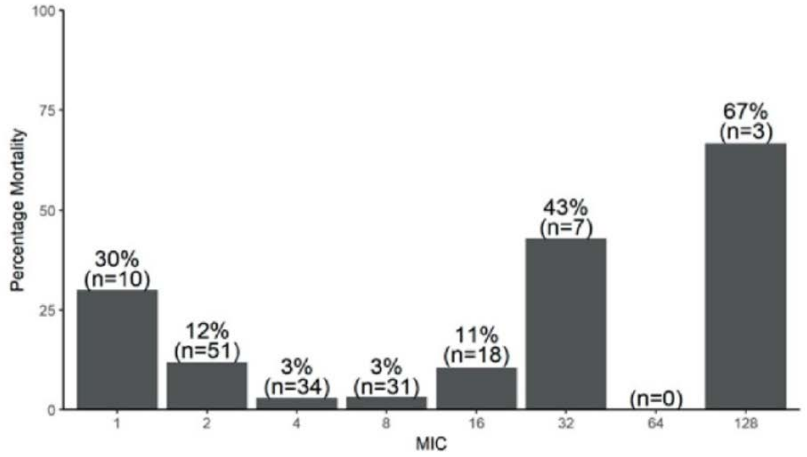

Figure 3. Percentage mortality in piperacillin-tazobactam arm stratified by MIC.

ECCMID 2019

Microbiological mITT

MY CALCULATIONS FROM PRESENTED DATA excluding non-susceptible isolates: Mortality

- MER: 6/164 (3.6%)
- TZP: 9/150 (6.0%)
- Difference (97.5% CI) 2.4 (-3.1 – 7.8)

Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients

B. Gutiérrez-Gutiérrez*, J. Rodríguez-Baño

Clinical Microbiology and Infection 25 (2019) 932–942

Table 1
Definitions used for the classification of patients in this review

Dimension	Classification	Conditions
Severity at presentation	Severe	Any of the following: Pitt score ≥4, APACHE II score >10, ICU admission, and presentation with severe sepsis or septic shock
	Non-severe	All others
Source of infection	High risk	High-inoculum Infections, drainage not possible or inadequate (e.g. pneumonia, endocarditis, inadequately drained deep-seated infections)
	Intermediate risk	Not included in high or low risk (e.g. vascular catheter Infection with catheter removal, drained biliary tract or intra-abdominal)
	Low risk	Urinary tract Infection without obstruction or released obstruction
Immune status	Severely immunocompromised	Any of the following: neutropenia (<500/μL), leukaemia, lymphoma, HIV infection with <200 CD4/μL, solid organ or hematopoietic stem cell transplantation, cytotoxic chemotherapy, steroids (>15 mg of prednisone daily for >2 weeks).
	Non-severe	All others

Group 1: Severe infection or non-severe + high-risk source and/or inmunocompromised

Group 2: Non-severe, intermediate-risk source, not immunocomprimised

Group 3: Non-severe, low-risk source, not immunocompromised

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Summary table of current options to treat infections due to ESBL-producing Enterobacteriaceae in different groups of patients

Group[1]	Characteristics of infection in each group	Options for treatment (dosing with normal renal function)
1	Severe infections; or Infections with a high-risk source; or/and Severely-immunocompromised patients	Imipenem (500 mg/6 h) Meropenem (1 g/8 h)
2	Non-severe infections from intermediate-risk source	Ertapenem (1 g/day) Piperacillin-tazobactam (4.5 g/6–8 hr in extended infusion) Imipenem (500 mg/8 hr) Meropenem (1 g/8 hr)
3	Non-severe urinary tract infection	Ertapenem (1 g/day) Piperacillin-tazobactam (4.5 g/6–8 hr in extended infusion) Amoxicillin-clavulanic acid (intravenous: 2.2 g/8 hr; oral for UTI: 1.250 g/8 hr) Aminoglycosides (amikacin: 15–20 mg/kg/day; gentamicin or tobramycin: 5–7 mg/kg/day) Plazomycin (15 mg/kg/day) Cephamycins (flomoxef: 1 g/8 hr; cefmetazole: 1 g/8 hr) Imipenem (500 mg/8 hr) Meropenem (1 g/8 hr) Fosfomycin iv (4 g/6 hr) Tromethamol-oral for non-bacteraemic UTIs (3 g/48 hr) Ciprofloxacin-oral for non-bacteraemic UTIs (400 mg/8–12 hr)

Second example: can I avoid the empirical of new drugs in some patients colonized with CPE?

