

Aminoglycosides used in combined treatment for multi-resistant Gram-negative bacteria

Combined antimicrobial therapy for multi-resistant Gram-negative bacteria

Mical Paul

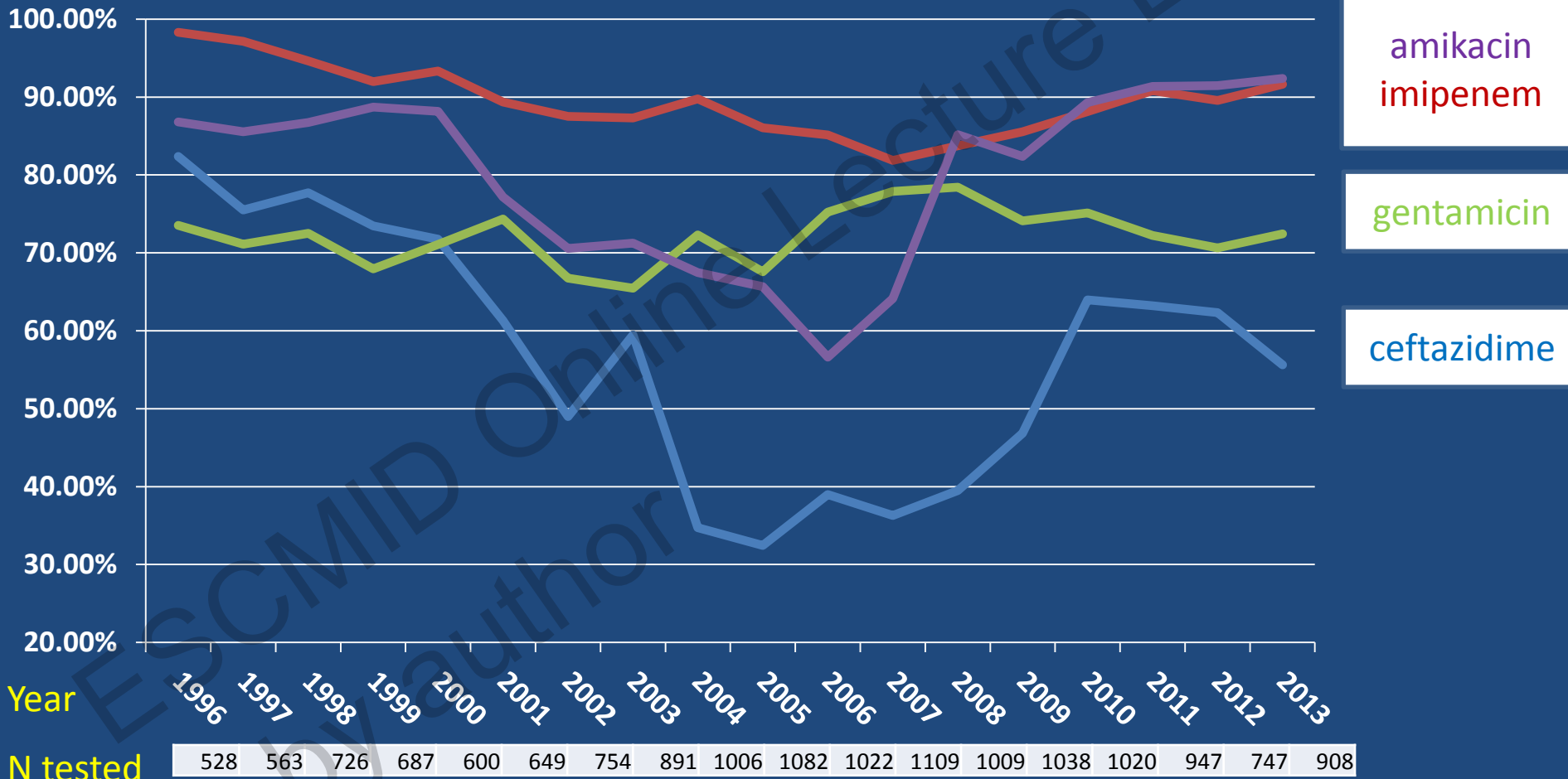
Rambam Health Care Campus

Topics

- Evidence on aminoglycoside monotherapy
- Aminoglycoside combination therapy against carbapenem-resistant Gram negatives
- Evidence on beta-lactam-aminoglycoside combination therapy
- Place of aminoglycoside combination therapy for the treatment of carbapenem-resistant Gram negatives in clinical practice

Coverage against Gram negatives

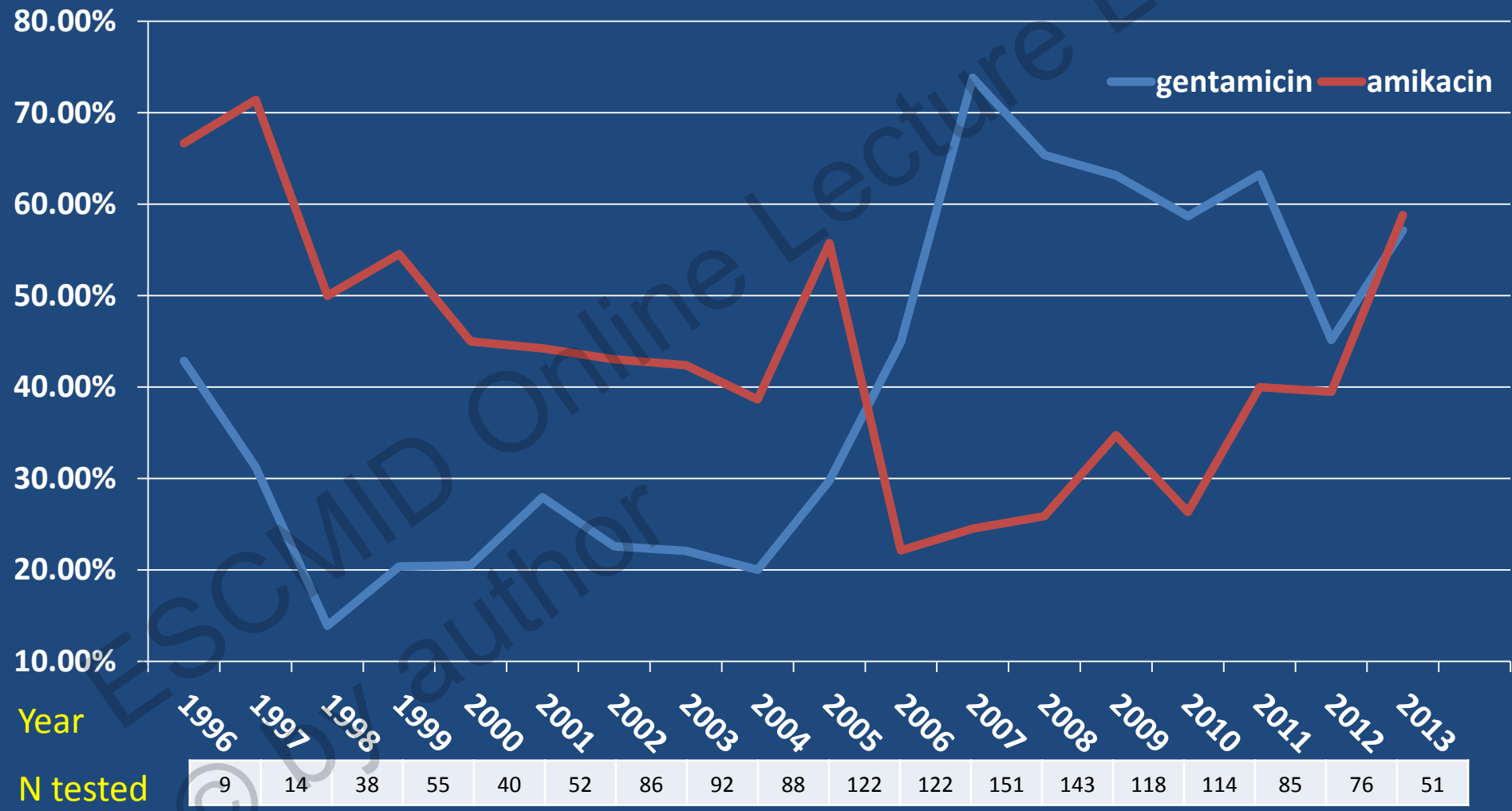
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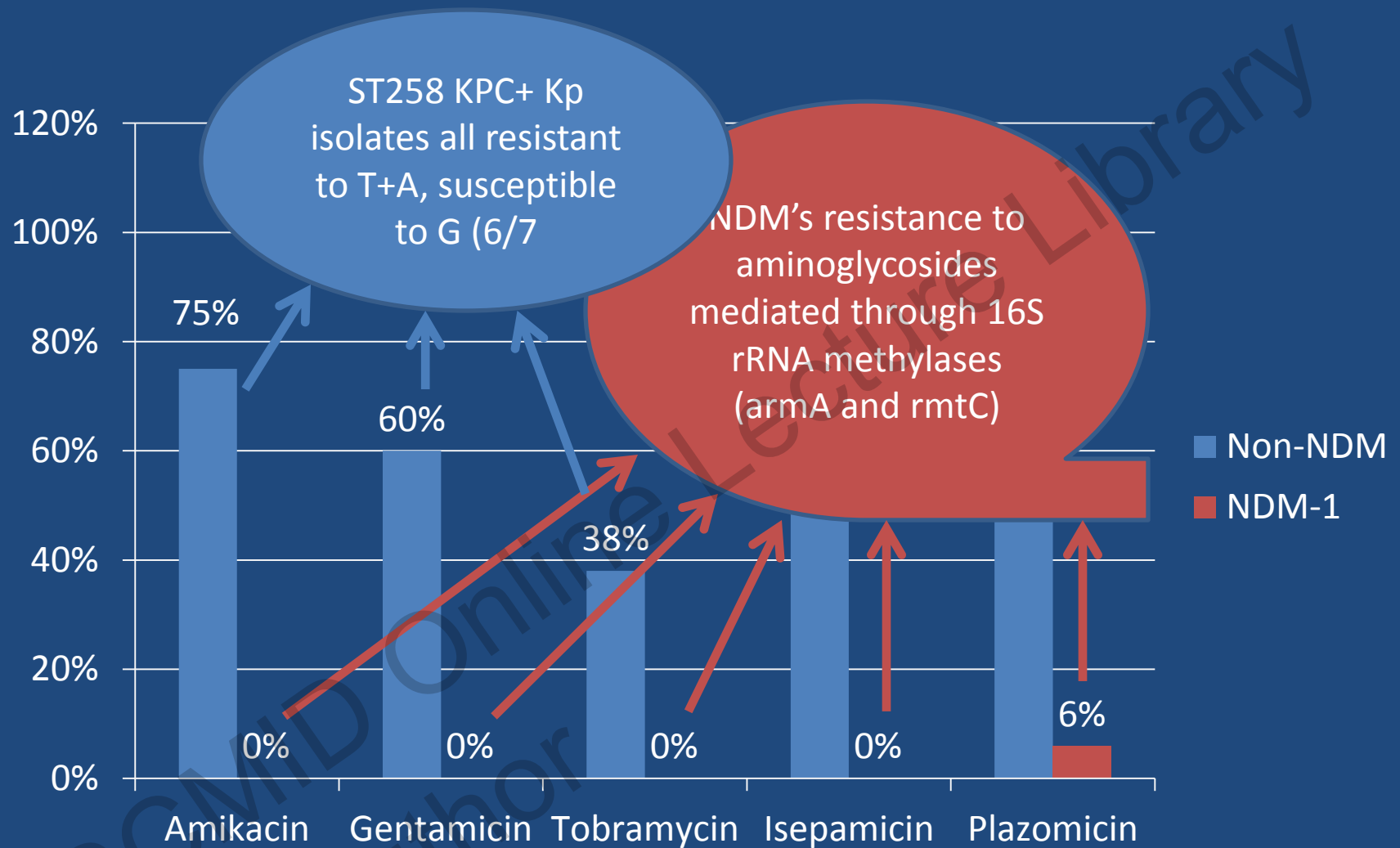
Patient-unique Gram-negative bacteremia, Rambam, Israel 1996-2013

