Treatment of serious infections due to MDR *Acinetobacter baumannii :*

Presentation of a multicenter randomised clinical trial

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R. Utili - Disclosures

Speaker activity for Novartis, MSD, Pfizer

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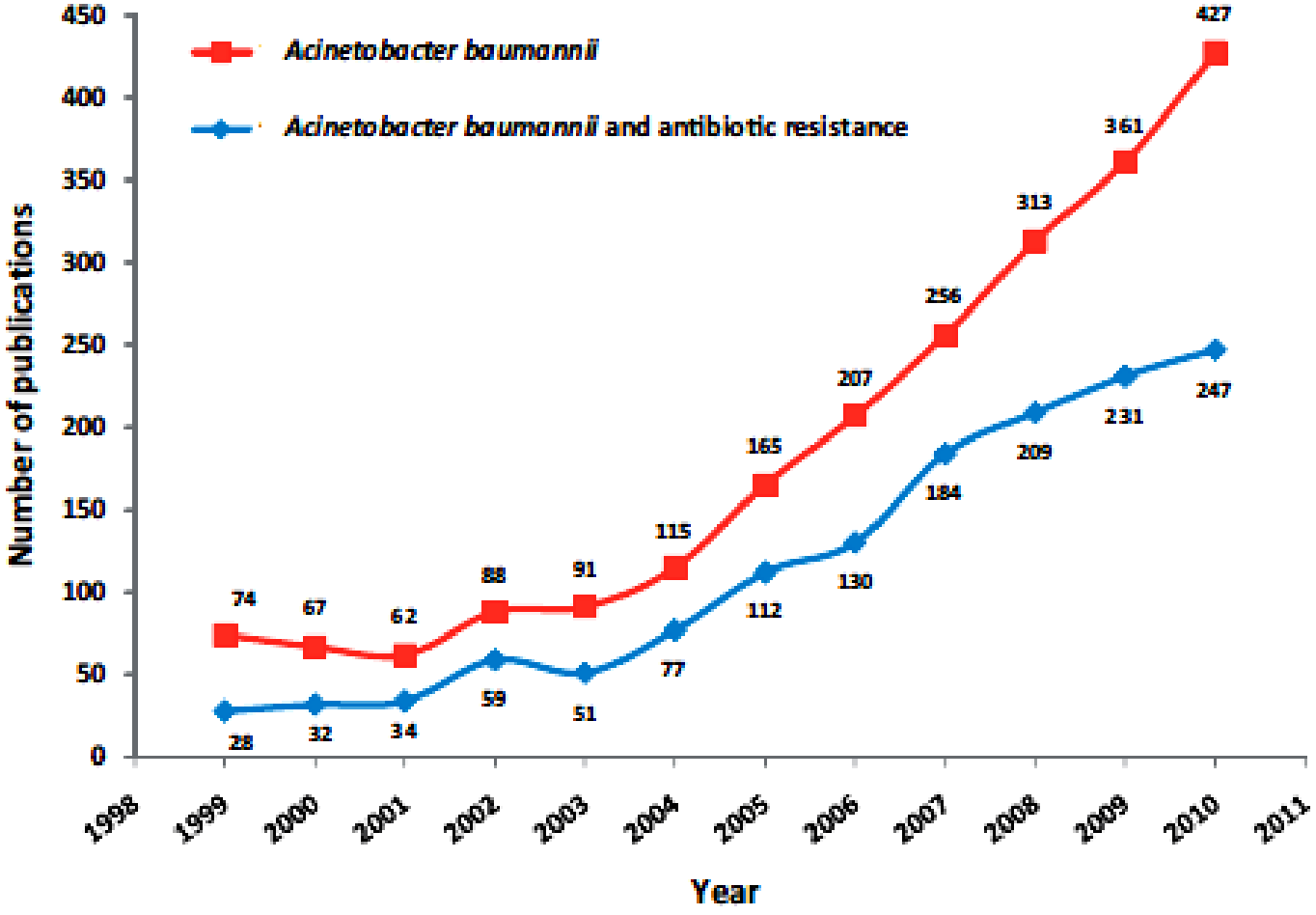


Fig. 1. Number of citations found in PubMed from 1999 to the end of 2010 using either '*Acinetobacter baumannii*' or '*Acinetobacter baumannii* and antibiotic resistance'.