Risks of Infection and Mortality Among Patients Colonized With *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Validation of Scores and Proposal for Management

Angela Cano,[1,a,b] Belén Gutiérrez-Gutiérrez,[2,a,b] Isabel Machuca,[1] Irene Gracia-Ahufinger,[3,b] Elena Pérez-Nadales,[4,b] Manuel Causse,[3,b] Juan José Castón,[1,b] Julia Guzman-Puche,[3] Julian Torre-Giménez,[1] Lara Kindelán,[1] Luis Martínez-Martínez,[3,b] Jesús Rodriguez-Baño,[2,b] and Julian Torre-Cisneros[1,b]

Clin Infect Dis 2018

TABLE 2. Logistic regression analysis of risk factors for CR-KP BSI development in rectal carriers

	OR (95% CI)	P-value	Risk score point
Admission to ICU	1.65 (1.05–2.59)	0.03	2
Invasive abdominal procedures	1.87 (1.16–3.04)	0.01	3
Chemotherapy/radiation therapy	3.07 (1.78–5.29)	<0.0001	4
Colonization at site besides stool (risk per each additional site)	3.37 (2.56–4.43)	<0.0001	5 per site

ICU, intensive care unit; OR, odds ratio.

Gianella et al, CMI 2014

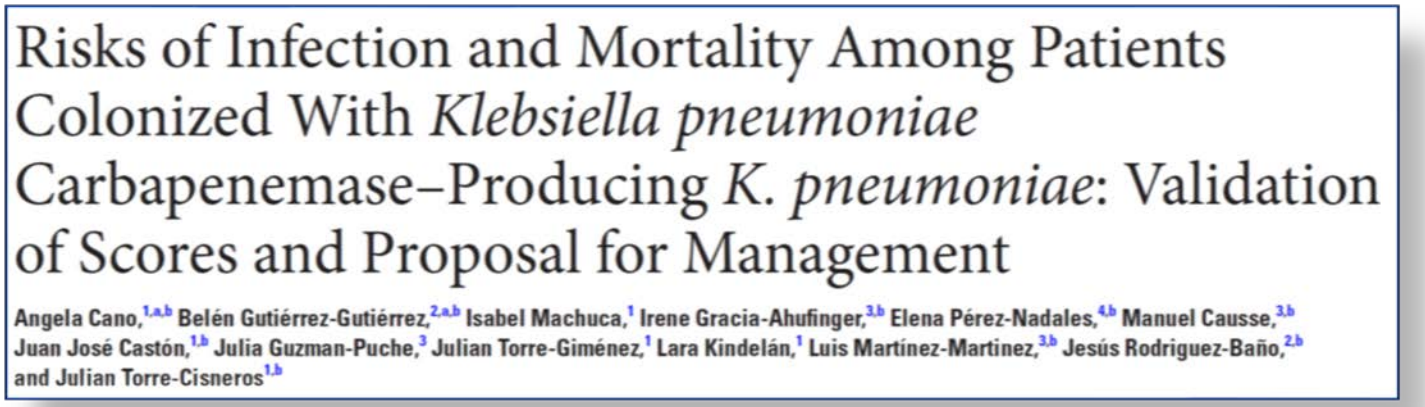
GIANELLA score
RISK OF INFECTION IN KPC-COLONIZED
Validation for any type of KPC infection
AUROC: 0.92 (95% CI 0.87–0.98)

TABLE 3. Assignment of Scores on the Basis of the Regression Coefficients Obtained for the Selected Variables Using Hierarchical Logistic Regression

