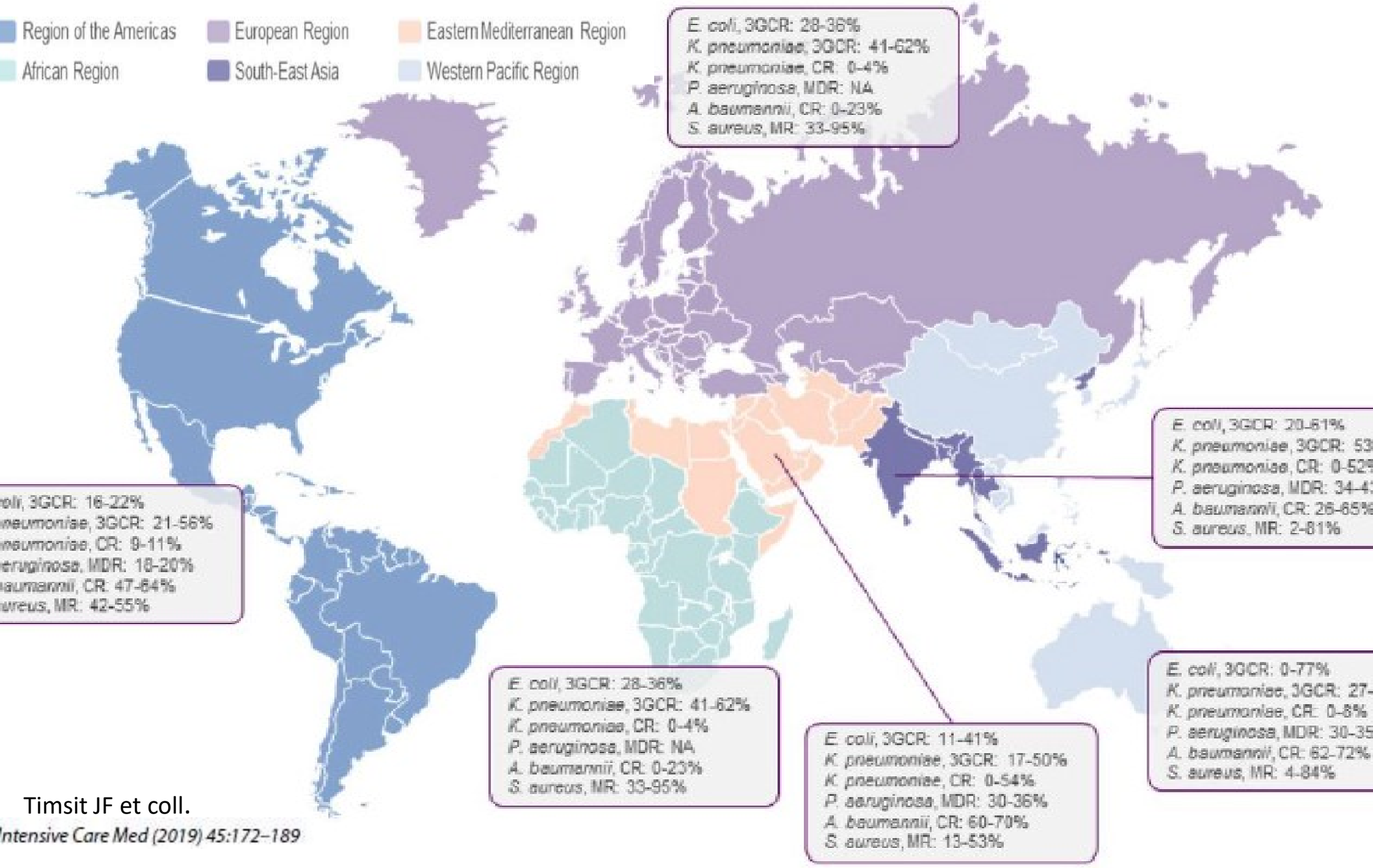
Infections à bacilles à Gram négatif multi-résistants: un défi permanent, nouvelles options thérapeutiques

Michel Wolff
Hôpital Sainte Anne Paris

ATR 30 novembre 2019

Liens d'intérêt

Type de lien	Compagnies
Expertises ponctuelles	Menarini
Orateur réunion scientifique	MSD, Pfizer
« Boards scientifiques »	MSD, Sanofi
« Chairman » DMC	MedImmune (AstraZeneca), INOTREM

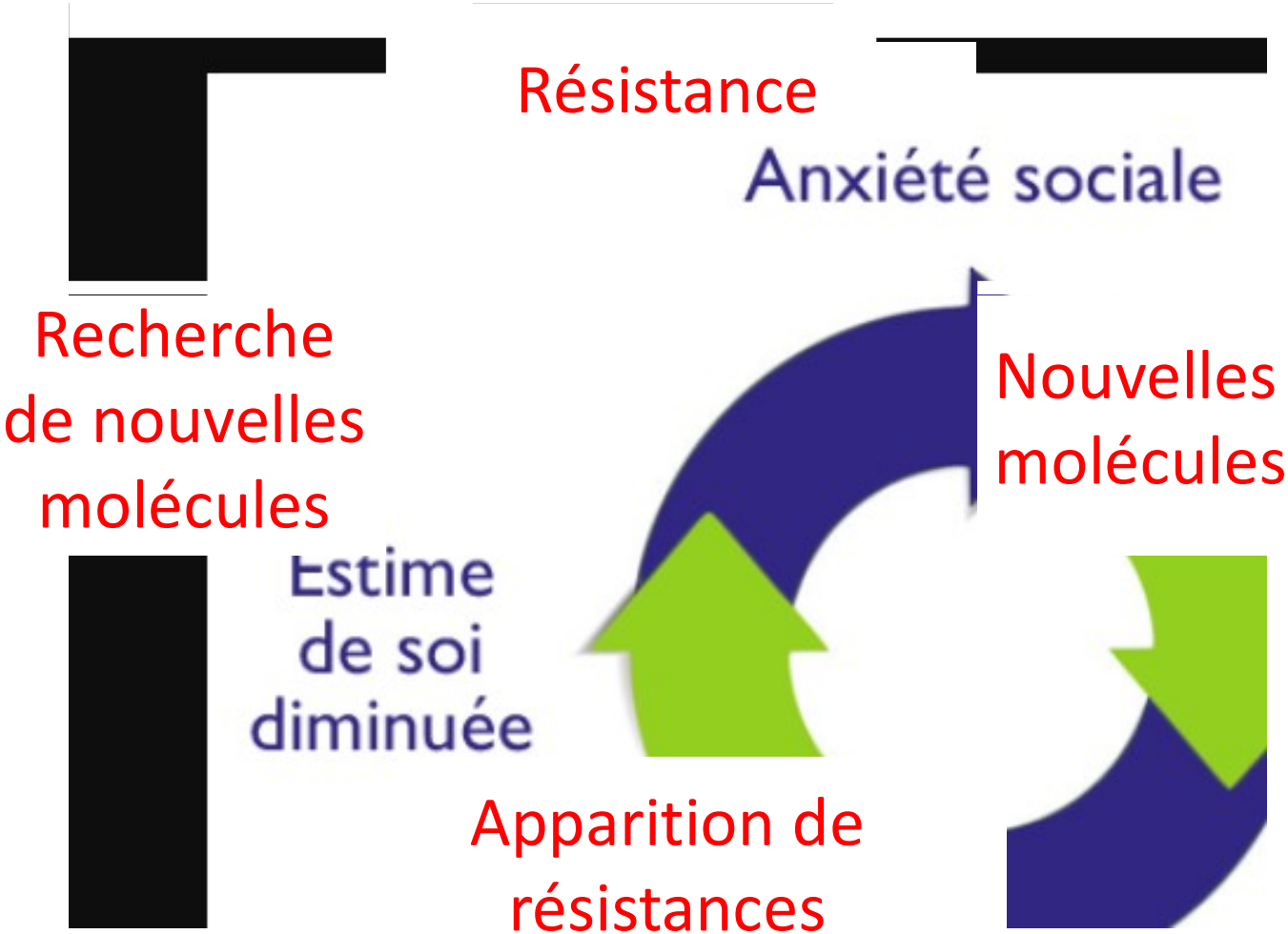


Timsit JF et coll.

Intensive Care Med (2019) 45:172–189

Rompre le cercle vicieux

révention
fections
révention
ansmission
roisée



« Antibioti
stewardshi

Intervention

All studies (N = 17)
Contact precautions (ie, at least use of dispo gowns and gloves) education/ monitoring
Active surveillance cultures[e]
Monitoring/audit of infection prevention and practices and feedback
Patient isolation or cohorting[f]
Hand hygiene education/monitoring
Environmental cleaning[g]
Antibiotic stewardship (eg, carbapenem rest
Environmental surveillance
Flagging positive patients in medical record promptly recognize readmissions/transfers
Daily chlorhexidine gluconate baths

