

Carbapenem Resistance, Initial Antibiotic Therapy and Mortality in *Klebsiella pneumoniae* Bacteremia: a Systematic Review and Meta-Analysis








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Disclosures

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Background

Mortality of patients with infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) is higher than those of patients with carbapenem-sensitive strains

Study or Subgroup	Carba-resistant		Carba-susceptible		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
1.1.1 Bacteremia							
Ben-David 2012	29	42	45	150	18.4%	2.30 [1.68, 3.16]	
Chang 2011	16	17	17	34	17.3%	1.88 [1.32, 2.69]	
Daikos 2007	7	13	5	43	6.0%	4.63 [1.76, 12.16]	
Daikos 2009	6	14	25	148	9.3%	2.54 [1.26, 5.12]	
Mouloudi 2010	25	37	9	22	12.2%	1.65 [0.95, 2.86]	
Patel 2008	48	99	20	99	14.9%	2.40 [1.54, 3.73]	
Subtotal (95% CI)		222		496	78.1%	2.19 [1.82, 2.63]	
Total events	131		121				
Heterogeneity: Tau ² = 0.00; Chi ² = 4.53, df = 5 (P = 0.48); I ² = 0%							
Test for overall effect: Z = 8.30 (P < 0.00001)							

Background

Debate about the reason for this observed difference:



Comorbidities

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Comorbidities



Increased
virulence

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Comorbidities



Increased
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Less effective and
more toxic drugs

Background

Debate about the reason for this observed difference:



Comorbidities



Increased
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Less effective and
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Time to adequate
treatment

Background

Debate about the reason for this observed difference:



Appropriateness of initial antibiotic treatment



Less effective and
more toxic drugs



Time to adequate
treatment

Study objectives

- To assess impact of carbapenem-resistance on mortality of adult patients with *Klebsiella pneumoniae* bacteremia
- To assess impact of appropriateness of initial antibiotic treatment (IAT) on mortality
- To determine whether the proportion of patients with carbapenem-resistant *K. pneumoniae* receiving appropriate IAT has changed over time

Methods: Literature search

Search strategy

- Search terms: *Klebsiella pneumoniae* AND carbapenem-resistance AND infection

Data sources

- Embase, MEDLINE, CINAHL, Wiley Cochrane
- Conference abstracts
- Contacting of authors in case of missing data

Methods: Study criteria

Inclusion

- Cohort and case-control studies reporting mortality for adult hospitalized patients (acute and intensive care) with carbapenem-resistant (CRKP) and carbapenem-sensitive *K. pneumoniae* (CSKP).
- Published between January 1994 and August 2016

Exclusion

- Studies with less than 10 patients per study group (in order to minimize the risk for outliers)

Methods: Analysis

Appropriate initial
antibiotic treatment

Meta-regression I
(time as co-variable)



Carbapenem-
resistance



Mortality

Meta-regression II
(IAT as co-variable)

Results

- 9180 unique references and 903 conference abstracts
- 15 included studies:
 - 9 cohort-studies, 6 case-control studies
 - US (4), Israel (3), Italy (3), Greece (2), Taiwan (2), Latin America (1)
 - Performed between 2004 and 2015
 - 14 studies in general acute and intensive care patient population, 1 study in hemato-oncologic patients

Results: Definitions

Mortality: 15 studies

- 9 studies: mortality within 14 to 30 days after diagnosis
- 6 studies: hospital- or ICU-related mortality

Appropriate IAT: 11 studies

- 4 studies: ≥ 1 active drug given before results of culture
- 4 studies: ≥ 1 active drug given within 48h after diagnosis
- 3 studies: not defined

