

Final Programme

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Clinical Microbiology
and Infectious Diseases

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ECCMID



25th

MEET-THE-EXPERT SESSION:

How and when to use non-conventional drugs for treatment of Gram-negative pathogens?

Haibo Qiu
Nanjing China

Non-Conventional Antimicrobial Treatment for MDR Bacterial Infections in ICU Setting

Focus on MDR *A. baumannii*

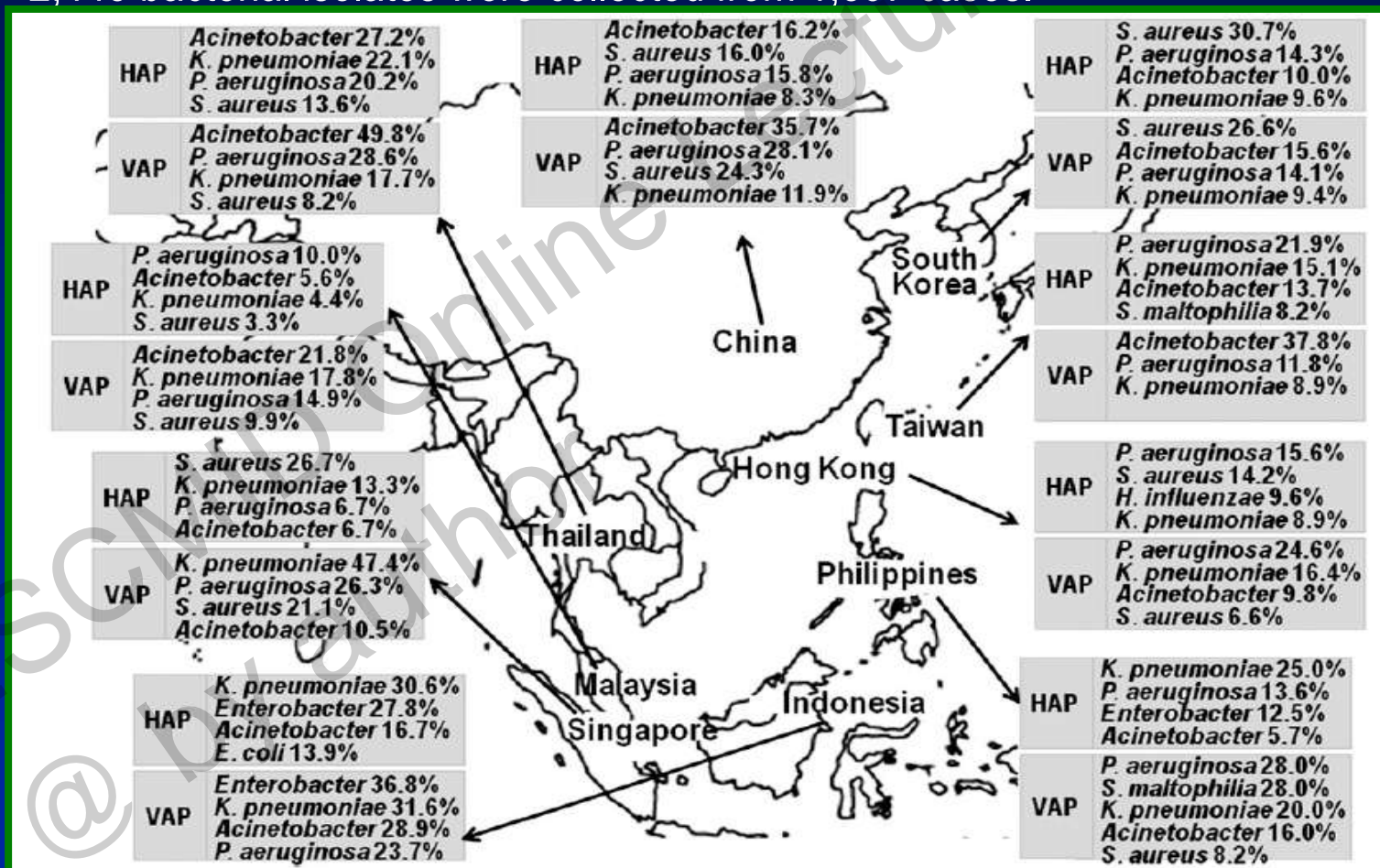
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Prevalence of MDR Nonfermenters in HAP or VAP in Asia

73 hospitals in 10 Asian countries from 2008–2009

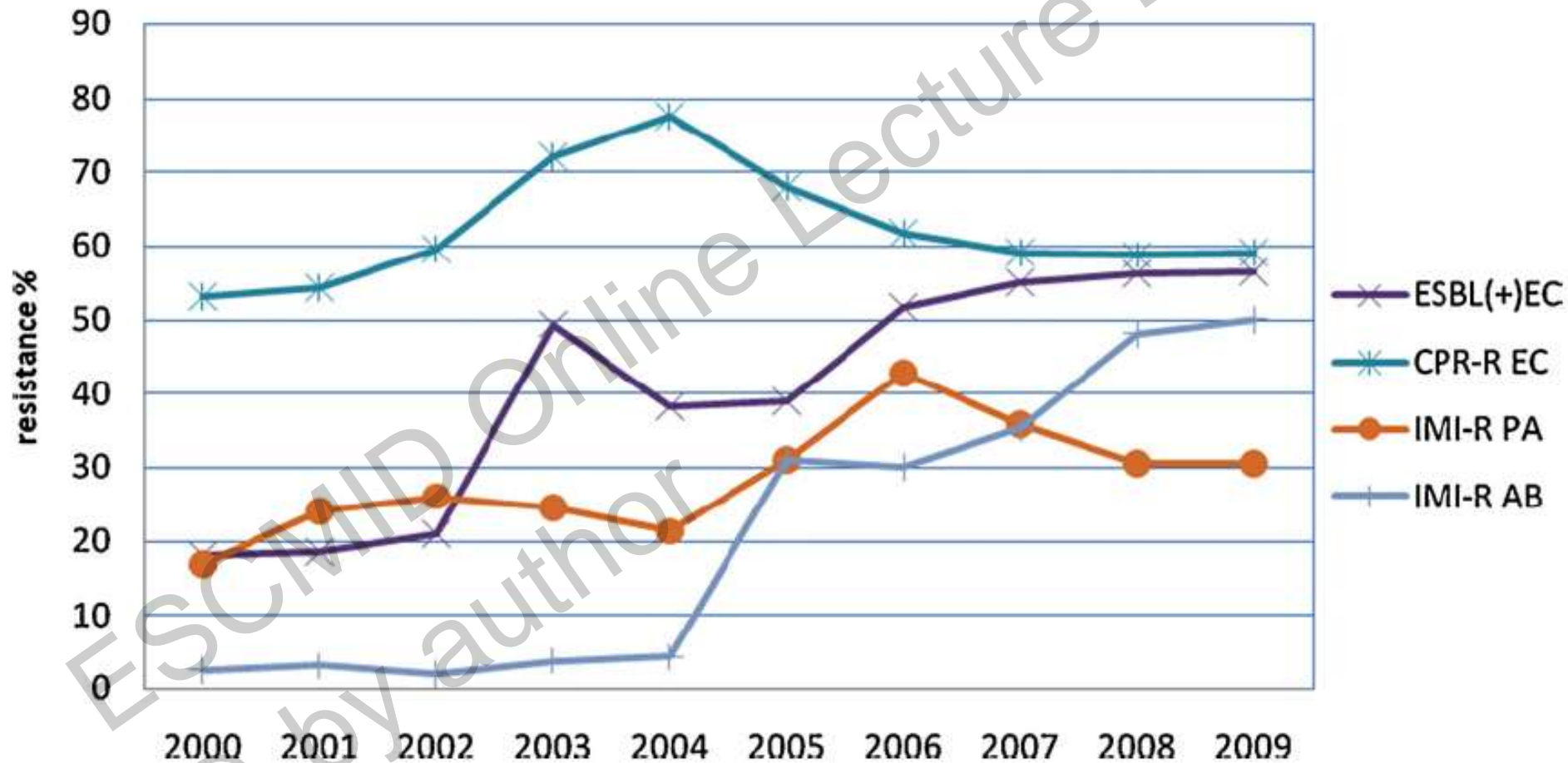
2,445 bacterial isolates were collected from 1,897 cases.



