Antibiothérapie *vintage*

ou comment des molécules délaissées ont une nouvelle vie

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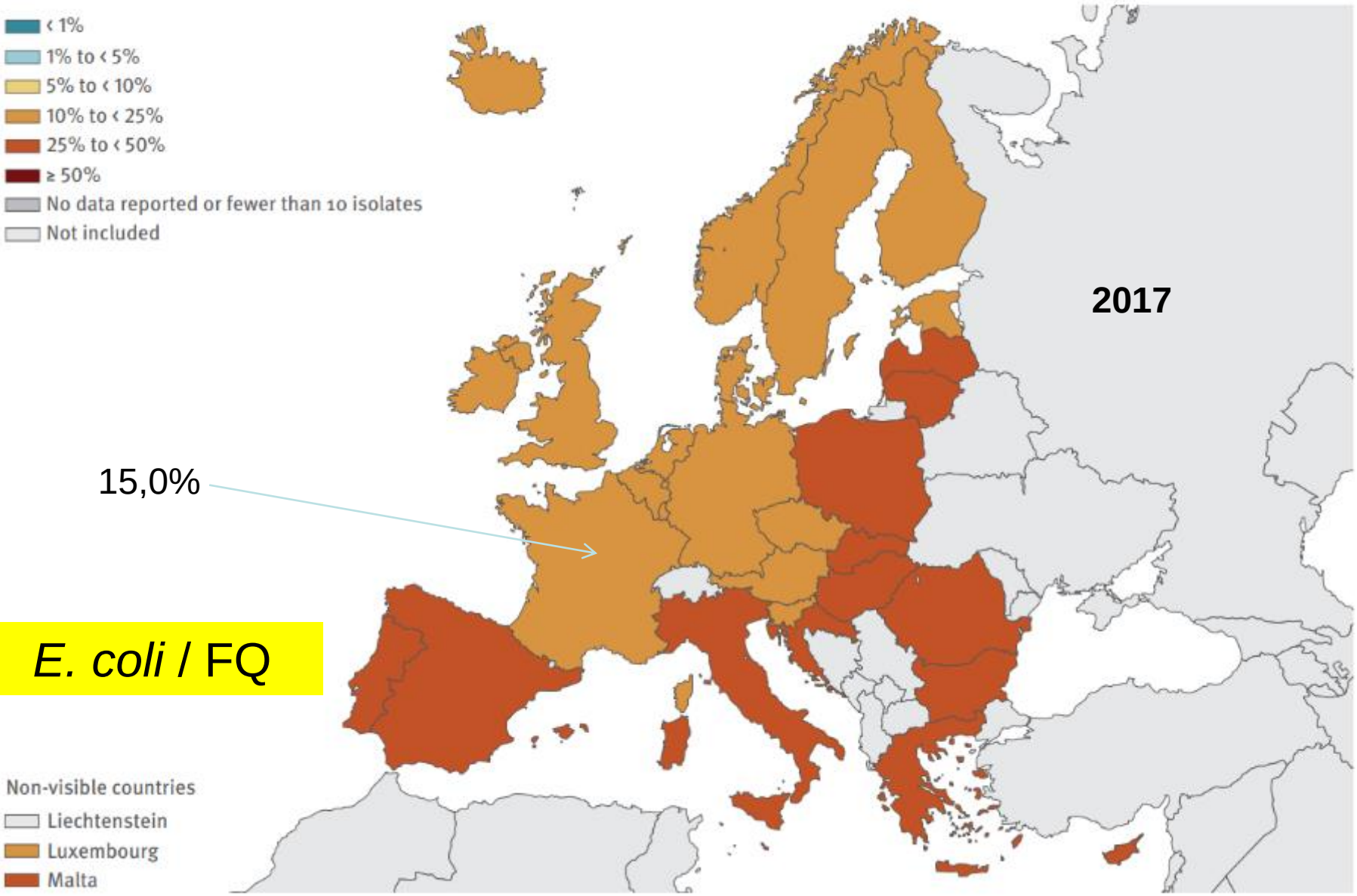
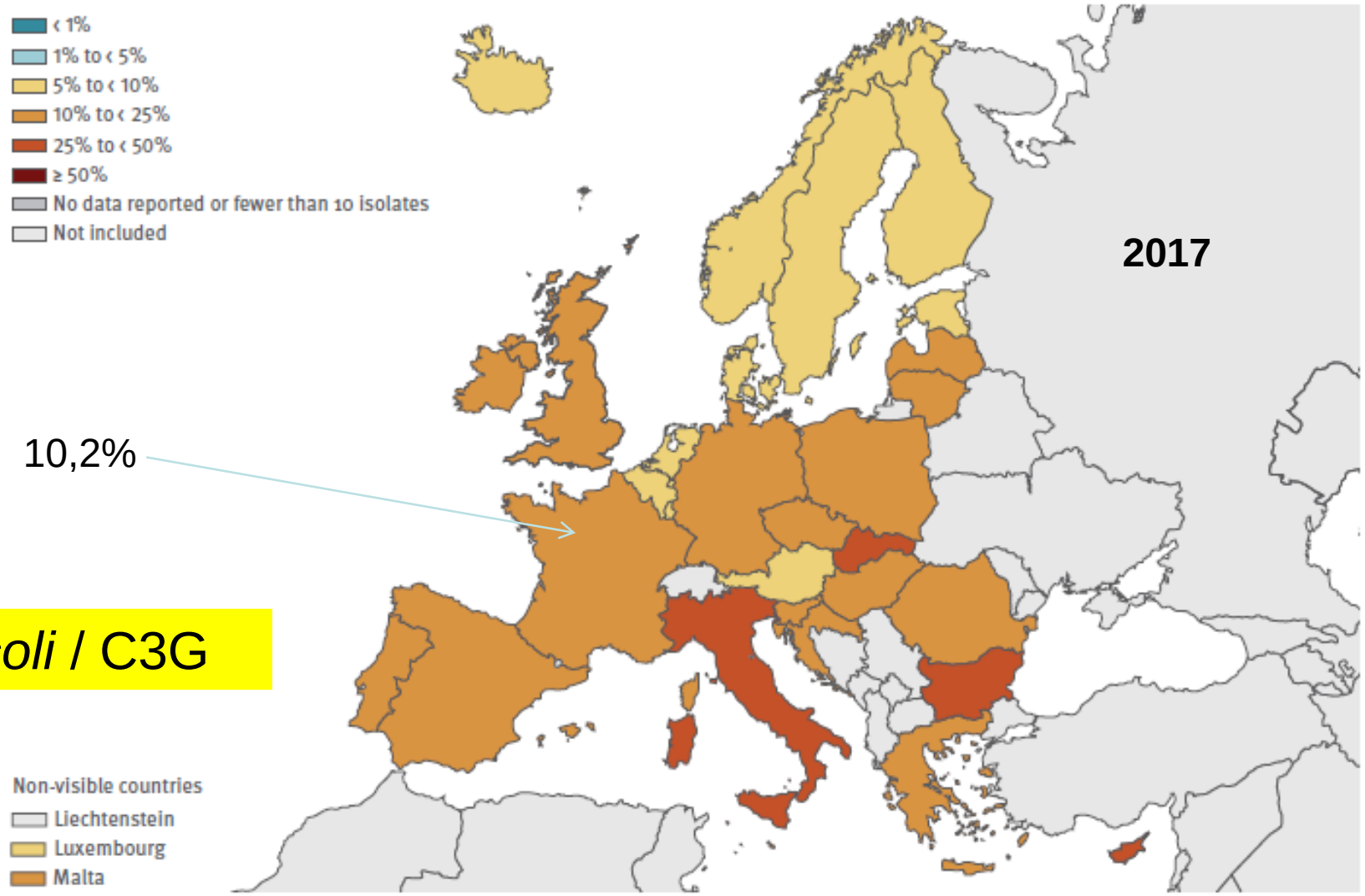
DU de thérapeutique anti-infectieuse
24 janvier 2019