Clinical Infectious Diseases

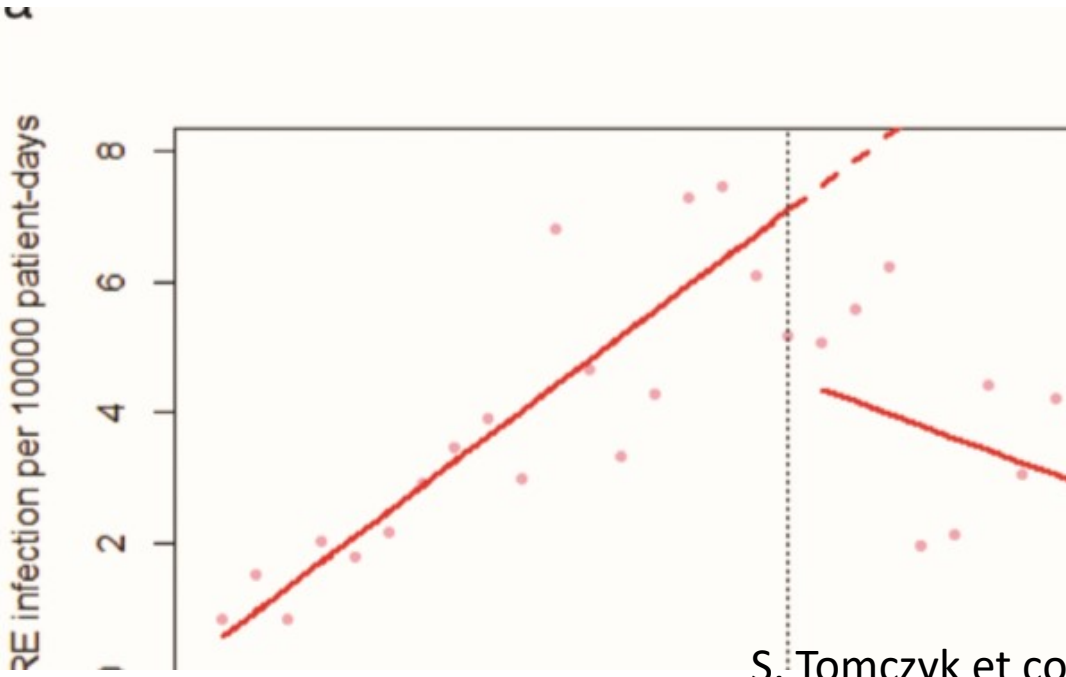
INVITED ARTICLE

IDSA Infectious Diseases Society of

HEALTHCARE EPIDEMIOLOGY: Robert A. Weinstein, Section Editor

Control of Carbapenem-resistant Enterobac *Acinetobacter baumannii*, and *Pseudomonas*

CID 2019:68 (1 March) • 88



S. Tomczyk et co

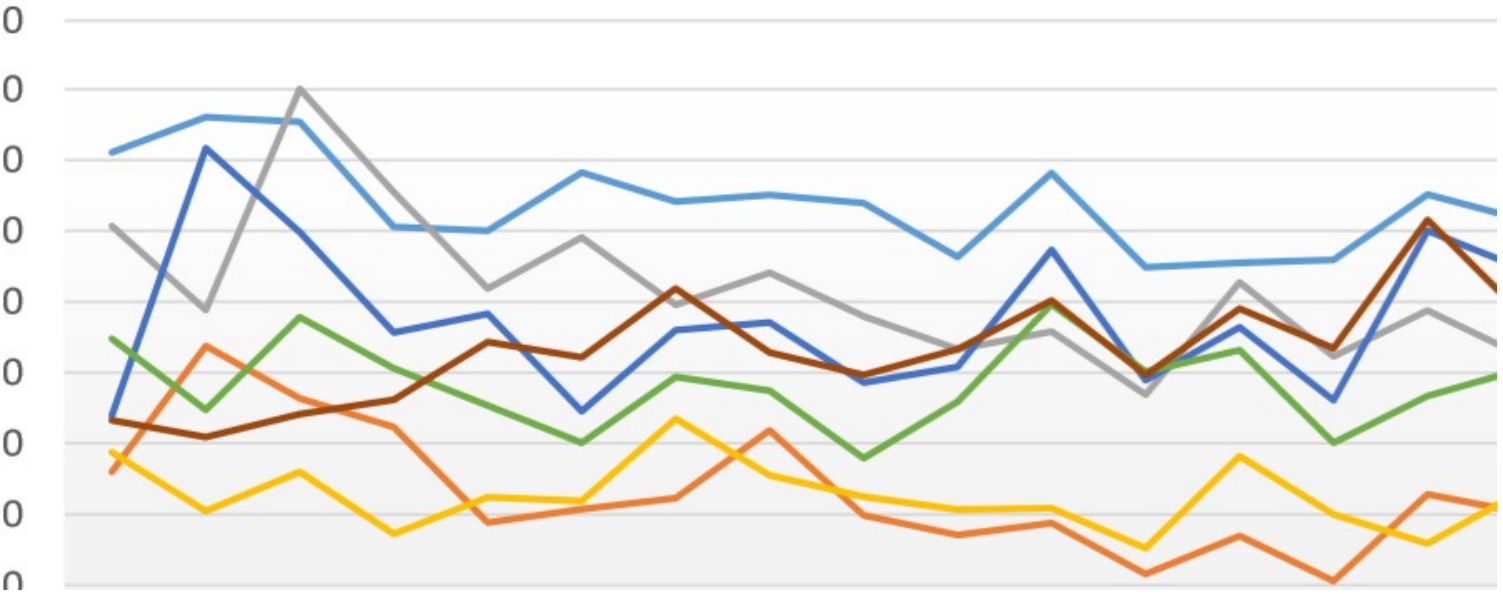
Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection
2019

journal homepage: www.clinicalmicrobiologyandinfectio

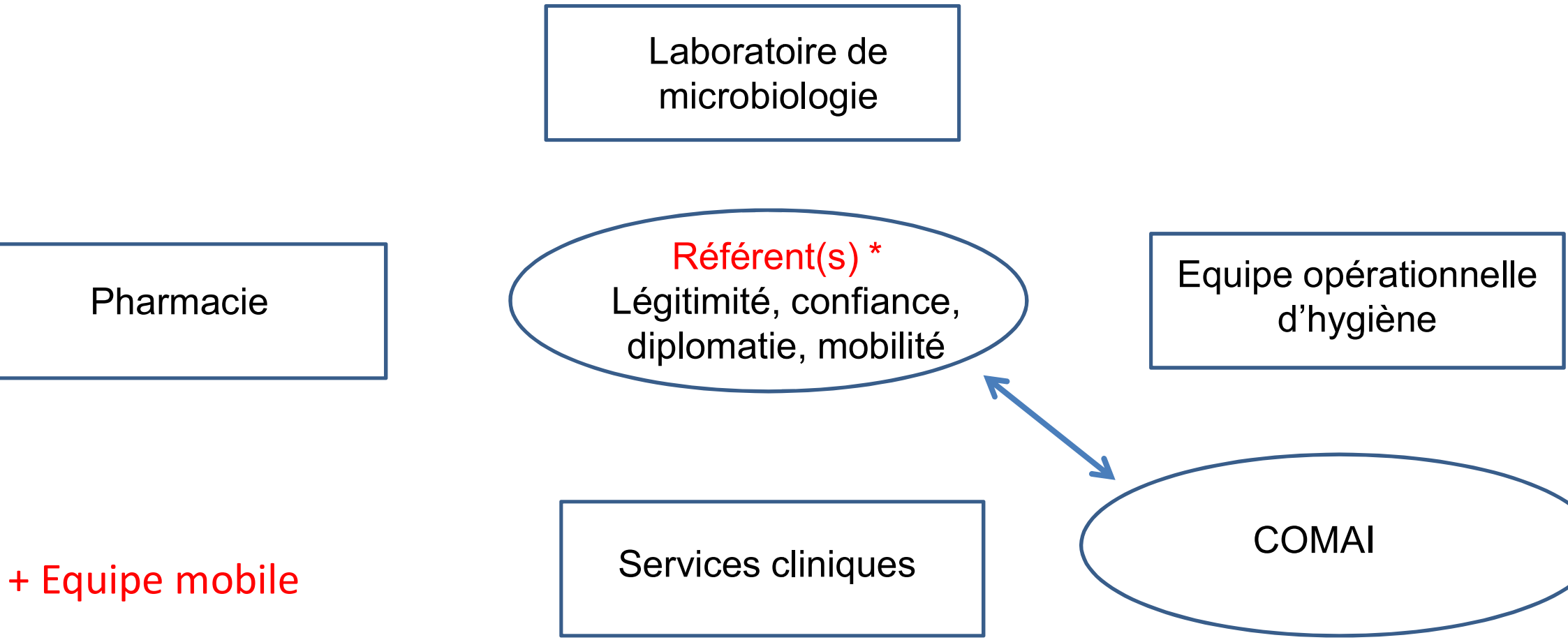
Original article



ID/1000 OBD	Trend QPC
ESBL-EC	**-1.4%**
CPE	**-5.6%**
MRSA	**-2.9%**
MDR-AB	-1.3%
ESBL-KP	-0.6%
MDR-PA	-0.4%

J Rodriguez-Bano et coll.

Un leadership et une approche multidisciplinair



Les nouvelles molécules : 6 dernières années

BL-IBL
Ceftolozane-tazobactam
Ceftazidime-avibactam

Céphalosporines
- Ceftaroline/ceftobiprole
- Cefiderocol

Glyco-lipopeptides
Dalbavancine
(Télavancine)

IDFR
Iclaprim

Cyclines
- Omadacycline
- Eravacycline

Pleuromutilines
Lefamuline

Oxazolidinones
Tédizolide

Fluoroquinolones
Délafloxacine

Aminosides
Plazomycine

β-lactamines/inhibiteurs de β-lactamases

	CEFTA-avibactam	CEFTO-tazobactam	IMI-relebactam	MERO/vaborbact
***eruginosa* résistant**				
nes	++	++	++	+
*p*C β -lactamase ⮝	++	++	++	++
mpes efflux	+/-	++	++	-
E				
X-M, TEM, SHV	++	+	++	++
***amp*C β-lactamase**	++	+/-	++	++

Entérobactéries résistantes aux C3 G et *P. aeruginosa* résistants

M. Wolff (communication personnelle), Bassetti M Curr Opin Infect Dis 2018, 31:177–1

Nosocomial pneumonia

	Ceftolozane-tazobactam (Aspect NP)	Ceftazidime-avibactam (Reprove)
opulation	HCAP/VAP (MV)	HCAP/VAP
patients	726	726
Dosing	2 g/1 g x 3	2 g/0,5g x 3
omparator	MERO: 1 g x 3	MERO: 1 g x 3
Status	Non-inferiority obtained	Non-inferiority obtained

MV: mechanical ventilation

REPROVE: BGN non sensibles à ceftazidime

alysis pulation	Study visit	Ceftazidime-avibactam	Meropenem	Difference (95% CI)
MITT	EOT	35/46 (76·1%)	39/54 (72·2%)	3·9 (–13·76, 20·82
	TOC	27/46 (58·7%)	27/54 (50·0%)	8·7 (–10·91, 27·56
IE	EOT	31/40 (77·5%)	36/49 (73·5%)	4·0 (–14·53, 21·67
	TOC	23/37 (62·2%)	21/41 (51·2%)	10·9 (–11·14, 31·9
E	EOT	26/33 (78·8%)	29/40 (72·5%)	6·3 (–14·22, 25·63
	TOC	21/30 (70·0%)	18/32 (56·3%)	13·8 (–10·49, 36·3

Torres A et coll.