A Systematic Review of Antibiotic Utilization in China

- 60~70% hospitalized patients prescribed antibiotics
- Studies of antibiotic prescribing patterns in China
 - Between 2000-August 2012
 - 57 studies with a total of 556.435 outpatient encounters
- 50.3% of outpatients prescribed antibiotics
 - 74.0% 1 antibiotic
 - 23.3% 2 antibiotics
 - 2.0% ≥3 antibiotics

Trends in Antimicrobial Resistance in China

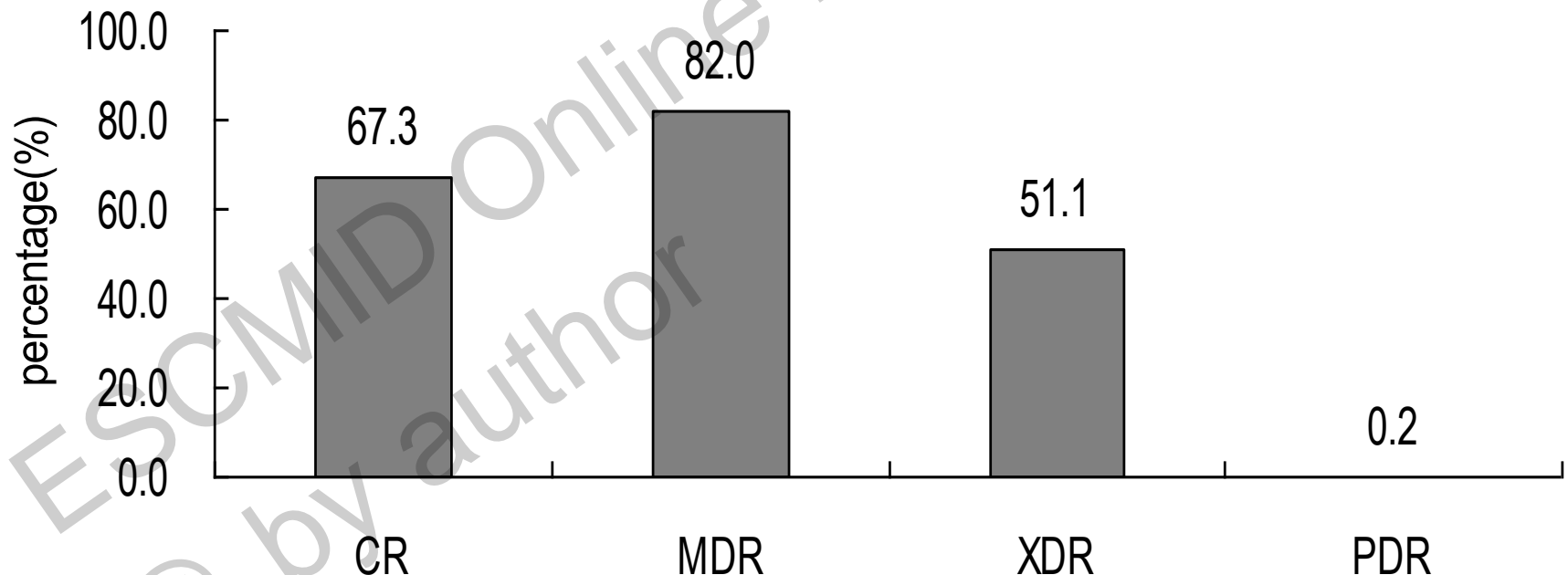


High Prevalence of MDR Acinetobacter in HAP or VAP in Asia

73 hospitals in 10 Asian countries from 2008–2009

2,445 bacterial isolates were collected from 1,897 cases.

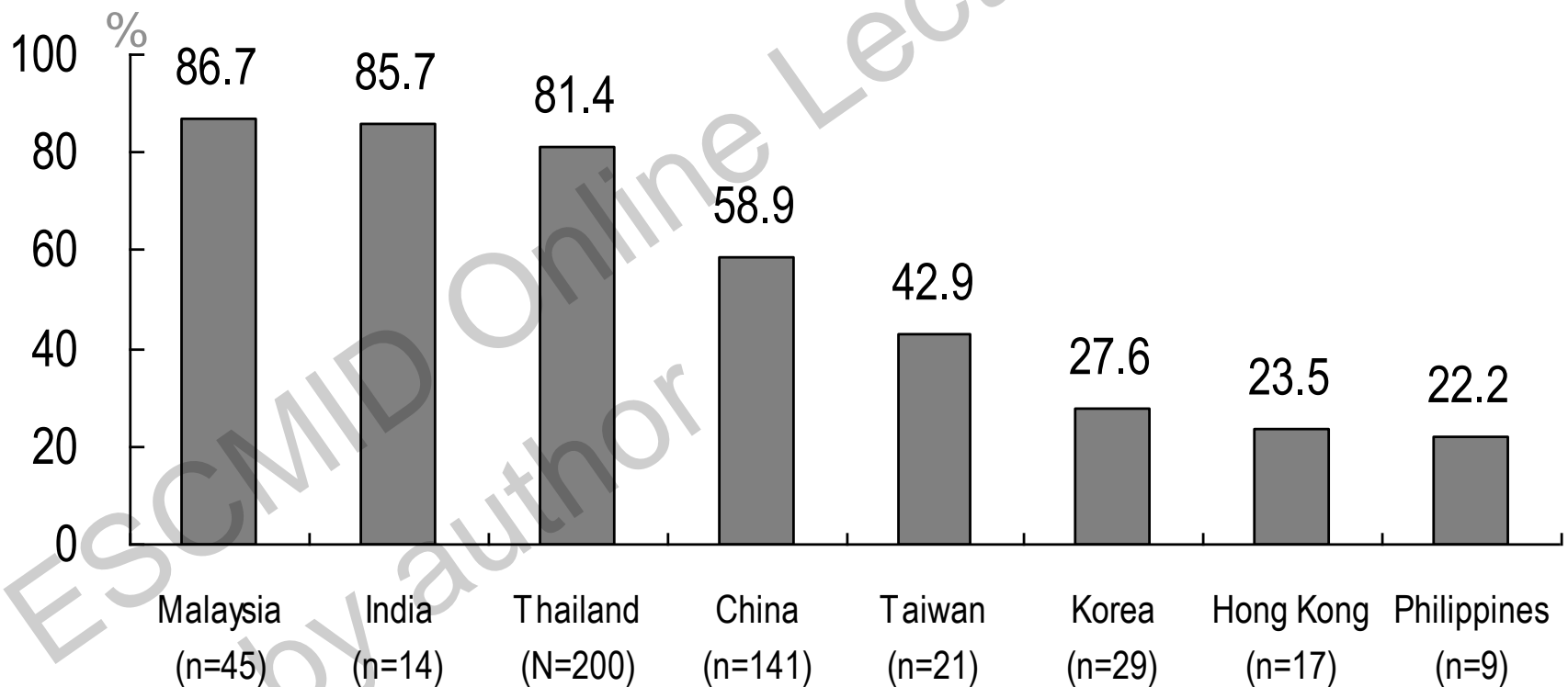
Incidence of Acinetobacter spp. resistant to antimicrobial agents