Variable	Regression coefficient (95% CI)	Score
Severe sepsis or septic shock	1.76 (1.01-2.50)	5
Pitt score ≥6	1.39 (0.54-2.25)	4
Charlson comorbidity index ≥2	0.93 (0.09-1.78)	3
Source of BSI other than urinary or biliary tract	0.92 (0-1.85)	3
Inappropriate early targeted therapy	0.69 (0.07-1.31)	2
Total points		*17*

Gutiérrez-Gutiérrez et al, Mayo Clin Proc 2017

INCREMENT score
RISK OF DEATH IN CPE INFECTION
Validation for any type of KPC infection
AUROC: 0.78 (95% CI 0.65–0.91)



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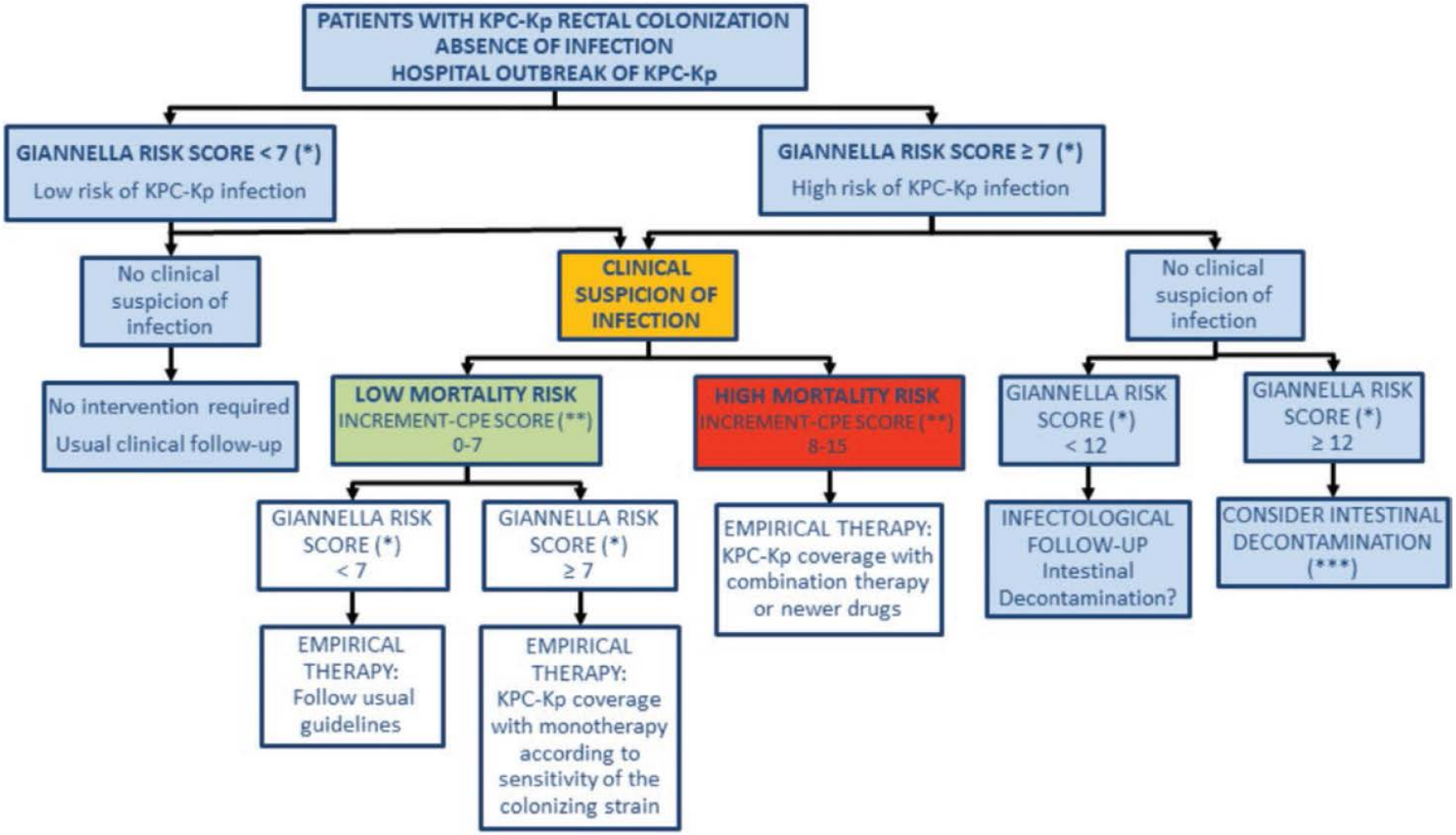
Clin Infect Dis 2018