Lancet Infect Dis 2018; 18: 285–95

Aspect NP: BGN résistants

	Ceftolozane–tazobactam group	Meropenem group
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)

MH Kolef et coll.

Clinical Infectious Diseases
MAJOR ARTICLE

IDSA
Infectious Diseases Society of Ar

Ceftolozane/Tazobactam vs Polymyxin or

VAP/HAP: 139/200: 69.5%

	C/T (n=100)	Coli/AG (n=100)	p	OR (95%CI
Clinical cure	81	61	0.002	2.72 (1.43–5.
ospital mortality	20	25	0.40	0.75 (0.38–1.
AKI	6	34	<0.001	0.12 (0.05–0.
Risk	2	8		
Injury	3	12		
Failure	1	14		
RTT	0	7		

Pogue JM et coll. 2019

β-lactamines/inhibiteurs de β-lactamases

	CEFTA-avibactam	CEFTO-tazobactam	IMI-relebactam	MERO/vaborbact
***eruginosa* résistant**				
nes	++	++	++	+
*p*C β -lactamase ↑	++	++	++	++
mpes efflux	+/-	++	++	-
E				
X-M, TEM, SHV	++	+	++	++
***amp*C β-lactamase**	++	+/-	++	++
bapénamases entérobactéries				
/CPE	++	-	++	++
A-48	++	- (sauf CAZ S)	?	-
talo-β-lactamases	-	-	-	-
RI (OXA-23)	-	-	-	-

M. Wolff (communication personnelle), Bassetti M Curr Opin Infect Dis 2018, 31:177–1

Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis

Han Zhong[a,1], Xian-Yuan Zhao[b,1], Zai-Li Zhang[a], Zhi-Chun Gu[a], Chi Zhang[a], Yuan Gao[b,*], Min Cui[a,*]

2018

CAZ-AVI versus comparateurs (carbapénèmes, colistine)
12 (9 RCT) 4951 patients

	RR	IC95%
Réponse clinique	0,99	0,96-1,02
Réponse clinique bactériémies	2,11	1,54-2,88
Eradication bactérienne	1,04	0,93-1,17
Réponse clinique CRE	1,61	1,13-2,29
Mortalité CRE	0,29	0,13-0,63

J Antimicrob Chemother 2018; **73**: 3170–3175
doi:10.1093/jac/dky295 Advance Access publication 7 August 2018

Journal of Antimicrobial Chemotherapy

Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Souza A, *et al*

Total number of patients	57
Demographic characteristics	
age, years, median (range)	64 (26–86)
sex male, *n* (%)	44 (77)
Charlson index, median (IQR)	3 (0–13)
neoplasia, *n* (%)	14 (24)
chronic renal disease, *n* (%)	12 (21)
creatinine clearance <30 mL/min, *n* (%)	7 (12)
surgery in the previous month, *n* (%)	33 (58)
Location at onset of infection	
ICU/reanimation unit, *n* (%)	22 (38)
surgical department, *n* (%)	16 (28)
Antibiotic treatment before CAZ/AVI	51 (89)

J Antimicrob Chemother 2018; **73**: 3170–3175
doi:10.1093/jac/dky295 Advance Access publication 7 August 2018

Journal of Antimicrobial Chemotherapy

Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Source of infection	
intra-abdominal, *n* (%)	16 (28)
pulmonary, *n* (%)	15 (26)
ventilator-associated, *n* (%)	7 (12)
urinary, *n* (%)	14 (25)
Bacteraemia, *n* (%)	26 (46)
Severity of infection	
sepsis/septic shock, *n* (%)	31 (54)
vasopressor use, *n* (%)	20 (35)
mechanical ventilation, *n* (%)	17 (30)
median APACHE-II (IQR)	24 (8–45)
INCREMENT-CPE score, median (IQR)	6 (2–13)

Monothérapie: 81%

Souza A, *et al*.

Principaux résultats

	Monothérapie (n=46)	Association (n=11)	p
Guérison clinique	37 (80)	7 (64)	0,44
Guérison microbio.	31 (67)	6 (54)	0,58
Mortalité J14	7 (15)	1 (9)	0,42
Mortalité J30	10 (22)	3 (27)	0,69
Rechute J90	4 (9)	2 (18)	0,35