Coverage against carbapenem-resistant GNBs

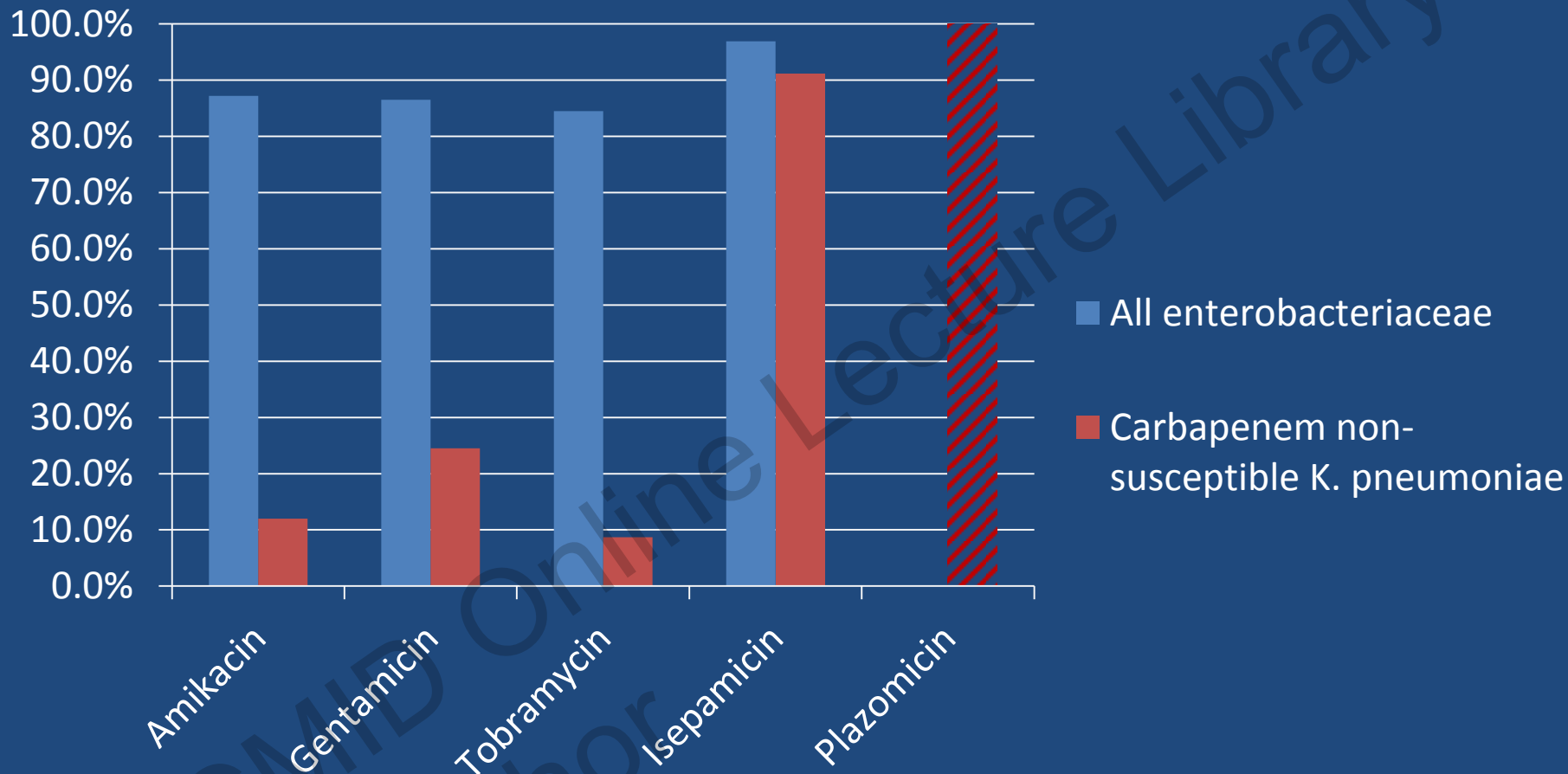
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Patient-unique CR Gram-negative bacteremia, Rambam, Israel 1996-2013



82 clinical carbapenem-resistant enterobacteriaceae isolates, UK, 2006-2009: KPC, SME, OXA-48, IMP, VIM, NDM, Porin ESBL, Porin AmpC



**Clinical enterobacteriaceae isolates, Greece, Crete 2004-2009;
Athens 2008-2010 (plazomicin)**

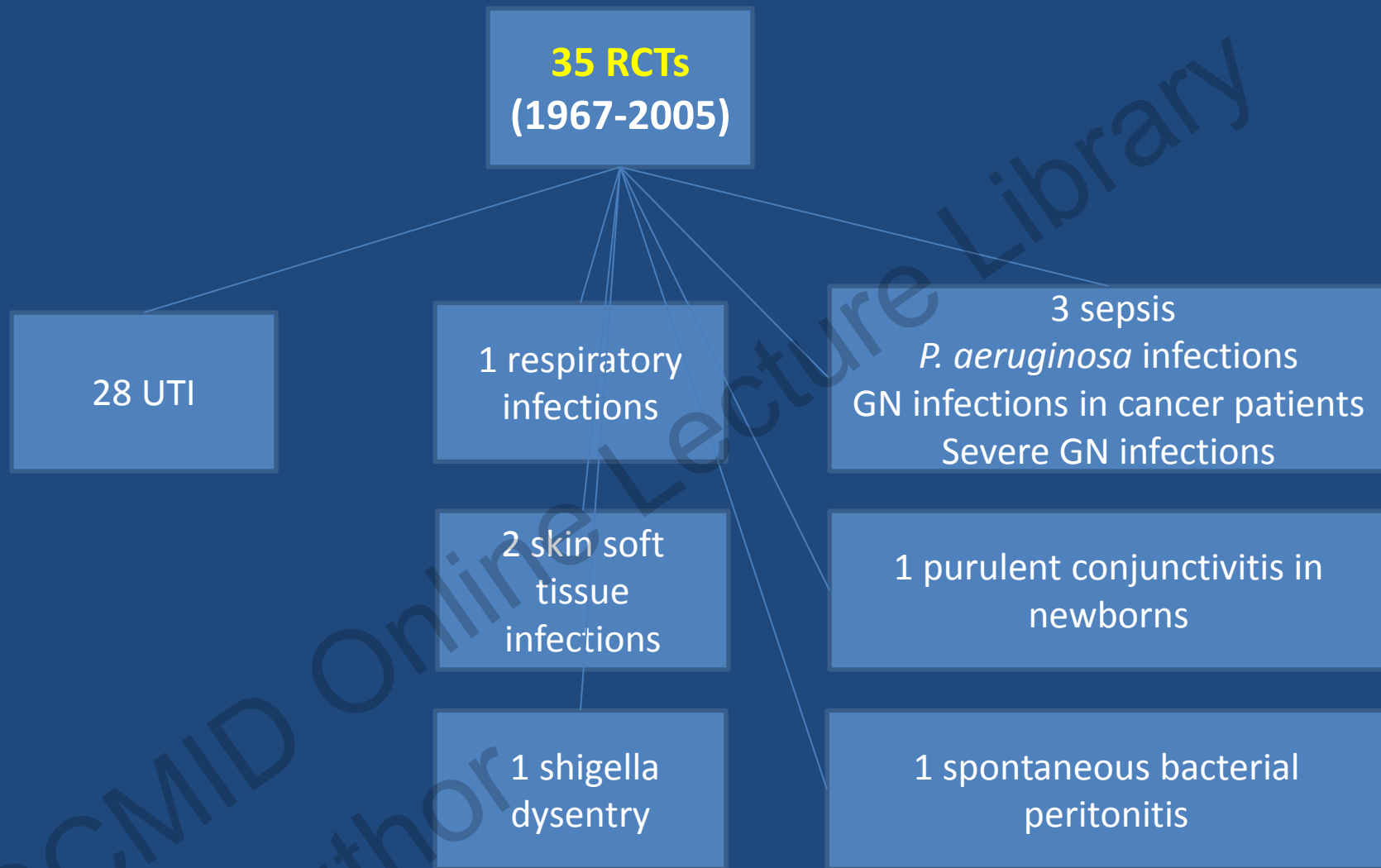
Maraki et al. Antimicrob Agents Chemother. 2012 Jun;56(6):3067-73;
Galani et al. J Chemother. 2012; 24(4): 191-4

Aminoglycoside coverage of MDRs/ XDRs

- Relatively conserved coverage
- Dependent on locally circulating isolates
 - Dominant carbapenem-resistant bacteria
 - Presence of aminoglycoside resistance mechanisms
 - Epidemiologically seems associated with carbapenem-resistance mechanisms in *K. pneumoniae*
- Dependent on usage of the specific aminoglycoside

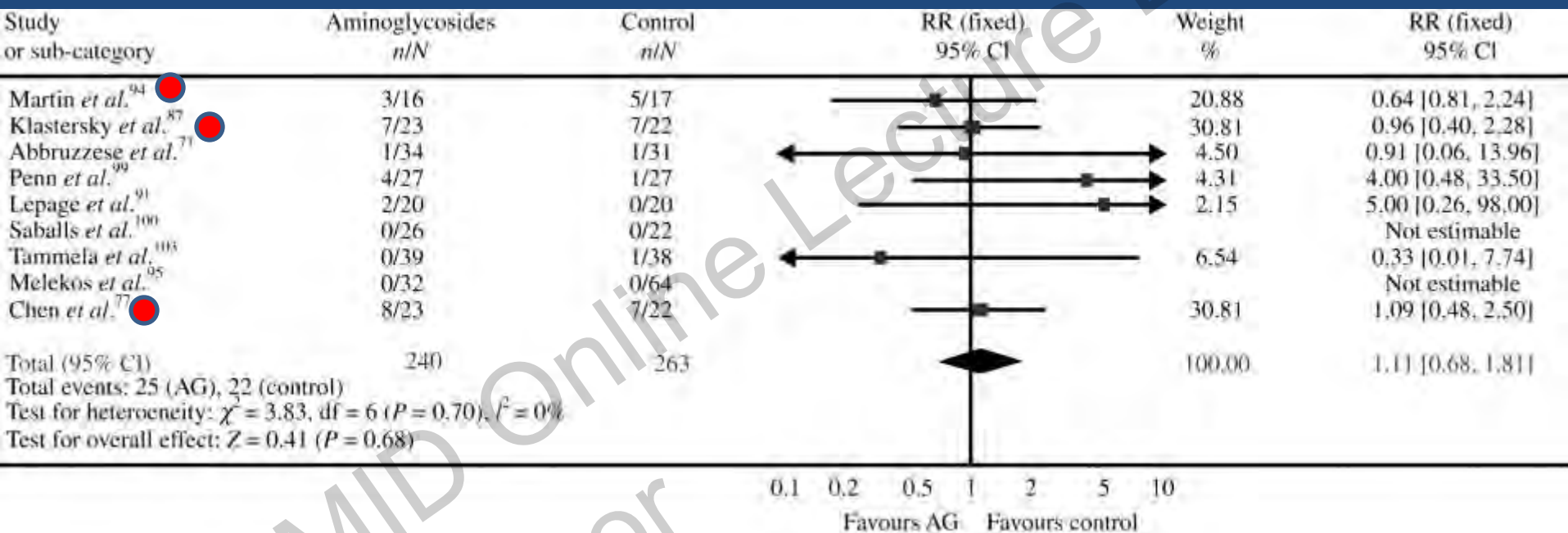
Evidence on aminoglycoside monotherapy

Systematic review of randomized controlled trials



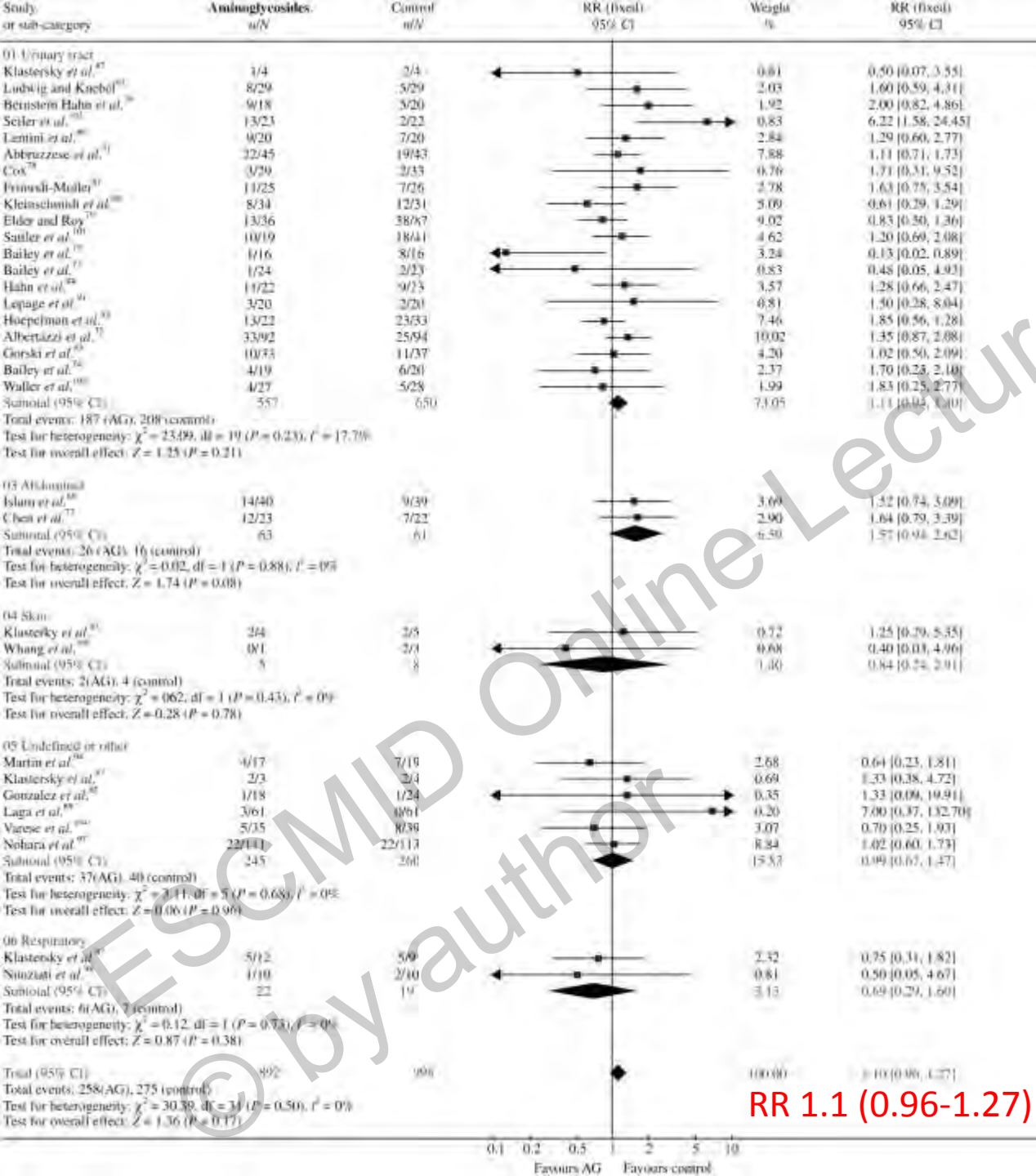
RCTs comparing aminoglycoside monotherapy vs. a non-aminoglycoside antibiotic regimen for the treatment of any infection