Results: Definitions

Carbapenem-resistance

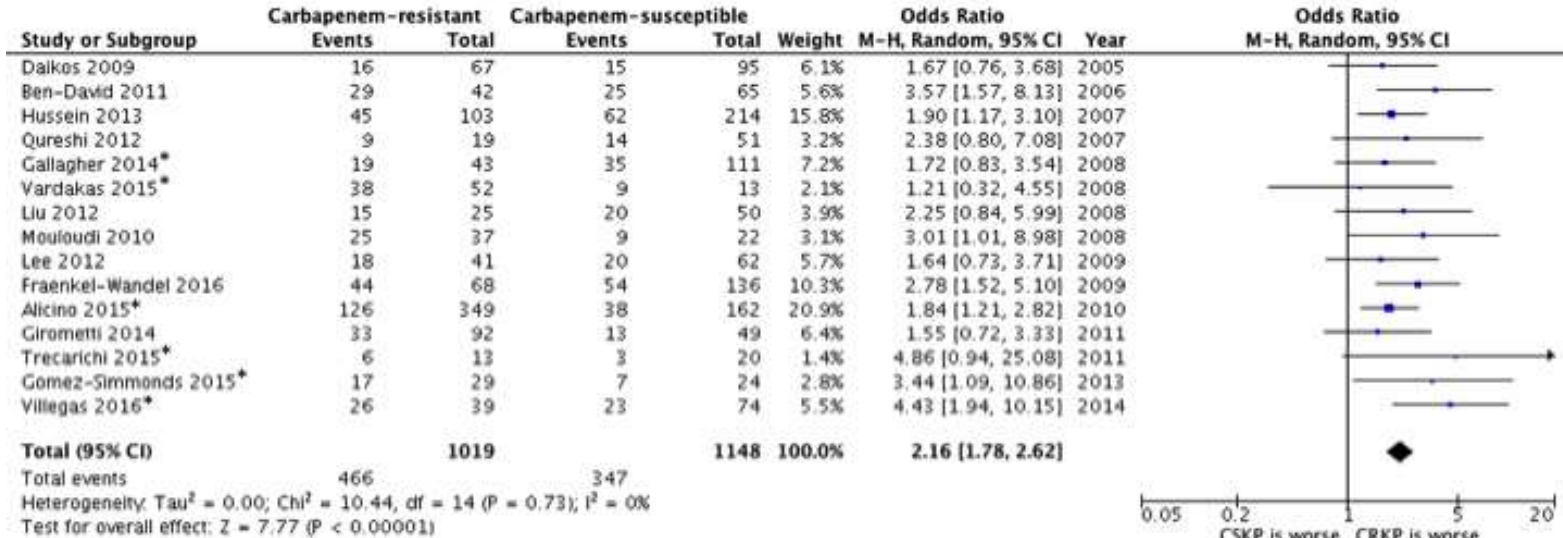
- 8 studies: non-susceptible/resistant to at least 1 carbapenem
- 3 studies: detection of a carbapenemase
- 4 studies: non-susceptible to at least 1 carbapenem AND detection of a carbapenemase

Comparison group

- 6 studies: carbapenem-susceptible
- 6 studies: carbapenem-susceptible AND ESBL/res to 3rd Gen Ceph
- 2 studies: carbapenem-susceptible and no carbapenemase
- 1 study: no carbapenemase

Results: Mortality of CRKP vs CSKP

Mortality: CRKP 46% CSKP 30%



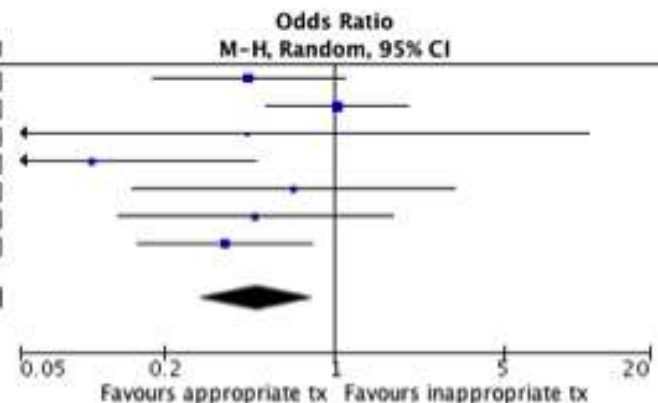
Subgroups: No difference between cohort (OR 2.16) and case-control studies (OR 2.18)