Imipenem-resistant *A.baumannii*

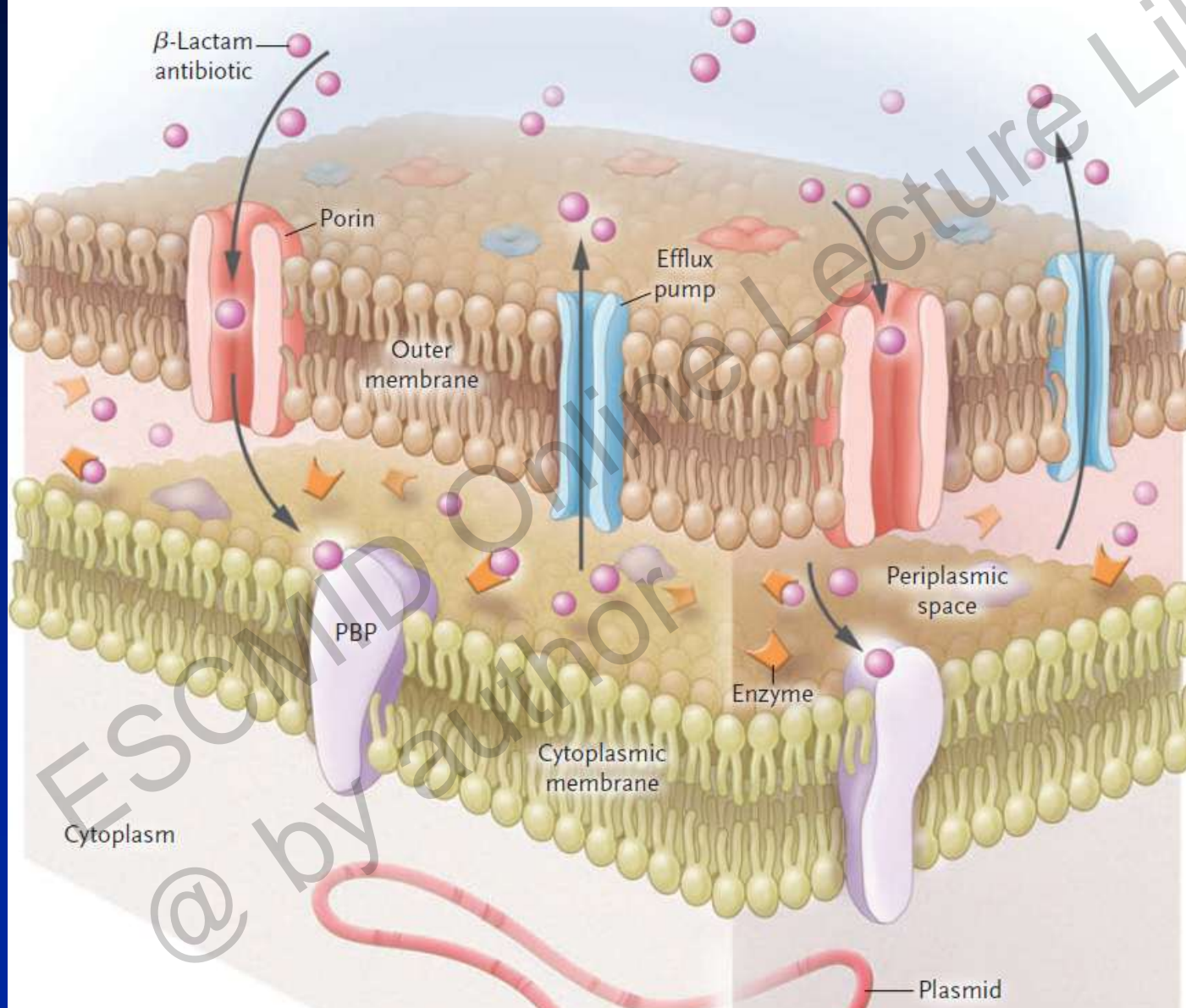
2,445 bacterial isolates were collected from 1,897 cases in Asia

High resistance rate of *Acinetobacter* spp. to imipenem ($MIC_{90} >64$ mg/L)