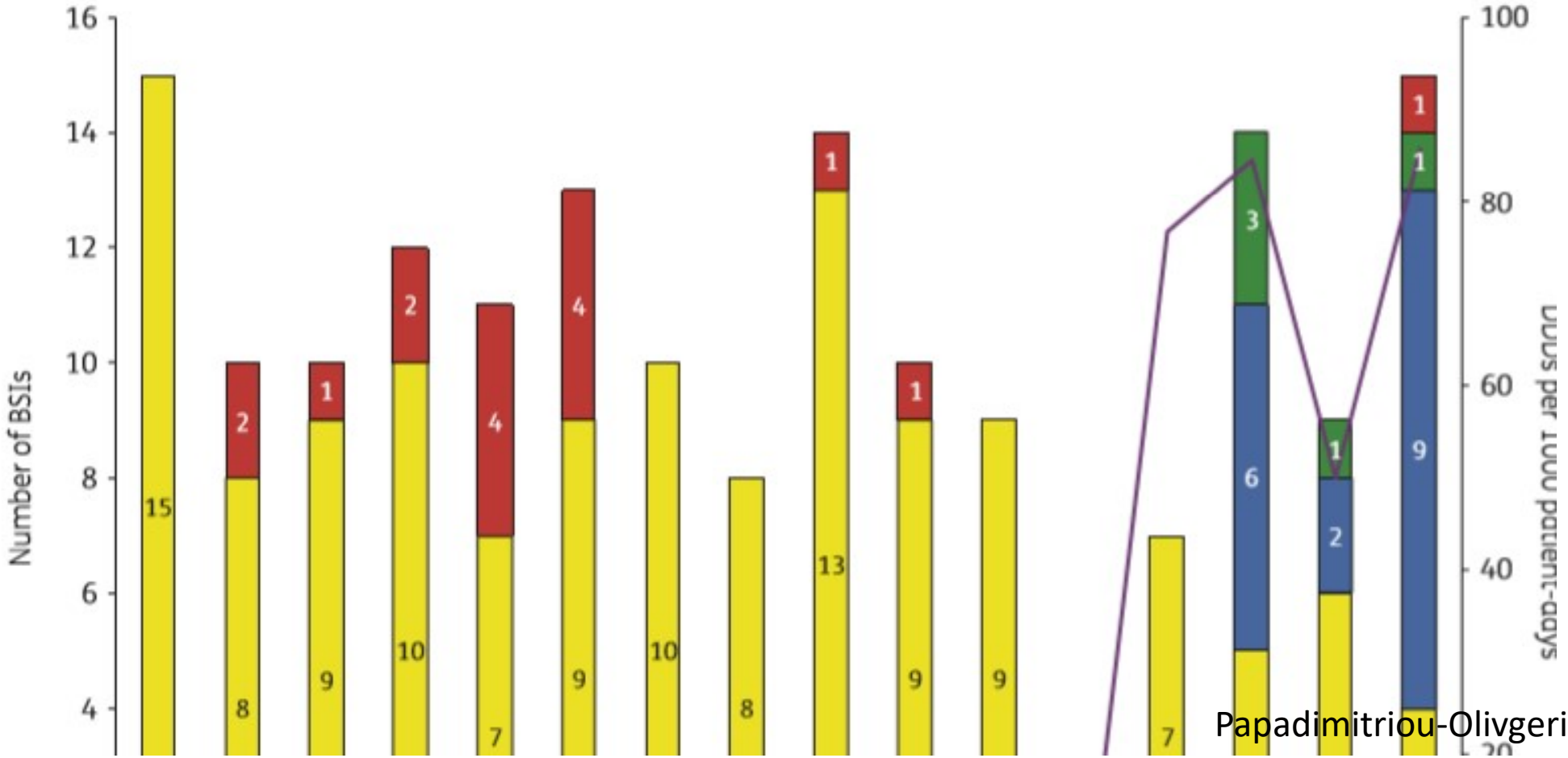
Pas d'émergence de souches résistantes

Facteur associé à la mortalité J14 en multivarié: INCREMENT- CPE > 7

2019

J Antimicrob Chemother
doi:10.1093/jac/dkz125

Reversal of carbapenemase-producing *Klebsiella pn*

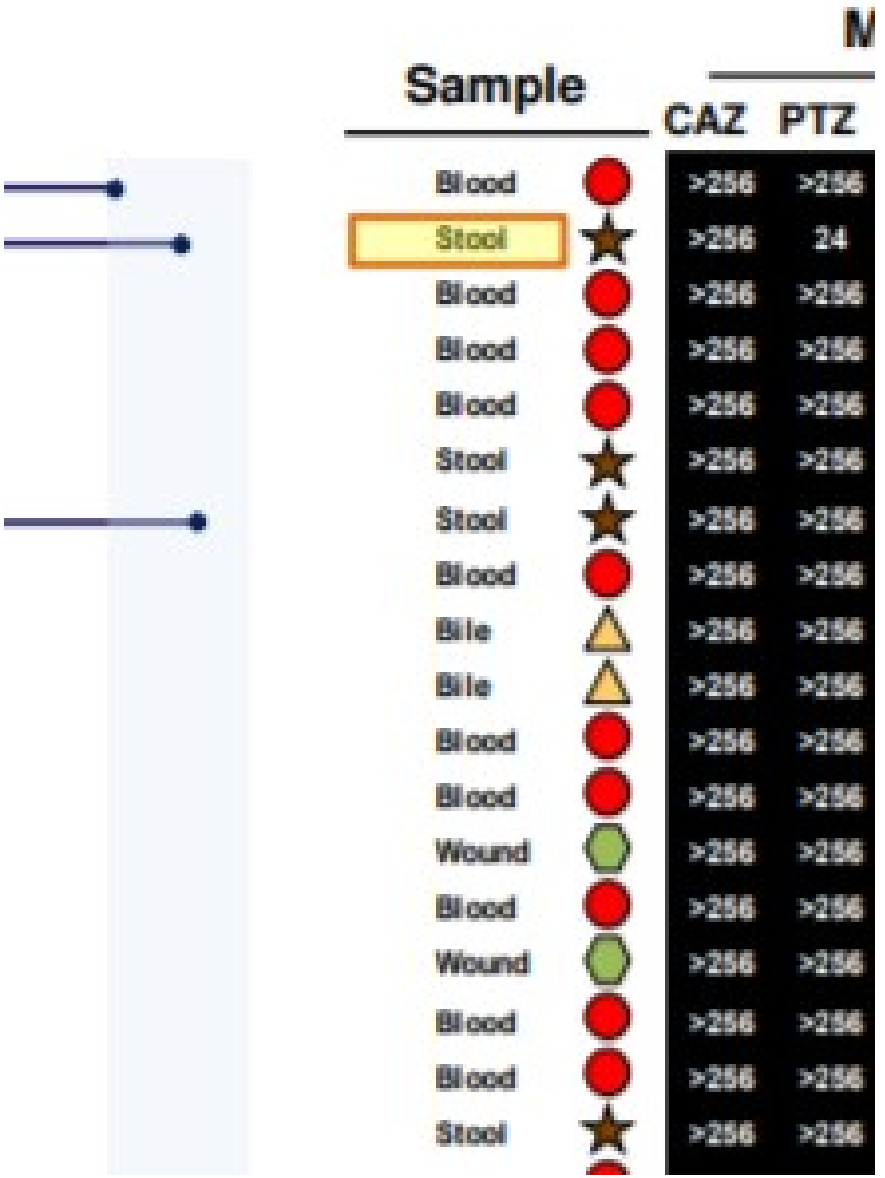


Papadimitriou-Olivgeri

C Accepted Manuscript Posted Online 21 October 2019

Research Article – Antimicrobial Agents and Chemothe

A 2.5-years within-patient evolution of a *Pseudom*

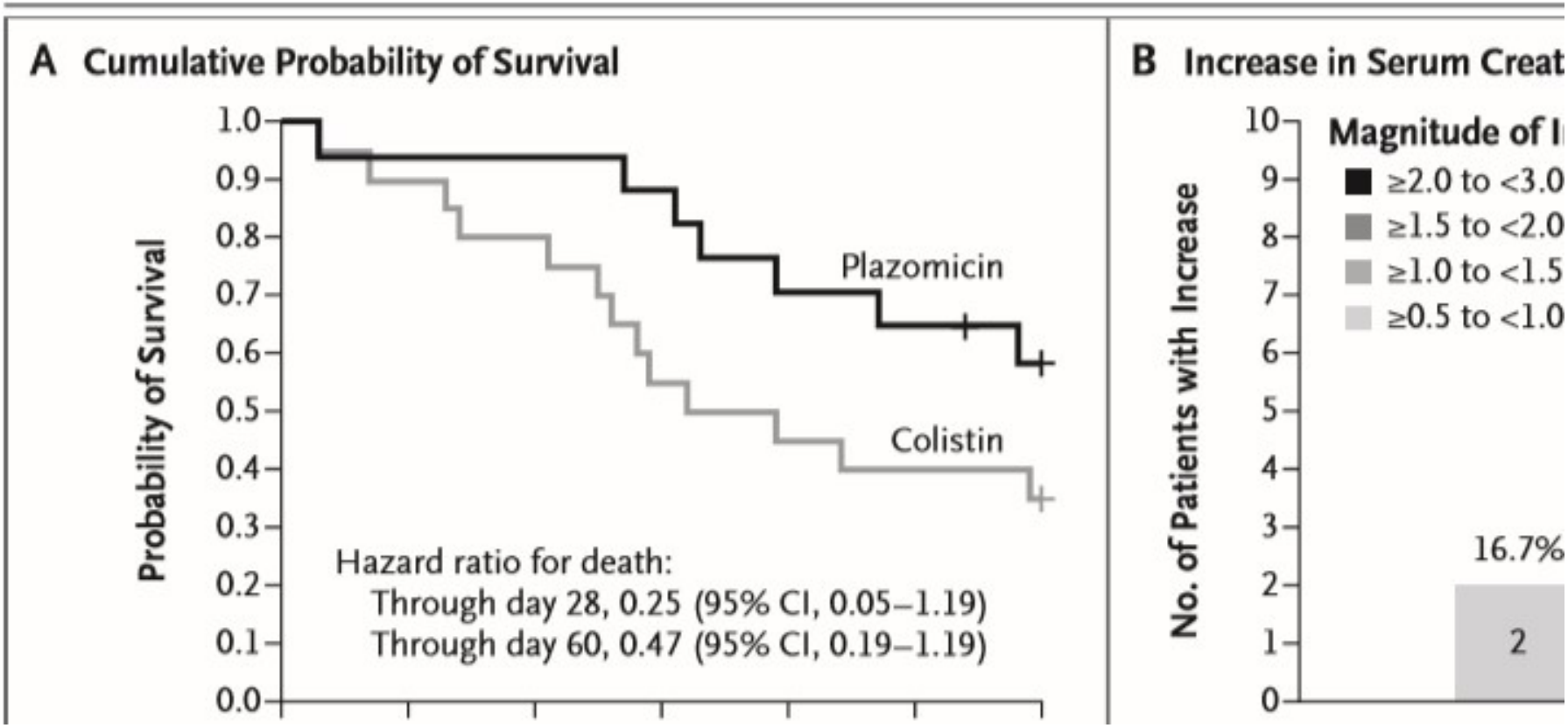


Antimicrobial

2018

Acquisition of Extended-Spectrum β-Lactama
to Resistance to Ceftolozane-Tazobactam Con

Pas de traitement préalable par C/T

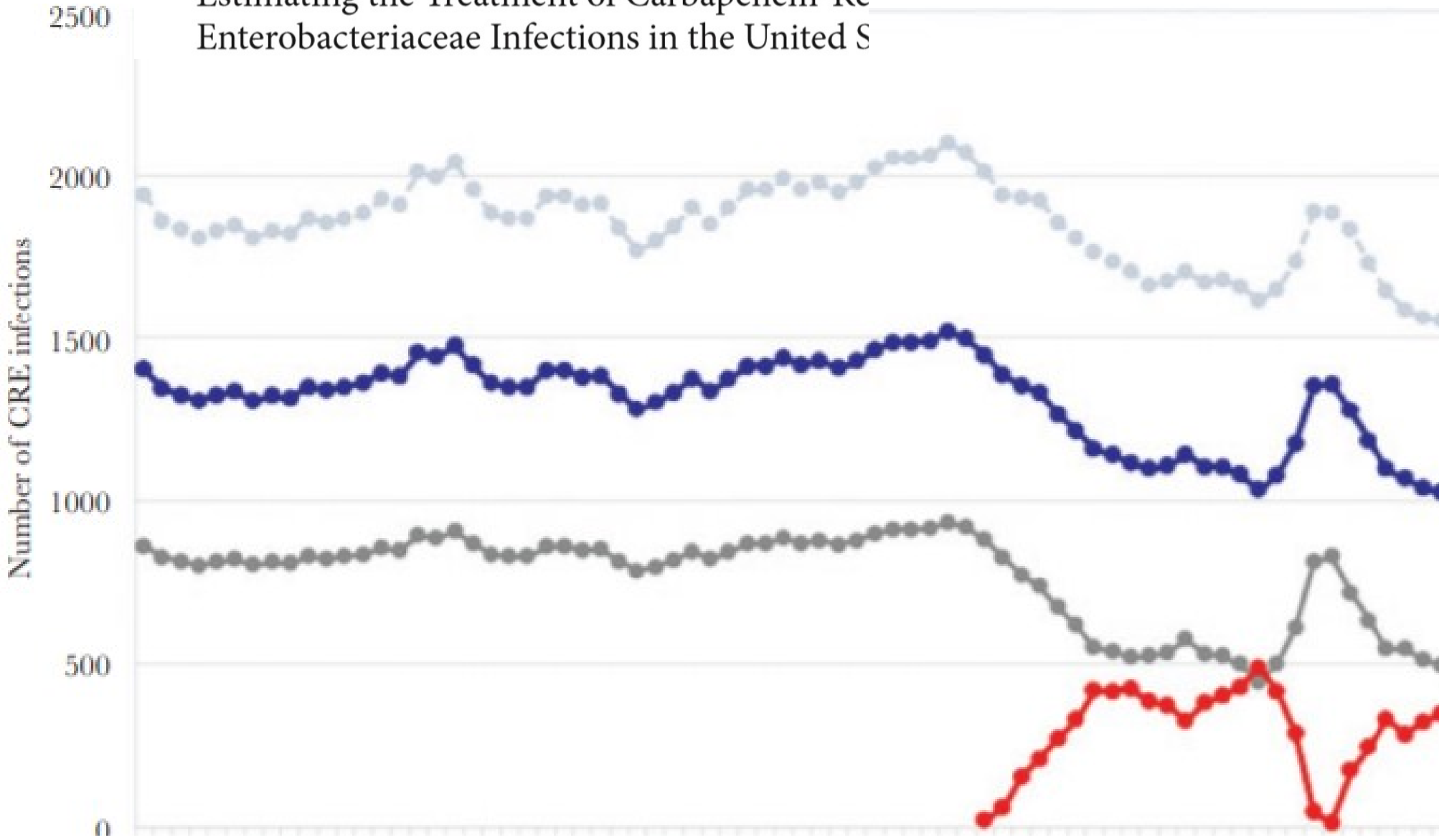

A Cumulative Probability of Survival
Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Plazomicin
Colistin
Hazard ratio for death:
Through day 28, 0.25 (95% CI, 0.05–1.19)
Through day 60, 0.47 (95% CI, 0.19–1.19)
B Increase in Serum Creat
No. of Patients with Increase
10
9
8
7
6
5
4
3
2
1
0
Magnitude of I
≥2.0 to <3.0
≥1.5 to <2.0
≥1.0 to <1.5
≥0.5 to <1.0
16.7%
2