Figure 3.2. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2017



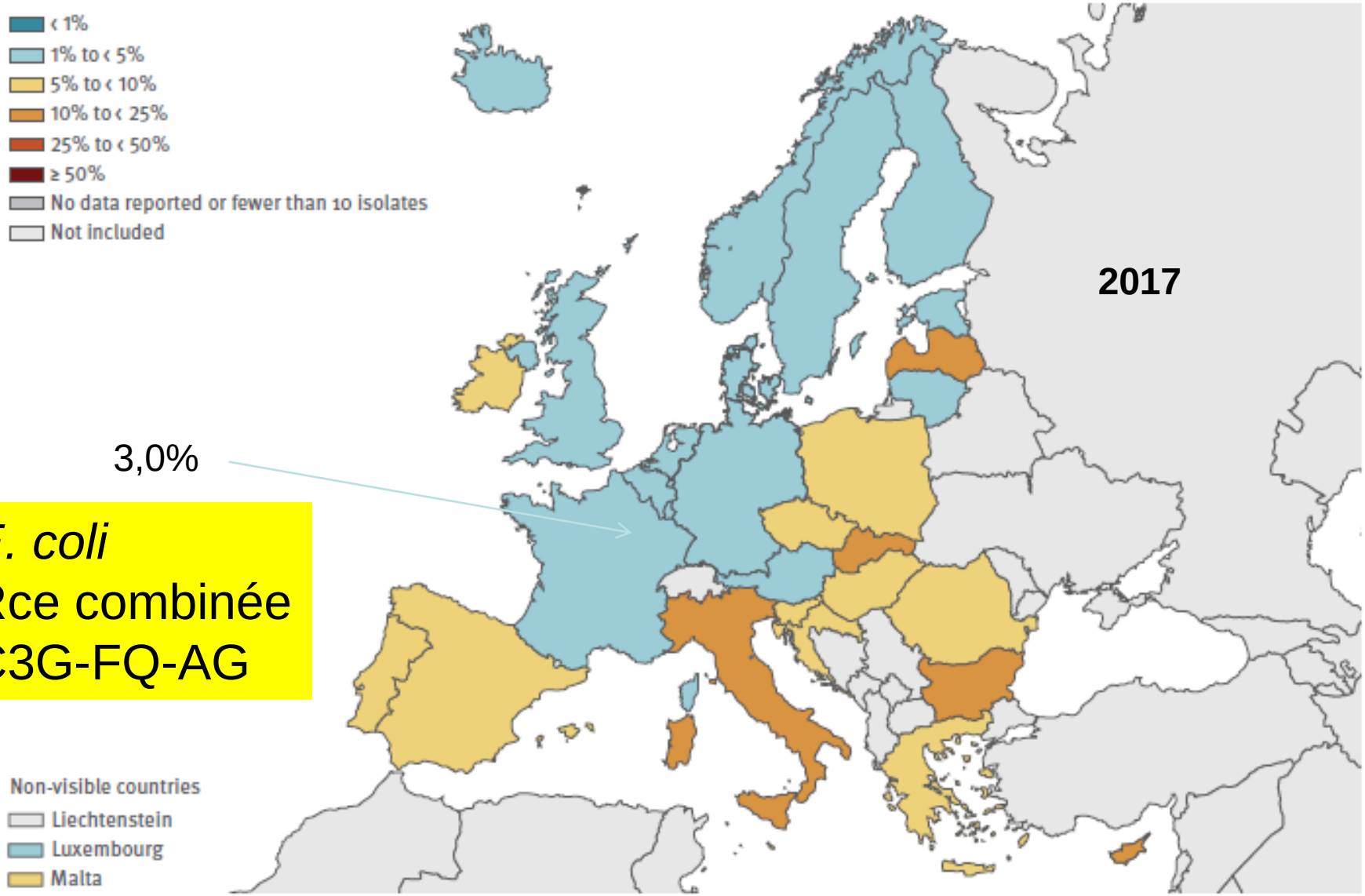
E. coli / FQ

Figure 3.3. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2017



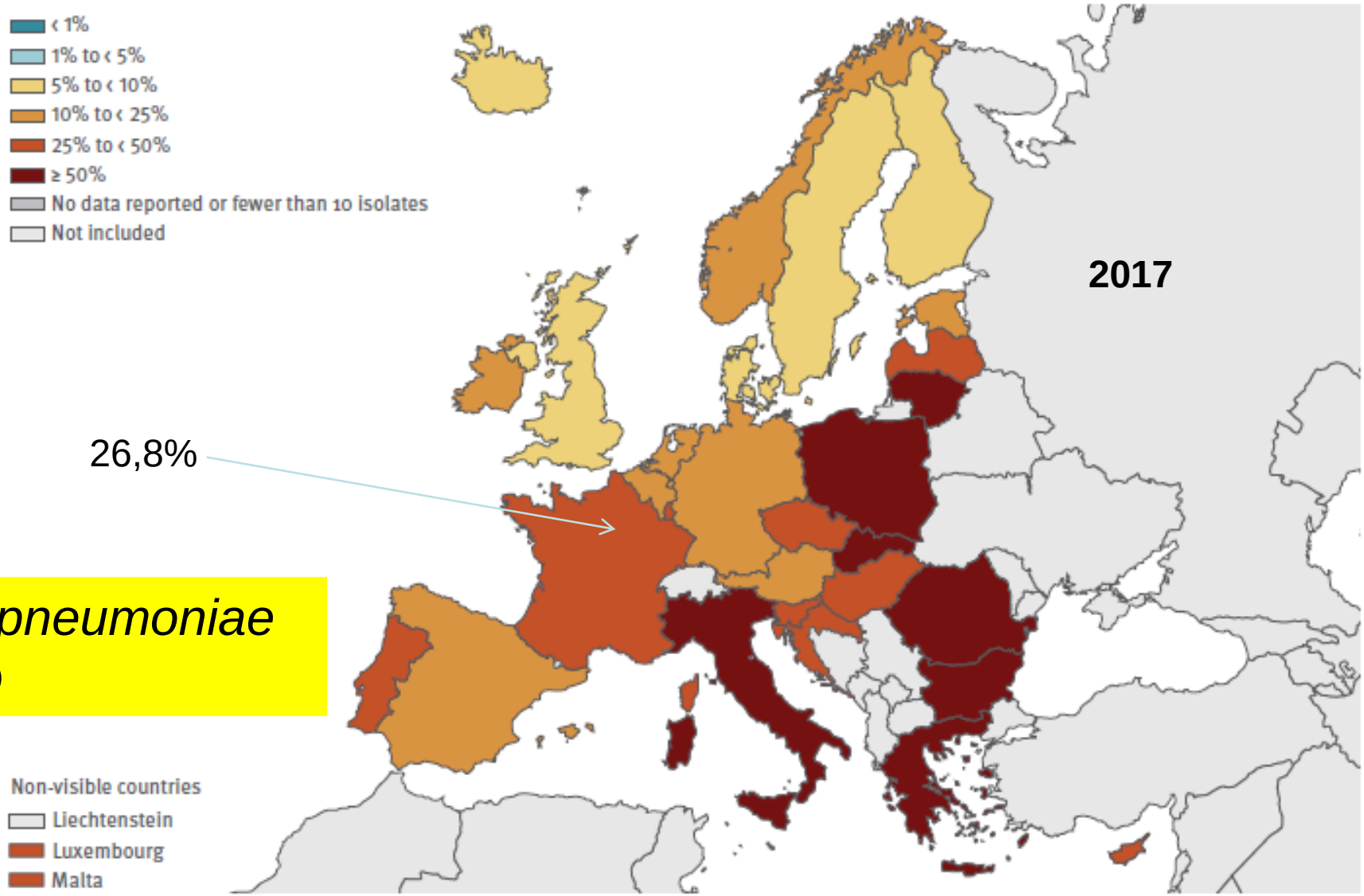
E. coli / C3G

Figure 3.6. *Escherichia coli*. Percentage (%) of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, by country, EU/EEA countries, 2017