Acinetobacter Infection

L. Silvia Munoz-Price, M.D., and Robert A. Weinstein, M.D.

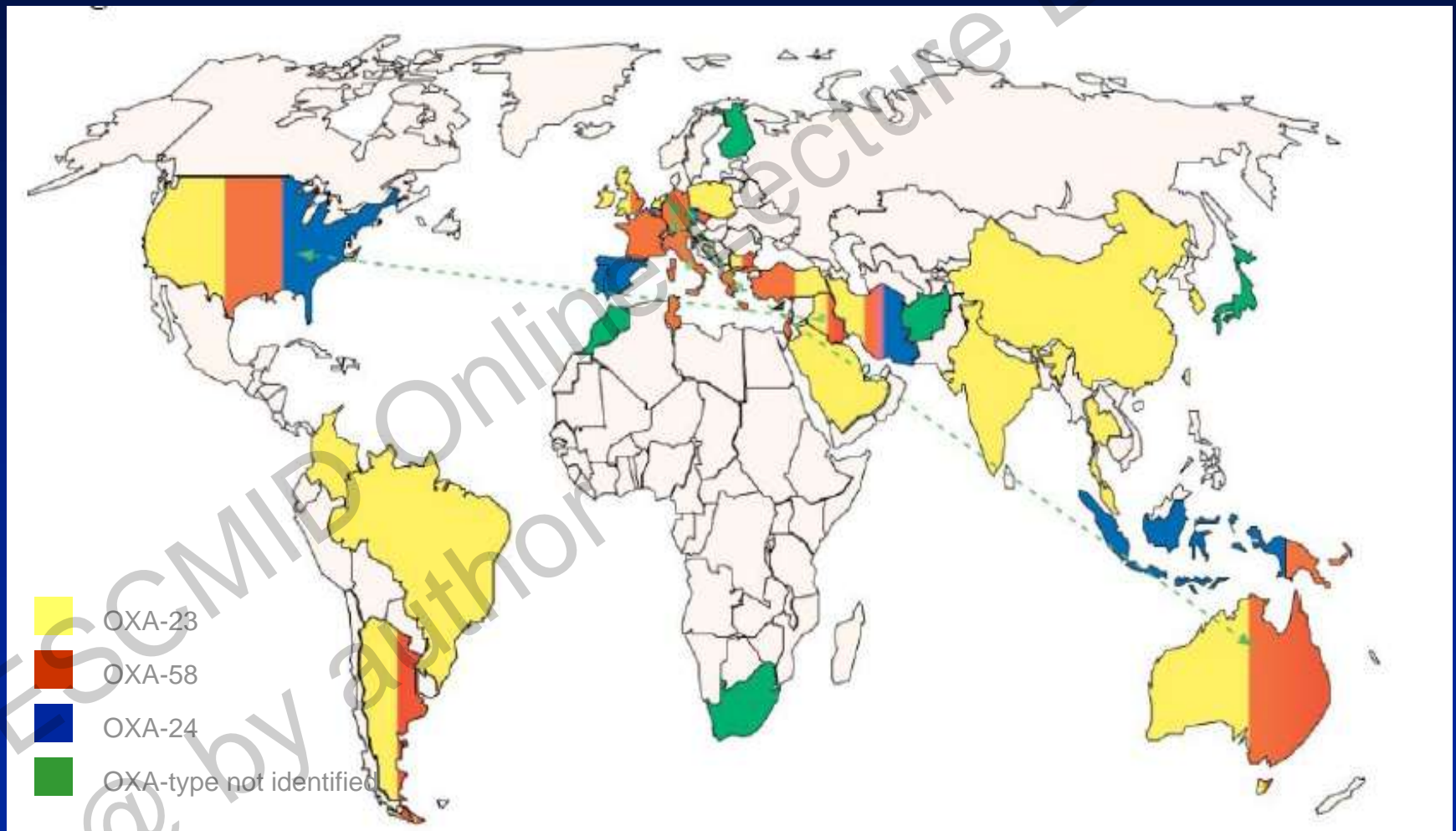


Carbapenem-resistant *Acinetobacter* spp.

Mechanisms

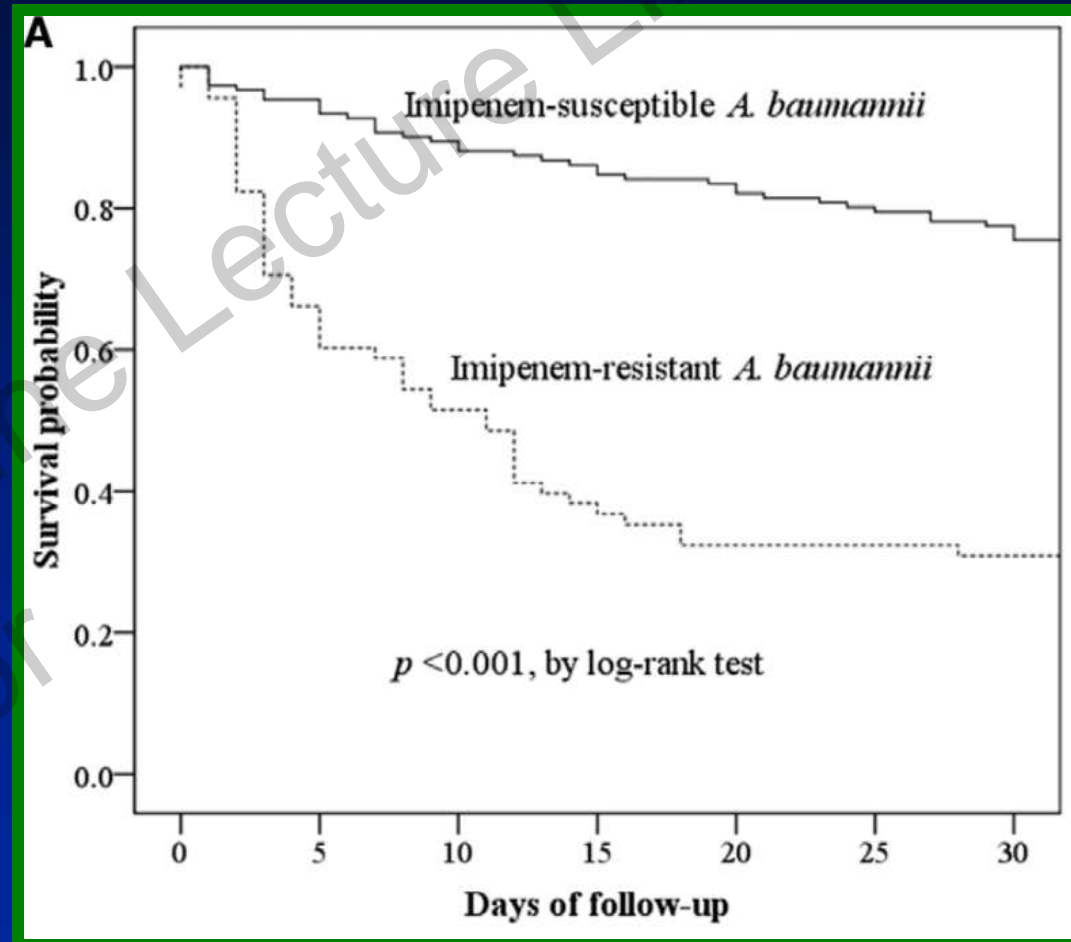
- Carbapenemases (most)
 - Class A: KPC, GES (-11, -12)
 - Class B: VIM, IMP, SIM, NDM (-1, -2)
 - Class D (CHDL): OXA-23, OXA-24, OXA-40, OXA-58, OXA-143; OXA-51 like (intrinsic)- ISAba 1,2,3..
- Decreased permeability of the outer membrane (loss or modification of porins)
 - CarO (29 kDa); 33- or 36-kDa OMPs, OprD-like OMP
- Modification of penicillin-binding proteins (rare)
- Efflux system (AdeABC)

Geographic Distribution and Genetic Characteristics of carbapenem-resistant *A. baumannii*



Understanding AB Outcomes : Bacteremia as a Paradigm

- ❑ Retrospective single center study
- ❑ Subjects: AB bacteremia
- ❑ Endpoint: 30 day Mortality
- ❑ n=298(25% CRAB)
- ❑ Crude mortality rate: 34%



SSC guidelines 2012

- Combination empirical therapy for Neutropenic patients with severe sepsis (grade 2B)

Patients with **difficult to treat multidrug-resistant bacterial pathogens such as Acinetobacter** and *Pseudomonas* spp. (grade 2B).

- *P. aeruginosa* bacteremia with respiratory failure and septic shock

Combination therapy: extended spectrum beta-lactam + aminoglycoside or fluoroquinolone (grade 1B).

- *Streptococcus pneumoniae* infections with septic shock

Combination: beta-lactam + macrolide (grade 1B).

Carbapenemase-Producing *A. baumannii* Options

Combined therapy

- Carbapenems
- Sulbactam
- Polymyxins
- Tigecycline
- Fosfomycin

Novel agents

- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Plazomicin(ACHN-490)
- Eravacycline (TP-434)
- DS-8587

A. Baumannii Infections

Therapeutic Strategy

Susceptible agent (s)



Carbapenems (MIC \leq 2mg/L)



Carbapenem (MIC \leq 32mg/L?)

Sulbactam-containing (ampicillin-, cefoperazone-)



Tigecycline or colistin in combination
(sulbactam, carbapenem...)

Severity
Resistance

Recommendations on Nosocomial Pneumonia caused by CR, XDR or PDR Ab.