Mc Kinnel JA

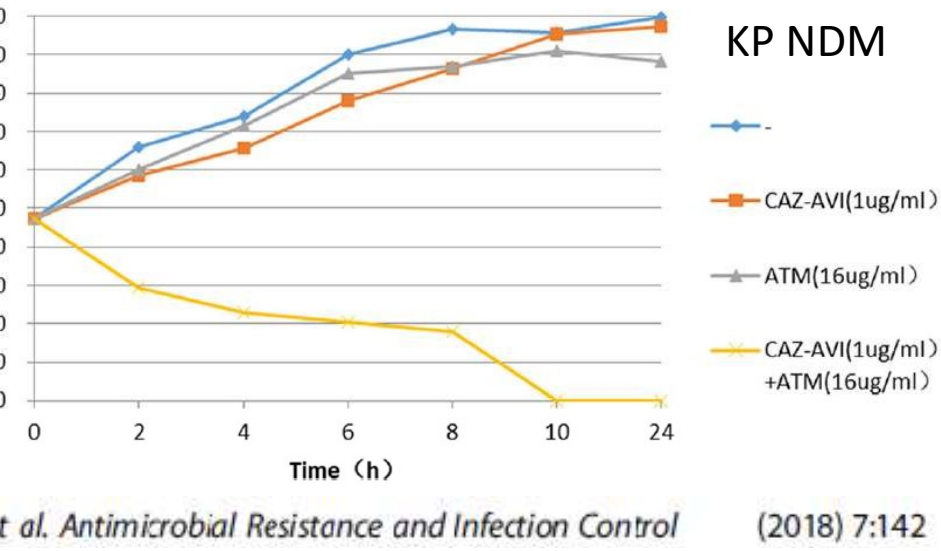
Open Forum Infectious Diseases 2019

MAJOR ARTICLE

Estimating the Treatment of Carbapenem-Re
Enterobacteriaceae Infections in the United S

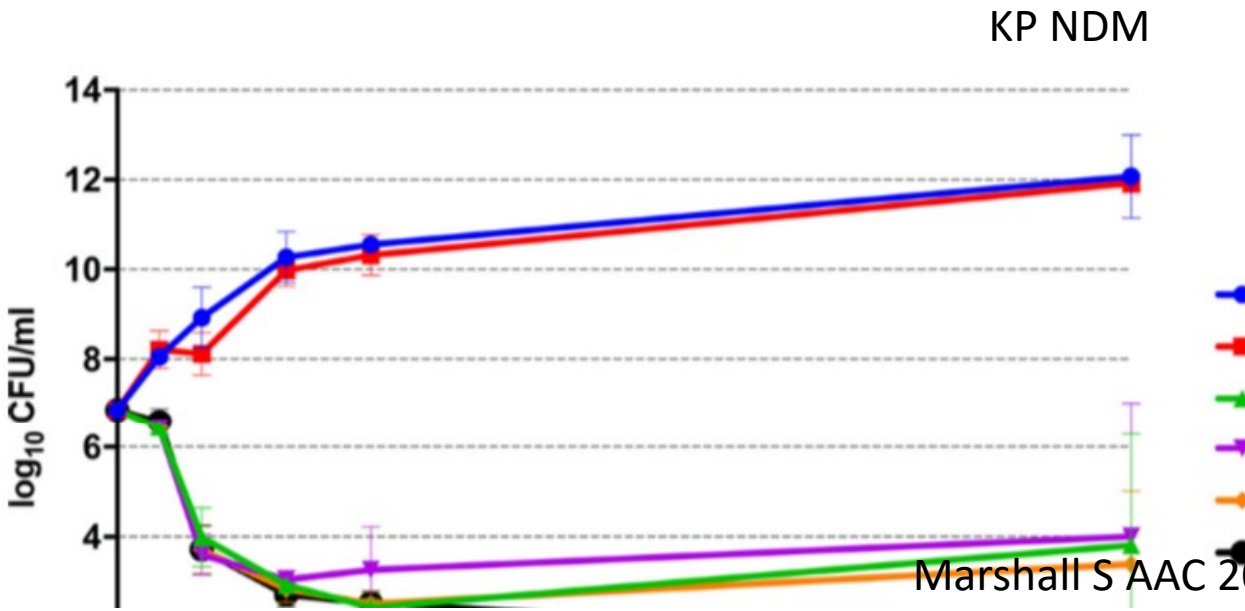


nfections graves à BGN MBL +: synergie CAZ-AVI/aztréonar



t al. Antimicrobial Resistance and Infection Control (2018) 7:142

Benchetrit L et coll 2019



Marshall S AAC 2

essful treatment of septic shock due to
1-producing *K. pneumoniae* using
zidime-avibactam combined with
onam in solid organ transplant recipients:
rt of 2 cases

Aztreonam plus Clavulanate, Tazobact

Synergie sur 50 Entérobactéries MBL+ = 8

(50% avec acide clavulanique)

Emeraud C AAC 2019

ort Communication

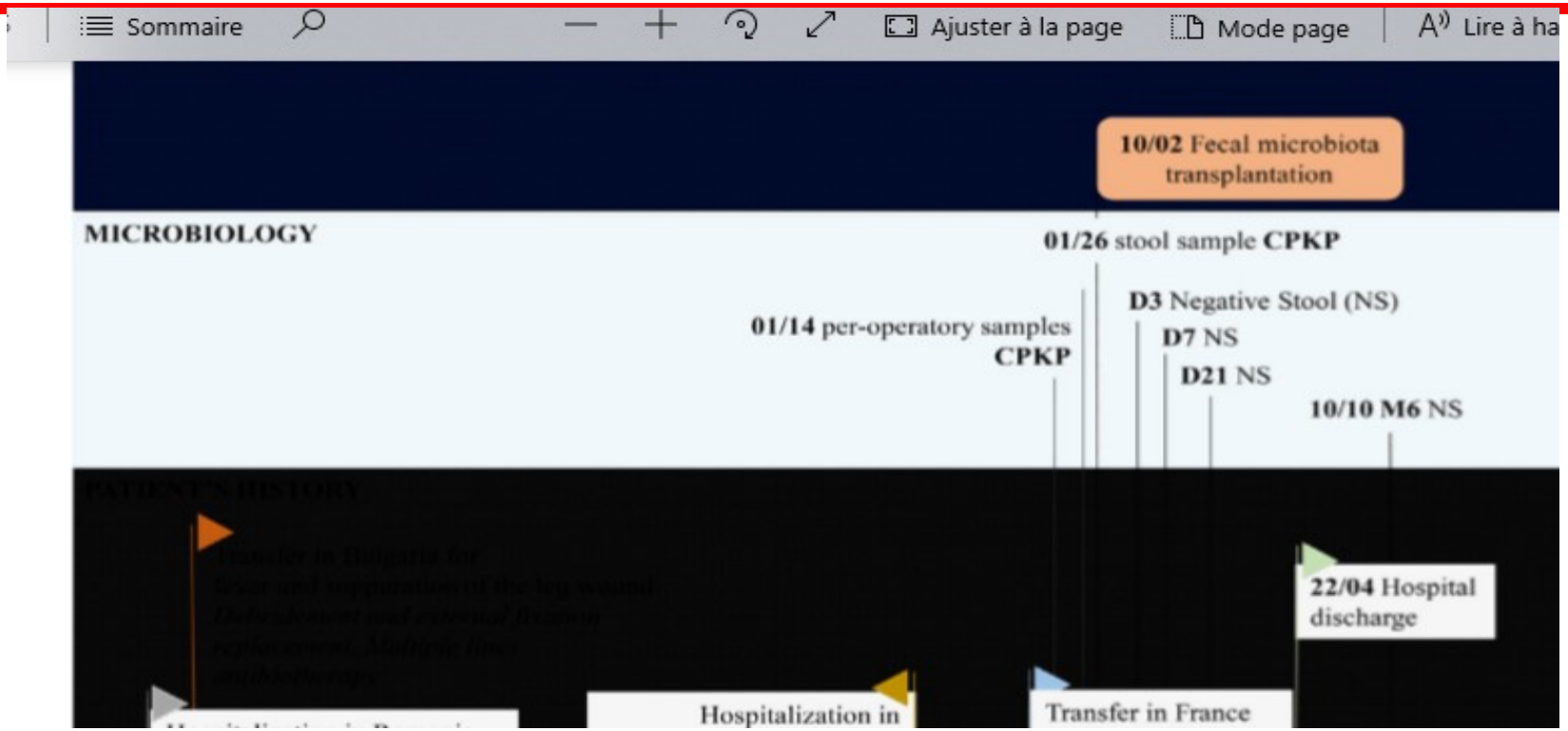
uccessful treatment and digestive decoloni
steitis caused by a carbapenemase-produci

Journal of Global Antimicrobial Resistance 18 (2019) 225–229

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resis

olistine IV (9 MUI puis 4,5 MUI x 2) + fosfomycine IV : 4 g x 3 + doxycycline
rale 100 mg/j pendant 3 mois puis transplantation fécale