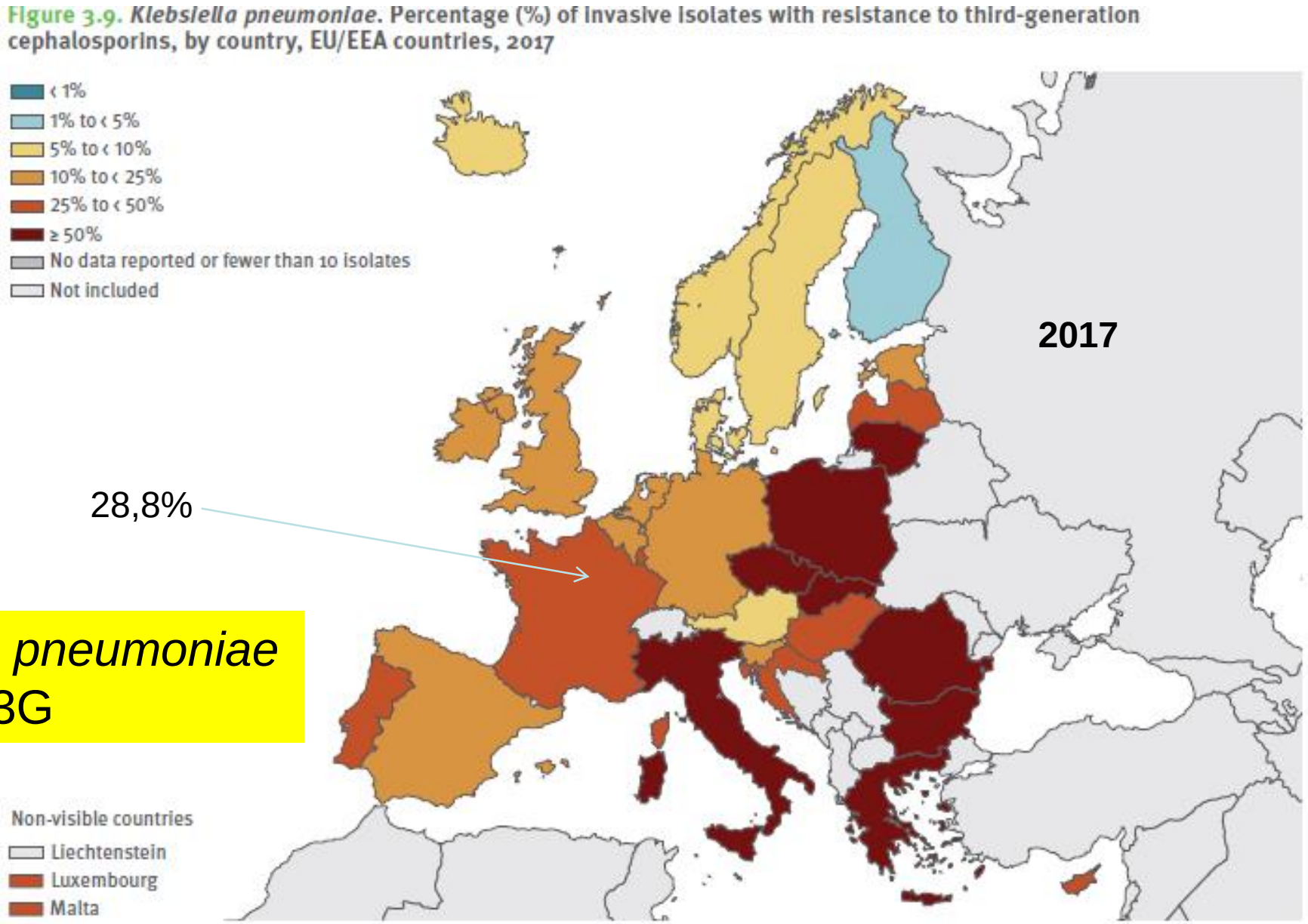


E. coli
Rce combinée
C3G-FQ-AG

Figure 3.8. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2017

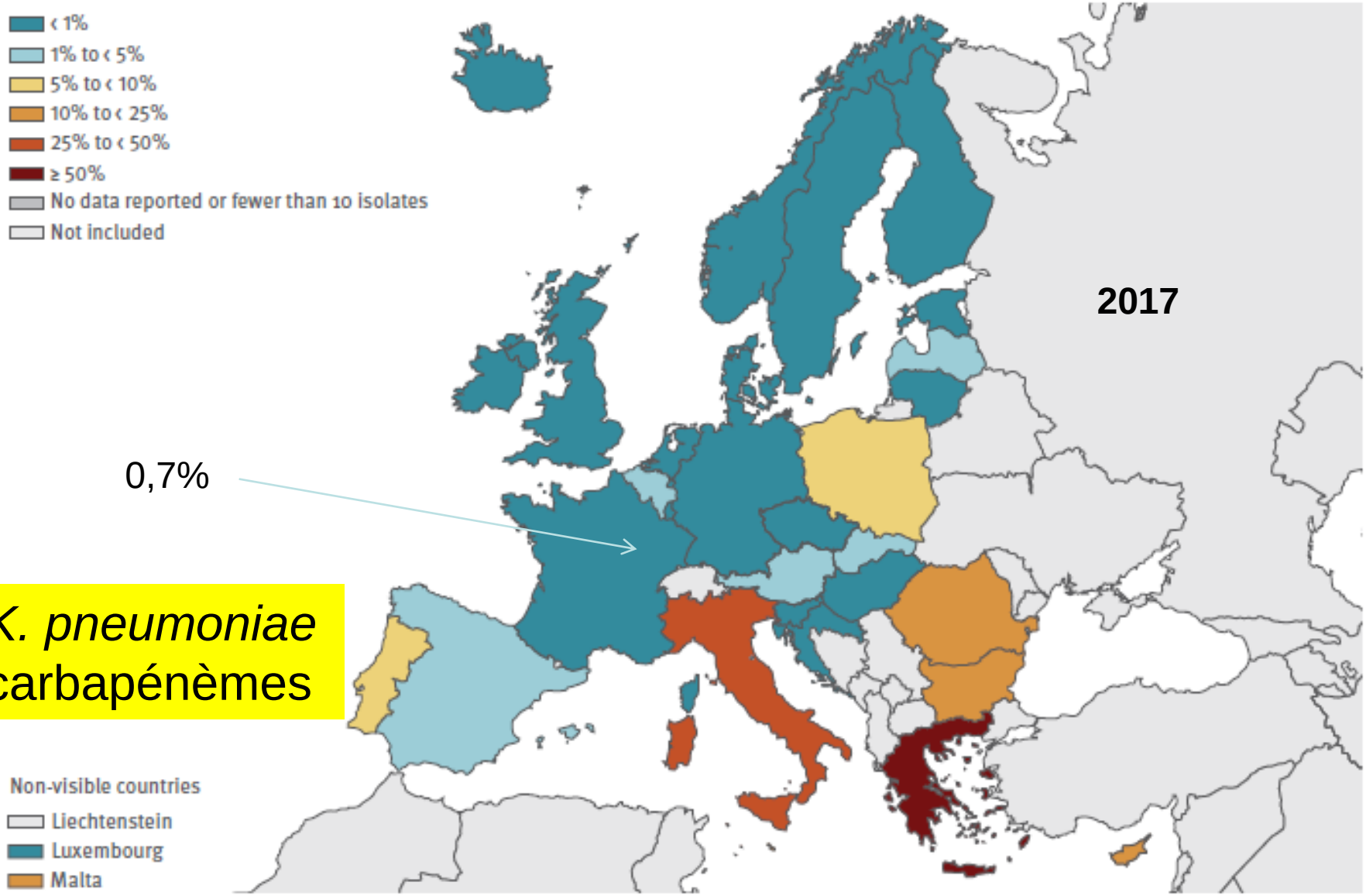


K. pneumoniae
FQ



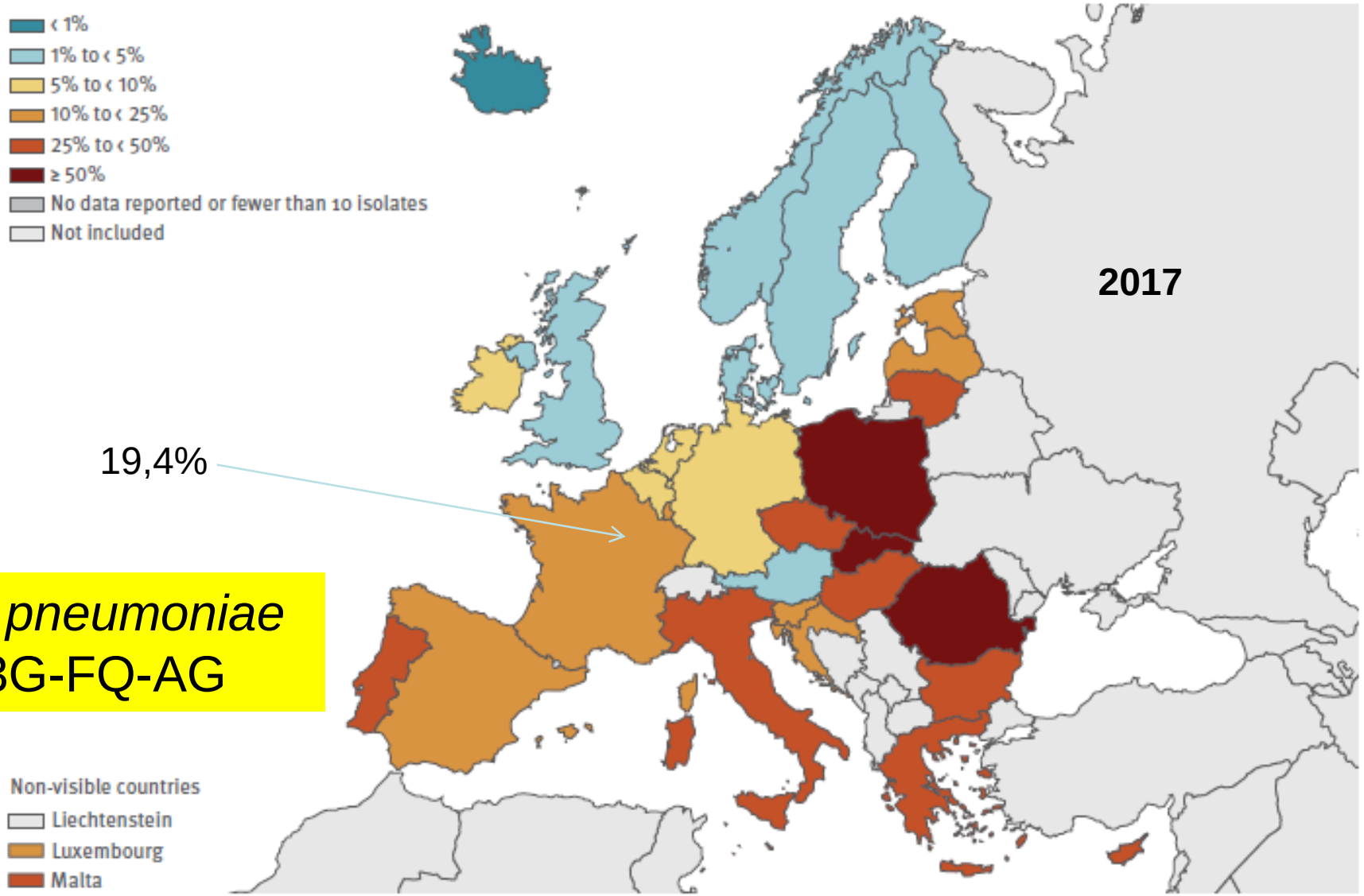
K. pneumoniae
C3G

Figure 3.11. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2017



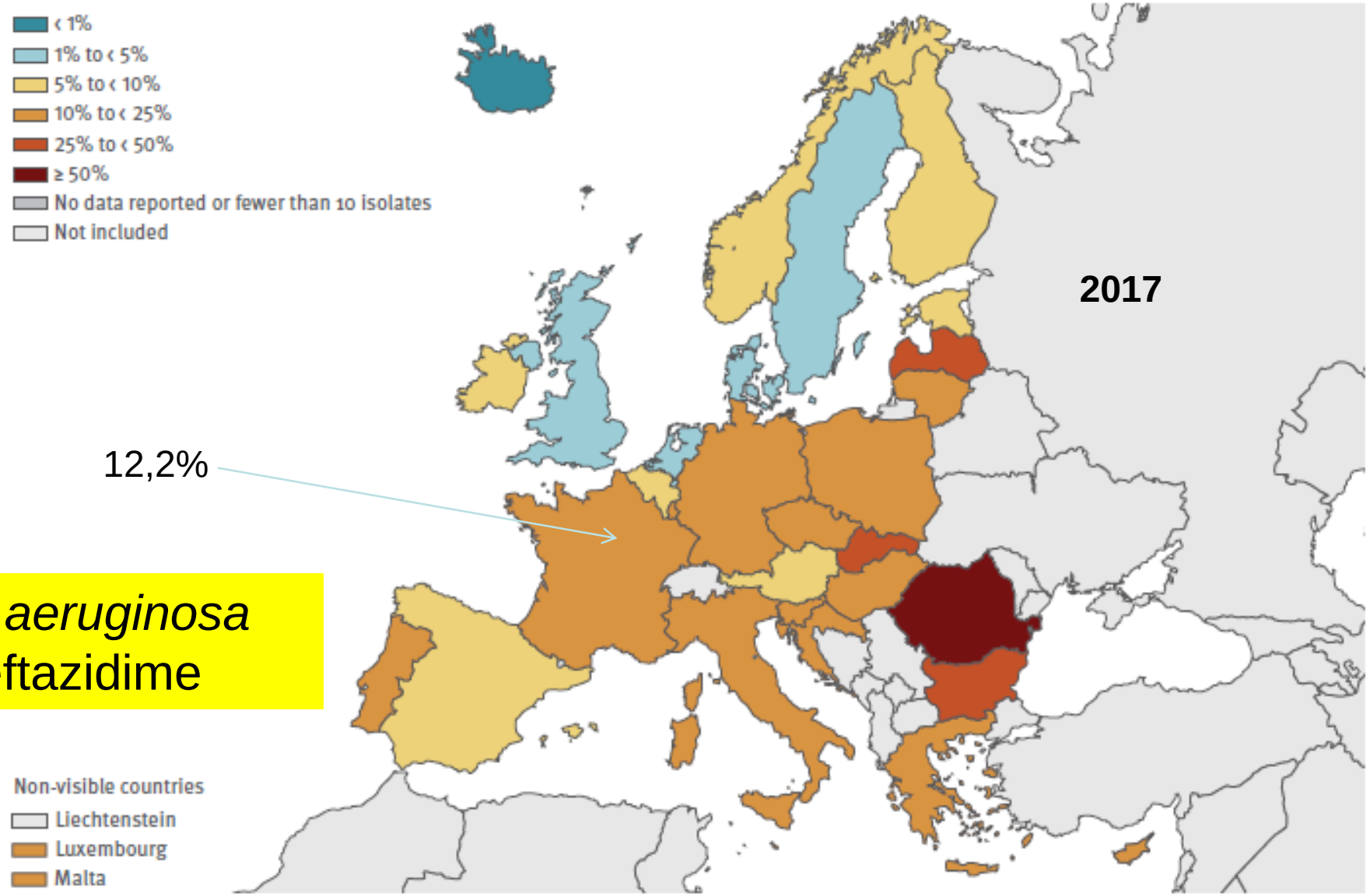
K. pneumoniae
carbapénèmes

Figure 3.12. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides, by country, EU/EEA countries, 2017



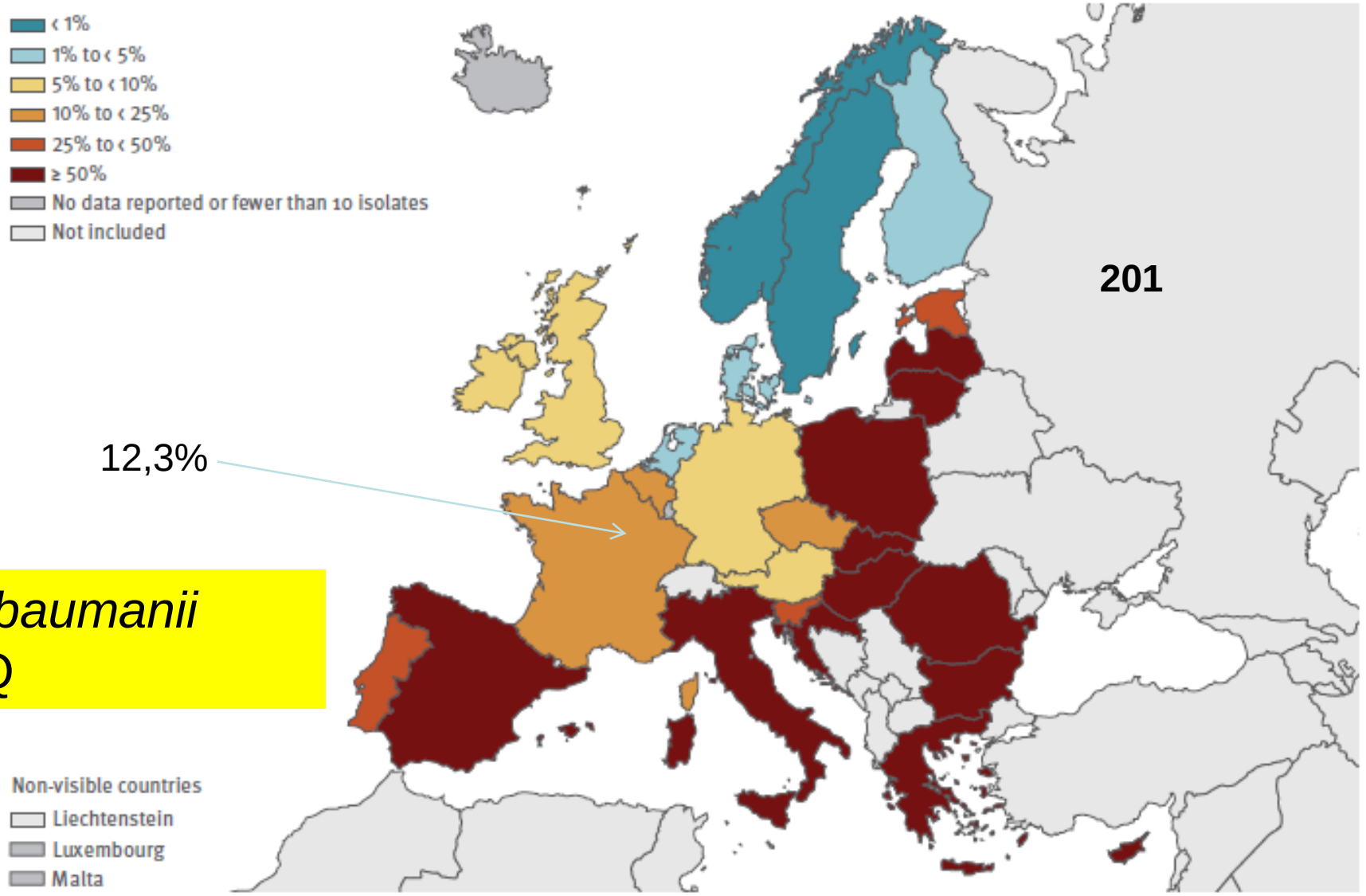
K. pneumoniae
C3G-FQ-AG

Figure 3.15. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to ceftazidime, by country, EU/EEA countries, 2017