Conventional agents

- Carbapenems (imipenem, meropenem and doripenem) prolonged infusion plus sulbactam (6-8g/d) or sulbactam-containing agents

Alternative agents

- IV colistin (2 MU every 8h) plus IV rifampicin (10 mg/kg) or carbapenem
- Tigecycline (high dose) plus carbapenem
- Tigecycline (high dose) plus colistin

Colistin dosing: high doses

A loading dose of 300 to 400 mg CBA followed by a maintenance dose of 150mg twice (CID 2013; 56: 398-404)

Meropenem and sulbactam against MDR Ab

Survival rates of BALB/c mice infected with Ab-153 (IMP-R *A.baumannii*) at 5 days after treatment with Saline, Sulbactam, Meropenem, Meropenem+sulbactam

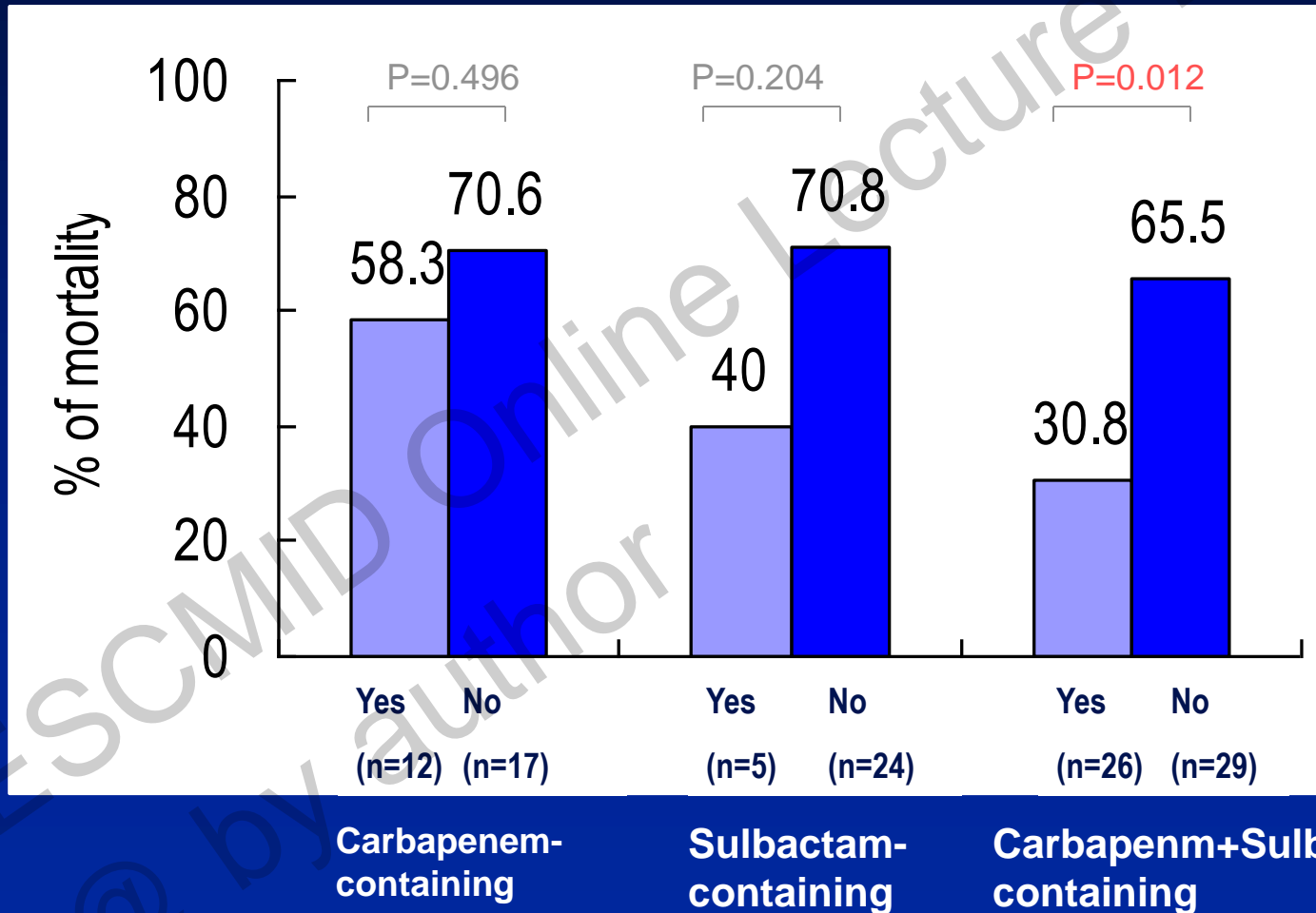
Initial inoculum (cfu)	Surviving mouse no./total mouse no. (%)			
	control	sulbactam	meropenem	sulbactam + meropenem
2.1×10^7	1/8 (12.5)	3/8 (37.5)	3/8 (37.5)	7/8 (87.5)
2.3×10^7	0/5 (0)	0/5 (0)	1/5 (20)	5/5 (100)
2.6×10^7	1/9 (11.1)	4/10 (40)	4/10 (40)	8/10 (80)
Total	2/22 (9.1) ^a	7/23 (30.4)	8/23 (34.8)	20/23 (87.0) ^b

^aControl versus sulbactam-treated group, $P = 0.054$; control versus meropenem-treated group, $P = 0.042$.

^bSulbactam-meropenem-treated group versus sulbactam-treated group, $P = 0.0002$; sulbactam-meropenem-treated group versus meropenem-treated group, $P = 0.0004$.