All-cause mortality



7 UTI RCTs – 10 events

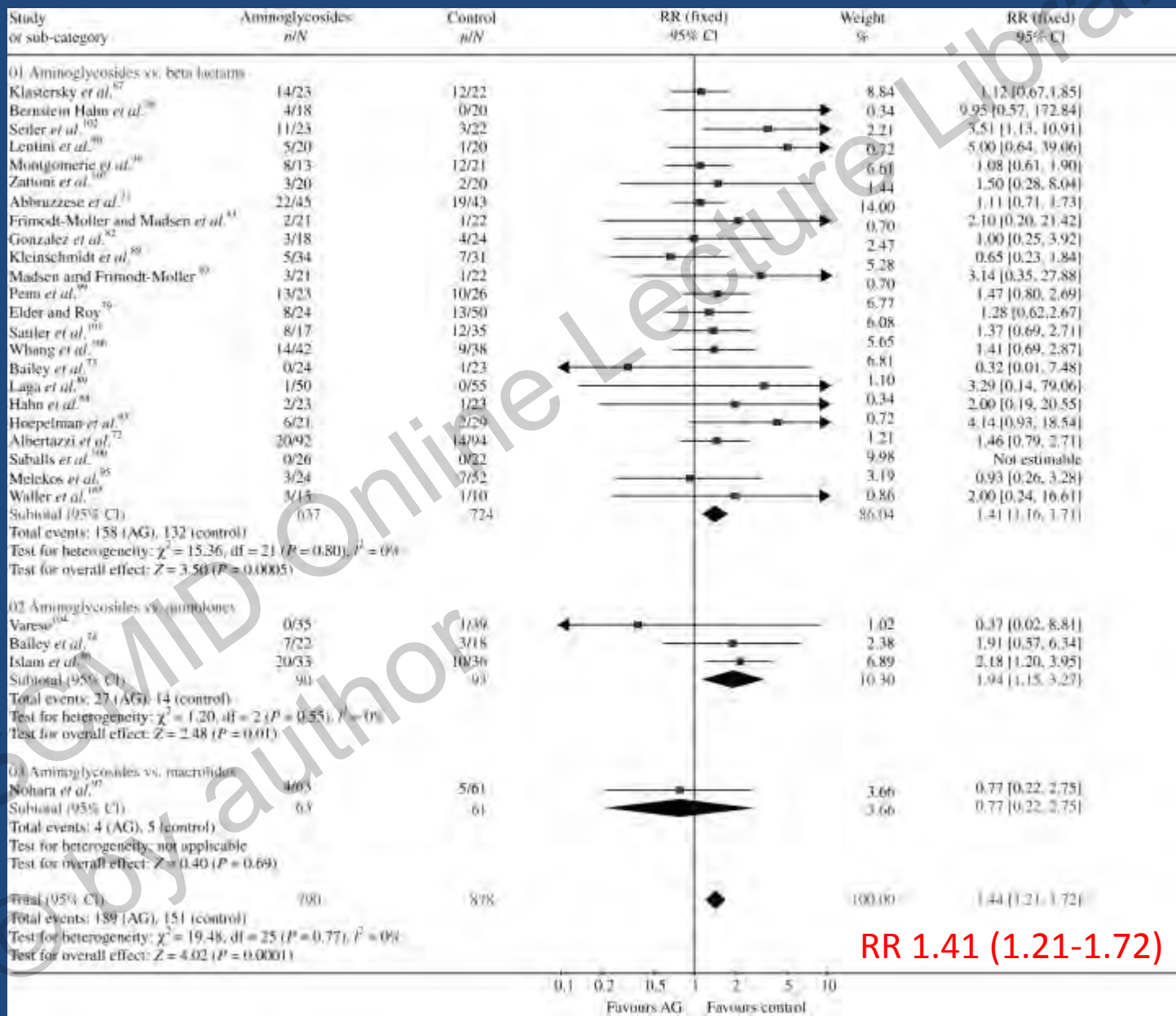
- 2 sepsis, 1 SBP RCTs – 37 events



Clinical failure, end of treatment

RR 1.1 (0.96-1.27)

Microbiological failure, end of treatment



Aminoglycoside monotherapy

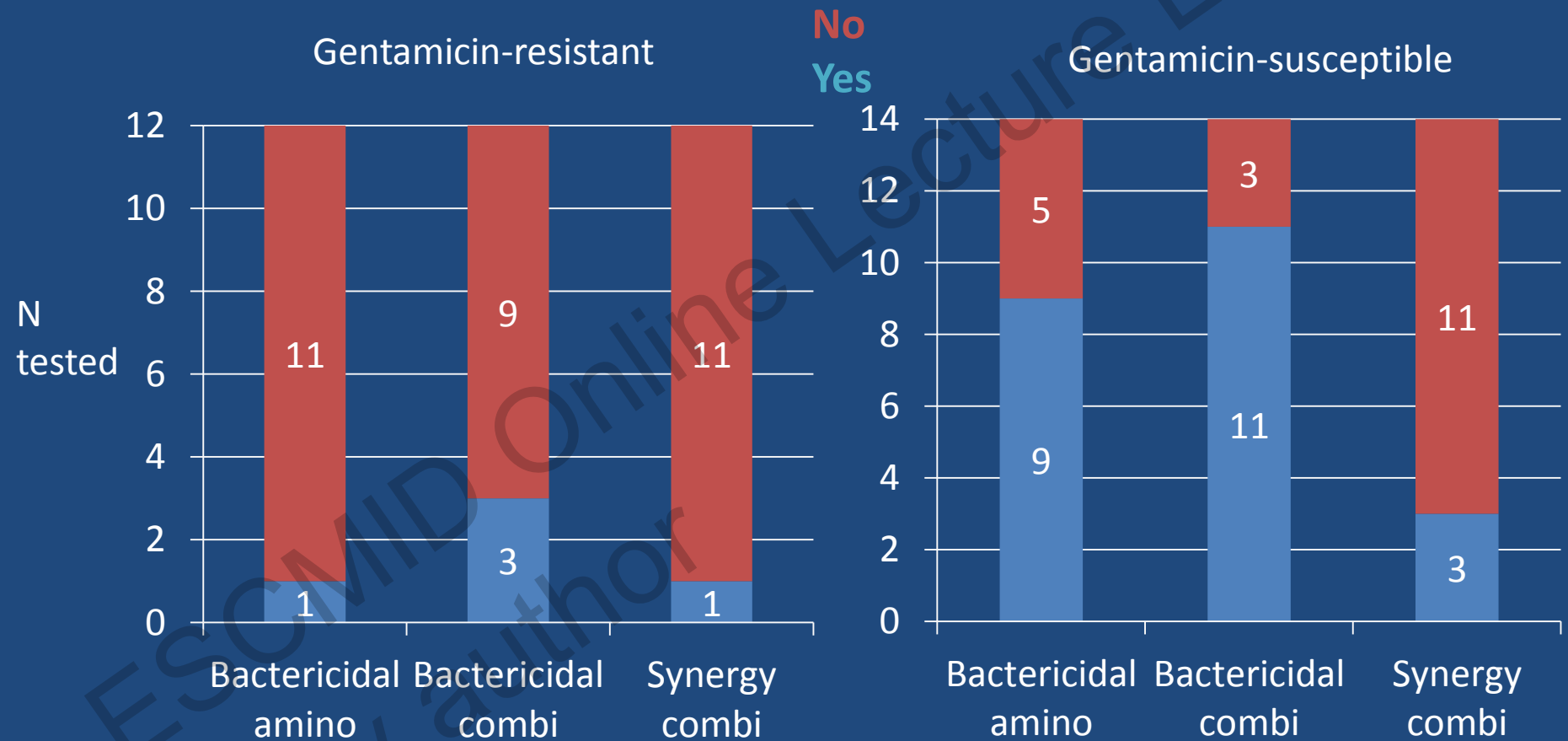
- For UTIs: no difference in clinical cure, no difference in relapse/ re-infection
 - The implications of higher rate of microbiological persistence unclear
- Little data overall and no contemporary data on effectiveness in severe sepsis
 - Probable inferior microbiological efficacy than beta-lactams and quinolone
- Overall much more support than colistin regarding effectiveness compared to other antibiotics

Aminoglycoside combination therapy against carbapenem- resistant Gram negatives

In vitro studies

Carbapenems-aminoglycosides

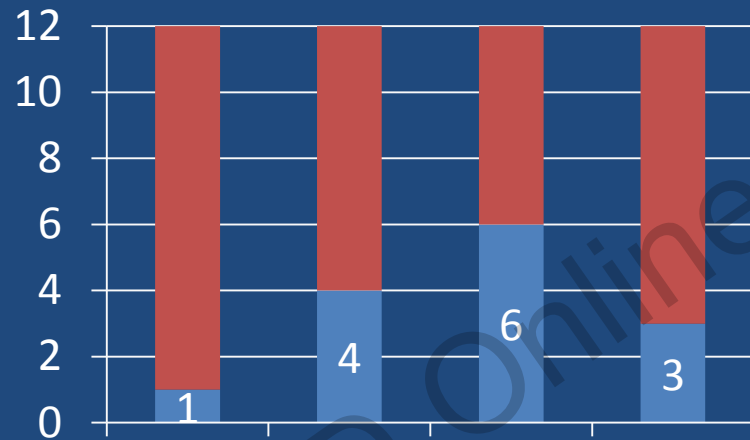
Doripenem-gentamicin, KPC producing *K. pneumoniae*



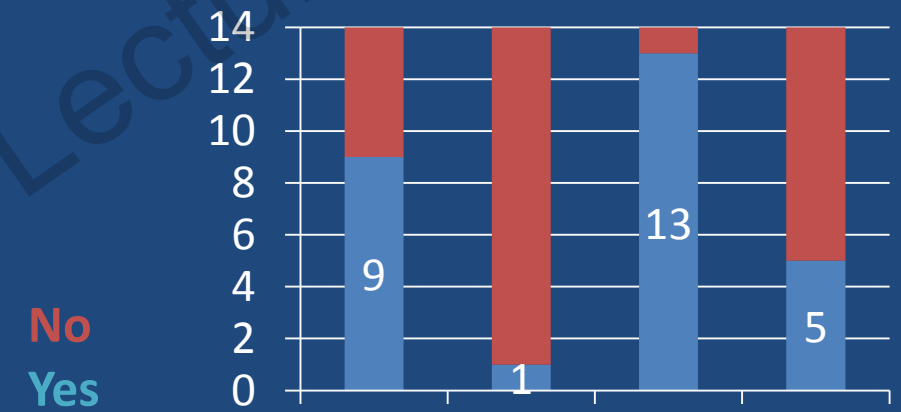
Polymyxin-aminoglycosides

Colistin-gentamicin, KPC producing *K. pneumoniae*

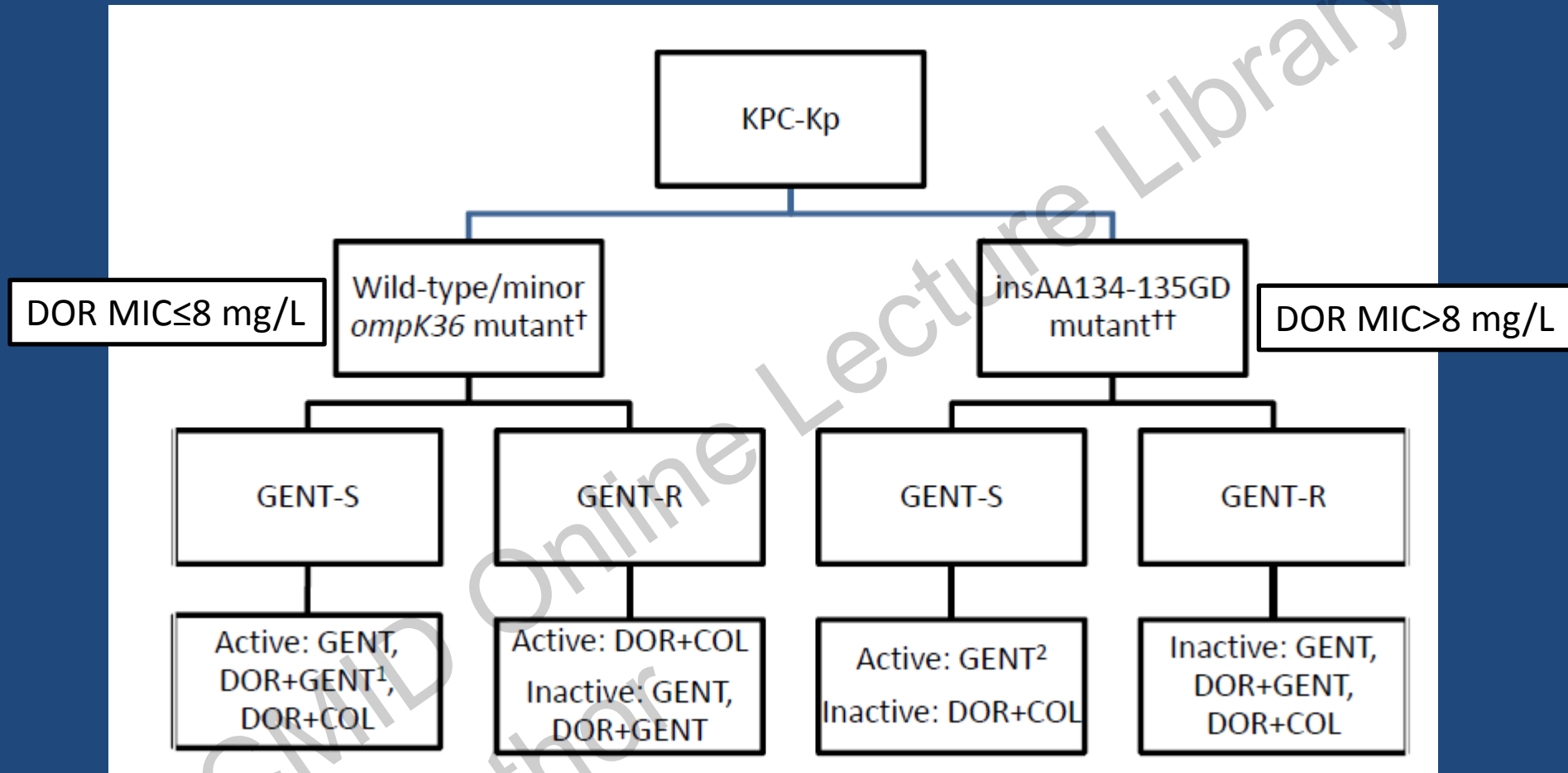
Gentamicin-resistant, colistin resistant