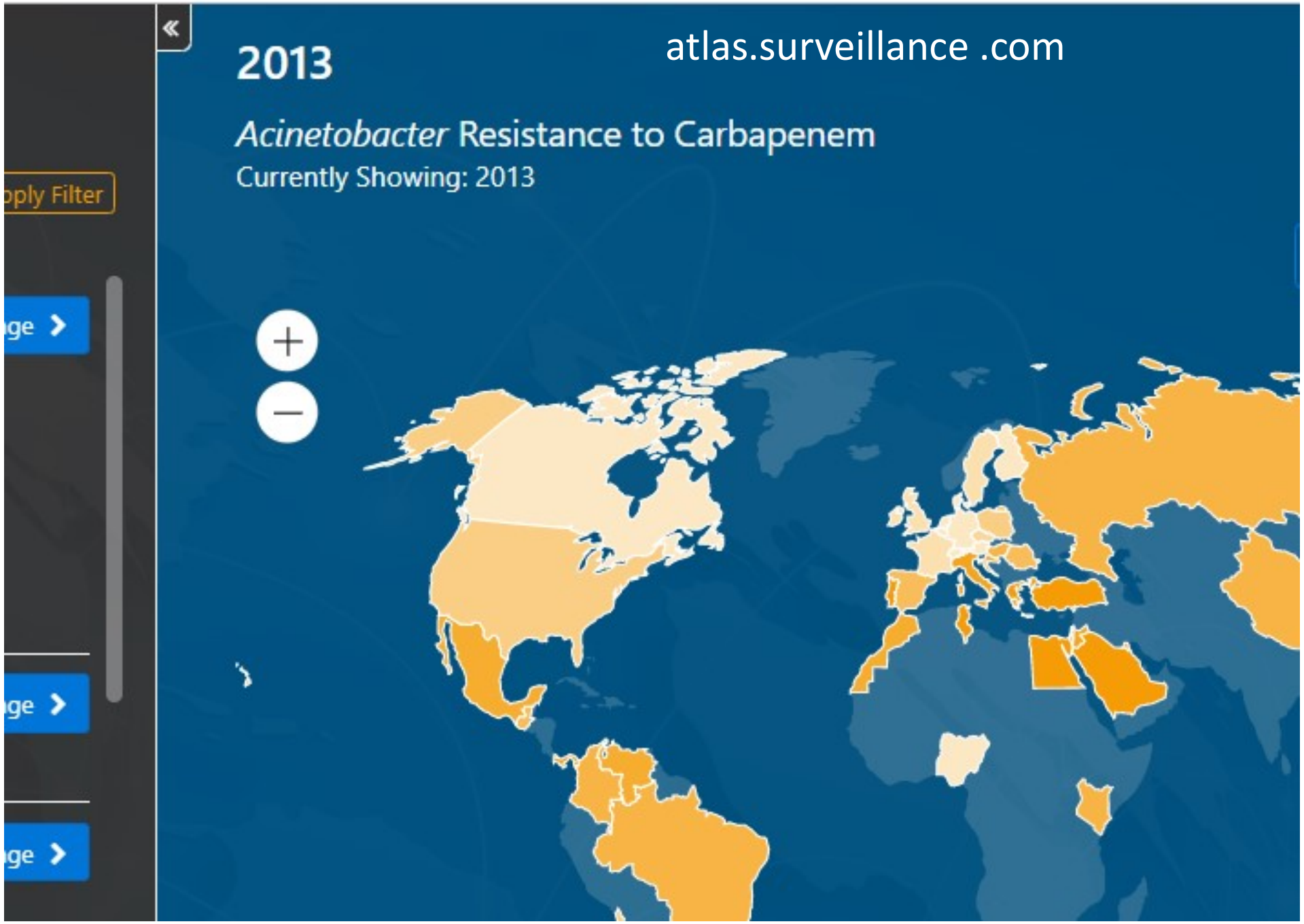
Diapositive 24

mW1 michel Wolff; 18/11/2019

β-lactamines/inhibiteurs de β-lactamases

	CEFTA-avibactam	CEFTO-tazobactam	IMI-relebactam	MERO/vaborbact
***eruginosa* résistant**				
nes	++	++	++	+
*p*C β -lactamase	++	++	++	++
npes efflux	+/-	++	++	-
E				
-M, TEM, SHV	++	+	++	++
***amp*C β-lactamase**	++	+/-	++	++
bapénamases entérobactéries				
/CPE	++	-	++	++
-48	++	- (sauf CAZ S)	?	-
tallo-β-lactamases	-	-	-	-
RI (OXA-23)	-	-	-	-

M. Wolff (communication personnelle), Bassetti M Curr Opin Infect Dis 2018, 31:177–1


2013
atlas.surveillance .com
Acinetobacter Resistance to Carbapenem
Currently Showing: 2013
pply Filter

Open Forum Infectious Diseases
SUPPLEMENT ARTICLE 2019;6(S1):S34–46
IDSA Infectious Diseases Society of America

Antimicrobial Susceptibility of *Acinetobacter ca*
Acinetobacter baumannii Complex and *Stenotro*
maltophilia Clinical Isolates: Results From the S

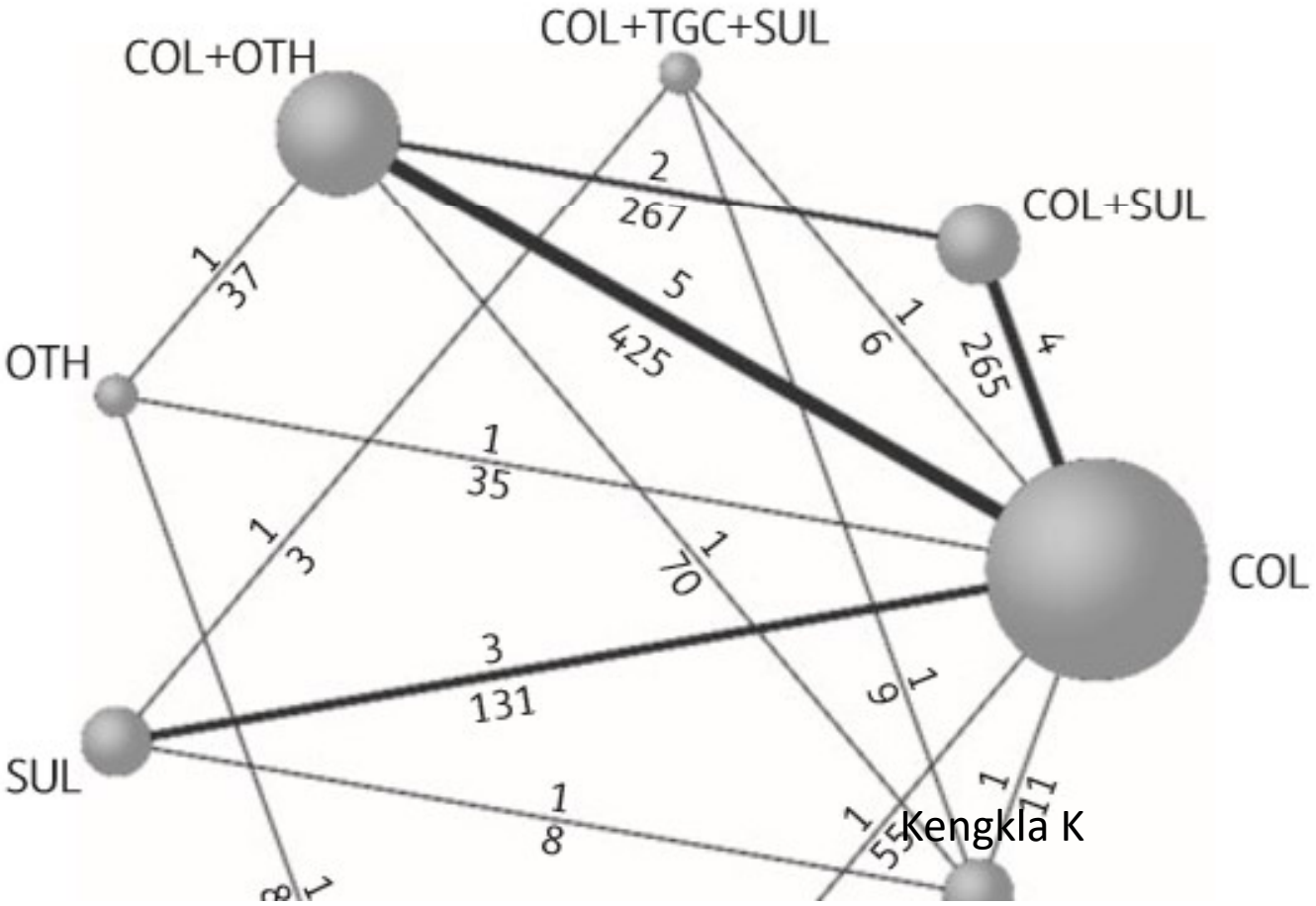
Acinetobacter % de souches XDR

	2009-2012	2013-2016
Asie-pacifique	80	73
Europe	71	79
Amérique latine	77	87
Amérique du nord	54	41