Difficulties in planning therapeutic trials for *A. baumannii* infections

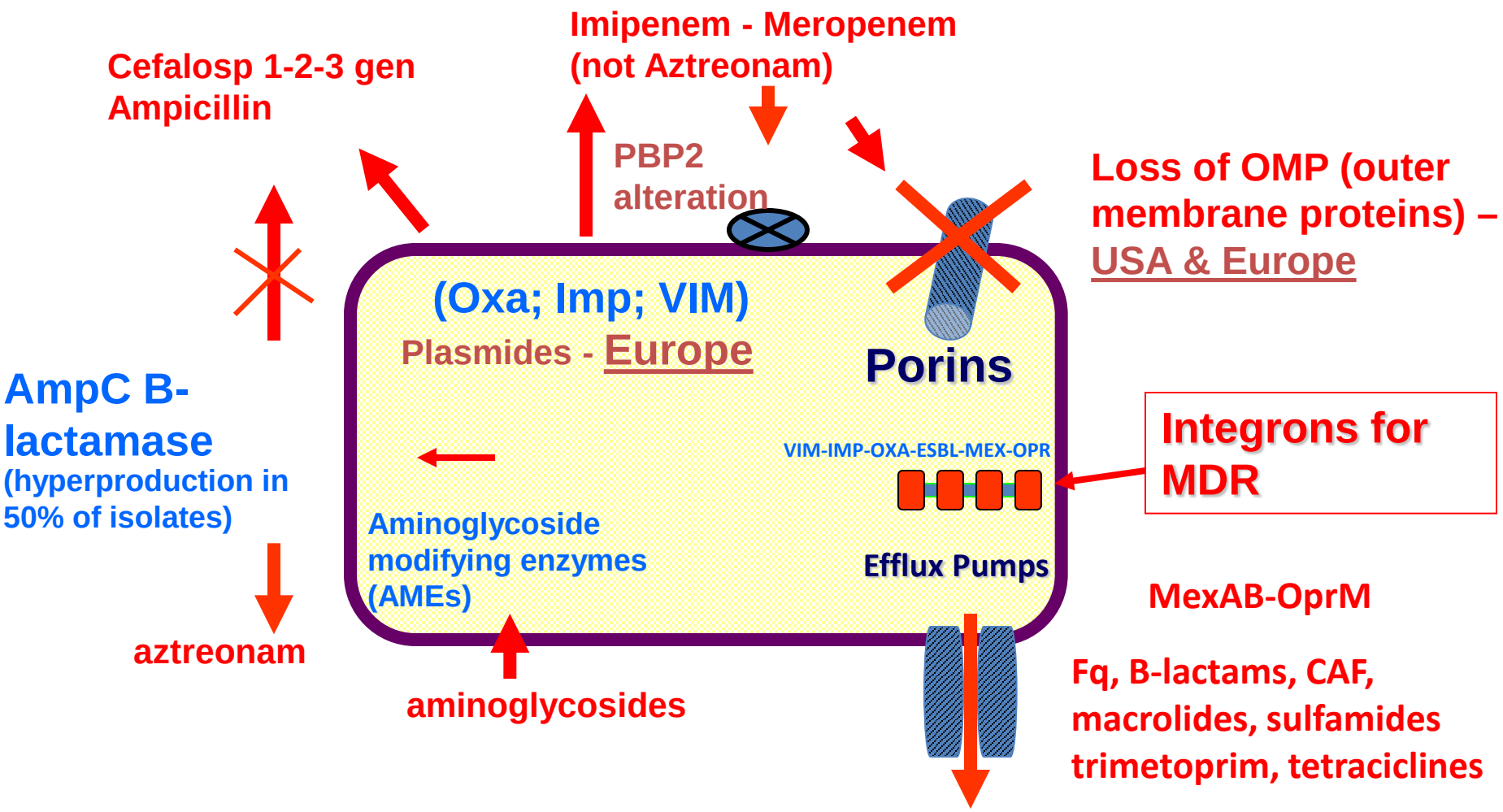
A. baumannii **infections (especially VAP) usually occurs late in the course of a severe disease (multiple comorbidities) in the ICUs**

Thus, patients may die for the Acinetobacter or with the Acinetobacter.

Crude mortality rate is high (40-60%)
Attributable mortality is a clinical judgment (risk of assessment bias)
it can only be estimated in a case control study

Need of strong outcomes to get reliable results , i.e.,
- 30 day mortality (including later f-u or out of hospital events)
- microbiological data collected at predetermined times
- lenght of hospitalisation

