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ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Preparing the future ESCMID guideline on infections due to MDR Gram-negative bacteria - a case-based discussion

Discussion panel:

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Case 5

03-01-2018

Empirical treatment: colistin 3 MU/8h + meropenem 2 g/8h (extended infusion)

Medical history

56 year-old men

- 2017: massive rectorragia requiring urgent colectomy (intestinal lymphoma); secondary peritonitis requiring reintervention (pip-taz; meropenem); CVC-BSI *S. epidermidis* (vanco); right nephrostomy (urether infiltration)
- 5 chemo cycles (last one 7 days before hospital admission)

- Recurrent UTIs (cipro, amoxi-clav)
- No allergies

Hospital admission

- Fever
- Purulent urine (nephrostomy bag)

Physical examination:

- T: 38,3°C, BP 76/44, HR 98, RR 14
- **Tests:**
  - WBC: 1.200 leucocytes/mm3 (960 neutrophils/mm3), lactate 2.8 mmol/L, creatinine 1.3 mg/dL; urine: nitrites (+), leucocytes (+++)
- Urine and blood culture performed
- **Rectal swab positive for KPC-producing *Klebsiella pneumoniae***

Case 5
Urine and blood culture

KPC producer

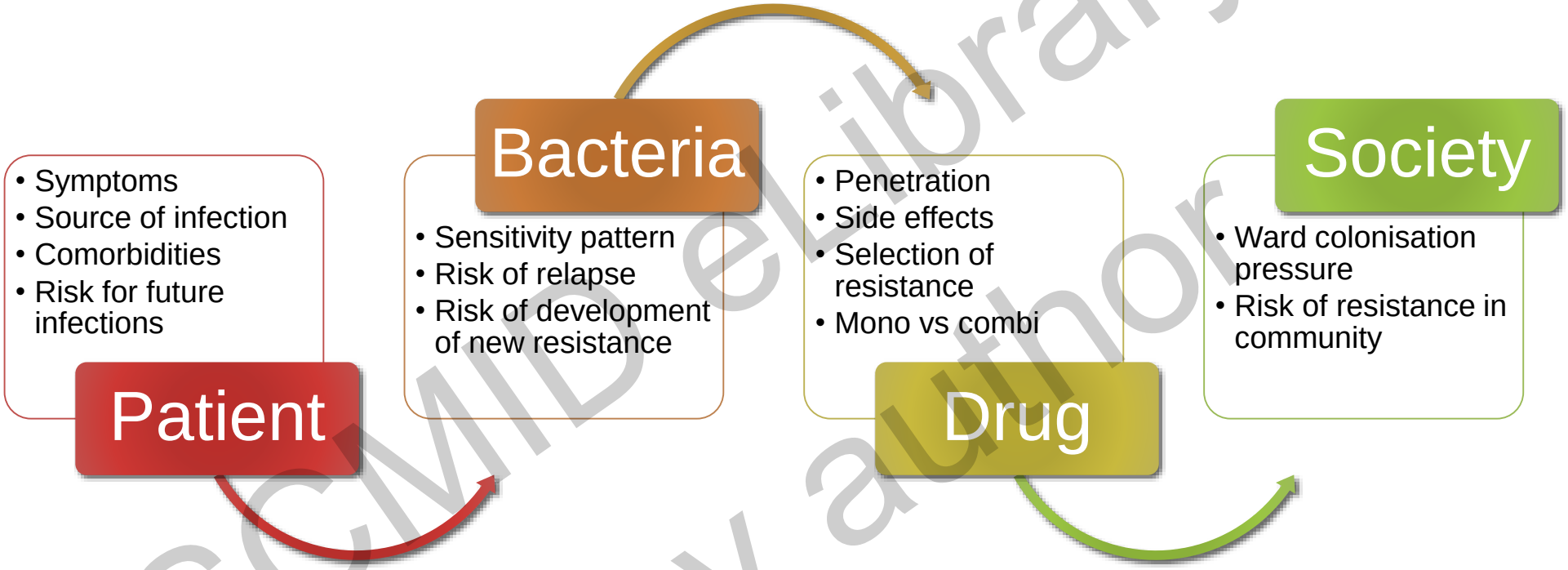
Klebsiella pneumoniae

Antibiogram	S/I/R	MIC (ug/ml)
Ampicillin	R	>16
Amoxicilin-clavulanic	R	>16/8