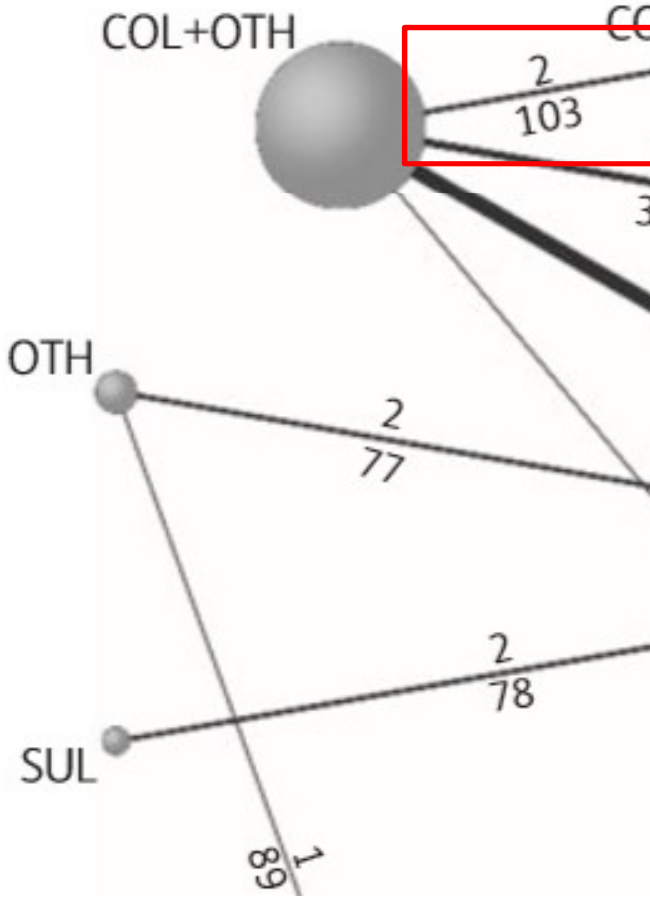
J Antimicrob Chemother 2018; **73**: 22–32
doi:10.1093/jac/dkx368 Advance Access publication 24 October 2017

Comparative efficacy and safety of treatment option

(a) Clinical cure



(b) Microbiological cure



Kengkla K

olistin alone versus colistin plus meropenem for trea
f severe infections caused by carbapenem-resistant

Paul M Lancet Infect Dis 2018; 18: 391–400

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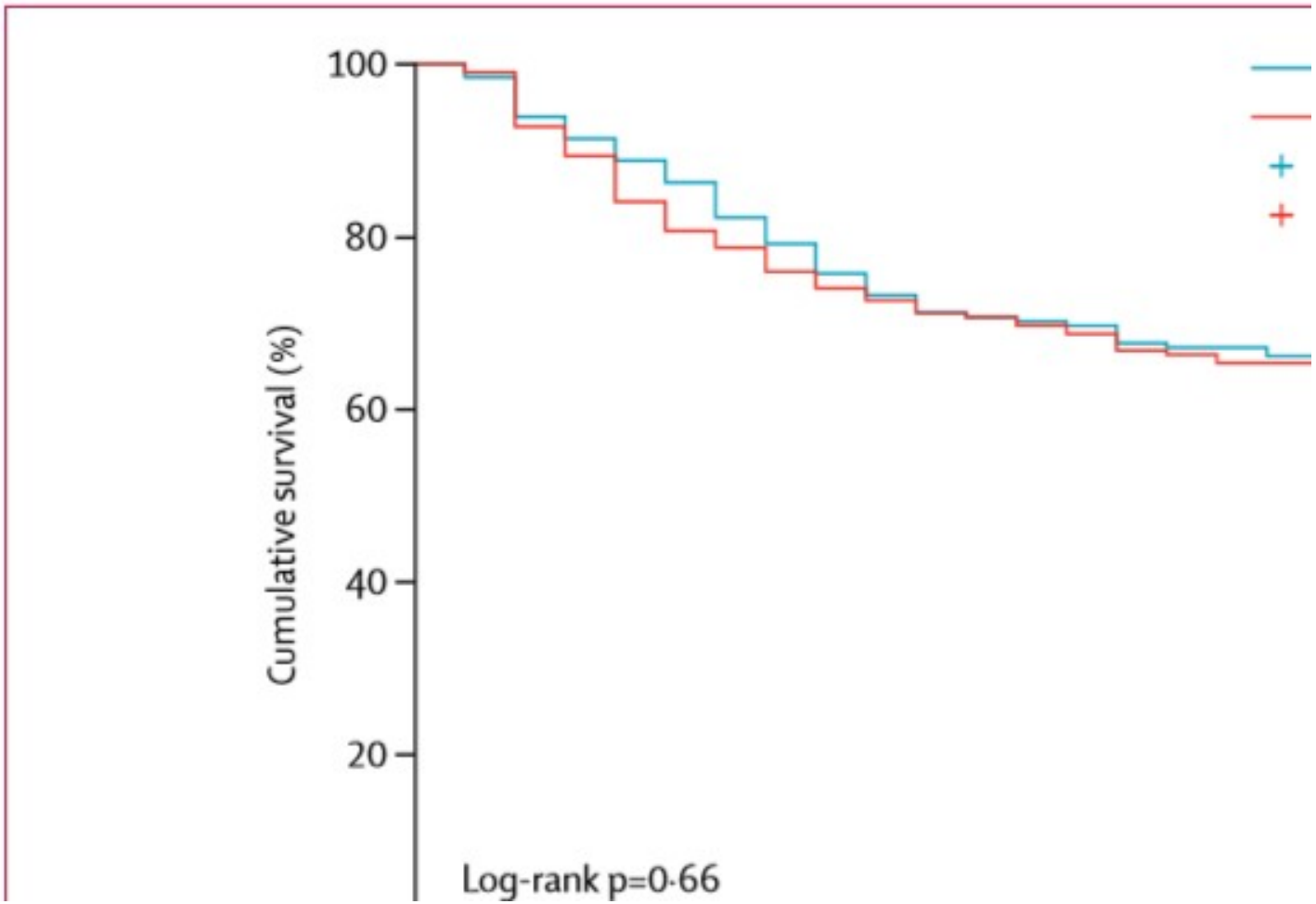
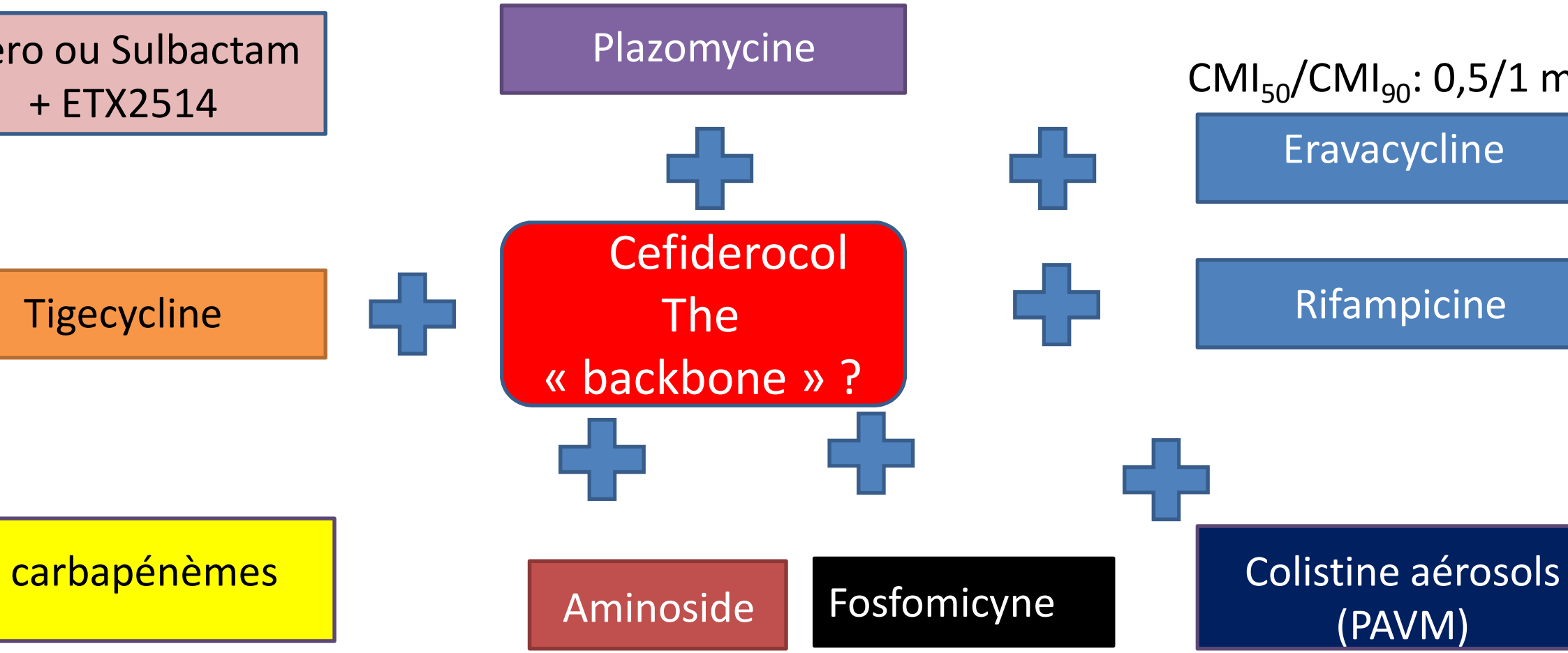
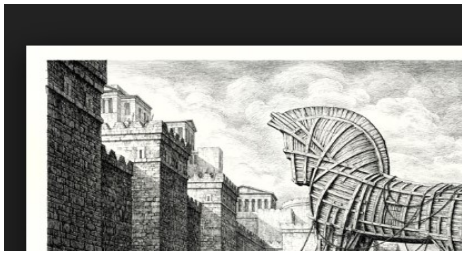


A. baumannii résistant aux carbapénemes le futur ?



M. Wolff (communication personnelle), * Seifert et coll. IJAA 2019;

Cefiderocol : *in-vitro* activity



	n isolates	MIC $_{50}$ mcg/ml	MIC$_{90}$ range mcg/m
*coli- M*ero R	72	2	0.015-4
pneumoniae-Mero R	689	4	0.004-32
*terobacte*r spp –Mero R	159	8	0.06-32
DR *P. aeruginosa*	262	2	0.002-32
DR *A. baumannii*	368	8	0.015- >256
DR *S. maltophilia*	218	0.25	0.015- >256
cepacia complex	40	0.12	0.002-32