Gentamicin-susceptible, colistin susceptible



No
Yes

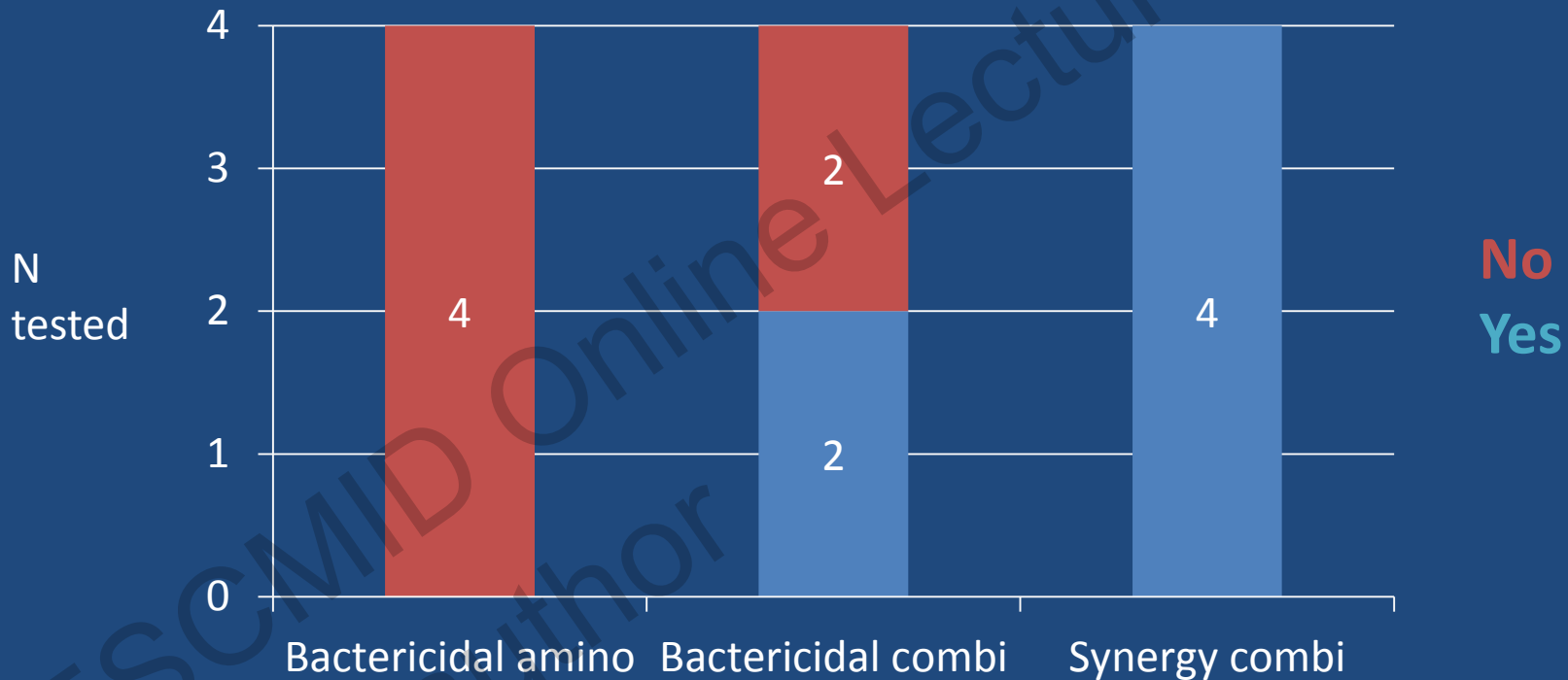


Proposed treatment algorithm of ST258, KPC-2 *K. pneumoniae* by *ompK36* mutants and gentamicin resistance

Carbapanems-aminoglycosides

meropenem-amikacin, KPC producing *K. pneumoniae*

Amikacin-resistant



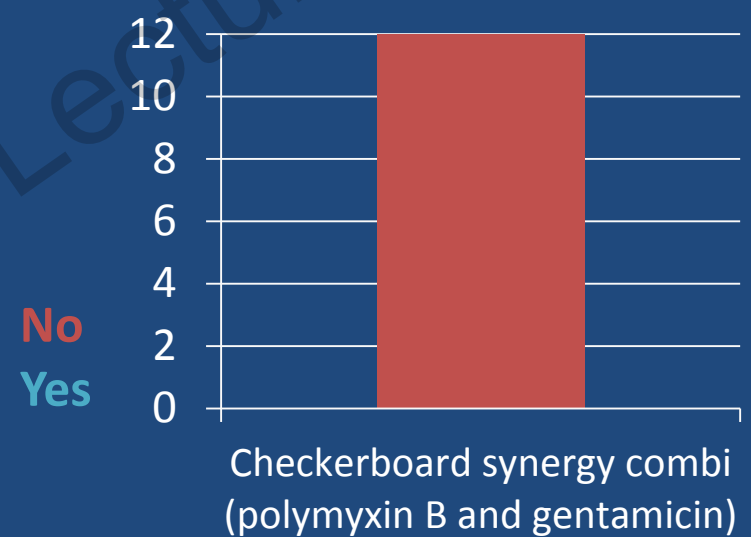
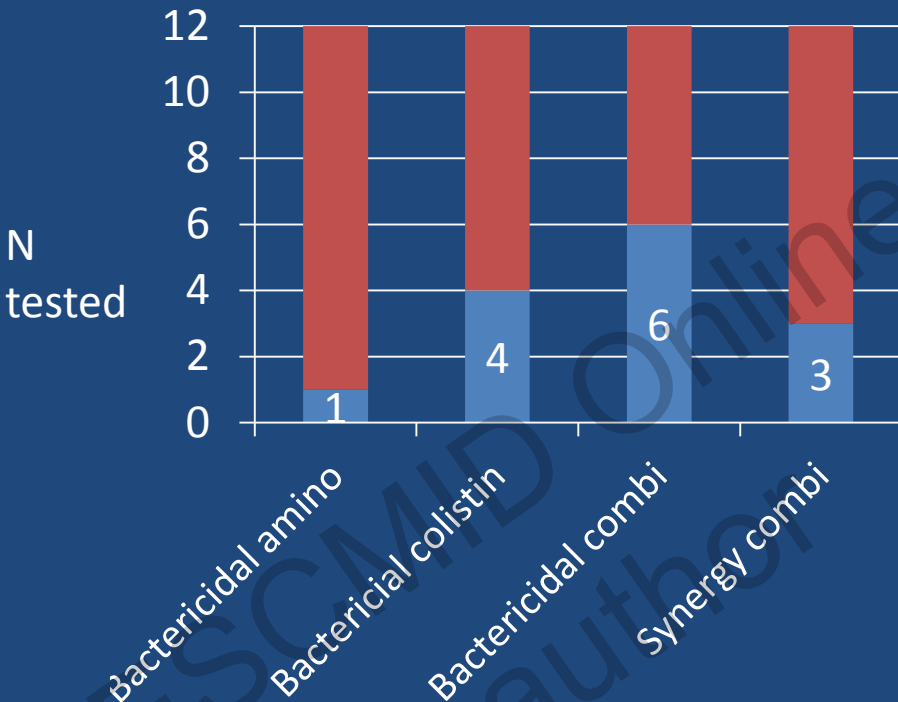
Le et al. J Clin Med Res. 2011; 3(3): 106-10; Long Beach, California, USA. 4 isolates with bla_{KPC-3} and genes encoding TEM-1 and SHV-11/-36, meropenem MIC ≥ 32 mg/L, amikacin MIC ≥ 32 mg/L.

Polymyxin-aminoglycosides

KPC producing *K. pneumoniae*

Gentamicin-resistant, colistin resistant

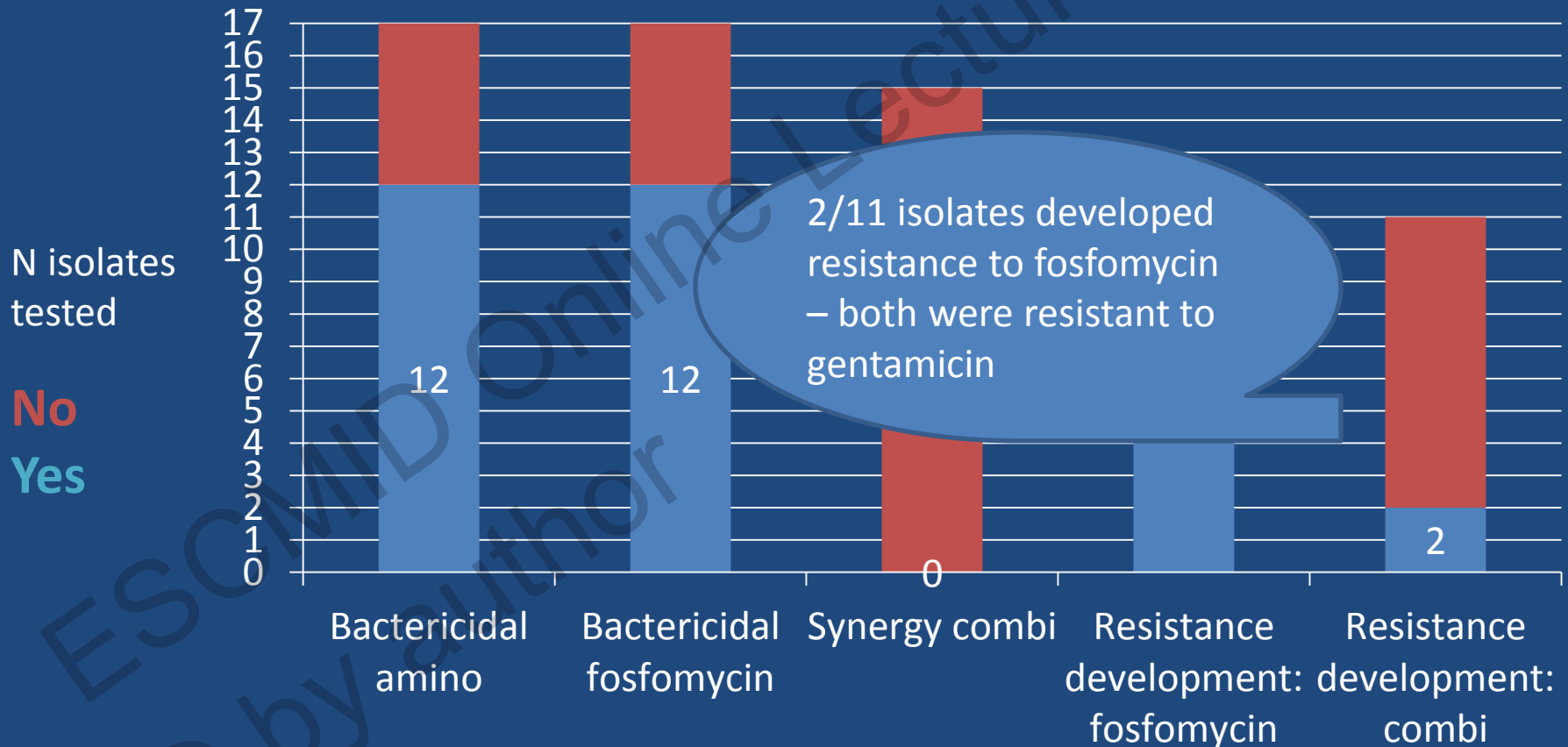
Gentamicin-resistant, polymyxin B resistant