A. baumannii: a 'successful pathogen'



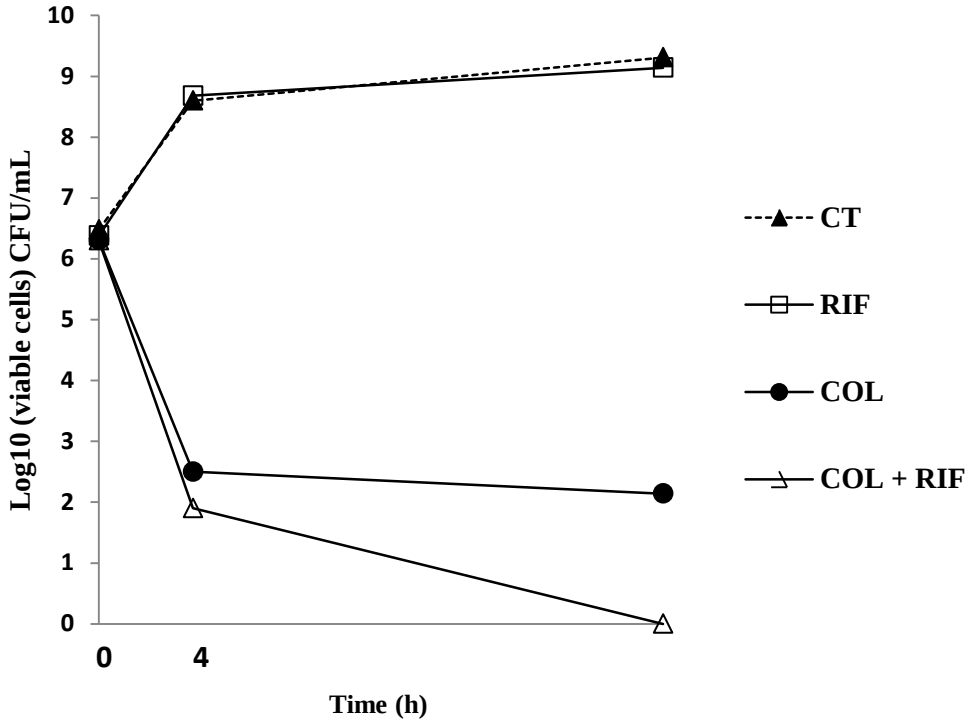
Adapted from Limanski JCM 2002; Urban CID 2003

Only option available

COLISTIN

- It acts by altering membrane permeability
- Poor lung diffusion
- Nephrotoxic
- Overall low efficacy when used as monotherapy
- Treatment is largely empiric

Antibiotic combinations
as an alternative approach to colistin monotherapy



Tripodi MF, Utili R et al. Int J Antimicrob Ag 2007

Co.R.A.b. study

Colistin vs Colistin+Rifampicin in A.baumannii infections

Open label, parallel,

randomized

5 clinical sites,

210 pts enrolled (2008-2011)

(Funded by the Italian Medicines Agency, AIFA;

ClinicalTrials.gov number, NCT01577862).

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Co.R.A.b. study

Colisitin vs Colistin+Rifampicin in A.baumannii infections

INCLUSION CRITERIA

- Age >18 y
- ICU admission
- Life-threatening infection (HAP, VAP, BSI, cIAI)
- Positive A.baumannii cultures
- XDR antibiotype
- Strain susceptible to colistin

EXCLUSION CRITERIA

- Previous treatment with colistin or rifampicin
- Hypersensitivity to either study drug
- Significant liver dysfunction (serum conjugated bilirubin >3 mg/dl).

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Typical antibiogram

Materiale **BRONCOASPIRATO** *Sito Prelievo*

Data Prelievo **29/01/2007**

Tipo di Esame **COLTURALE**

R I S U L T A T O

Microrganismo #1: Acinetobacter baumannii (acibau)

Antibiotics	acibau(1)	
Amikacina	>=64	R
+Amoxicillina/A.CLAV.		R
+Ampicillina		R
Aztreonam	>=64	R
Cefepime	>=64	R
+Cefotaxime		R
Cefpirome	>=64	R
Ceftazidime	>=64	R
+Ceftriaxone		R
Ciprofloxacina	>=4	R
Gentamicina	>=16	R
Imipenem	>=16	R
Meropenem	>=16	R
+Mezlocillina		R
Netilmicina	>=32	R
Pefloxacina	>=16	R
Piperacillina	>=128	R
Piperacillina/tazoba	>=128	R
Ticarcillina	>=128	R
Ticarcillina/A.CLAV.	>=128	R
Tobramicina	>=16	R
Trimetoprim/Sulfam.	>=320	R
+Amoxicillina		R
Colistina	<=0,5	**S**
Isepamicina	>=64	R

Co.R.A.b. study

Treatment arms

Colistin monotherapy

- Colistimethate sodium
- 2 MU (=160 mg), q8h, i.v.
- Treatment duration: 10-21 d.

Colistin + Rifampicin combination

- Colistimethate sodium, same dose
- Rifampicin, 600 mg q12h, i.v.
- Treatment duration: 10-26 d.