Piperacillin-tazobactam	R	>64/4
Cephuroxime	R	>16
Cefotaxime	R	>16
Ceftazidime	R	>16
Ceftazidime-avibactam	S	≤1
Cefefepim	R	> 8
Ertapenem	R	>1
Meropenem	R	>16
Amikacin	R	>32
Gentamicin	R	>4
Tobramycin	R	>4
Ciprofloxacyn	R	>2
Tmp/Smx	R	>4/76
Colistine	S	≤1
Tigecycline	S	≤1

Fosfomycin susceptible

Question for a smart audience
How would you treat?

1. Colistin
2. Colistin and Meropenem
3. Colistin and Tigecyclin
4. Colistin, Tigecyclin, and Meropenem
5. Ceftazidime-avibactam
6. Ceftazidime-avibactam and Colistin / Meropenem



Patient

- Symptoms
- Source of infection
- Comorbidities
- Risk for future infections

- Mild symptomatic
- Urinary tract source of infection
- No allergies
- Not severe neutropenia
- Age < 60 y.o.
- Right nephrostomy
- **Intestinal lymphoma**
- **Recurrent UTIs**

Society

- Ward colonisation pressure
- Risk of resistance in community

- Impact of usage of colistin / cefta-avibactam / tigecycline on selecting ward´s resistance rates
- Risk of spreading resistance in the **community** (home discharge / **LTCF**)

Bacteria

- Sensitivity pattern
- Risk of relapse
- Risk of development of new resistance

- **KPC producer**
- **Meropenem MIC**
- Risk of relapse of KP
- Risk of development of resistance

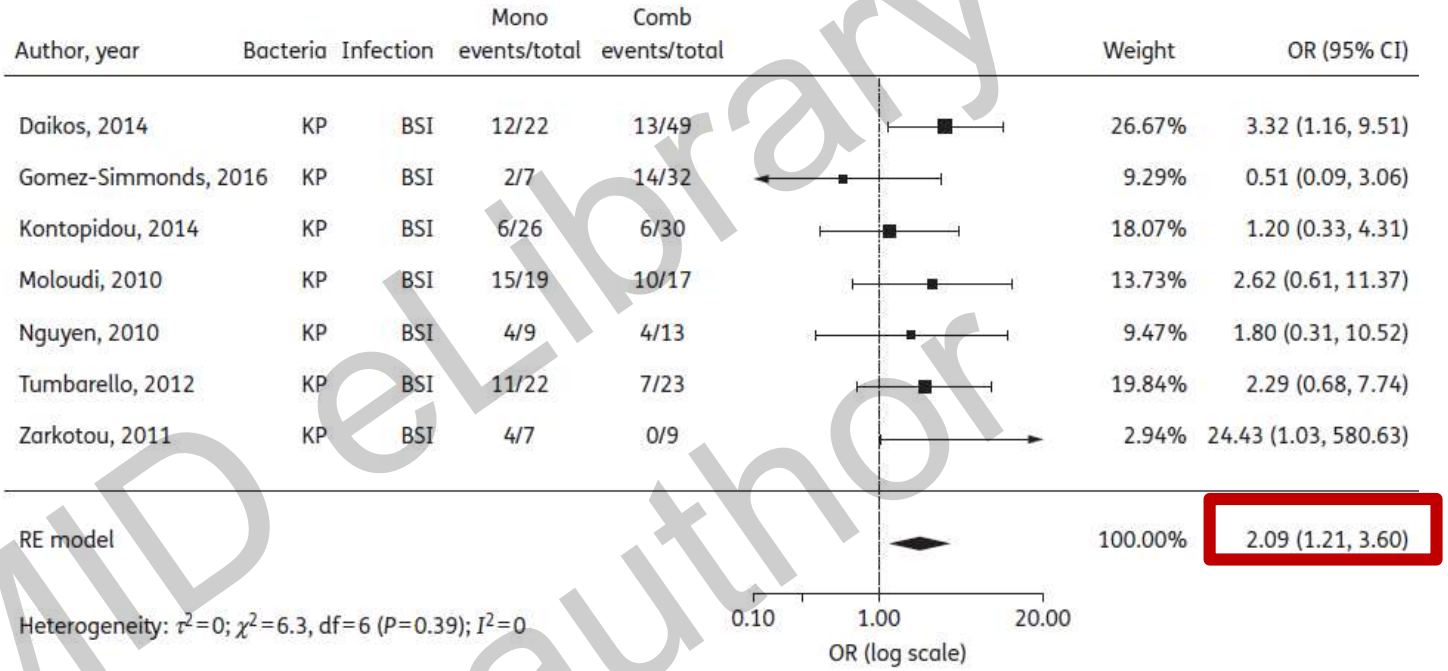
- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