Jernigan et al. Antimicrob Agents Chemother. 2012; 56(6): 3395-8. Pittsburgh, USA
Elemam et al. J Clin Microbiol. 2010; 48(10): 3558-62. New York, NY, USA

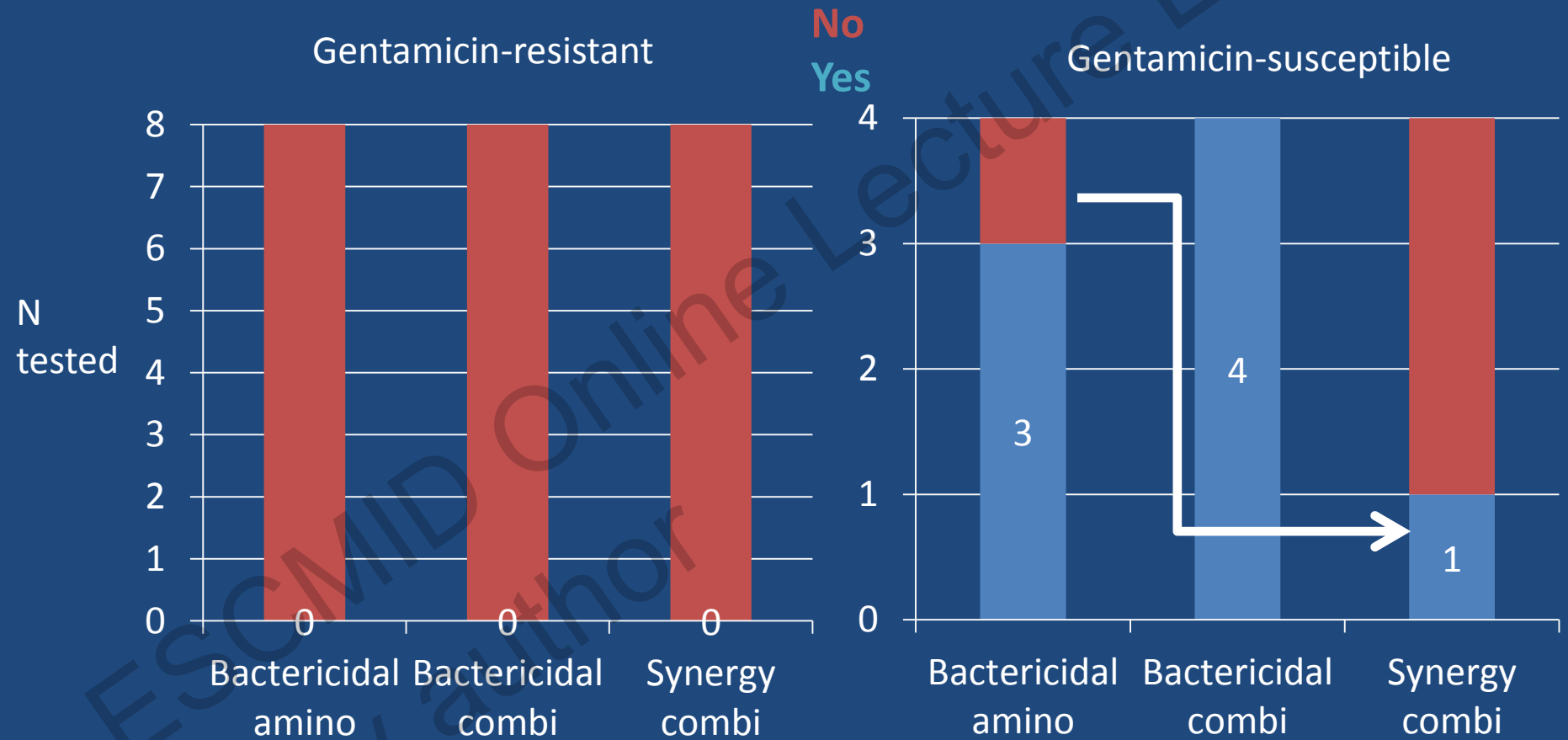
Fosfomicin-aminoglycoside

fosfomicin-gentamicin, KPC-2 *K. pneumoniae*



Carbapenems-aminoglycosides

Imipenem-gentamicin, carbapenem-resistant *A. baumannii*



Carbapenems-aminoglycosides

Imipenem-gentamicin, carbapenem-resistant *Acinetobacter sp.*

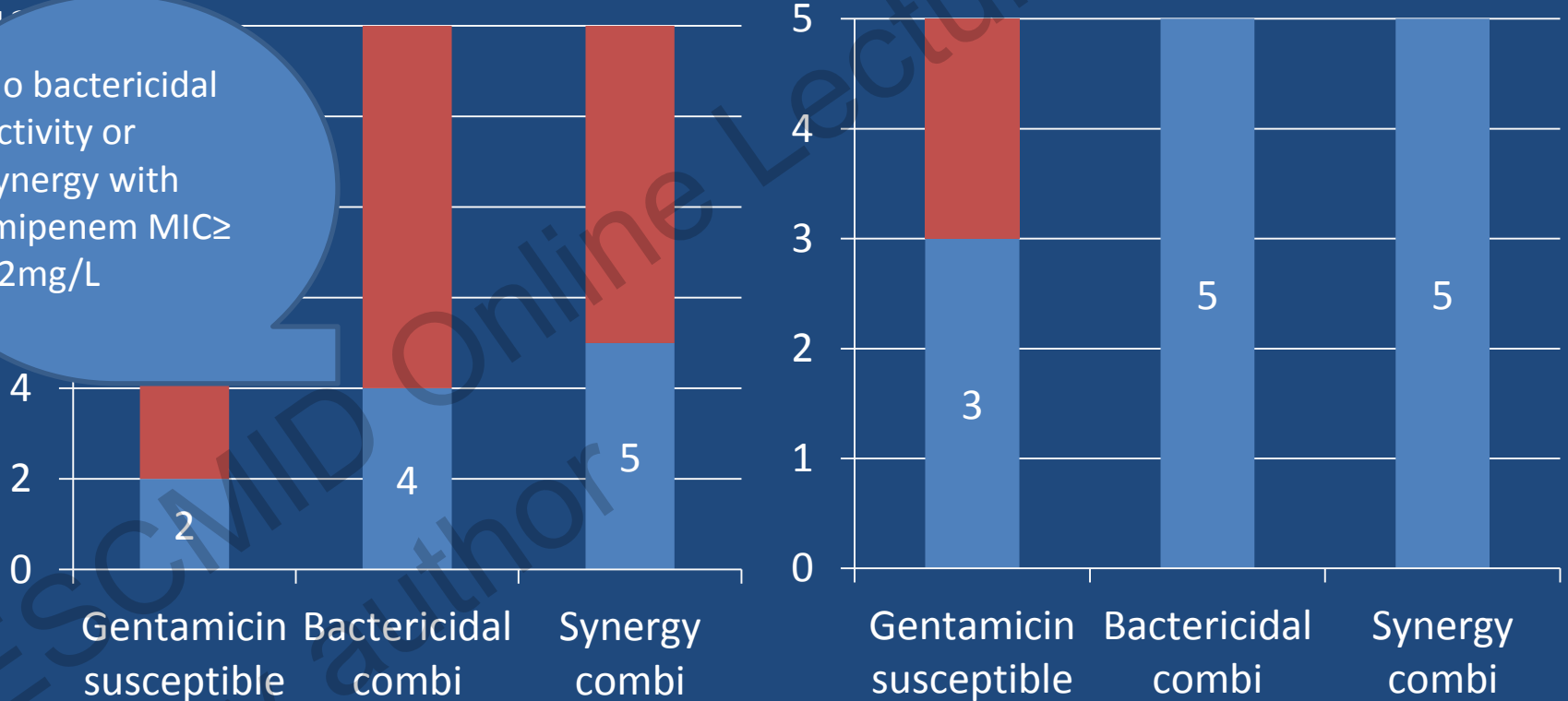
Acinetobacter baumannii
(genospecies 2}

No

Yes

Acinetobacter genospecies
13TU or genospecies 3

No bactericidal
activity or
synergy with
imipenem MIC \geq
32mg/L



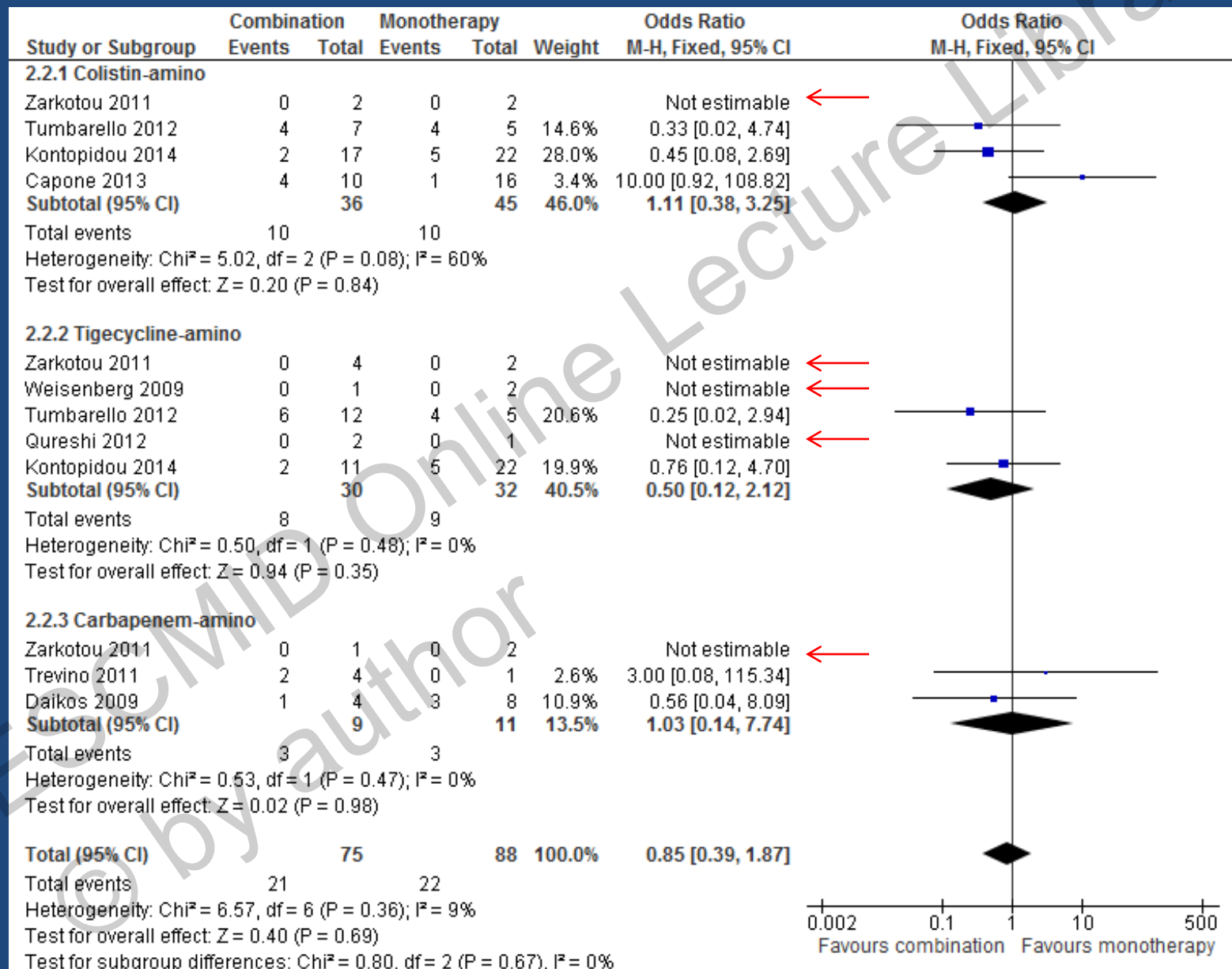
Aminoglycoside combinations against carbapenem resistant GNB: in-vitro studies

- Very little data
- Small or no benefit over most active single drug
 - Combinations with carbapenems dependent on the carbapenem's MIC within the non-susceptible range
 - Colistin-aminoglycoside combinations may be advantageous over each alone when susceptible
 - Resistance development?