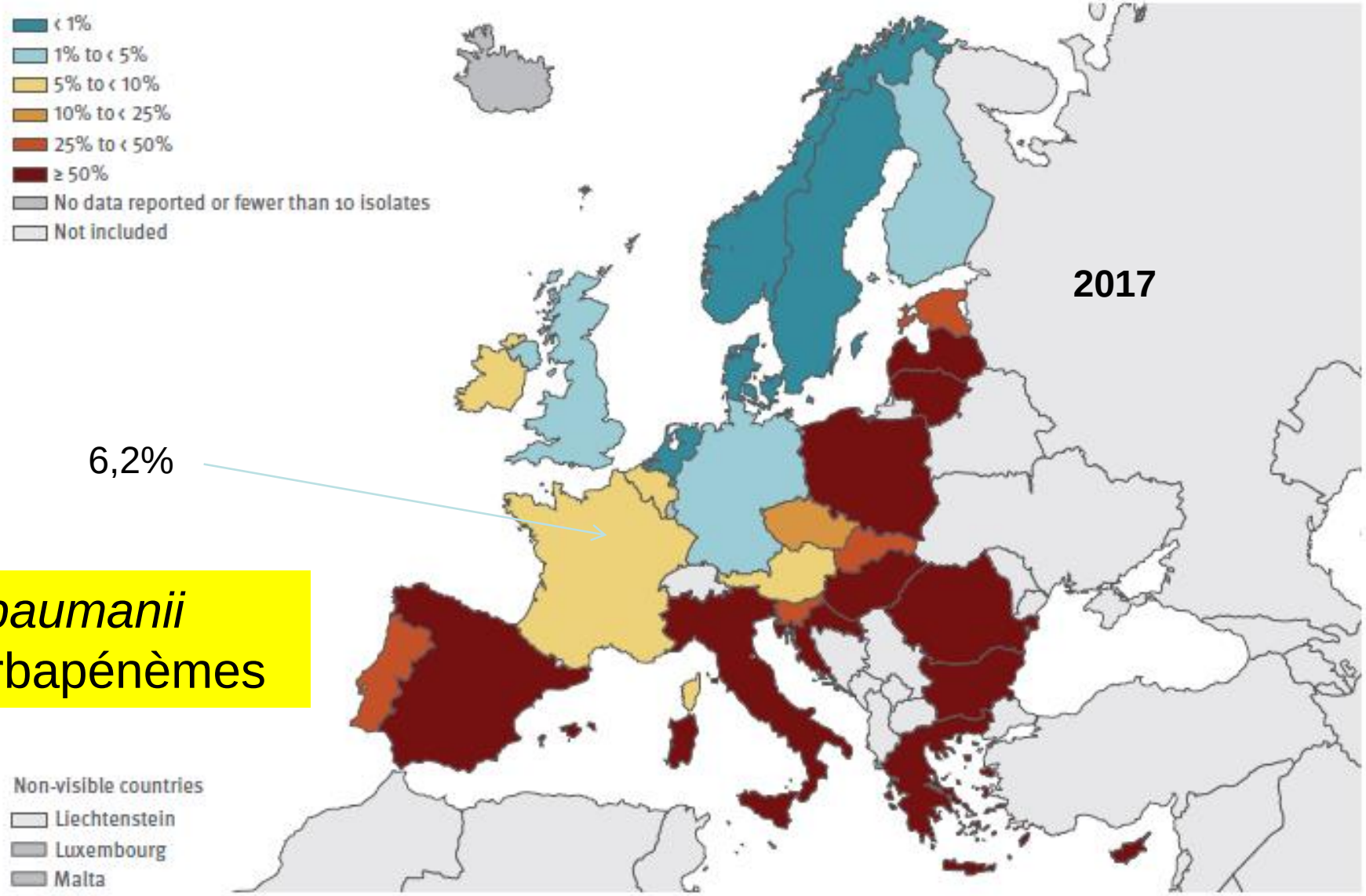
P. aeruginosa
ceftazidime

Figure 3.20. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2017



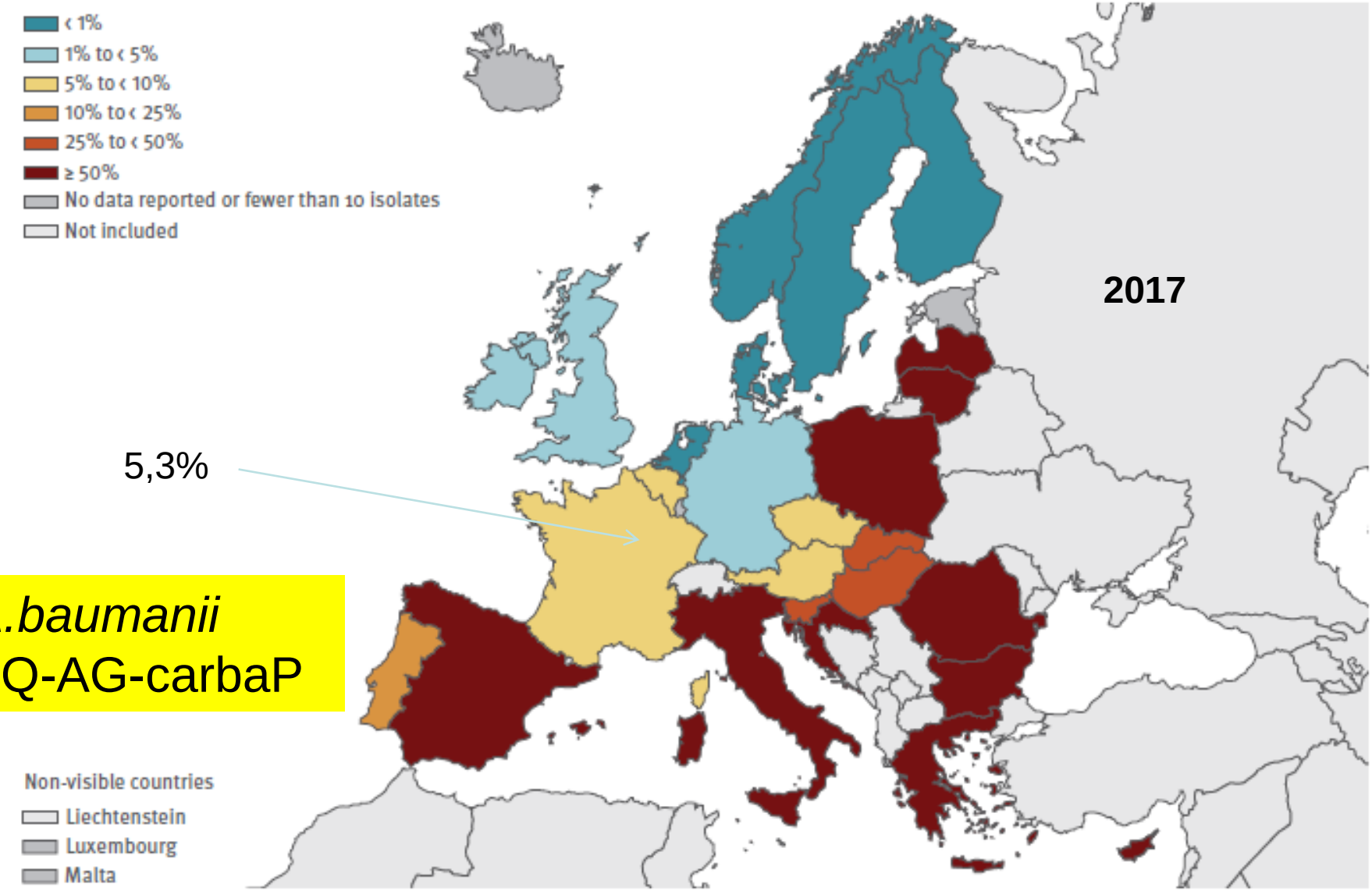
A.baumanii
FQ

Figure 3.22. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2017



A.baumanii
carbapénèmes

Figure 3.23. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems, by country, EU/EEA countries, 2017



A.baumanii
FQ-AG-carbaP

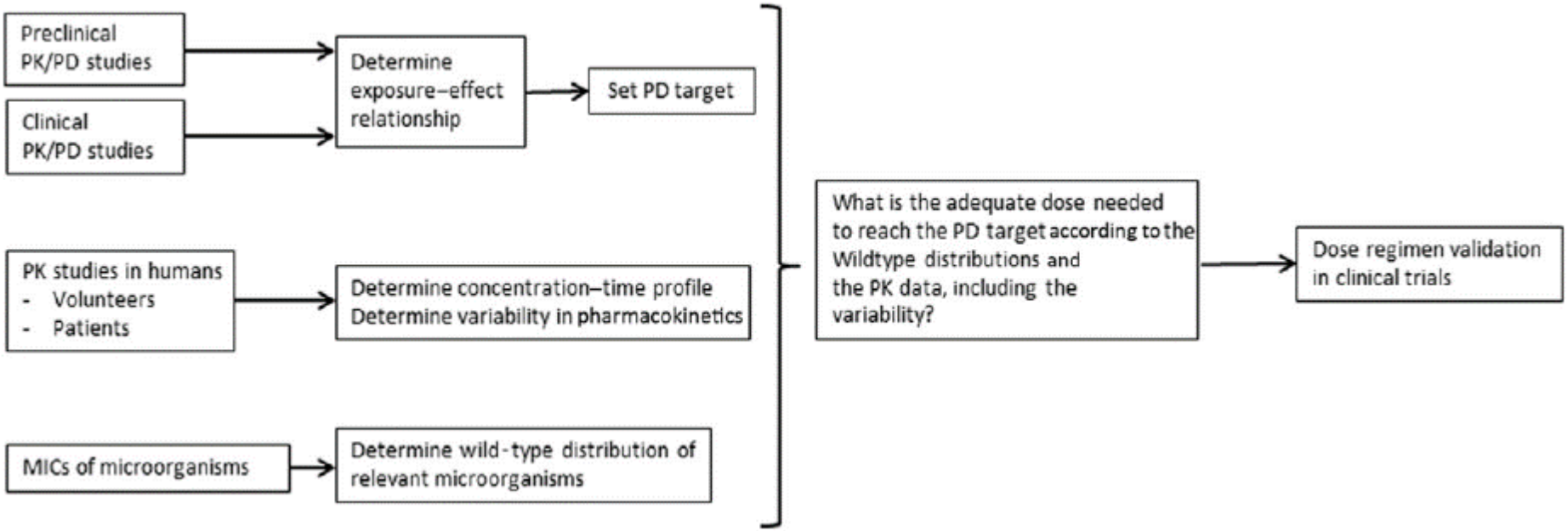
Mode de retour de certains ATB

- **On les pensait plus toxiques qu'ils ne sont**
  - Colimycine
- **Ils ne sont pas apparentés aux grandes familles contre lesquelles se sont développées les résistances**
  - Phénicolés
  - Colimycine
  - « vieux » anti-tuberculeux
  - Fosfomycine
- **Ils « résistent aux résistances » mieux que les autres**
  - Témocilline et béta-lactamases
- **Des travaux de PK/PD permettent de les utiliser de façon plus rationnelle**
  - Alors qu'on ne disposait auparavant que de données anciennes

Problèmes communs

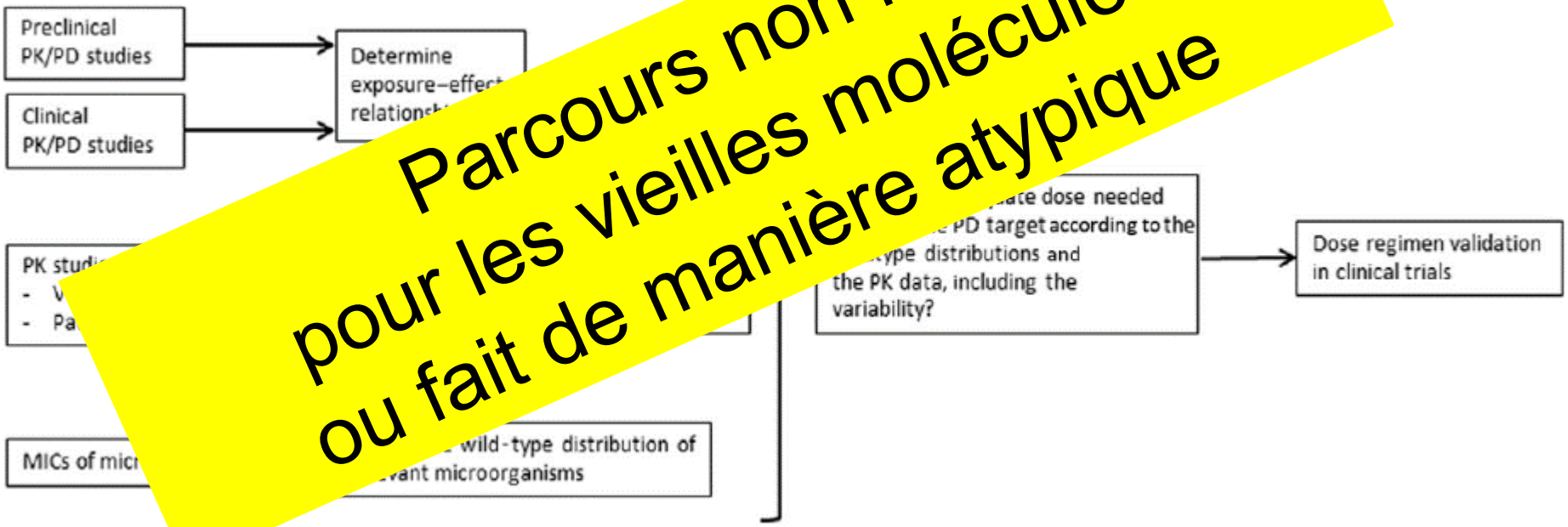
- Pas de données aussi précises qu'avec les antibiotiques plus récents
  - Études de PK datant de 50 ans ou plus
  - Pas d'essais cliniques randomisés
- Brevets expirés
  - Donc très peu de fonds privés pour le développement
- Les données récentes proviennent d'études peu satisfaisantes
  - Registre / recueil prospectif sans comparateur
  - Étude rétrospective

Parcours idéal d'un ATB



PD : pharmacodynamie
PK : pharmacocinétique

Parcours idéal d'un ATB



Parcours non fait
pour les vieilles molécules
ou fait de manière atypique

PD : pharmacodynamie
PK : pharmacocinétique

Antibiotiques abordés aujourd'hui

- Polymyxines
- Fosfomycine
- Témocilline
- Phénicolés

J Antimicrob Chemother 2011; **66**: 2070–2074
doi:10.1093/jac/dkr239 Advance Access publication 29 June 2011

Journal of Antimicrobial Chemotherapy

Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09)

Ana C. Gales[1]*, Ronald N. Jones[2] and Hélio S. Sader[1,2]

[1]Division of Infectious Diseases, Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo, Brazil; [2]JMI Laboratories, North Liberty, IA, USA