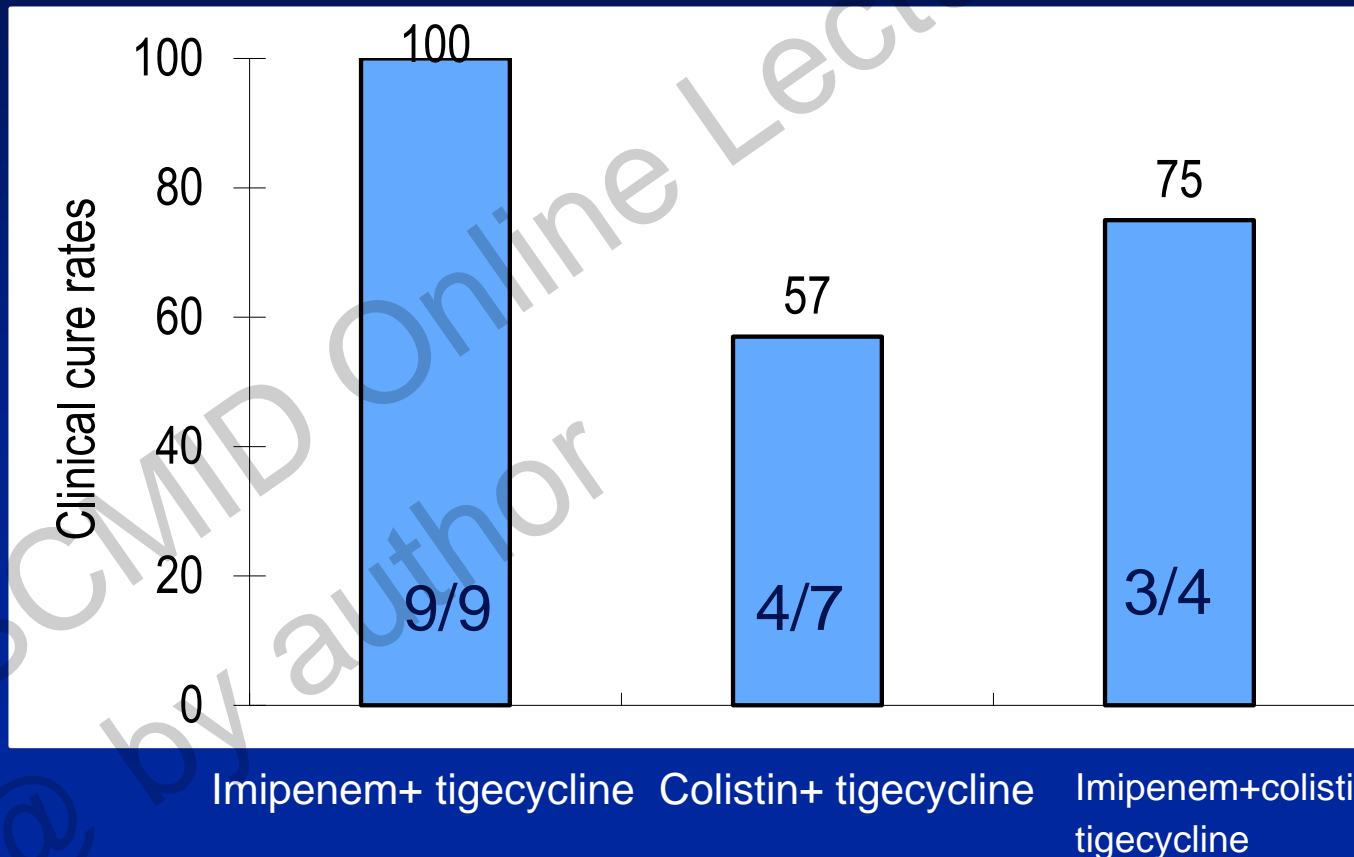
Bacteremia due to CRAB (XDRAB)

- 55 patients, NTUH, 2003-2004

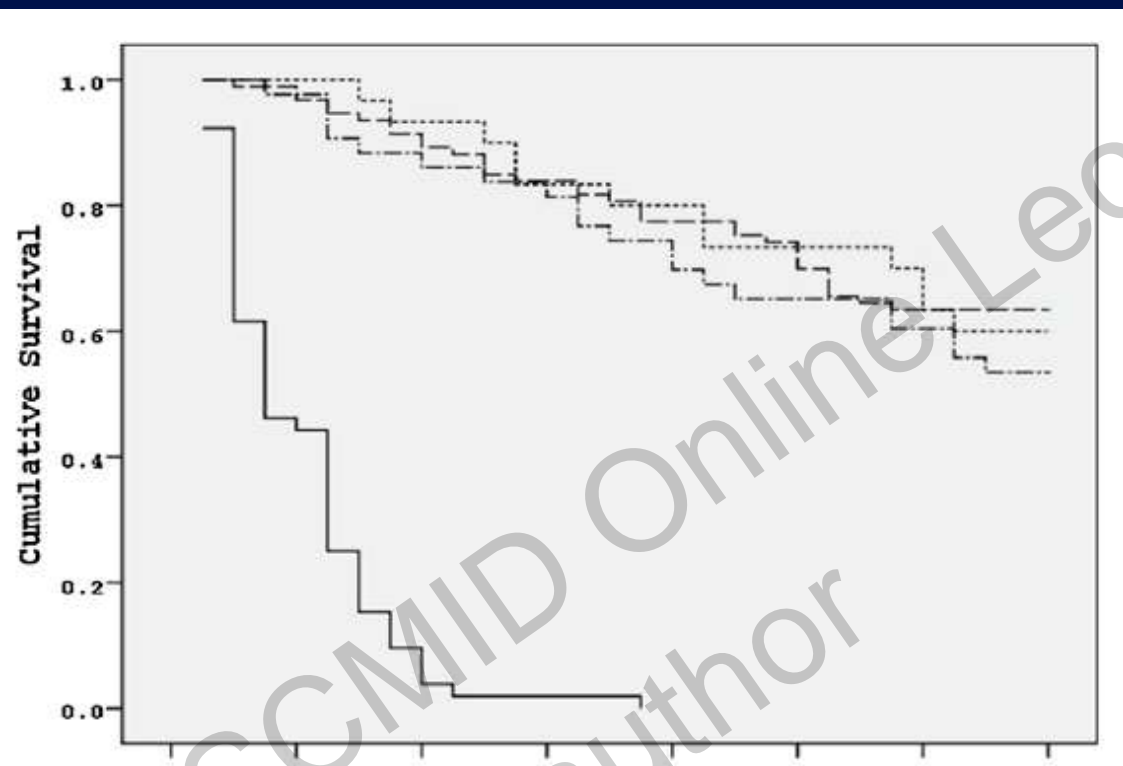


Tigecycline plus Imipenem

No statistically significant differences were noted for clinical resolution ($p=0.061$) or microbial eradication ($p=0.47$) based on the antibiotic regimens used.



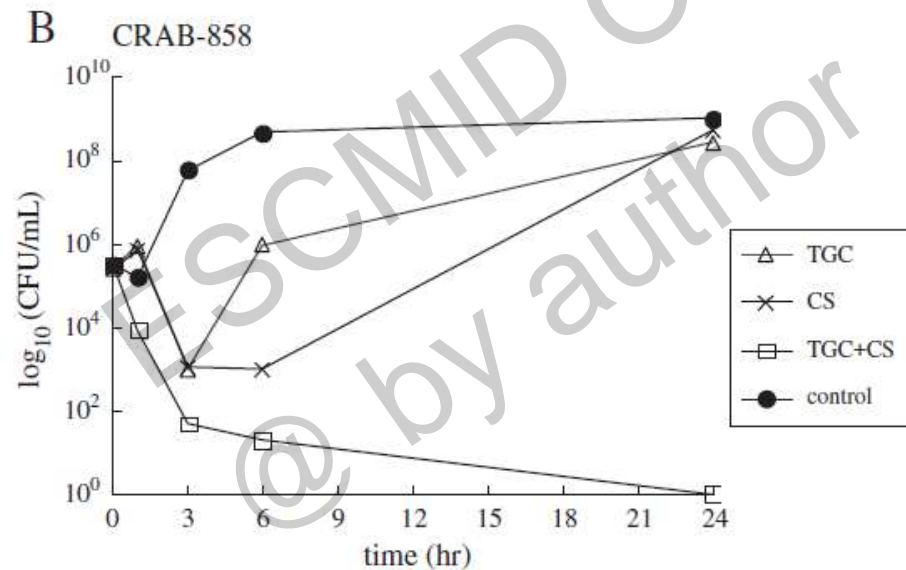
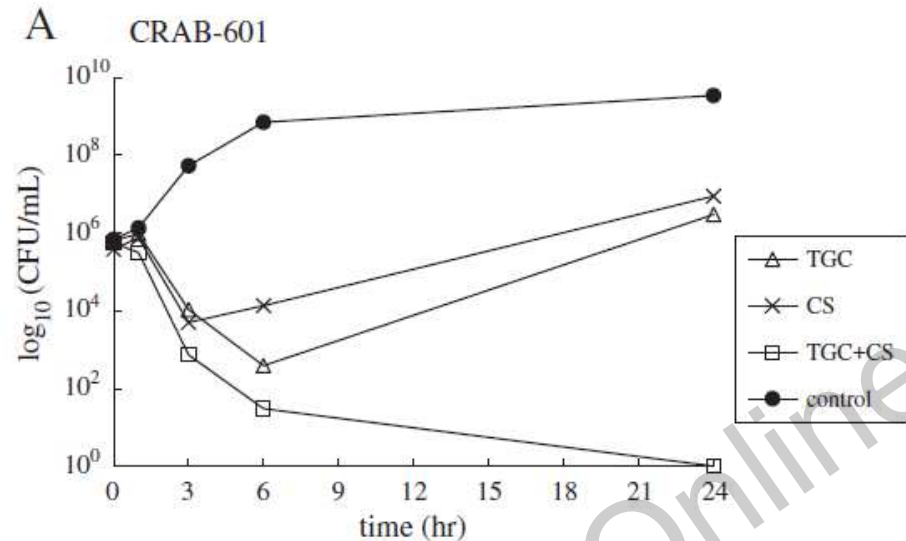
Colistin-based treatment for Extensively Drug-resistant Ab. pneumonia