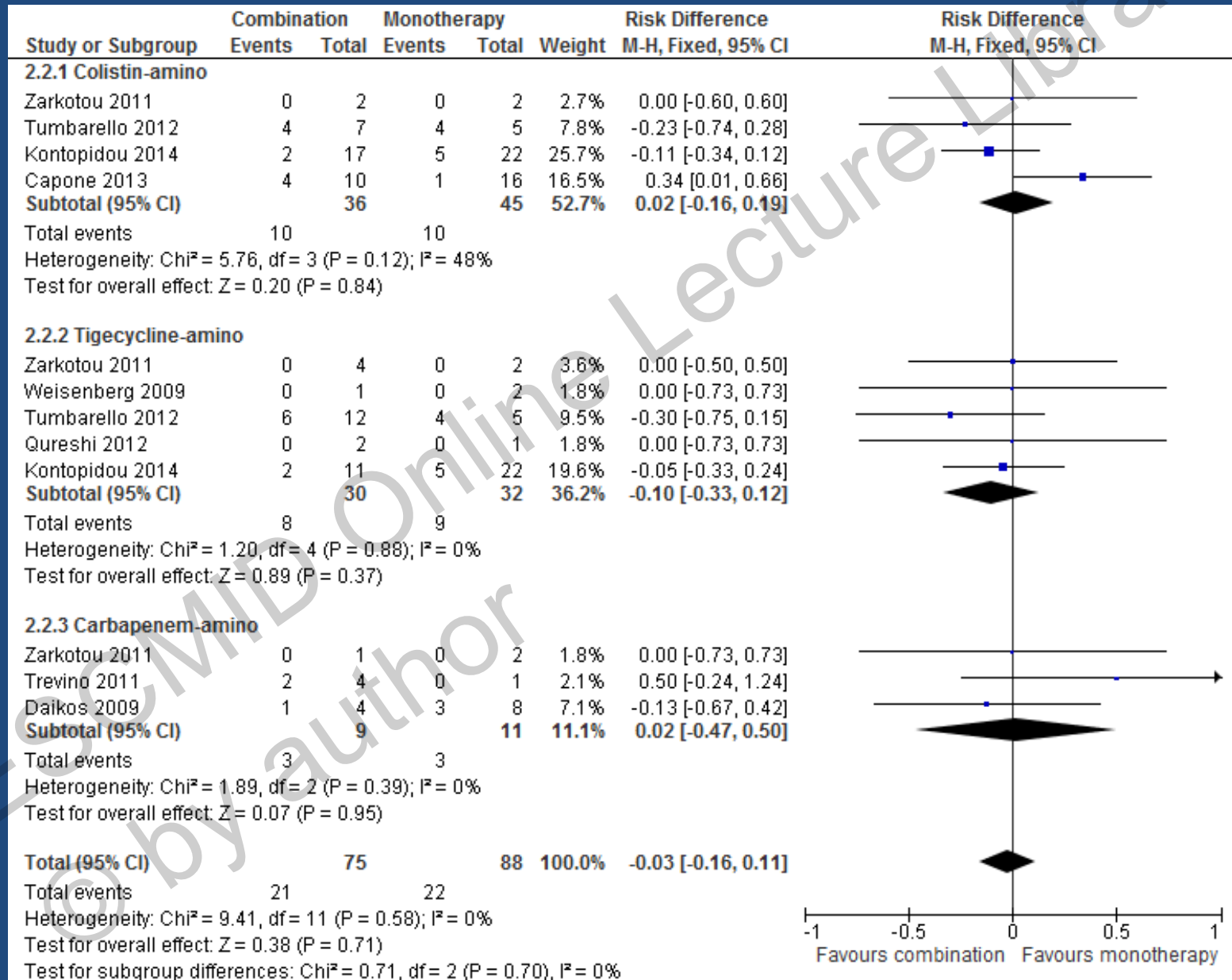
Aminoglycoside combination therapy against carbapenem- resistant Gram negatives

Clinical studies

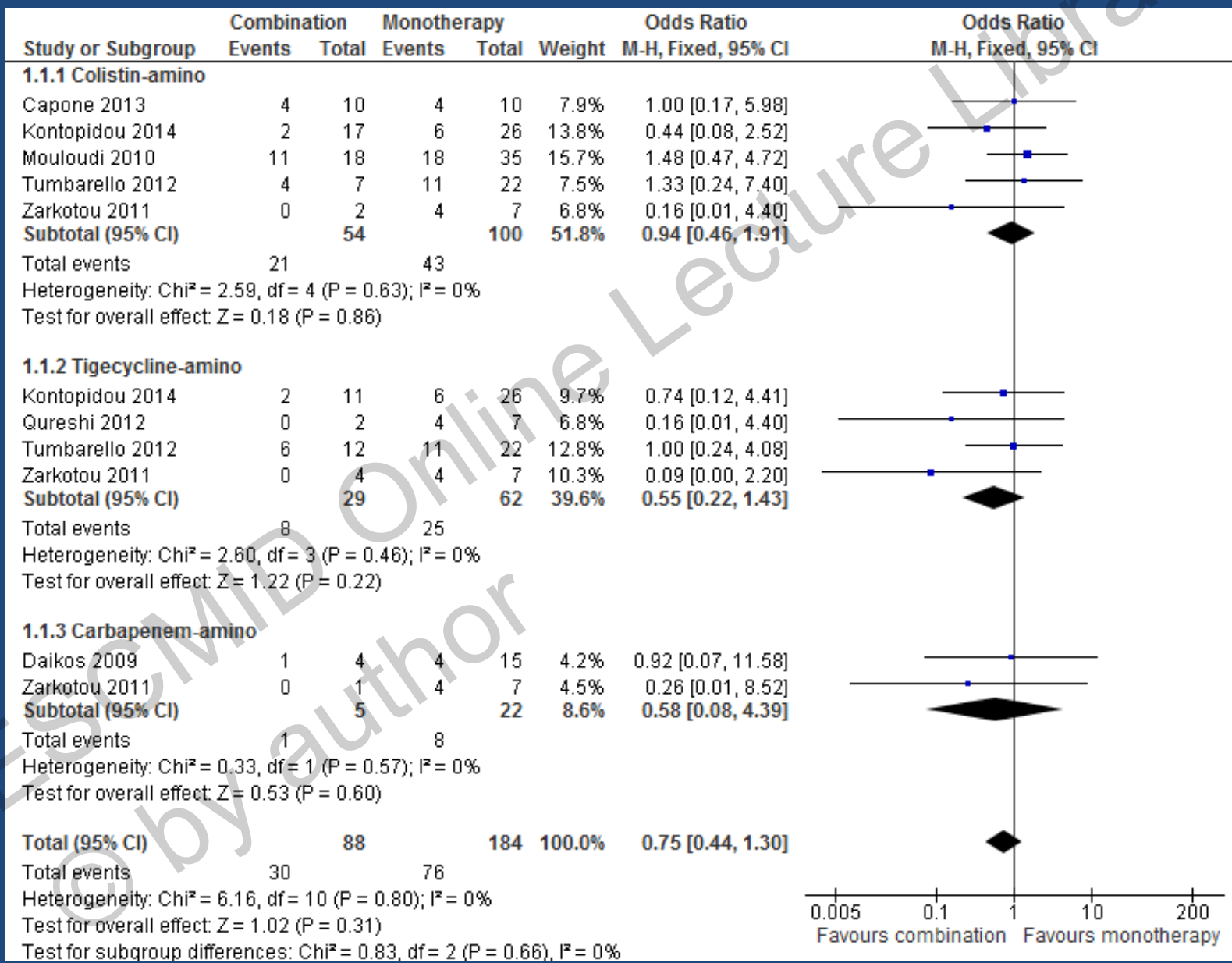
All cause mortality: aminoglycoside-based combination vs. aminoglycoside monotherapy



All cause mortality: aminoglycoside-based combination vs. aminoglycoside monotherapy



All cause mortality: aminoglycoside-based combination vs. colistin monotherapy



Aminoglycoside combinations against carbapenem resistant GNB: clinical studies



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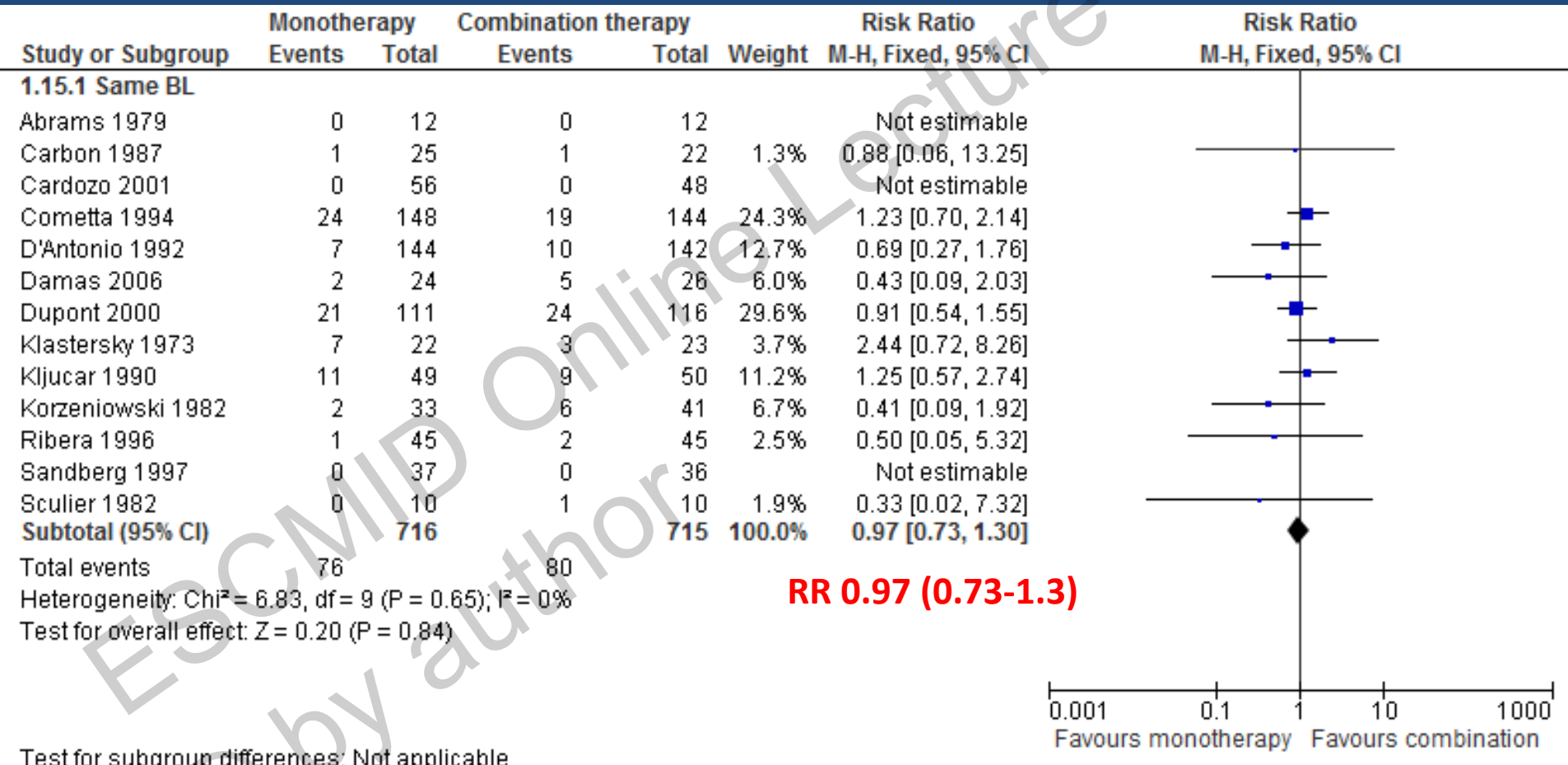
Evidence on beta-lactam-aminoglycoside combination therapy

Systematic review of randomized controlled trials

Systematic review methods

- Included randomized controlled trials comparing any beta-lactam monotherapy vs. any beta-lactam-aminoglycoside combination for sepsis in non-neutropenic patients
 - Separate analysis for trials comparing same and different beta-lactams
- Non-restrictive search, Cochrane methodology
- In total, 69 RCTs were included
 - 22 RCTs compared the same beta-lactam

All-cause mortality: same beta-lactams



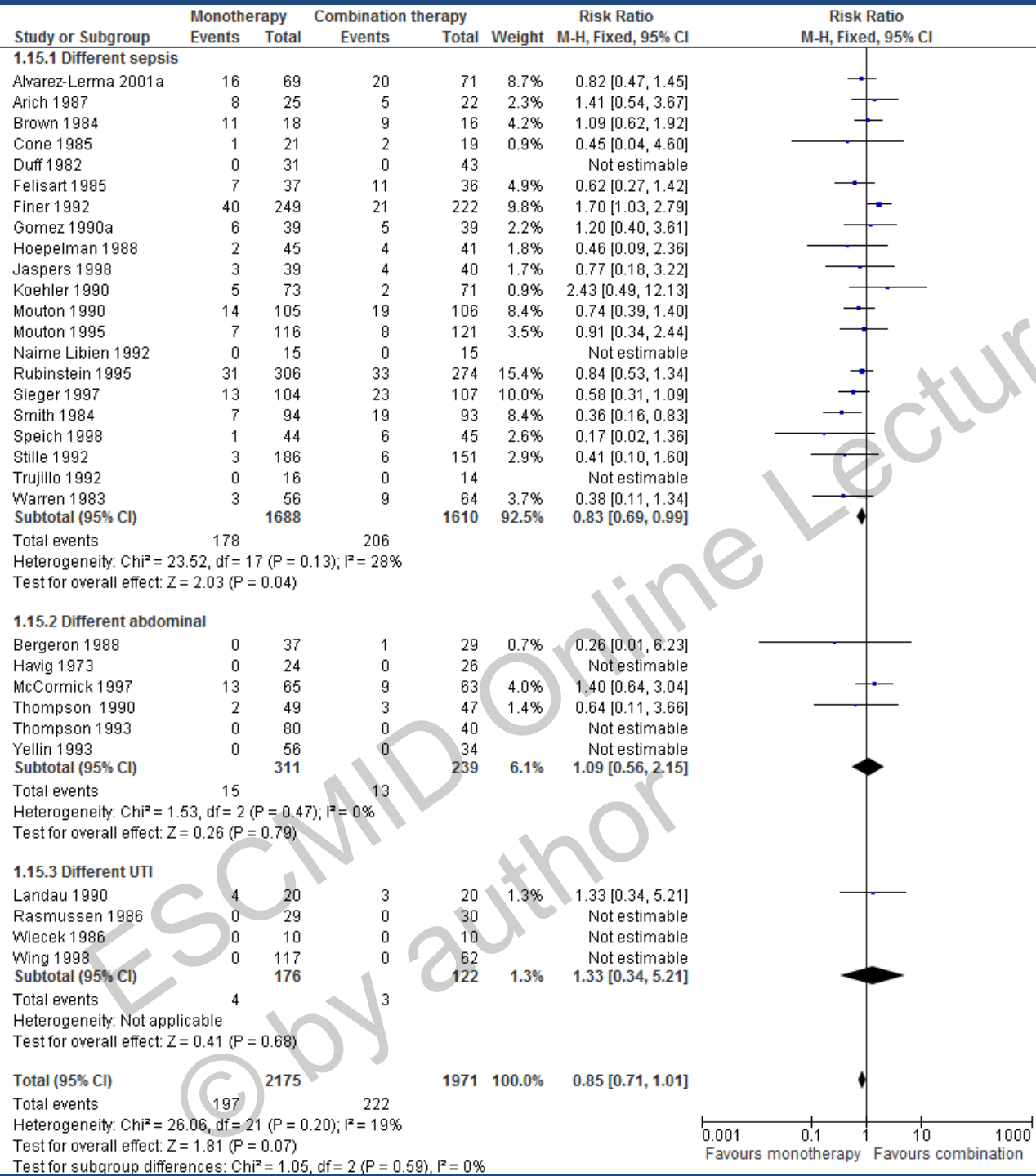
All-cause mortality, different beta-lactams