BSI (285 patients)

OR 2.09, 95%CI **1.21–3.6**

1. Monotherapy vs combination therapy



Zusman O, 2017: 7 retrospective cohort studies

- Mortality was significantly higher with polymyxin mono vs combi (tige/ amino/ fosfo); 285 patients, no heterogeneity; very low quality

BSAC guidelines 2018 (SR 2012, Medline up to 2014, some references added Oct 2016-June 2017)

Recommendation by antibiotic and bacteria

- **Severe infections use combination**

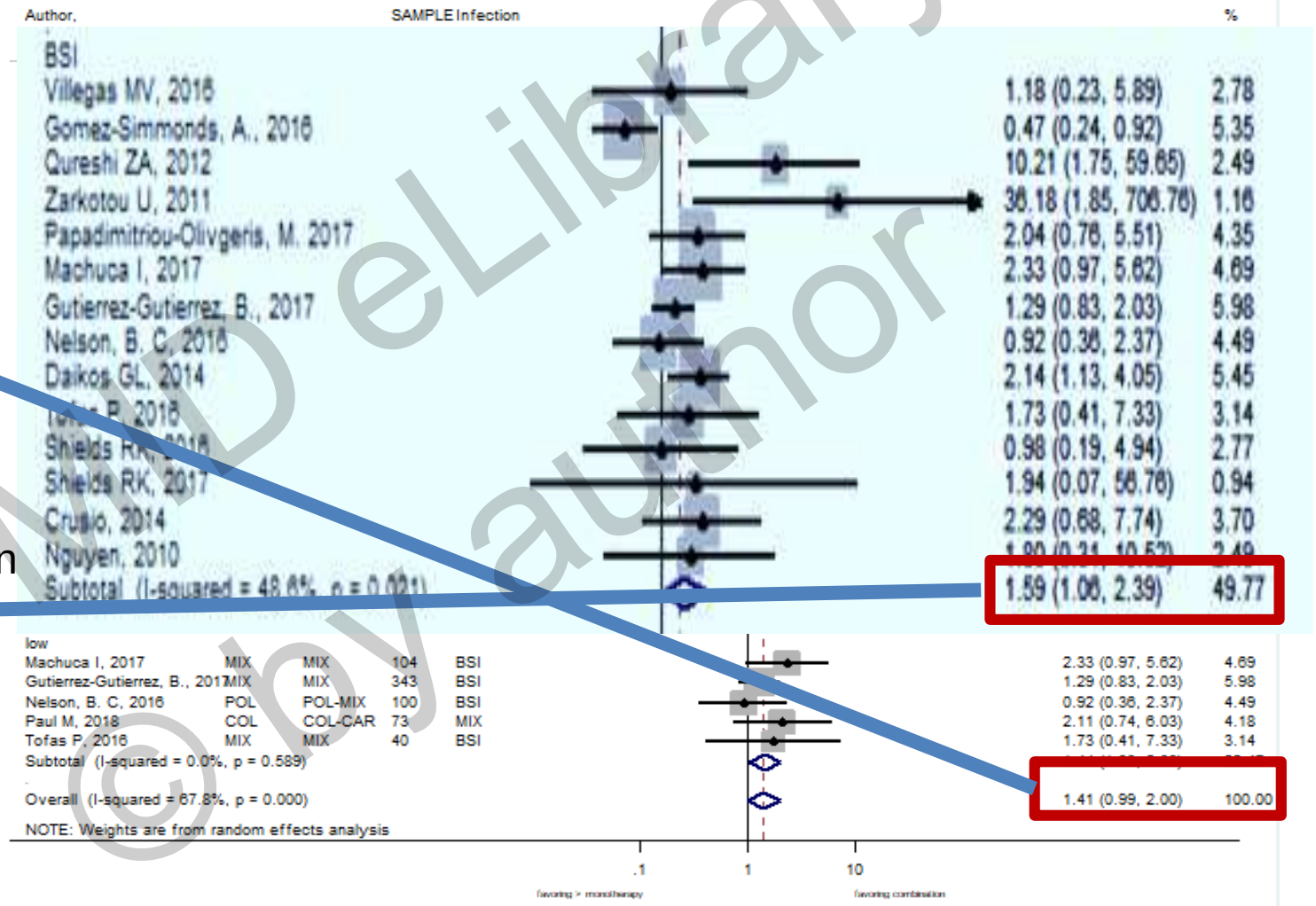
- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