- A retrospective cohort study
- 236 adult patients with XDR-Ab pneumonia
- CL + TC: Colistin + tigecycline (n = 43)
- CL+SB: Colistin + high-dose sulbactam (n = 93)
- CL + CB: Colistin + high-dose prolonged infusion carbapenem (n = 30)

Three colistin-based two-drug combination regimens may be treatment options for XDR-Ab pneumonia.

Imipenem-resistant Ab.



Tigecycline + colistin

Imipenem 64mg/L

Tigecycline 0.5mg/L

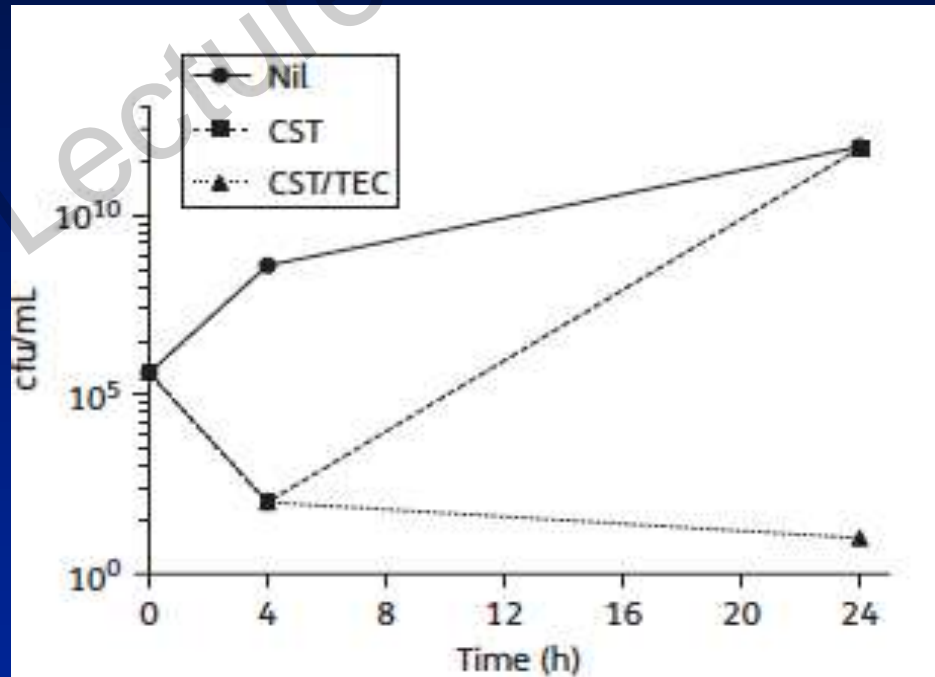
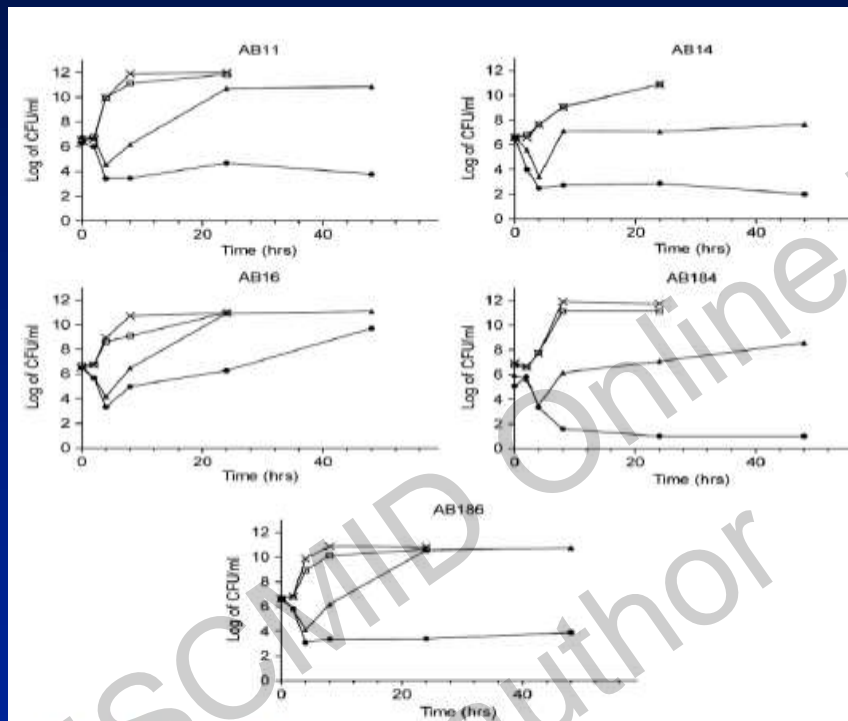
Colistin 2mg/L

Imipenem 128mg/L

Tigecycline 2mg/L

Colistin 0.5mg/L

Synergy with Colistin and Glycopeptides vs MDR *Acinetobacter*



2. Time-kill assay performed on AB14 in the presence of 1 mg/L colistin (CST); and 1 mg/L colistin+20 mg/L teicoplanin (CST/TEC). The y-axis is CFU/mL. The x-axis is Time (h). The legend indicates: Nil (solid line with circles), CST (dashed line with squares), and CST/TEC (dotted line with triangles).

Synergistic effect : Sulbactam with fosfomycin

Testing of coupled antimicrobial agents against carbapenem-resistant *A. baumannii* (CRAB) clinical isolates by checkerboard technique.