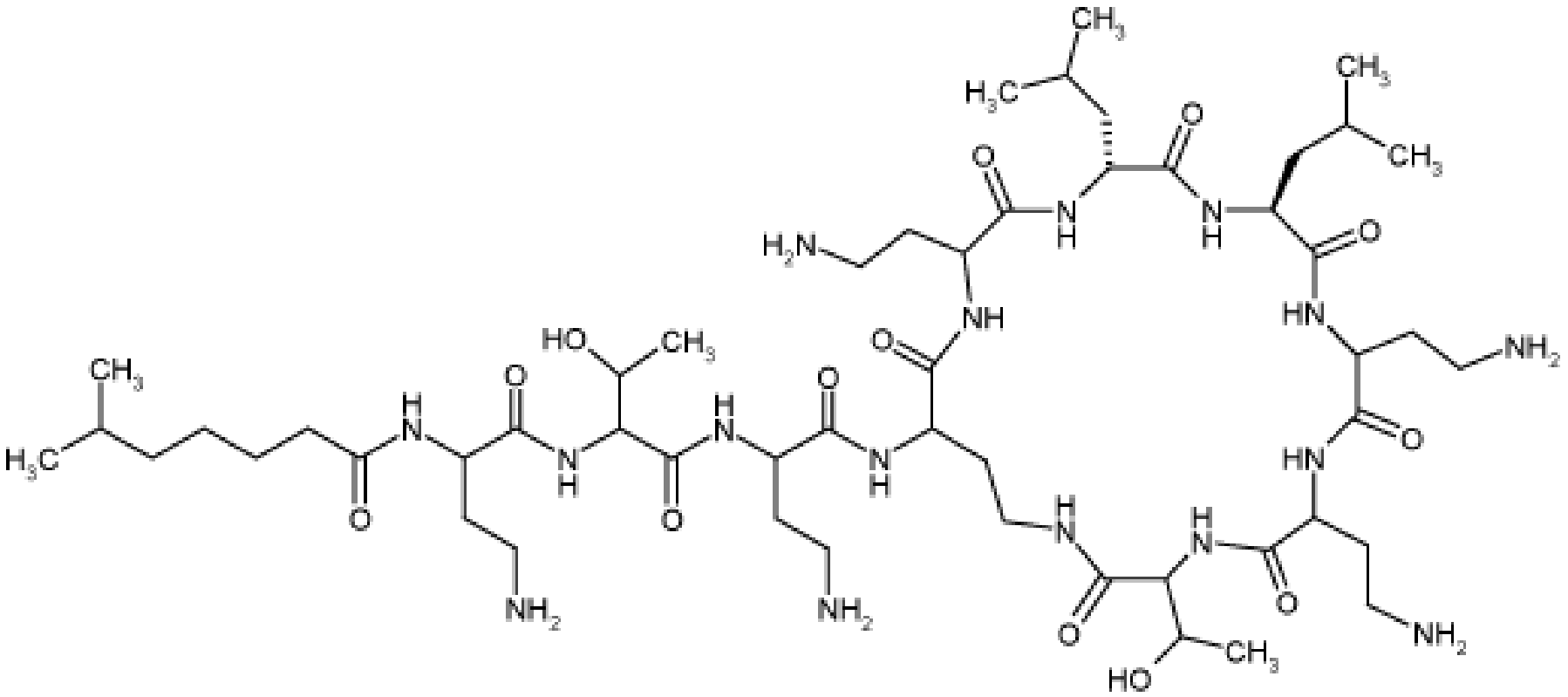
Geographical region	Percentage susceptible[a] (no. of isolates tested)				
	2006	2007	2008	2009	all years
Acinetobacter spp.					
North America	(171)	(226)	(177)	(160)	(734)
colistin	97.7	98.2	98.3	97.5	98.0
polymyxin B	98.8	99.6	98.3	98.7	98.9
imipenem	77.8	61.5	68.4	62.5	67.2
Europe[b]	(201)	(253)	(225)	(264)	(943)
colistin	99.5	99.2	99.6	98.1	99.1
polymyxin B	100.0	99.6	100.0	98.9	99.6
imipenem	64.7	58.1	46.2	45.1	53.0
Latin America	(230)	(288)	(303)	(236)	(1057)
colistin	99.1	99.3	98.4	98.7	98.9
polymyxin B	99.6	99.7	98.4	98.7	99.1
imipenem	73.0	58.0	39.6	23.7	48.3
Asia-Pacific[c]	(544)	(669)	(397)	(342)	(1952)
colistin	—[d]	98.4	99.0	98.3	98.3
polymyxin B	99.3	99.1	100.0	97.4	99.3
imipenem	59.4	69.4	48.6	37.4	56.8
all regions	(1146)	(1436)	(1102)	(1002)	(4686)
colistin	98.8	98.7	98.8	97.9	98.6
polymyxin B	99.4	99.4	99.3	98.8	99.2
imipenem	65.8	63.9	48.8	40.2	55.7

Geographical region	Percentage susceptible[a] (no. of isolates tested)				
	2006	2007	2008	2009	all years
E. coli					
North America	(974)	(1135)	(1085)	(1261)	(4455)
colistin	99.9	100.0	99.9	100.0	99.9
polymyxin B	99.9	100.0	99.9	100.0	99.9
imipenem	100.0	100.0	100.0	100.0	100.0
Europe[b]	(1748)	(1913)	(1783)	(1813)	(7254)
colistin	99.9	99.5	99.7	99.7	99.7
polymyxin B	100.0	99.6	99.7	99.8	99.8
imipenem	100.0	100.0	100.0	100.0	100.0
Latin America	(349)	(493)	(508)	(415)	(1850)
colistin	100.0	100.0	100.0	99.8	99.9
polymyxin B	100.0	100.0	100.0	100.0	100.0
imipenem	100.0	99.8	100.0	100.0	100.0
Asia-Pacific[c]	(919)	(1208)	(645)	(701)	(3473)
colistin	—[d]	99.8	99.8	99.7	99.8
polymyxin B	100.0	99.8	99.9	99.7	99.9
imipenem	99.9	99.6	99.5	99.7	99.7
all regions	(4075)	(4749)	(4021)	(4190)	(17035)
colistin	99.9	99.8	99.8	99.8	99.9
polymyxin B	100.0	99.8	99.8	99.9	99.9
imipenem	100.0	99.9	99.9	100.0	99.9

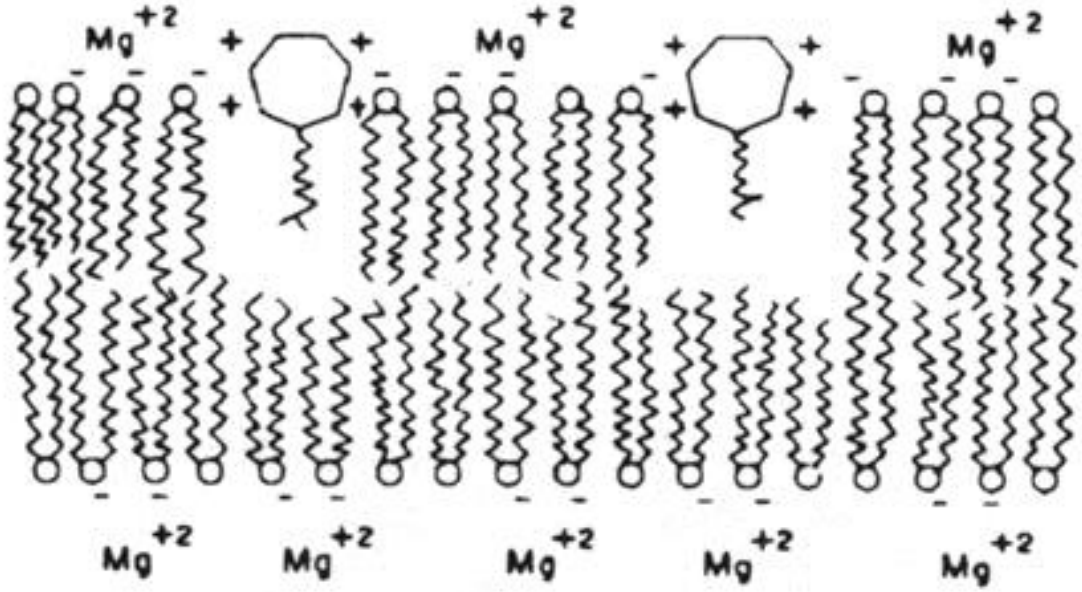
Geographical region	Percentage susceptible[a] (no. of isolates tested)				
	2006	2007	2008	2009	all years
P. aeruginosa					
North America	(488)	(630)	(489)	(514)	(2121)
colistin	100.0	99.8	100.0	99.6	99.9
polymyxin B	100.0	100.0	100.0	99.8	99.8
imipenem	83.6	78.6	78.5	82.7	80.6
Europe[b]	(618)	(770)	(632)	(626)	(2646)
colistin	99.2	100.0	99.5	99.5	99.6
polymyxin B	99.4	100.0	99.7	99.5	99.7
imipenem	75.6	76.5	77.4	70.9	75.2
Latin America	(390)	(355)	(376)	(341)	(1462)
colistin	99.7	99.7	100.0	99.4	99.7
polymyxin B	100.0	100.0	100.0	99.4	99.9
imipenem	64.9	59.7	63.0	58.4	61.6
Asia-Pacific[c]	(719)	(1248)	(426)	(508)	(2901)
colistin	—[d]	99.3	99.8	99.2	99.4
polymyxin B	100.0	99.8	99.8	99.6	99.8
imipenem	74.1	76.0	77.2	73.6	75.3
all regions	(2215)	(3003)	(1923)	(1989)	(9130)
colistin	99.6	99.6	99.8	99.5	99.6
polymyxin B	99.8	99.9	99.8	99.6	99.8
imipenem	74.6	74.8	74.8	72.5	74.3

Polymyxines

- Découvertes en 1947
  - À partir d'un *Paecilomyces* initialement
- Arrêt de l'utilisation dans les années 70
  - Du fait de leur neuro- et néphrotoxicité
- Regain d'intérêt du fait des résistances
- Pas de développement approprié aux standards actuels
  - En efficacité
  - En tolérance
  - En production industrielle

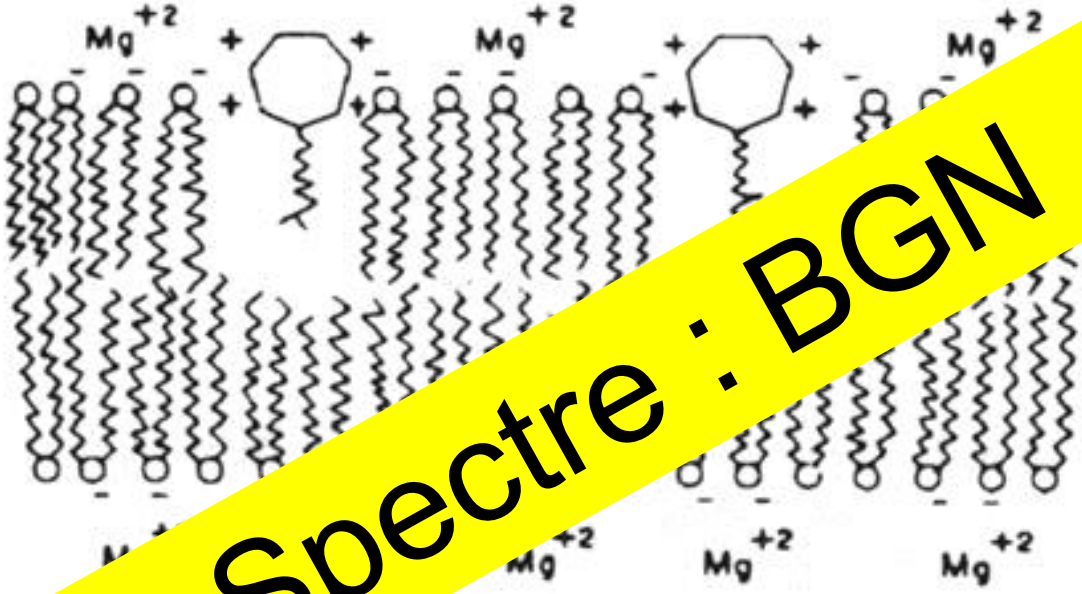


Mécanisme d'action



Hypothetical model for interaction of polymyxin with a phospholipid bilayer. It is proposed that the fatty acid tail of the peptide penetrates the hydrophobic domain of the bilayer, with the peptide amino groups interacting electrostatically with phospholipid phosphates. (*From Storm et al: Annu Rev Biochem 46:723, 1977.*)

Mécanisme d'action



Spectre : BGN

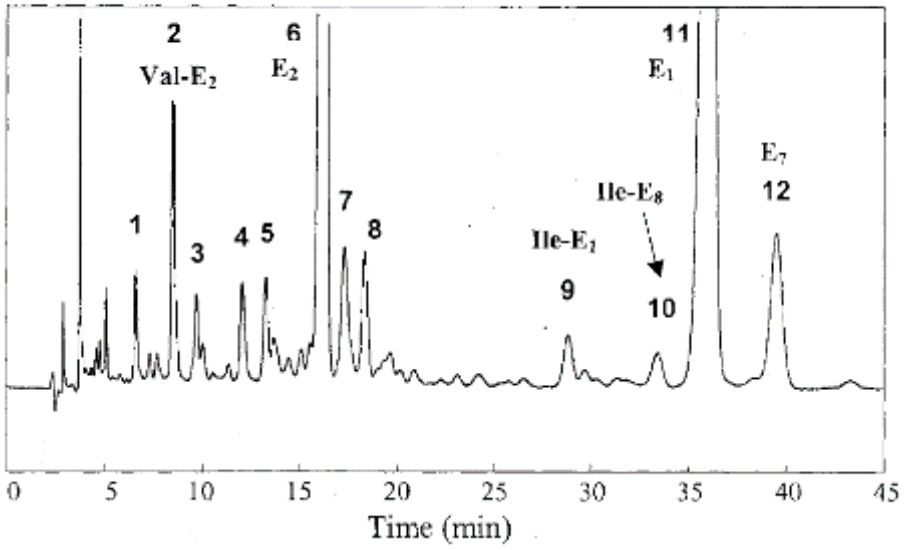
al model for interaction of polymyxin with a phospholip t is proposed that the fatty acid tail of the peptide penetra he hydrophobic domain of the bilayer, with the peptide amino groups interacting electrostatically with phospholipid phosphates. (*From Storm et al: Annu Rev Biochem 46:723, 1977.*)

Différents facteurs de complexité

- Il y a plusieurs polymyxines
- Elles ont plusieurs métabolites
- Il existe une prodrogue de certaines
- Il existe une expression
  - En mg de drogue
  - En mg de prodrogue
  - En unités internationales d'activité antibactérienne
- Les tests de sensibilités sont imparfaits

- 5 polymyxines différentes
  - A à E
- Composés hétérogènes
- Fermentation par *Bacillus polymyxa*

Fig. 2. Chromatogram of 50 μg colistin sulphate commercial sample.