Results: Mortality appropriate vs inappropriate IAT

Mortality: Appropriate IAT 33% Inappropriate IAT 48%

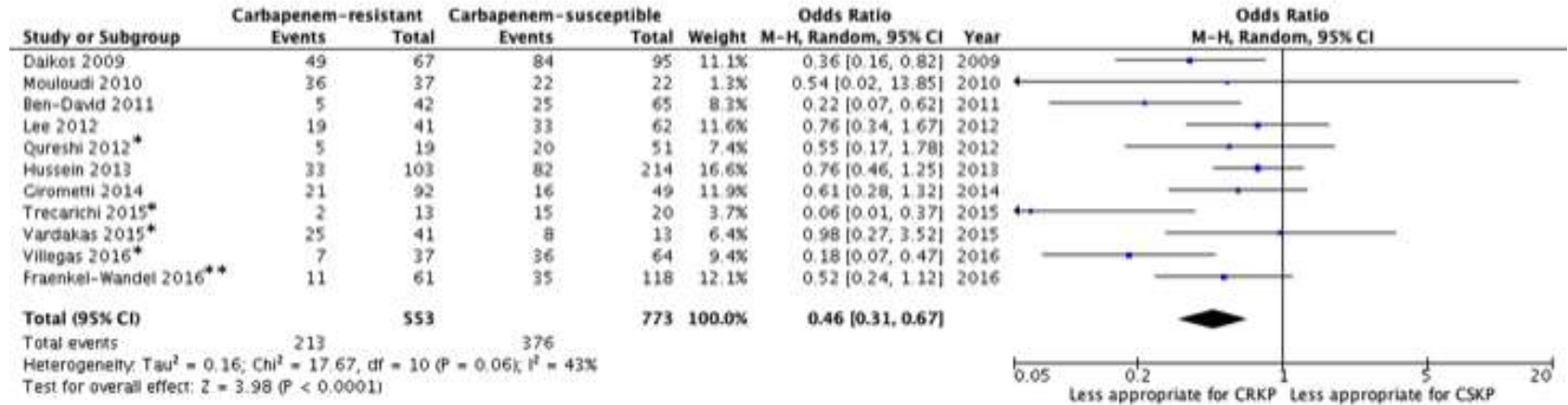
Study or Subgroup	Appropriate therapy		Inappropriate therapy		Weight	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Dalkos 2009	22	133	9	29	19.3%	0.44	[0.18, 1.09]
Fraenkel-Wandel 2016**	21	46	60	133	25.7%	1.02	[0.52, 2.00]
Mouloudi 2010	33	58	1	1	2.6%	0.44	[0.02, 11.20]
Qureshi 2012*	2	25	21	45	9.4%	0.10	[0.02, 0.47]
Trecarichi 2015*	4	17	5	16	9.6%	0.68	[0.15, 3.16]
Vardakas 2015*	22	33	17	21	12.2%	0.47	[0.13, 1.74]
Villegas 2016*	13	43	32	58	21.2%	0.35	[0.15, 0.81]
Total (95% CI)		355		303	100.0%	0.48	[0.28, 0.82]

Total events 117 145
Heterogeneity: Tau² = 0.18; Chi² = 9.37, df = 6 (P = 0.15); I² = 36%
Test for overall effect: Z = 2.69 (P = 0.007)