Strains	FICI for combined antimicrobial agents ^a				
	Colistin + sulbactam	Colistin + imipenem	Colistin + fosfomycin	Sulbactam + imipenem	Sulbactam + fosfomycin
AB23	0.96 (I)	0.94 (I)	1.17 (I)	0.63 (I)	0.32 (S)
AB54	1.54 (I)	0.56 (I)	1.04 (I)	0.52 (I)	0.49 (S)
AB164	0.87 (I)	0.89 (I)	1.38 (I)	0.62 (I)	0.48 (S)
AB167	1.10 (I)	0.62 (I)	0.94 (I)	0.85 (I)	0.37 (S)
AB198	0.94 (I)	0.52 (I)	0.85 (I)	0.75 (I)	0.28 (S)
AB307	0.71 (I)	0.99 (I)	1.08 (I)	1.27 (I)	1.04 (I)
AB313	0.75 (I)	0.71 (I)	0.49 (S)	0.51 (I)	0.47 (S)
AB315	0.92 (I)	1.04 (I)	1.08 (I)	0.92 (I)	1.08 (I)

FICI, fractional inhibitory concentration index; ≤ 0.5 , synergistic, S; $> 0.5-4.0$, indifferent, I; and > 4 , antagonistic effect, AT

Carbapenemase-producing *A. baumannii*

60 patients with CRAB infections

- M/F: 36/24; mean age 64; Mean APACHE II score: 19
- VAP (n=45) and bacteremia (n=15)

Mortality

- 100% died among patients (n=15) died prior to appropriate empirical therapy
- 55.6% died among patients (n=45) with appropriate definite therapy

Antibiotic regimens

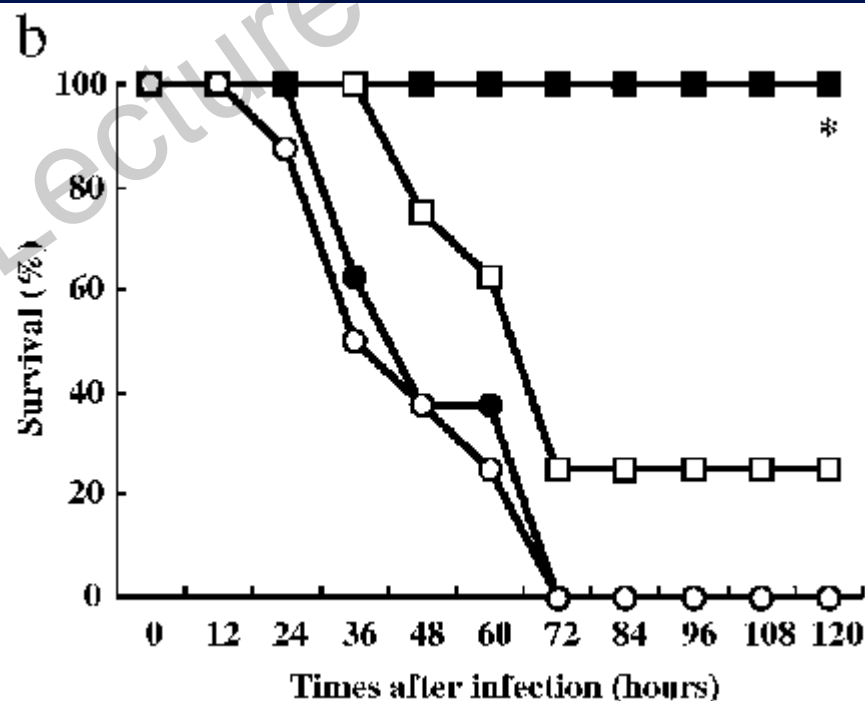
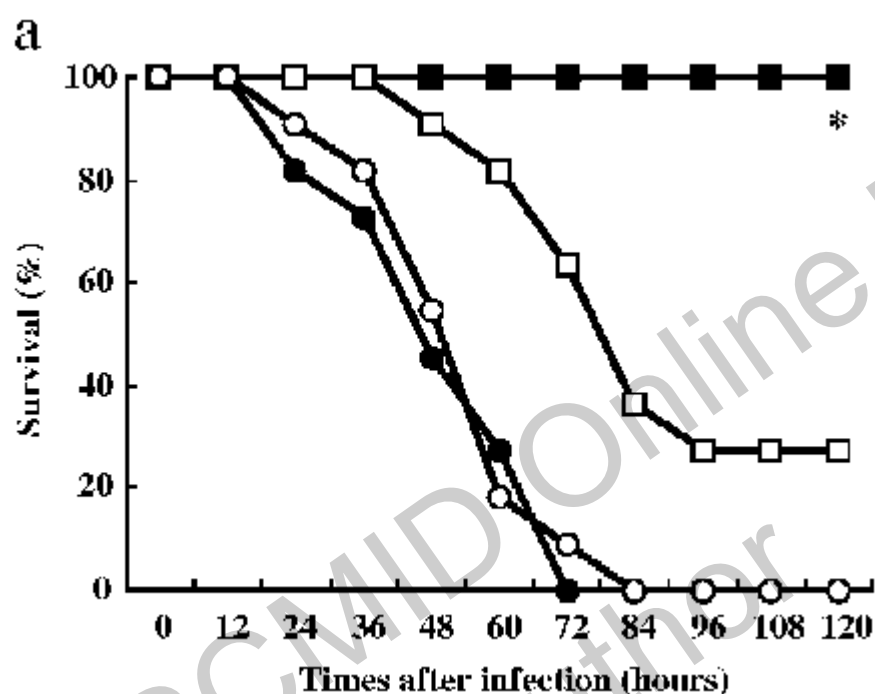
- Colistin/ tigecycline (n=20), colistin/ netilmicin (12)
- Colistin/ meropenem (3), tigecycline/ meropenem (6), or colistin monotherapy (4)

Antimicrobial regime from XDR *A. baumannii*

Combination with two drugs	Combination with three drugs
<p data-bbox="117 375 548 429">Sulbatam based:</p> <ul data-bbox="162 454 707 672" style="list-style-type: none"><li data-bbox="162 454 562 515">Plus tigecycline<li data-bbox="162 532 707 594">Plus Doxyeycline and Carbapenem <p data-bbox="117 772 600 826">Tigecycline based:</p> <ul data-bbox="146 851 595 1069" style="list-style-type: none"><li data-bbox="146 851 504 912">Plus sulbatam<li data-bbox="146 929 595 991">Plus Carbapenem<li data-bbox="146 1008 475 1069">Plus collistin <p data-bbox="117 1169 519 1223">Collistin based:</p> <ul data-bbox="162 1248 610 1383" style="list-style-type: none"><li data-bbox="162 1248 610 1309">Plus Carbapenem<li data-bbox="162 1326 562 1388">Plus tigecycline	<p data-bbox="1051 375 1721 515">Sulbatam Plus Tigecycline Plus Carbapenem</p> <p data-bbox="1051 615 1740 755">Sulbatam Plus Doxyeycline and Carbapenem</p> <p data-bbox="1051 855 1736 995">Carbapenem Plus Rifapicin and Colistin or Tobumycin</p>

Therapeutic potential of EDTA –Ga⁺ for MDA AB

Metallo-beta-lactamase \longrightarrow Zinc in active site \longrightarrow EDTA Chelating



P. aeruginosa mouse pneumonia model in the setting of hyperoxia.
intranasal administration (a) and subcutaneous administration (b)

Control (open circles)

Ca-EDTA (closed circles)

IPM (open squares)

IPM plus Ca-EDTA (closed squares)

Take home message

- **Worldwide emergence of *A. baumannii* strains resistant to carbapenems and colistin**
- **CRAB associated with considerable hospital cost and attributable mortality**
- **Choice of combination agents should be guided by results of in vitro antibiotic susceptibility testing**
Carbapenem, sulbactam, colistin, tigecycline, rifampin
- **Combination of colistin with other existing compounds in well-controlled clinical studies is critical**
- **New drugs are currently in the pipeline?**

Thank you....

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