2017-2018 evidence

1.44 (1.03 – 2.00)
in favour of combination
(low risk of bias)

1.59 (1.06 – 2.39)
in favour of combination
(BSI)



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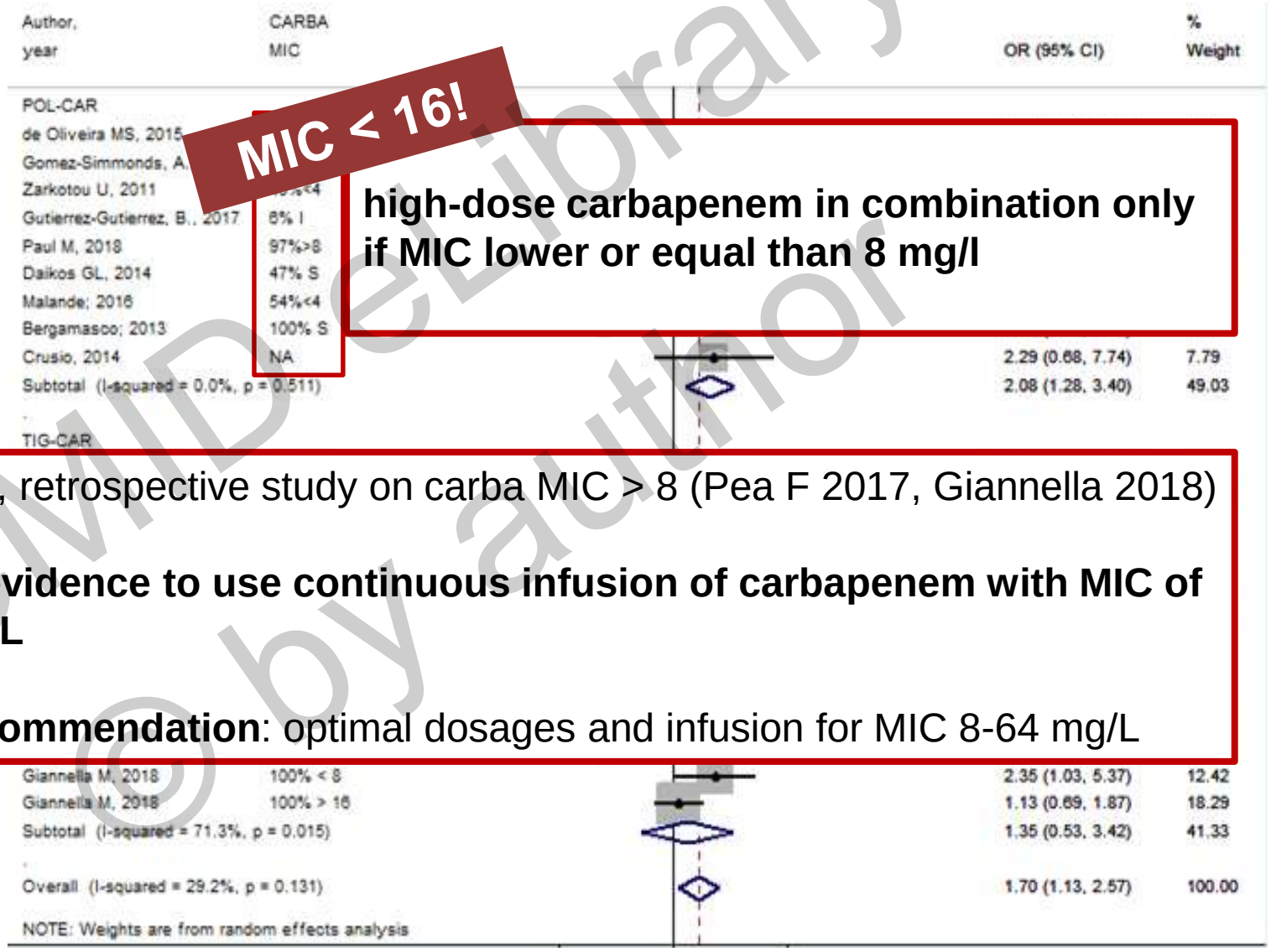
Carrara E, ESCMID GL (28 studies) 2018

- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

Monotherapy vs combination therapy
Combination with carbapenems



MIC < 16!

high-dose carbapenem in combination only if MIC lower or equal than 8 mg/l

2 uncontrolled, retrospective study on carba MIC > 8 (Pea F 2017, Giannella 2018)

Not enough evidence to use continuous infusion of carbapenem with MIC of .8 and .64mg/L

Research recommendation: optimal dosages and infusion for MIC 8-64 mg/L

ESCMID

Carrara E, ESCMID GL (14 studies) 2018

COLISTIN

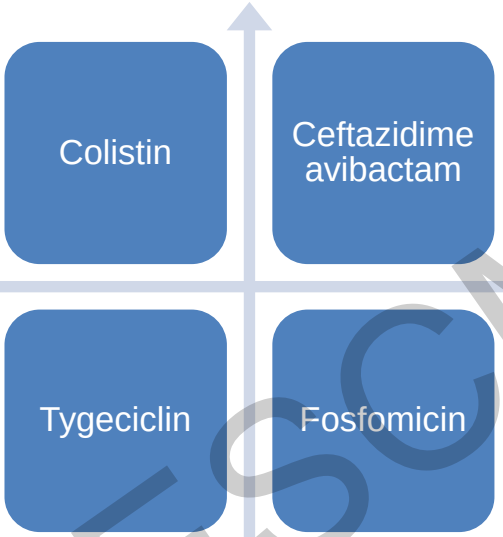
- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

Certainty assessment						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
14	observational studies	serious	not serious	not serious	not serious	none

⊕◯◯◯ VERY LOW

12 OBSERVATIONAL STUDIES ON MIXED INFECTIONS
2 OBSERVATIONAL STUDIES ON UTI



KPC-CR-KP-BSI

1. Colistin could be considered in combination therapy in BSI-KPC-CR-KP (possible combination in this patient tigecycline, fosfomycin, and ceftazidime-avibactam)

2. Dosing: evidence incomplete for a recommendation (SHEA polymyxin consensus under development)

Research recommendation: loading doses, high dosages and combination, and serum level monitoring

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CEFTAZIDIME-AVIBACTAM

- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2.1 ceftazidime/avibactam						
7	observational studies	very serious	not serious	not serious	not serious	none

⊕◯◯◯ VERY LOW

4 uncontrolled studies on CR-KP

Shields, 2016: 31 patients; overall clinical success rate: 59%

KPC-CR-KP-BSI

1. Cefta-avibactam could be considered in combination (mono)-therapy in BSI-KPC-CR-KP. **Very limited quality of evidence**