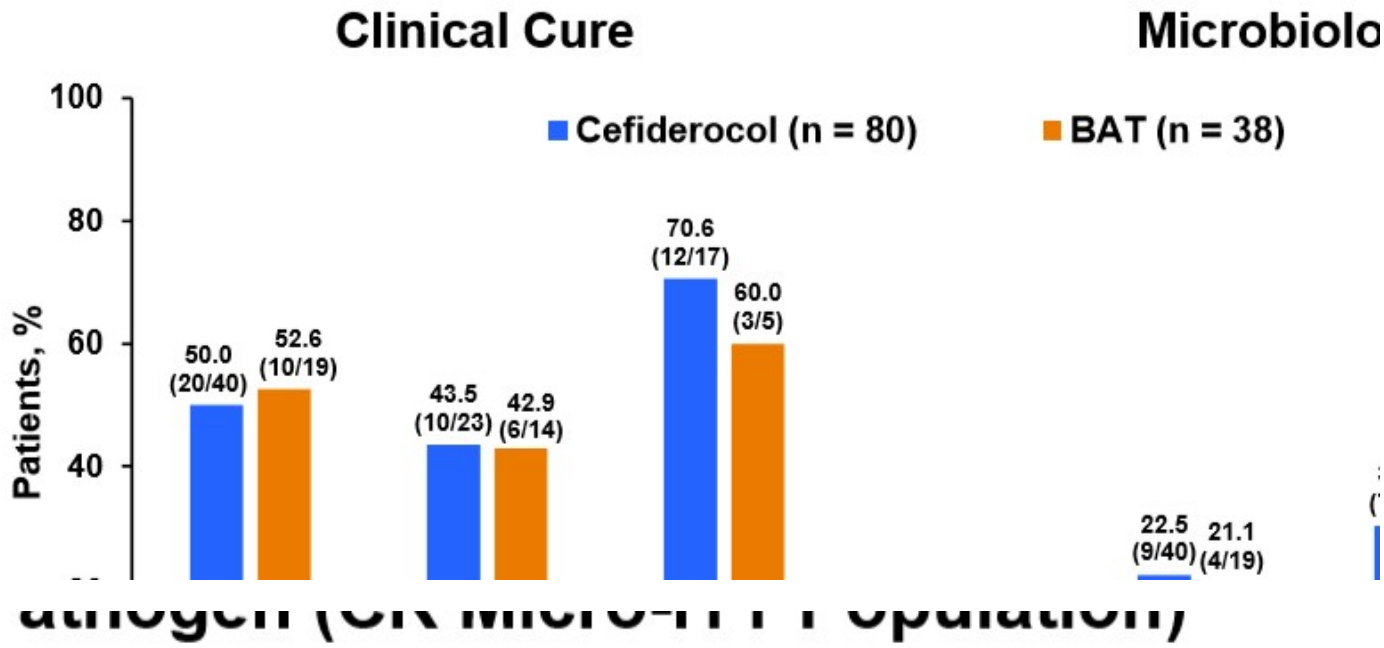
s stable vis-à-vis des différentes carbapénèmases (KPC, NDM, VIM, IMP, OXA)

Jim Lewis, Infectious Disease Forum, Rome 16 November 201

Cefiderocol

October 16, 2019

Figure 22 **CREDIBLE-CR Primary Endpoints at TO Site (CR Micro-ITT Population)**



Pathogen (CR Micro-ITT Population)

TOC	Cefiderocol n = 80 n/N (%)	
Clinical cure		
CR *A. baumannii*	16/37 (43.2)	

Ne pas oublier les molécules anciennes ou à spectre plus étroit: ex EBLSE: HAS France 2019

Molécules	Utilisation
Pipéracilline-Tazobactam (4g x 4/24h)	HAP-VAP non graves ou en relais si CMI (milieu liquide) ≤ 4 mg/L)
Céfoxitine: 4-6 g/24h	Infections urinaires à *E.coli*
Temocilline: 4-6 g/24h	Infections urinaires
Amoxicilline-acide clavulanique: 2 g x 3	Infections urinaires

Les nouvelles approches anti-infectieuses

Approches	Limites
Anti-virulence	Ciblée : *P. aeruginosa*, *S. aureus*, *C. diffi*
Phagothérapie Vaccins	Peu adaptés aux situations aigues
Nanoparticules	Très exploratoire mais une révolution future ???
Microbiote digestif - Probiotiques - Manipulations chimiques - Transplantation fécale	Nous sommes à la fin du commencement...

Sites suggérés ▾ clear1x1[1].gif

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾

Home > Search Results > Study Record Detail

Trial record **6 of 27** for: evade

◂ Previous Study | Return to List | Next Study ▸

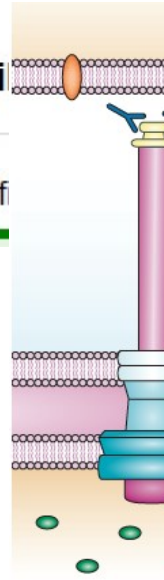
Effort to Prevent Nosocomial Pneumonia Caused by Pseudomonas Aeruginosa in Mechanically Venti

ClinicalTrials.gov Identif

Intervention Model: Parallel /

Masking: Quadrup

Primary Purpose: Preventi



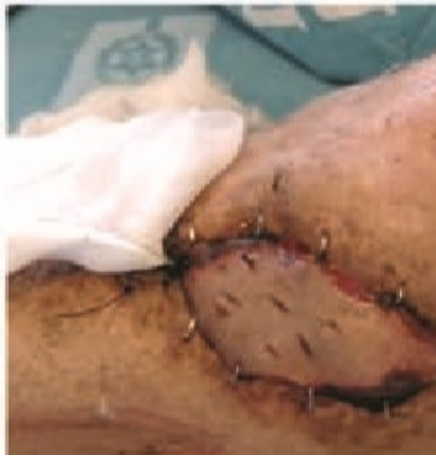
- Etude de phase II, preuve de concept
- Tolérance et efficacité d'une dose unique d'anticorps anti-PcrV pour la prévention des PAVM à *P. aeruginosa* chez les malades colonisés
- n de patients à inclure: 429

Clinical Infectious Diseases® 2019;XX(XX):1–4

Clinical Infectious Diseases

BRIEF REPORT

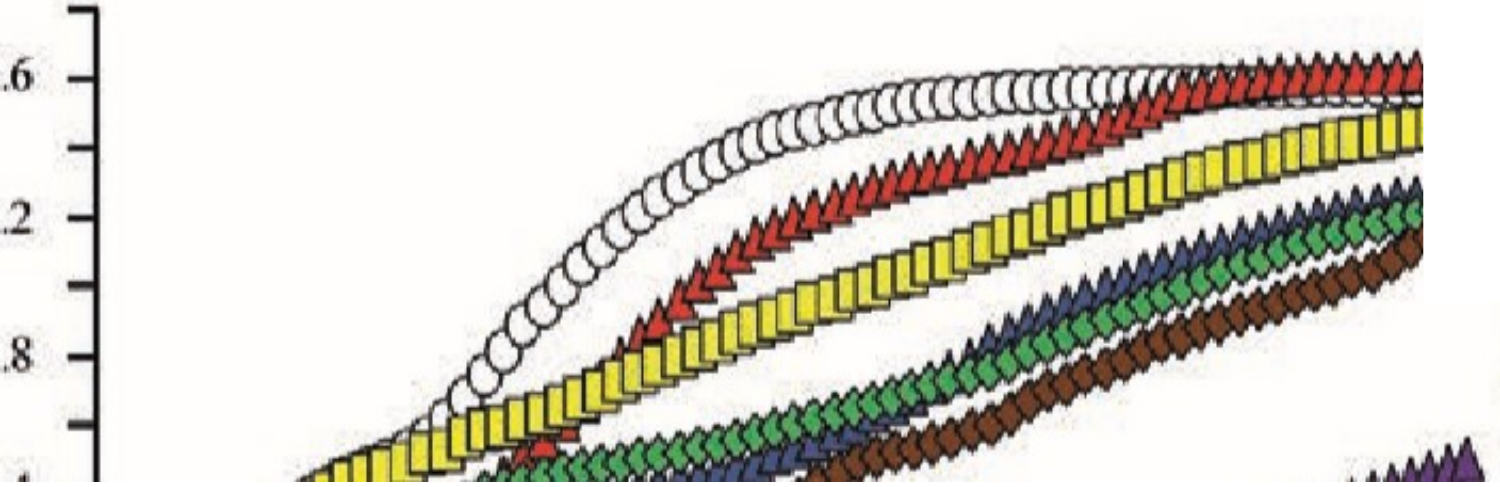
R Nir-Paz et *al*.

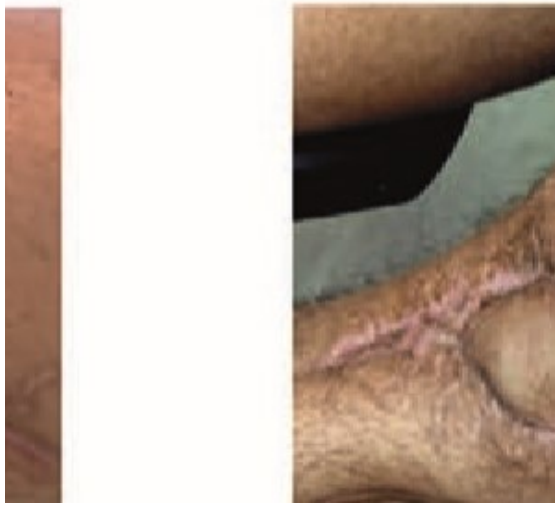


Successful Treatment of Antibi
resistant, Poly-microbial Bone

A. baumannii XDR

B. *AbKT722*





Conclusions

L’arrivée de nouvelles molécules permet d’envisager un peu plus sereinement le traitement des infections graves à bactéries multi et hautement résistantes

L’utilisation de ces nouvelles molécules doit s’inscrire dans le cadre du bon usage des antibiotiques (probabiliste raisonné, documenté++, désescalade…) et de la prévention (infection et transmission croisée)

Des thérapeutiques « non antibiotiques » sont en cours de développement.

L’avenir dira si elles pourront jouer un rôle important dans la prévention ou le traitement d’infections graves.