- **Asymptomatic carrier: decision for follow-up according to Gianella score**
  - <7 (low risk of infection): no intervention
  - ≥7 (high risk of infection): consider decolonization with gentamicin, mostly if GRS ≥12 (Machuca et al, JAC 2016)

- **Infection: empirical therapy according to INCREMENT and Gianella scores**
  - Increment <7 + Gianella <7: standard treatment
  - Increment <7 + Gianella ≥7: monotherapy against KPC-Kp
  - Increment ≥7: combination therapy against KPC-Kp



Cano et al, CID 2018

Challenges in the treatment of MDRO

- As attending physician
  - How should I treat this patient
  - How will my decision impact the next patients
- As scientist
  - How can I produce evidence for decisions

The quality of studies evaluating antimicrobial stewardship interventions: a systematic review

V.A. Schweitzer [1,*], I. van Heijl [2], C.H. van Werkhoven [1], J. Islam [3], K.D. Hendriks-Spoor [2], J. Bielicki [4], M.J.M. Bonten [5], A.S. Walker [6], M.J. Llewelyn [3]on behalf of the Consensus on Antimicrobial Stewardship Evaluations (CASE) study group[†]

Clinical Microbiology and Infection 25 (2019) 555–561

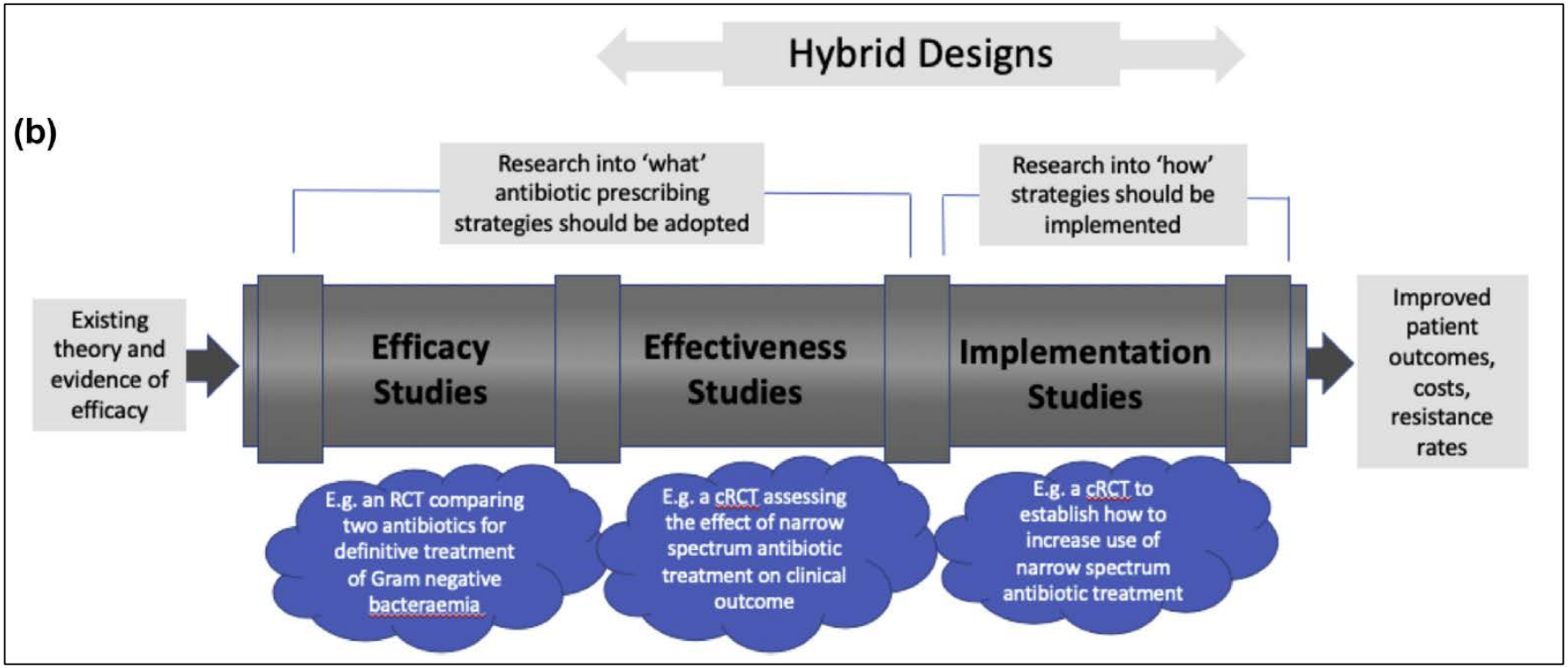
Implications: Overall quality of antimicrobial stewardship studies is low and has not improved over time. Most studies do not report clinical and microbiological outcome data. Studies conducted in the community setting were associated with better quality. These limitations should inform the design of future stewardship evaluations so that a robust evidence base can be built to guide clinical practice.