Sepsis
RR 0.83 (0.69-0.99)

Abdominal

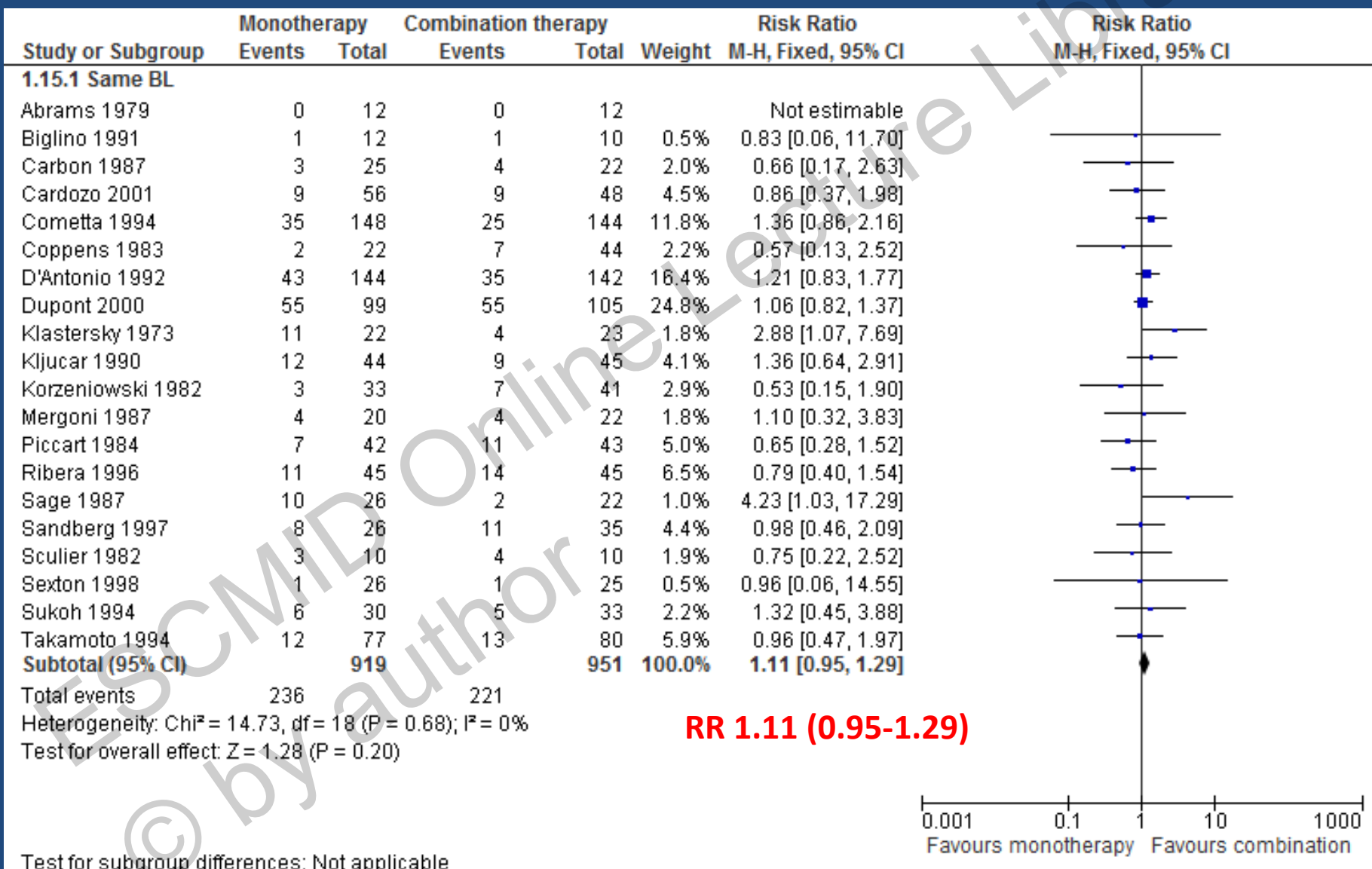
UTI

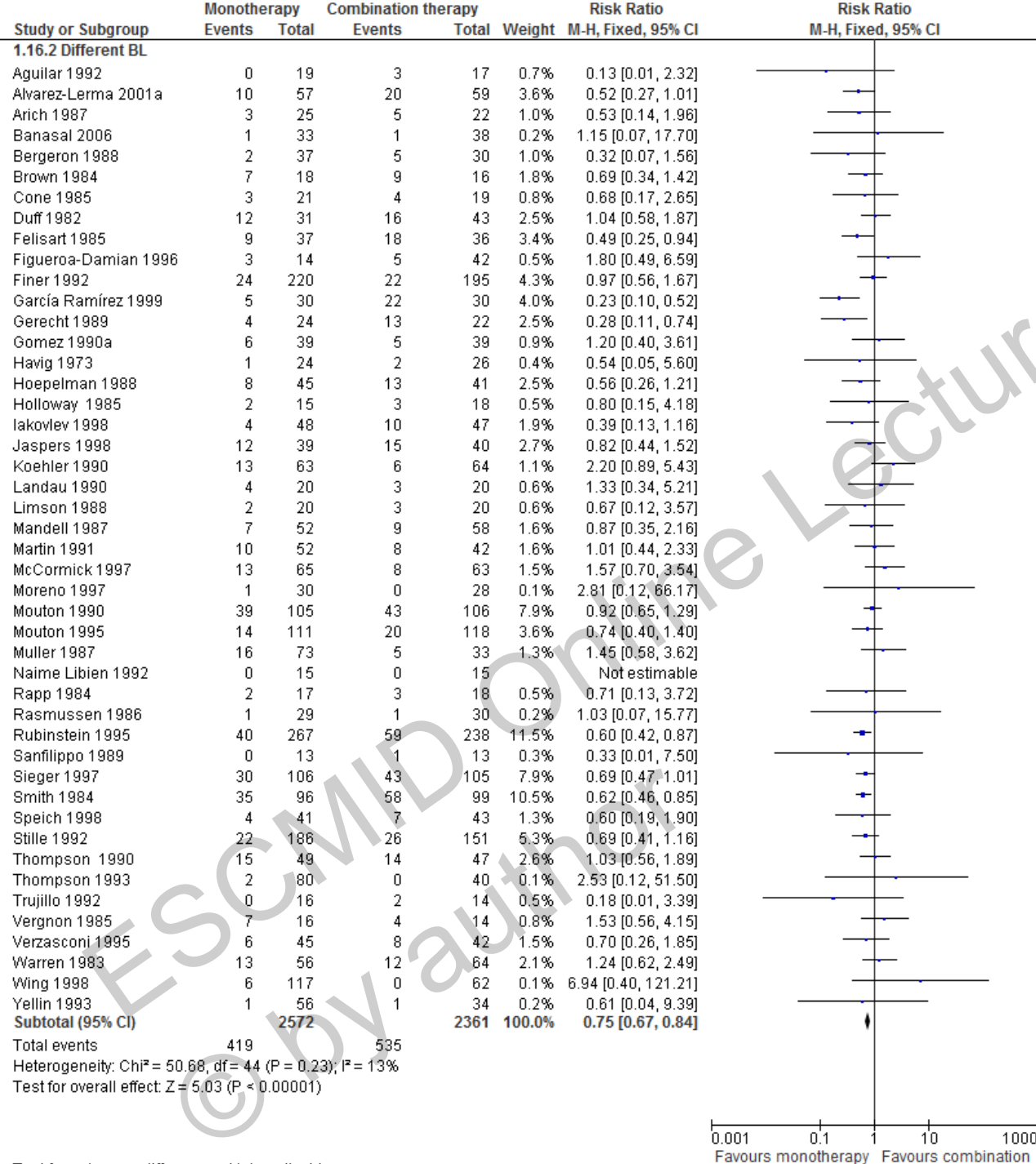
Overall
RR 0.85 (0.71-1.01)



0.001 0.1 1 10 1000
Favours monotherapy Favours combination

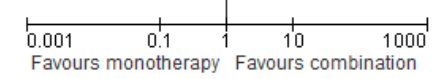
Treatment failure: same beta-lactams





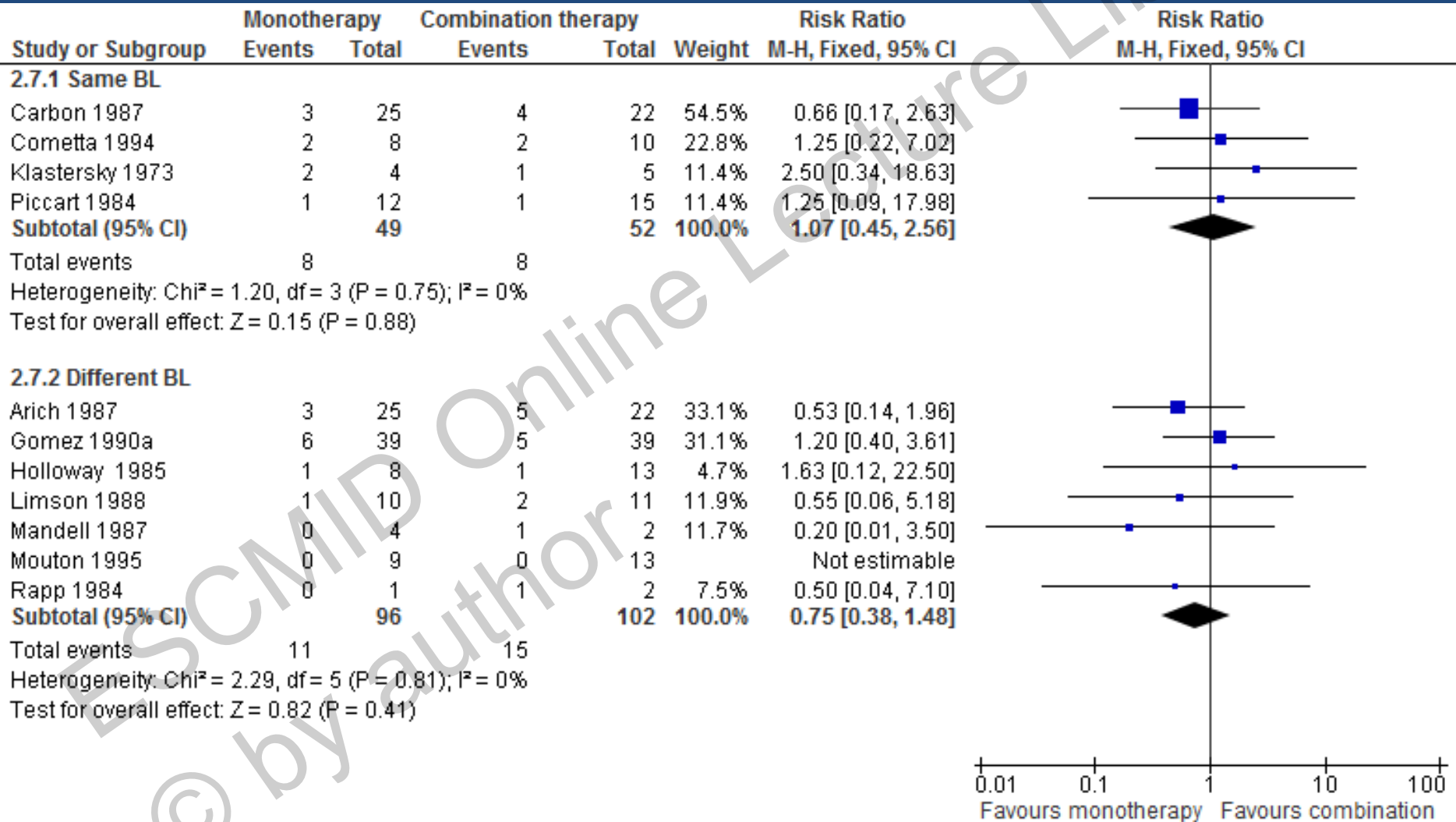
Treatment failure, different beta-lactams

Overall RR 0.75 (0.67-0.84)



Test for subgroup differences: Not applicable

Treatment failure: Gram-negative bacteremia



Beta-lactam – aminoglycoside combination therapy

- No benefit shown in RCTs comparing one beta-lactam vs. the same beta-lactam with an aminoglycoside (both covering)
- Advantage to broad spectrum beta-lactam monotherapy vs. different beta-lactam with an aminoglycoside (regimens with similar coverage)
- Paucity of data on patients with Gram-negative bacteremia (100 patients same, 200 different)
- Lack of data on specific pathogens

Place of aminoglycoside
combination therapy for the
treatment of carbapenem-resistant
Gram negatives in clinical practice



Empirical treatment

- Aminoglycosides retain relatively good coverage
- Evidence for aminoglycoside monotherapy in UTIs
- Lack of evidence colistin aminoglycoside monotherapy for severe non-UTI infections

Definitive treatment

- Aminoglycoside combination therapy lacks clinical advantage overall
- Data limited for CR GNBs and not suggestive of advantage for highly resistant isolates
- Aminoglycoside-colistin for highly carbapenem-resistant isolates?