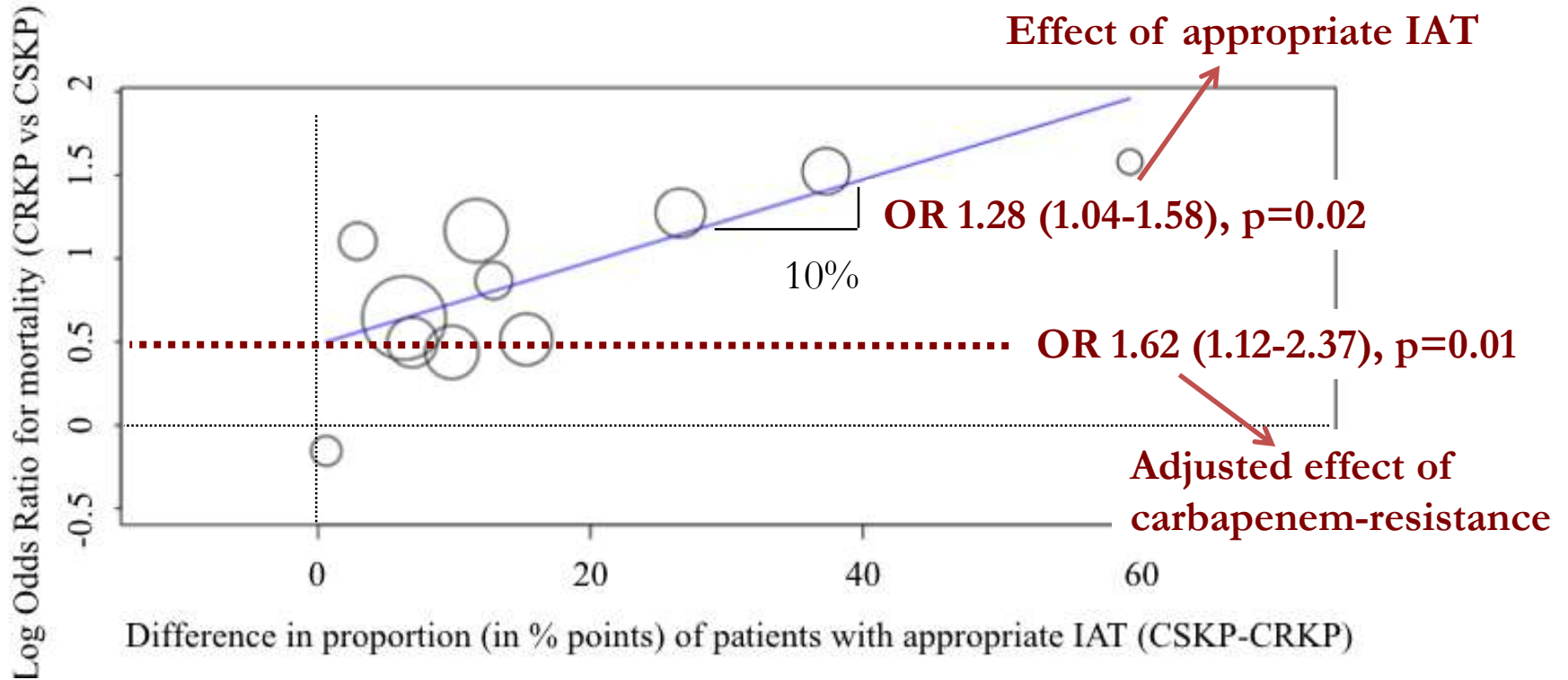
Results: Carbapenem-resistance and appropriate IAT

Appropriate IAT: CRKP 39% CSKP 49%



Meta-regression I with study year as co-variable: No trend over time

Results: Meta-regression II



Key points

1. Mortality of adult patients with CRKP bacteremia is increased compared to those with CSKP
2. Patients with CRKP are less likely to receive appropriate initial antibiotic treatment, which itself is associated with increased mortality
3. Meta-regression shows that appropriateness of IAT is a major independent contributor to the increased mortality in CRKP patients

Thank you



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Discussion

How to improve appropriateness of IAT without unnecessarily treating patients with broad-spectrum antibiotics?

- Introduction of rapid diagnostic tests into clinical practice to reduce time to appropriate therapy
- Integration of more complex risk stratification scores into decisions regarding empiric antibiotic treatment

Limitations

- Observational studies
- Pooling of adjusted ORs for carbapenem-resistance and mortality not possible due to lack of data
- Heterogeneous definitions used
- Meta-regression: Residual confounding on study and patient level