Consensus statement

Optimizing design of research to evaluate antibiotic stewardship interventions: consensus recommendations of a multinational working group

V.A. Schweitzer [1], C.H. van Werkhoven [1], J. Rodríguez Baño [2], J. Bielicki [3], S. Harbarth [4], M. Hulscher [5], B. Huttner [4], J. Islam [6], P. Little [7], C. Pulcini [8], A. Savoldi [9, 10], E. Tacconelli [9, 10], J.-F. Timsit [11, 12], M. van Smeden [13], M. Wolkewitz [14], M.J.M. Bonten [15], A.S. Walker [16, 17], M.J. Llewelyn [7, *], on behalf of Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working Group on Design of Antimicrobial Stewardship Evaluations

Clin Microbiol Infect 2019



Challenges for RCTs in the field…

- How specific should it be? (pathogen, mechanism of resistance, type of infection, type of patient)
- Pragmatism (real life) in management
- Outcomes
  - Cure somehow subjective → need to blind
  - Mortality (not sensitive enough for some infections)
- Empirical (inclusion of non-target bacteria) or definitive (impact of empirical therapy)?
- Funds…

Challenges for observationals in the field…

- Exposure
  - Changes in treatment during the course
  - Survivor bias
- Confounding
  - Variables assessed
  - Methods for confouding control
- Assessment for soft outcomes

Improved treatment of multidrug-resistant bacterial infections: utility of clinical studies

Esther Bettiol*[,1], Wouter C Rottier[2], Maria Dolores del Toro[3,4], Stephan Harbarth[1], Marc J Bonten[2,5] & Jesús Rodríguez-Baño[3,4]; on behalf of the COMBACTE consortium

Future Microbiol. (2014) 9(6), 757–771

How to test individualized decisions?

- Comparator?
- Ethics?
- Predefined pathway for indivualized decisions?

Some ongoing studies at HUVM…

- Observationals
  - EURECA (CRE) (≈2,000 patients)
  - PROBAC (nationwide, bloodstream infections) (≈6,000 patients)
- RCT
  - FOREST (fosfomycin in bacteraemic UTI)
  - SIMPLIFY (de-escalation in BSI due to enterobacteria)
  - NO-BACT (intervention in patients with negative blood cultures)
  - Submitted for funding: ASTARTE (temocillin for BSI due to ceph-R enterobacteria)

Conclusions

- As attending physicians
  - The big 3: CRE, XDR *P. aeruginosa* and *A. baumannii*
  - New antibiotics are probably better in some situations but old antibiotics are still useful in others
  - If we don't preserve the new antibiotics we will soon loose them
  - Individualization is key for the individual patient and for stewardship

- As scientists
  - Evaluating and performing studies is difficult…
  - …but we must try

Two final recommendations (non-evidence based)

- Come to ECCMID 2020
- Participate in ESCMID activities!!

Ackowledgements