Empirical treatment

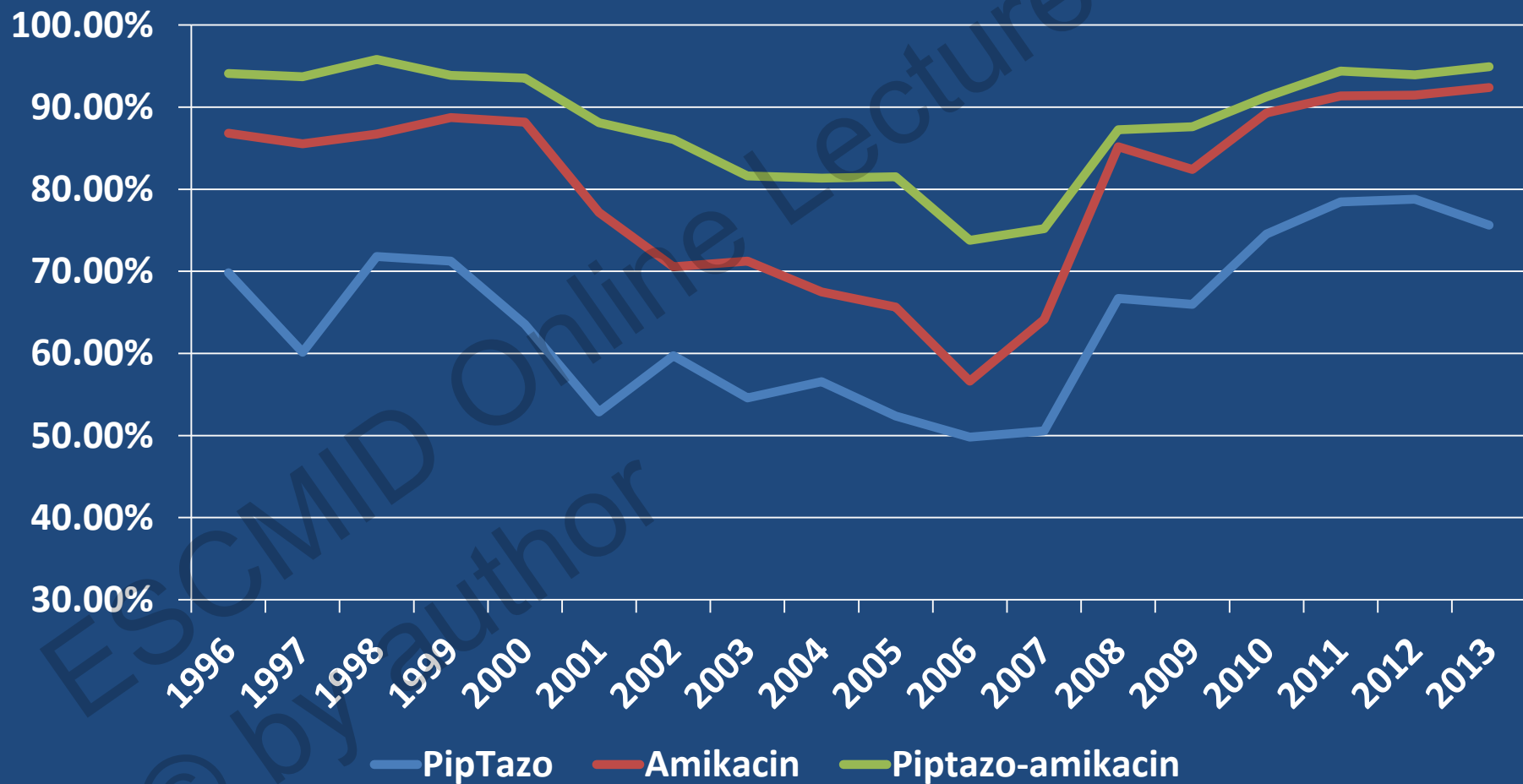
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Definitive treatment

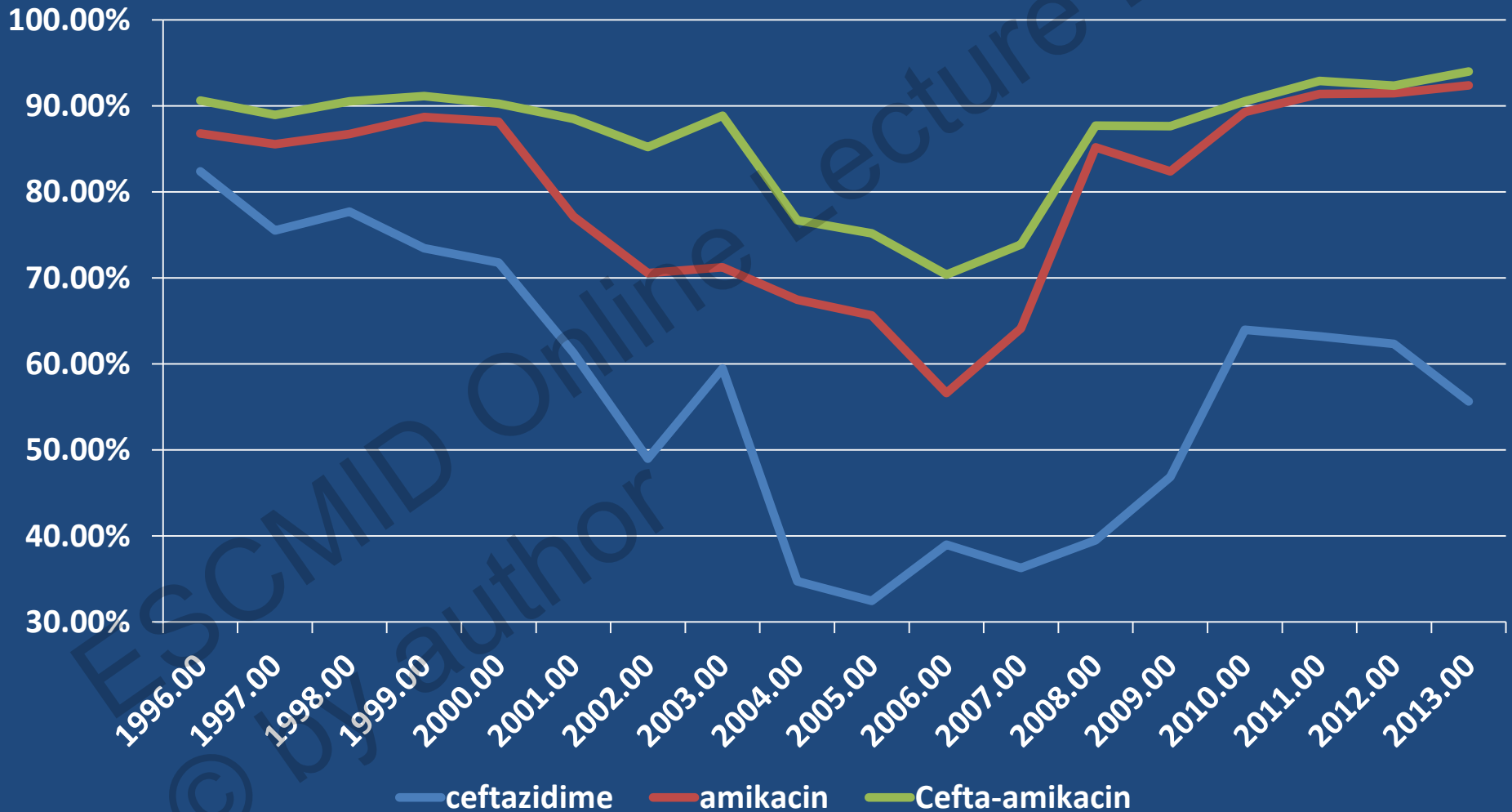
- Aminoglycoside combination therapy lacks clinical advantage overall
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- Aminoglycoside-colistin for highly carbapenem-resistant isolates?

Combination coverage

Piperacillin-tazobactam - amikacin

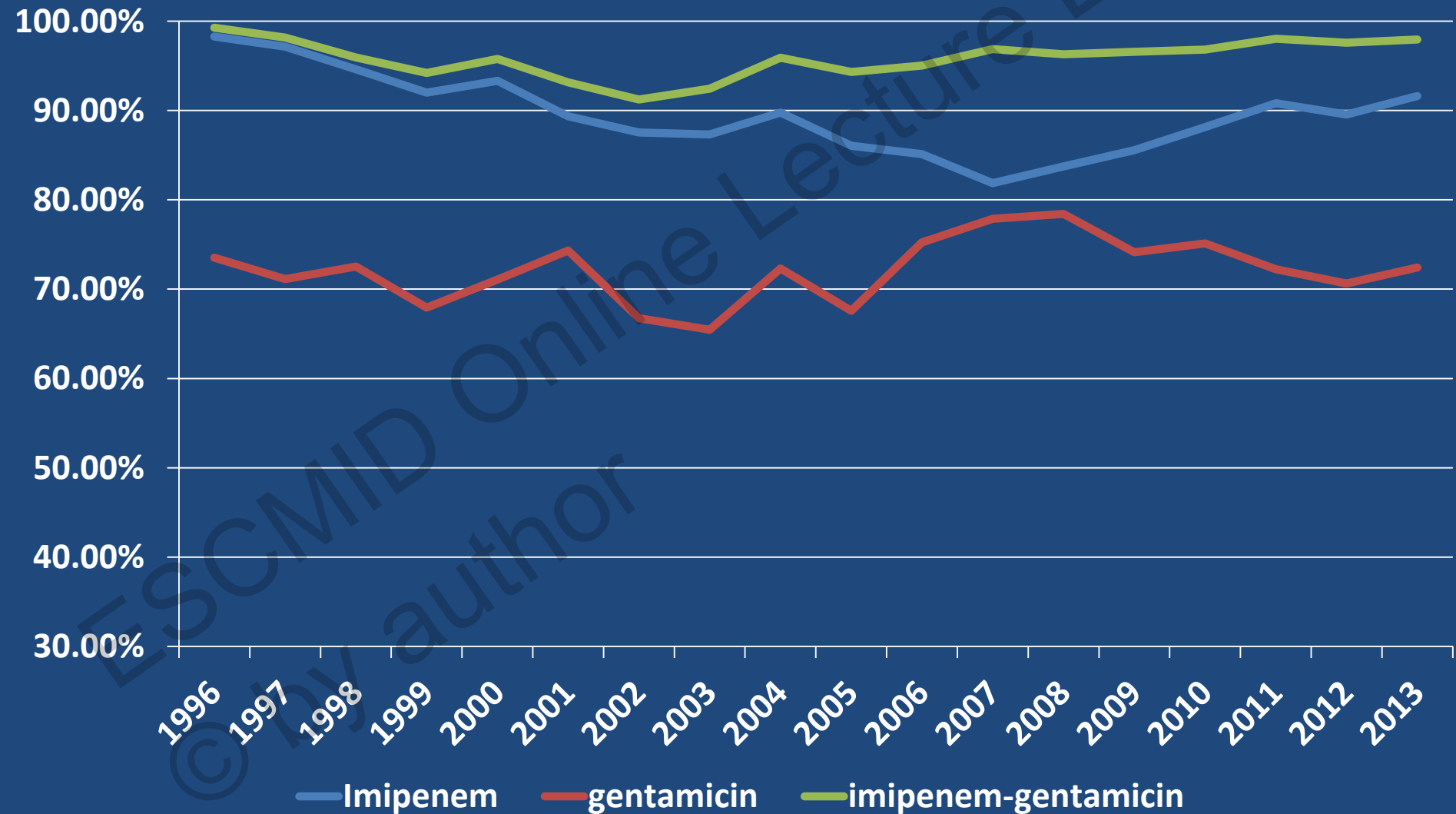


Combination coverage ceftazidime - amikacin



Combination coverage

Imipenem - gentamicin



Data summary and suggestions

- The empirical addition of an aminoglycoside to beta-lactams can increase spectrum of coverage
 - Local and temporal epidemiology
- Definitive addition of aminoglycosides to covering beta-lactams has no advantage
- Definitive addition of aminoglycosides to non-covering carbapenems probably has no advantage

Studies needed

- Comparison of aminoglycoside monotherapy vs. colistin monotherapy for XDR GNB susceptible only to both
- Aminoglycoside-colistin combination therapy for XDR GNB susceptible only to both
 - Less toxic aminoglycosides/ polymyxin?

Thank you

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