2. **Resistance emerging in 10% of treated patients**. KPC-3-producing Klebsiella spp. are vulnerable to mutations in the blaKPC-3 gene causing resistance

Comparison: 99 colistin (46% BSI)
30-day mortality: 9% vs 32%
Most patients received additional anti-CRE agents

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- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
BSI and mortality					
observational studies [5,6,9,10]	very serious [c]	not serious	not serious	not serious	none

TIGECYCLIN

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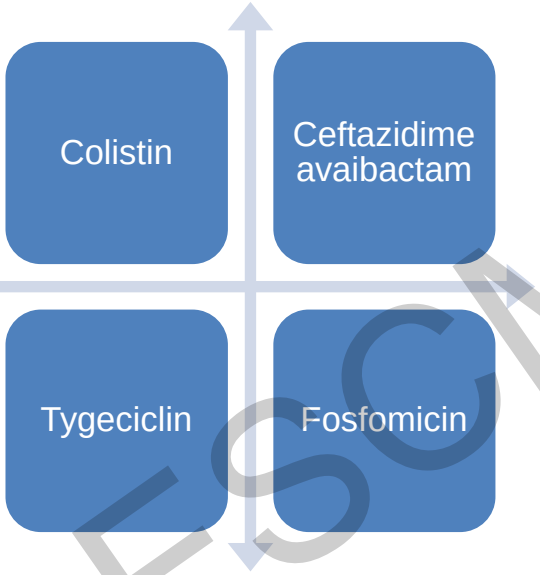
VERY LOW



KPC-CR-KP-BSI

4 small retrospective cohorts
No advantage in combination
High mortality rate in CR-KP BSI

Balandin-Moreno, 2014 (16 patients, mixed infections): no difference

De Pascale, 2014 (100 patients, mixed aetiology / infections): HD performed better in VAP subgroup

Verdakas, 2015 (22 patients): no difference

- **High Dosage (HD)**: **not enough data for a recommendation**
- **Research recommendation**: high dosages in selected populations

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- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Drug

Certainty assessment						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
fosfomycin ev						
4	observational studies [1,2,3,4]	very serious [a]	not serious	not serious	not serious	none

FOSFOMYCIN

⊕○○○
VERY LOW

KPC-CR-KP-BSI

4 observational studies (combination)

Michalopoulos, 2010: 11 critically ill patients / mixed KPC infections
- 30-day mortality 9%

Pontikis, 2014: 23 ICU patients / mixed infections
- Overall mortality: 44%

Karageorgopoulos, 2012: 3 patients KPC-BSI
- All 3 developed resistance to fosfomycin during treatment

- **Not enough data for a recommendation**

Could be considered for a salvage therapy for susceptible KPC-CR-KP
- **Research recommendation**: optimal dosages and indications

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Question for the smart audience after a (hopefully) smart presentation
How would you treat?

KPC-CR-KP-BSI

1. Colistin
2. Tigecycline
3. Colistin and Tigecyclin
4. Tigecyclin and meropenem
5. Ceftazidime-avibactam
6. Ceftazidime-avibactam and colistin / meropenem

Final selection

KPC-CR-KP-BSI (genta-R)

How long can we discuss in case of low / very low evidence? How much we are influenced by personal experience, working setting and availability of diagnostic and budget?

1. Ceftazidime-avibactam and Colistin
2. Ceftazidime-avibactam
3. Tigecycline and Colistin

Take home message

KPC-CR-KP-BSI

Summary of evidence

- 28 studies: **1 RCT** and 27 observational studies (23 retrospective, 4 prospective)
- Certainty of assessment for all outcomes: **Very low**
- **Heterogenenity** of setting, population, dosages, and combination

What else?

- Enhanced infection control essential! (EUCIC decolonisation GL, Tuesday 13:30 Hall A)
- Clinical studies on loading dosages, dosages, duration, and combined effect of specific drugs are urgently needed
- **Networking** for research **among high endemic countries and within the same country** could make a difference