Orwa 2001

Polymyxine E

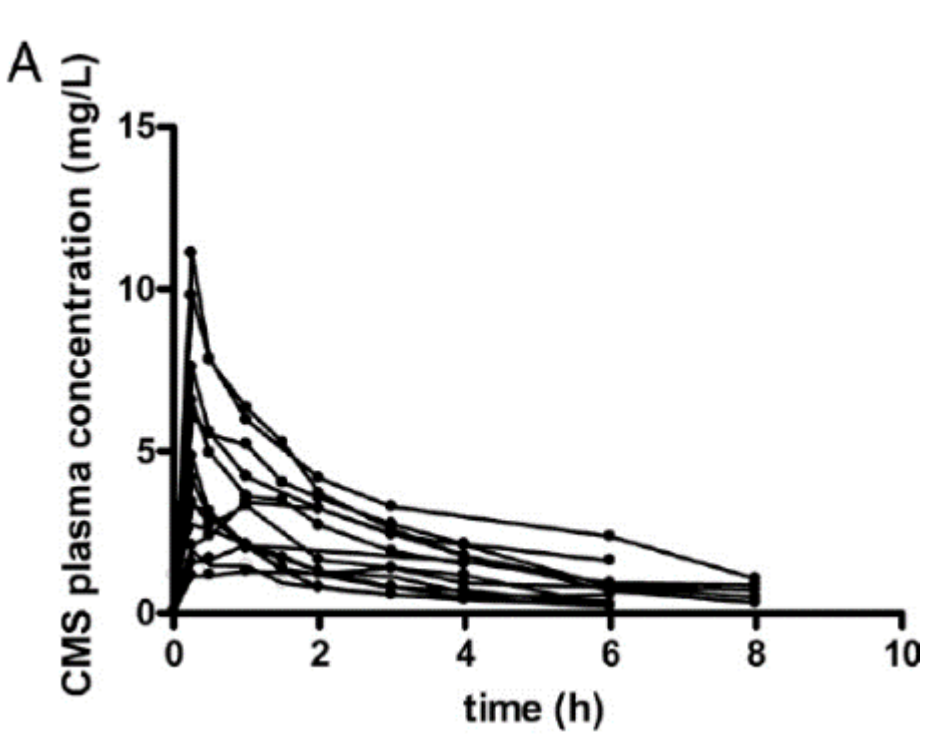
- La plus utilisée
- Dite aussi **colistine**
- Mélange de différents polypeptides
  - En particulier polymyxines E1 et E2
    (colistines A et B)
- Préparation commerciale IV
  - **Colistiméthate de sodium**
  - Prodrogue (inactive et moins toxique) de la colistine
    - Hydrolyse in vivo
  - 1mg = 12500 unités
- Préparation commerciale PO
  - Sulfate de colistine … plus disponible depuis 2012

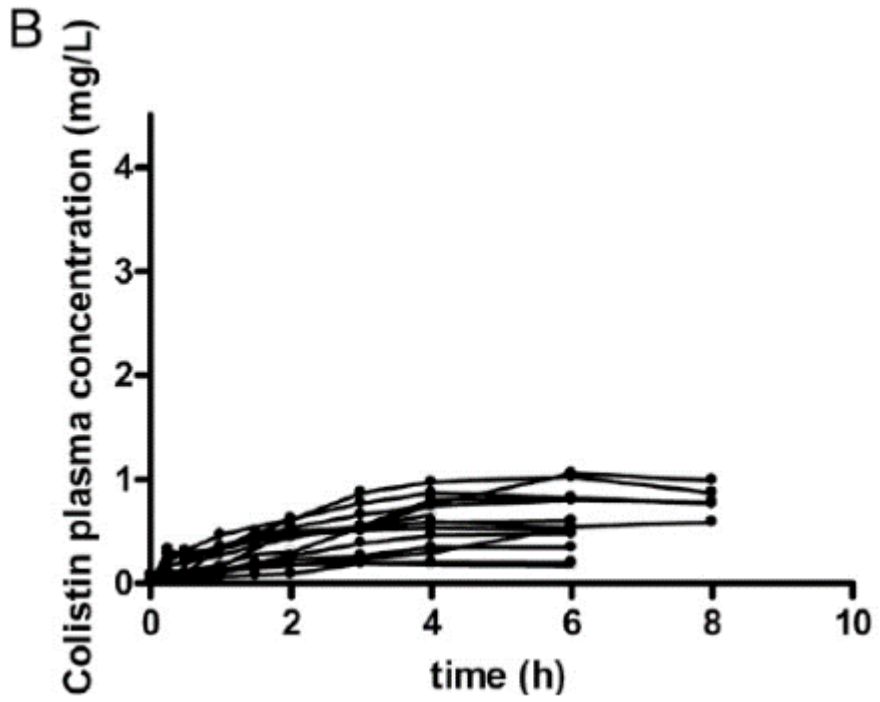
Polymyxine B

- Regroupe en fait 30 polypeptides différents
- Disponible uniquement en topique
- Donc pas/peu utilisée