Randomization

- Centre site
- Simplified Acute Physiology Score (SAPS) II <40 or ≥40

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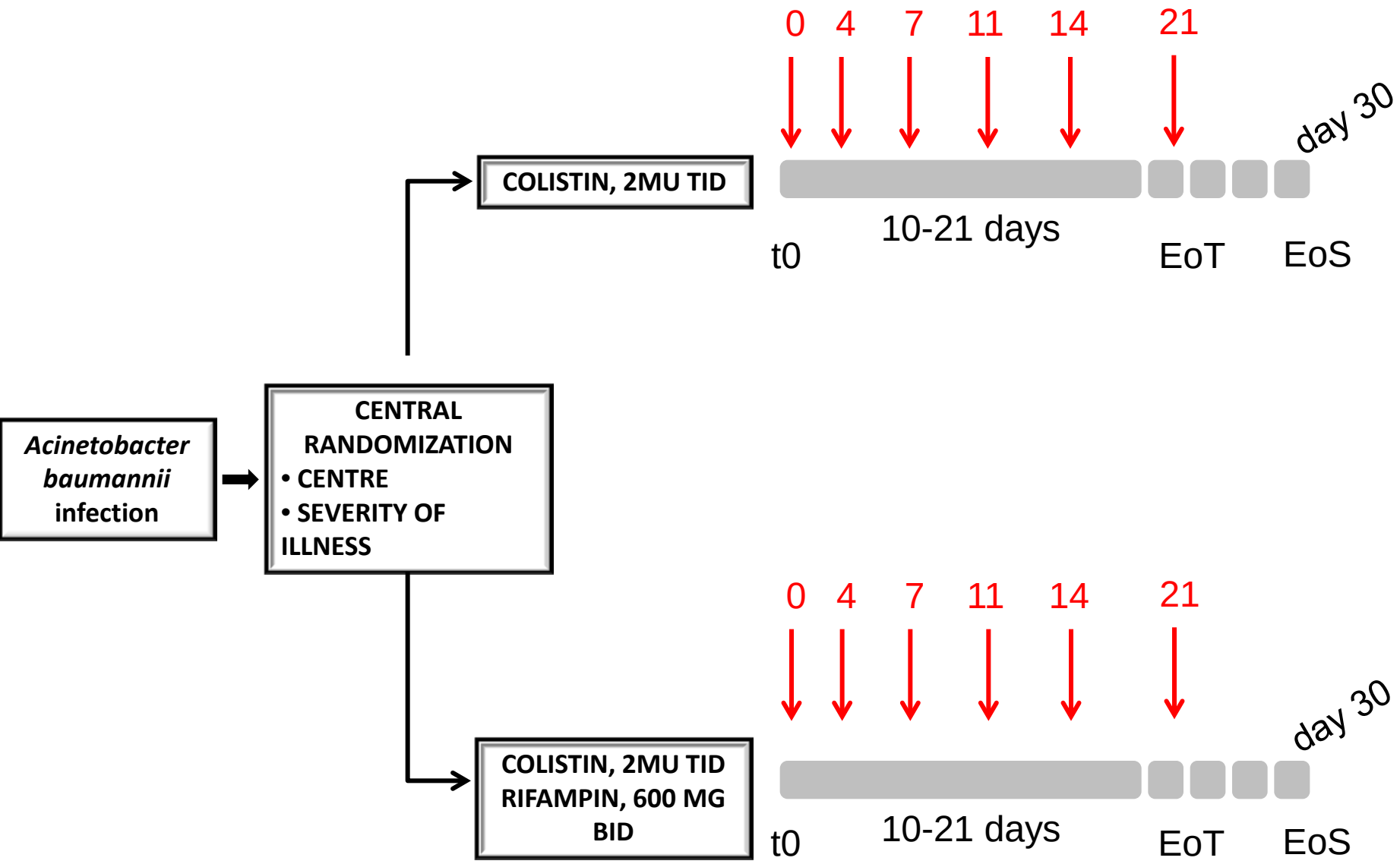
COLISTIN AND RIFAMPICIN FOR XDR-ACINETOBACTER



t0: baseline; EoT: end of treatment; EoS: end of study;

Sample size

The study was designed to identify an absolute mortality reduction of 20%.

Assuming a raw 30-day mortality rate of 60% in the control group,

a two-tailed significance level of 0.05, a power of 0.8, an allocation ratio of 1:1 and a drop-out rate of 10%,

207 patients had to be enrolled (East software v. 4).

Co.R.A.b. study

Primary end point

30-day crude mortality

(death for any cause within 30 days from randomization)

Secondary end points

- **disease-specific death**
- **microbiological eradication**
- **hospitalization length**
- **emergence of resistance to colistin during treatment**

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Safety evaluation

- **renal dysfunction possibly related to colistin**
- **neurotoxicity, possibly related to colistin**
- **hepatic dysfunction, possibly related to rifampicin**

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The end