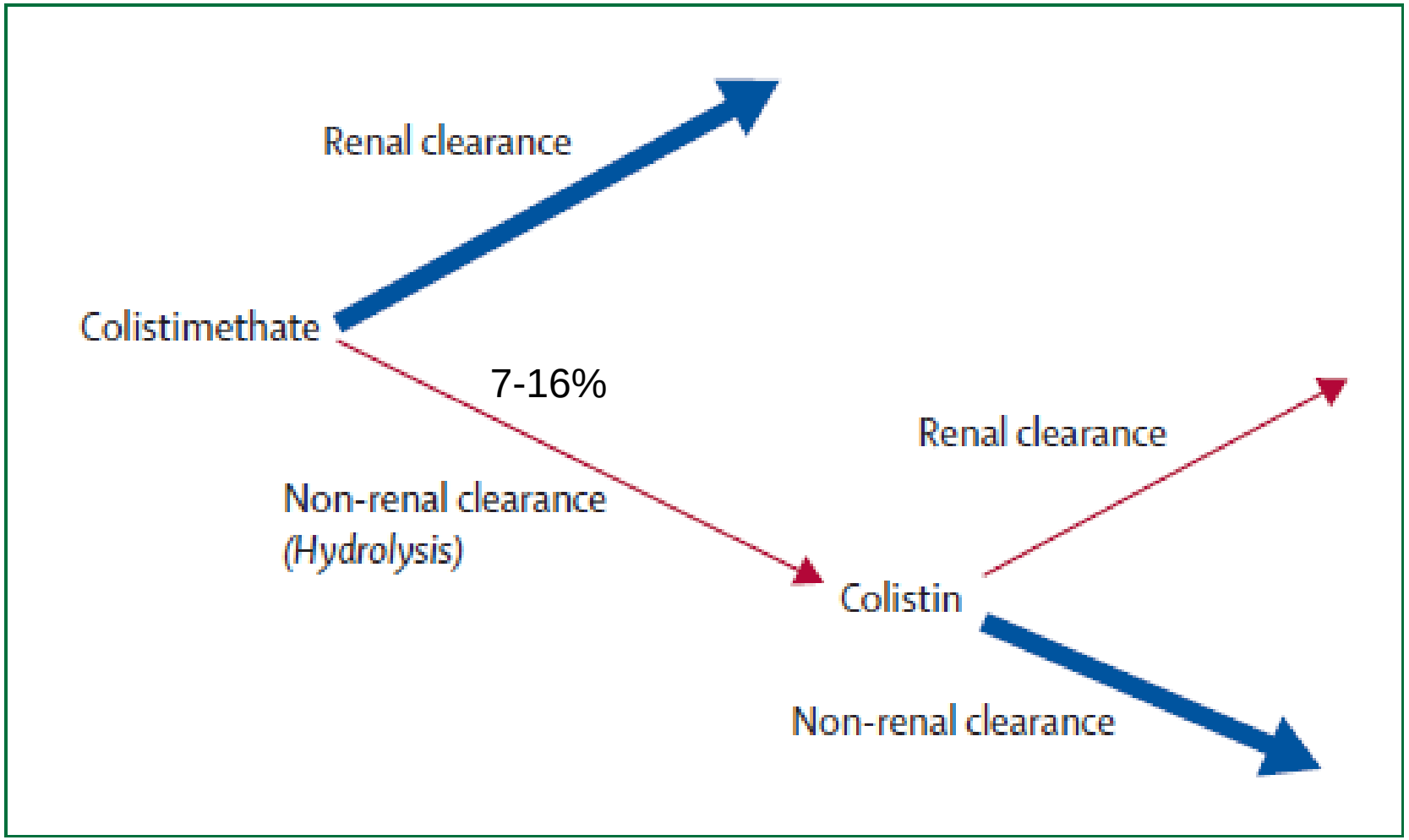
CMS = prodrogue …

très partiellement et lentement métabolisée



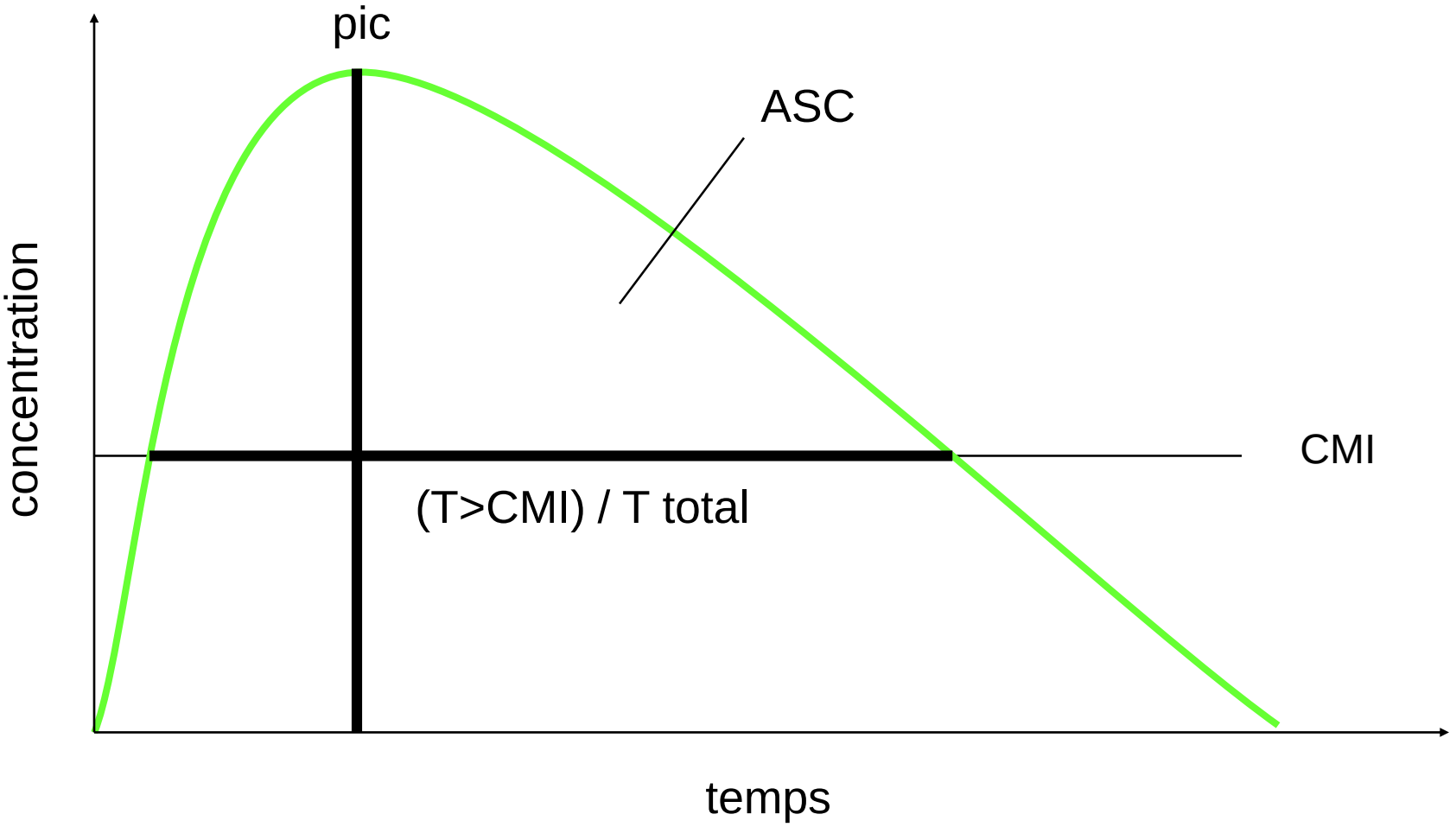


Plachouras 2009



L’hydrolyse produit une 30aine de molécules différentes
… Dont « la » colistine

Pharmacocinétique
Pharmacodynamique



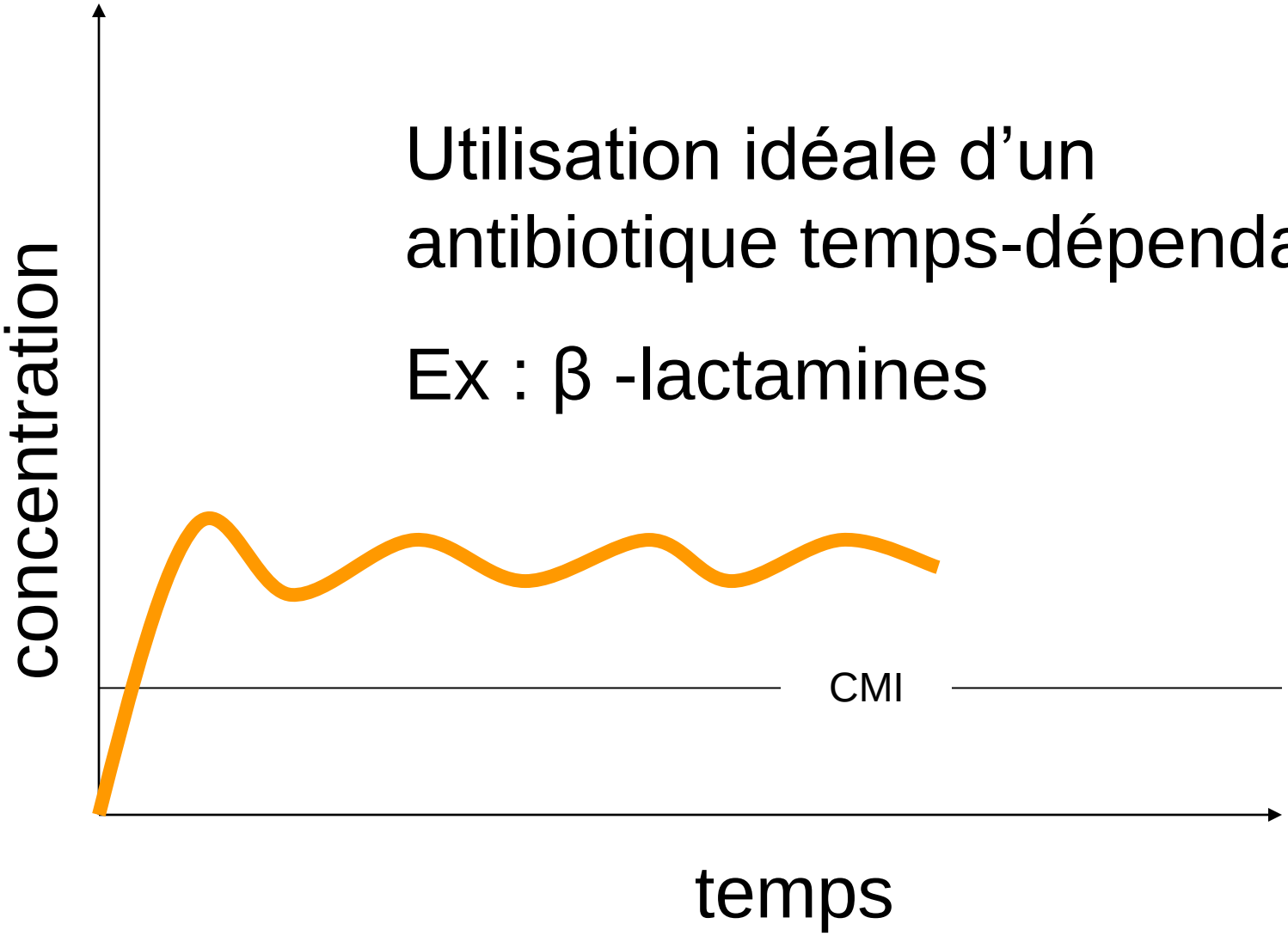
Bactéricidie temps-dépendant

- Paramètre le plus important : Tps > CMI
  - β-lactamines
  - Glycopeptides

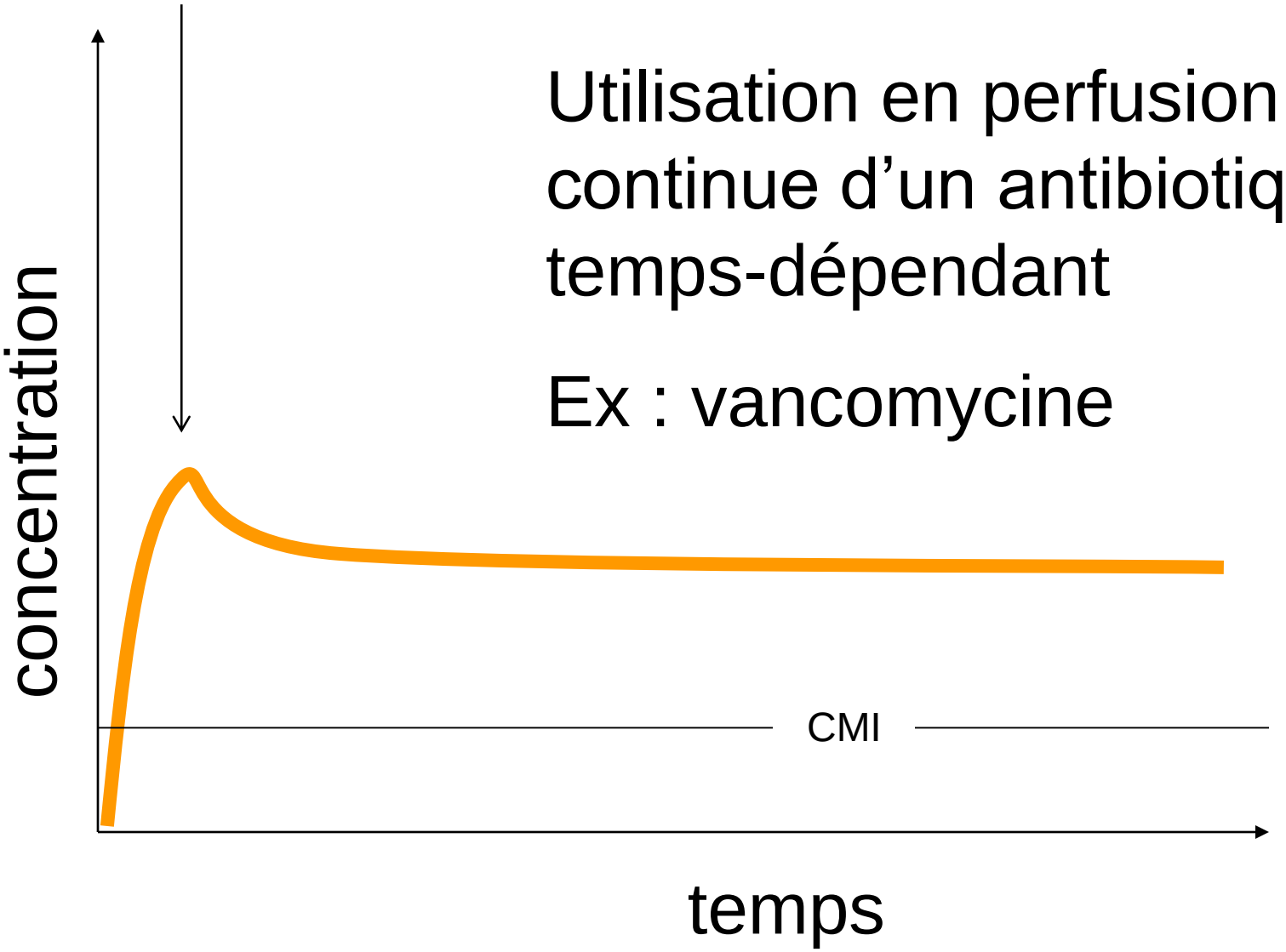
- administration fréquente (4-6/J)
  voire continue
  (en fonction de la demi-vie)

Utilisation idéale d’un antibiotique temps-dépendant

Ex : β -lactamines



Dose de charge



Utilisation en perfusion continue d'un antibiotique temps-dépendant

Ex : vancomycine

Bactéricidie dose-dépendante

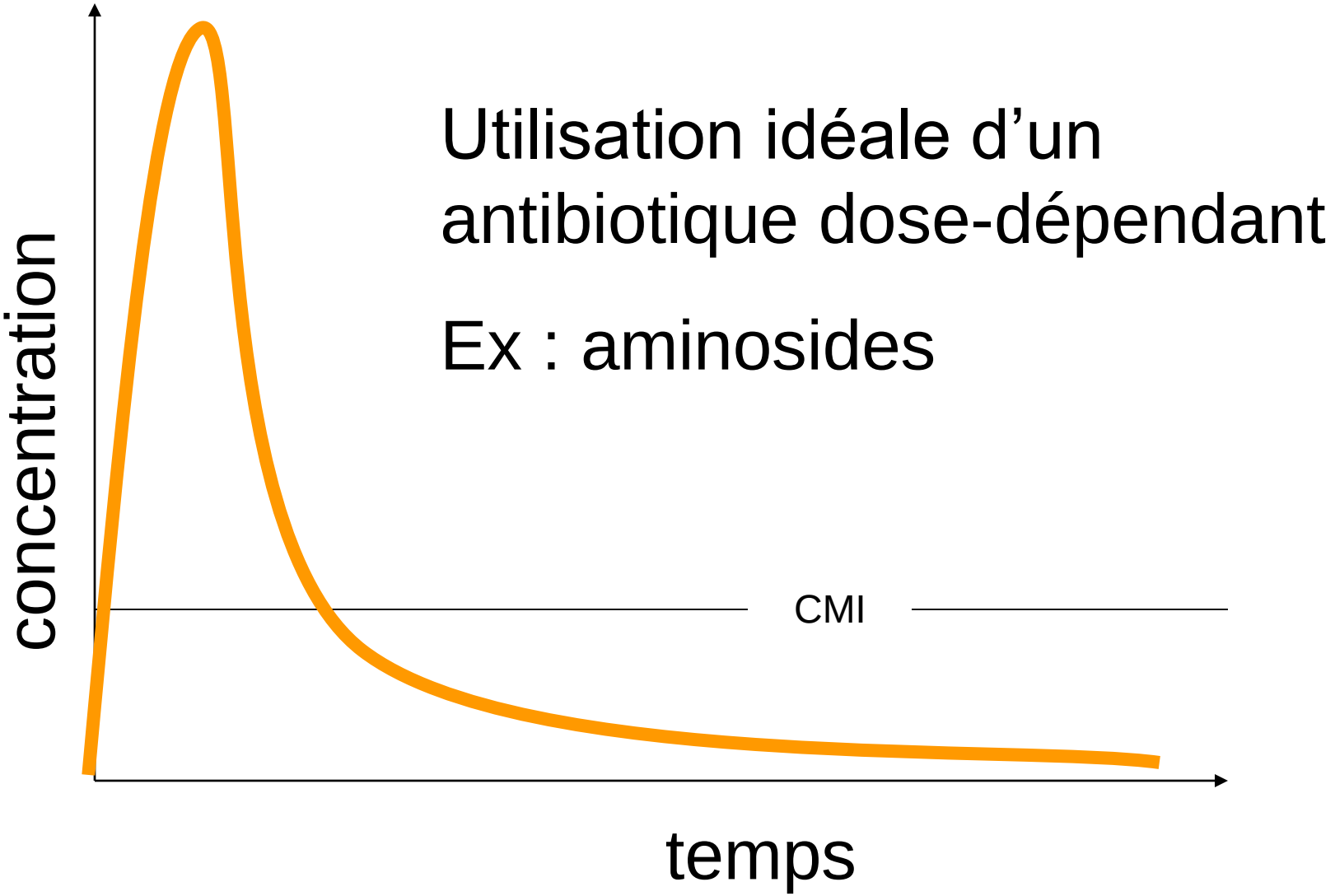
- Paramètre le plus important :
  AUC / CMI ou Cmax/CMI
  - Fluoroquinolones
  - Aminosides
  - Rifampicine

- Administration 1 à 2 fois par jour

Bactéricidie dose-dépendante

- Paramètre le plus important : Cmax/CMI
  - Aminosides

- Administration 1 fois par jour



Utilisation idéale d’un antibiotique dose-dépendant

Ex : aminosides

Bactéricidie AUC- dépendante

- Paramètre le plus important : AUC / CMI
  - Fluoroquinolones
  - Rifampicine

- Administration 1 à 2 fois par jour

Colimycine : pharmacodynamie

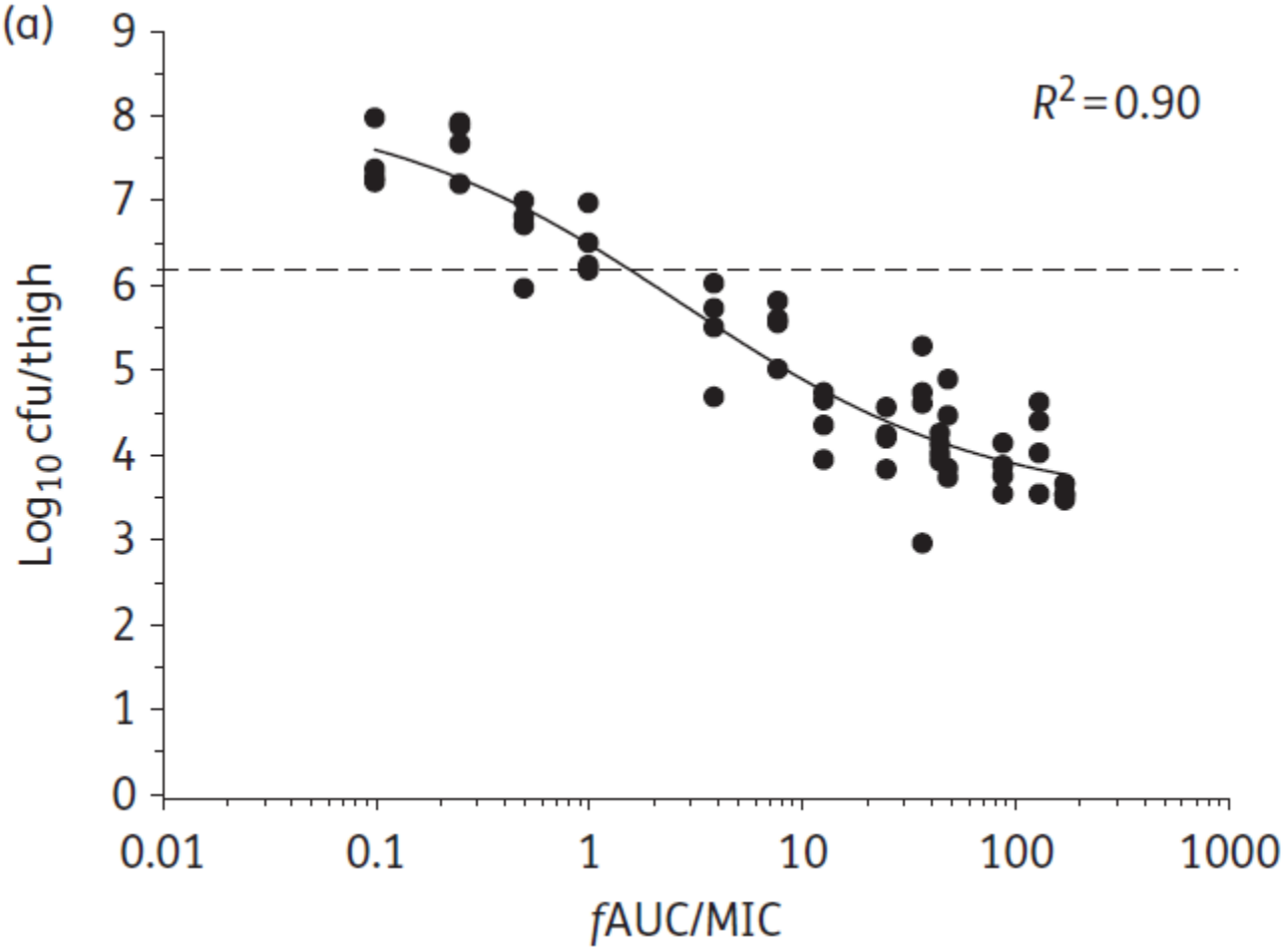
- Bactéricide
- AUC/MIC

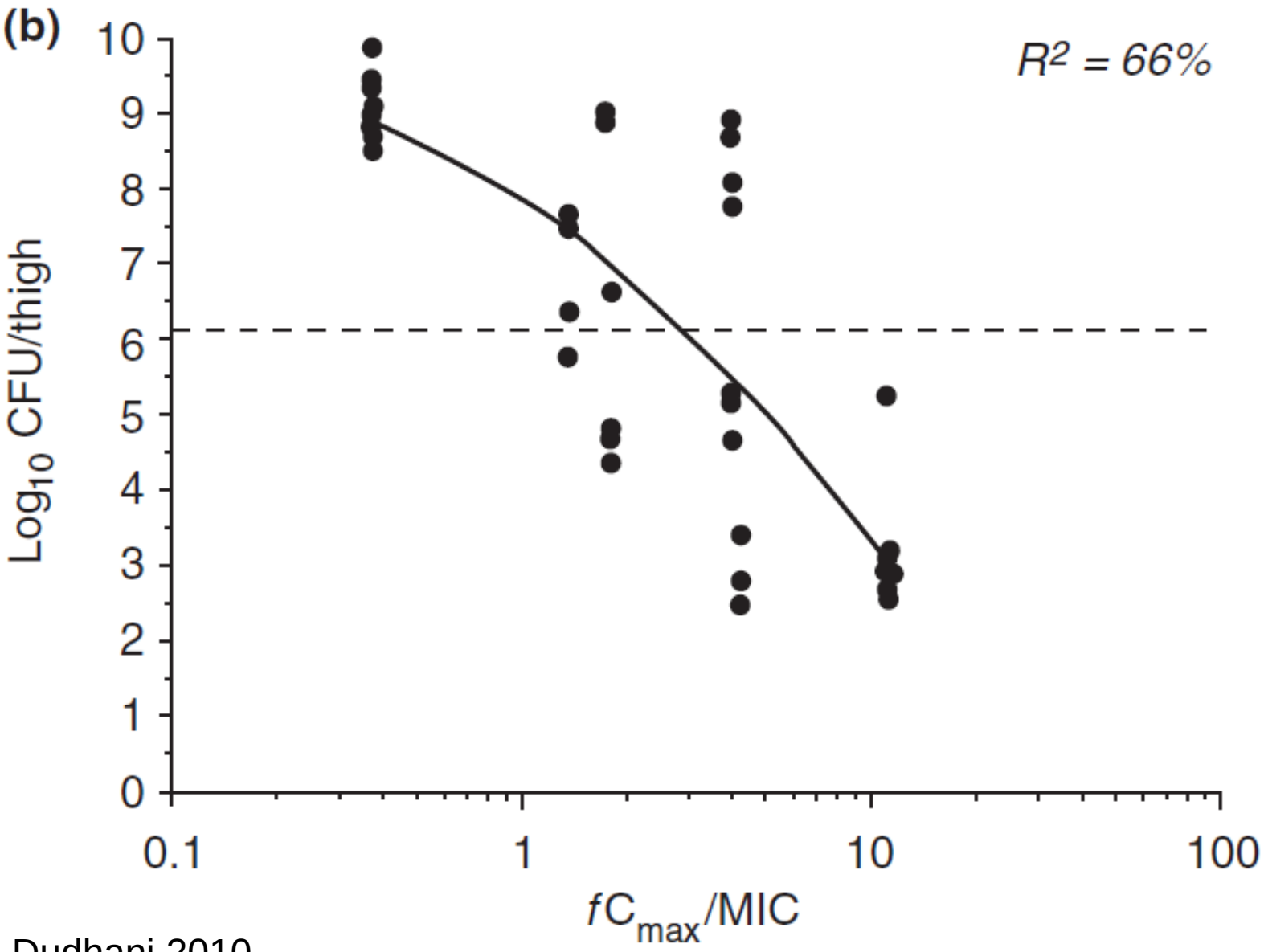
J Antimicrob Chemother 2010; **65**: 1984–1990
doi:10.1093/jac/dkq226 Advance Access publication 23 June 2010

Journal of Antimicrobial Chemotherapy

fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models

Rajesh V. Dudhani[1], John D. Turnidge[2,3], Roger L. Nation[1]† and Jian Li[1]*†





Dudhani 2010

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2006, p. 2946–2950 Vol. 50, No. 9
0066-4804/06/$08.00+0 doi:10.1128/AAC.00103-06

Heteroresistance to Colistin in Multidrug-Resistant *Acinetobacter baumannii*

Jian Li,[1]* Craig R. Rayner,[1] Roger L. Nation,[1] Roxanne J. Owen,[1] Denis Spelman,[2] Kar Eng Tan,[1] and Lisa Liolios[2]

Facility for Anti-infective Drug Development and Innovation, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia,[1] and Department of Microbiology and Infectious Diseases Unit, Alfred Hospital, Melbourne, Victoria, Australia[2]

Received 25 January 2006/Returned for modification 3 May 2006/Accepted 13 June 2006

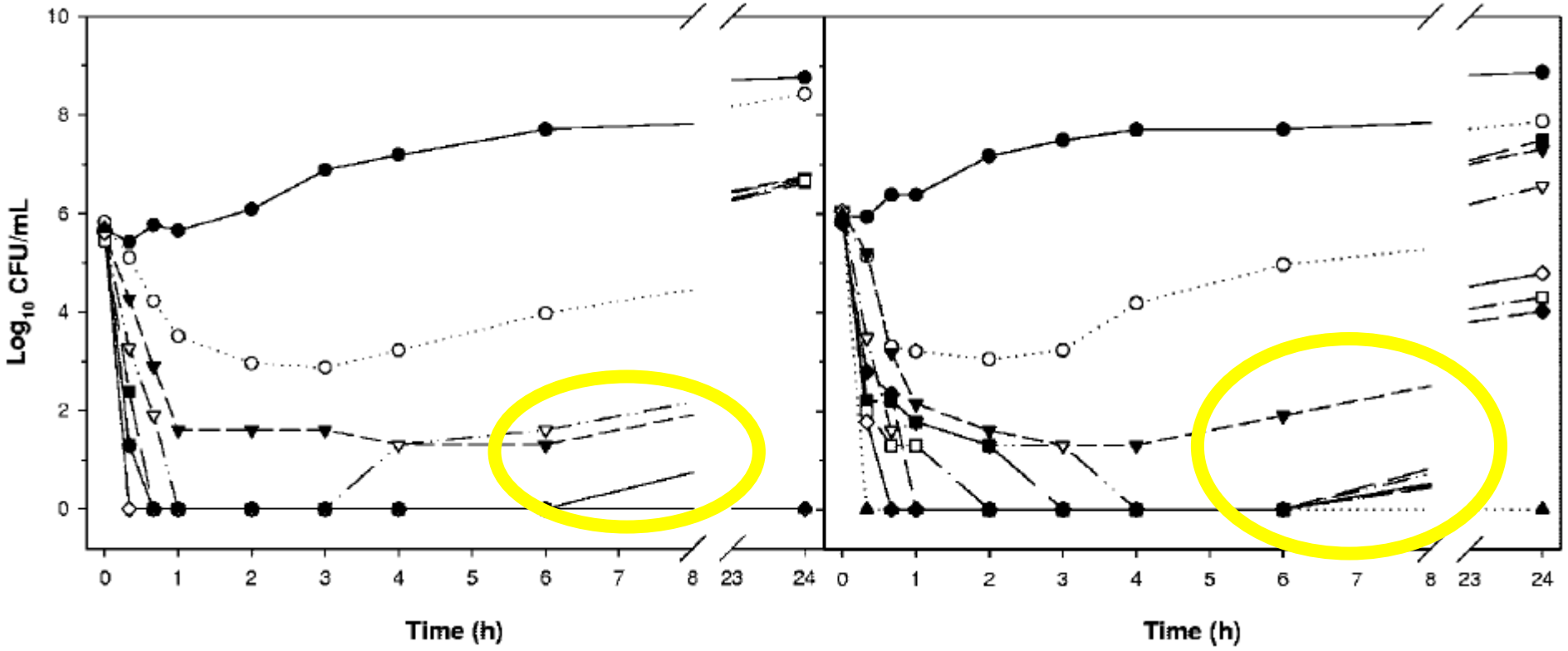


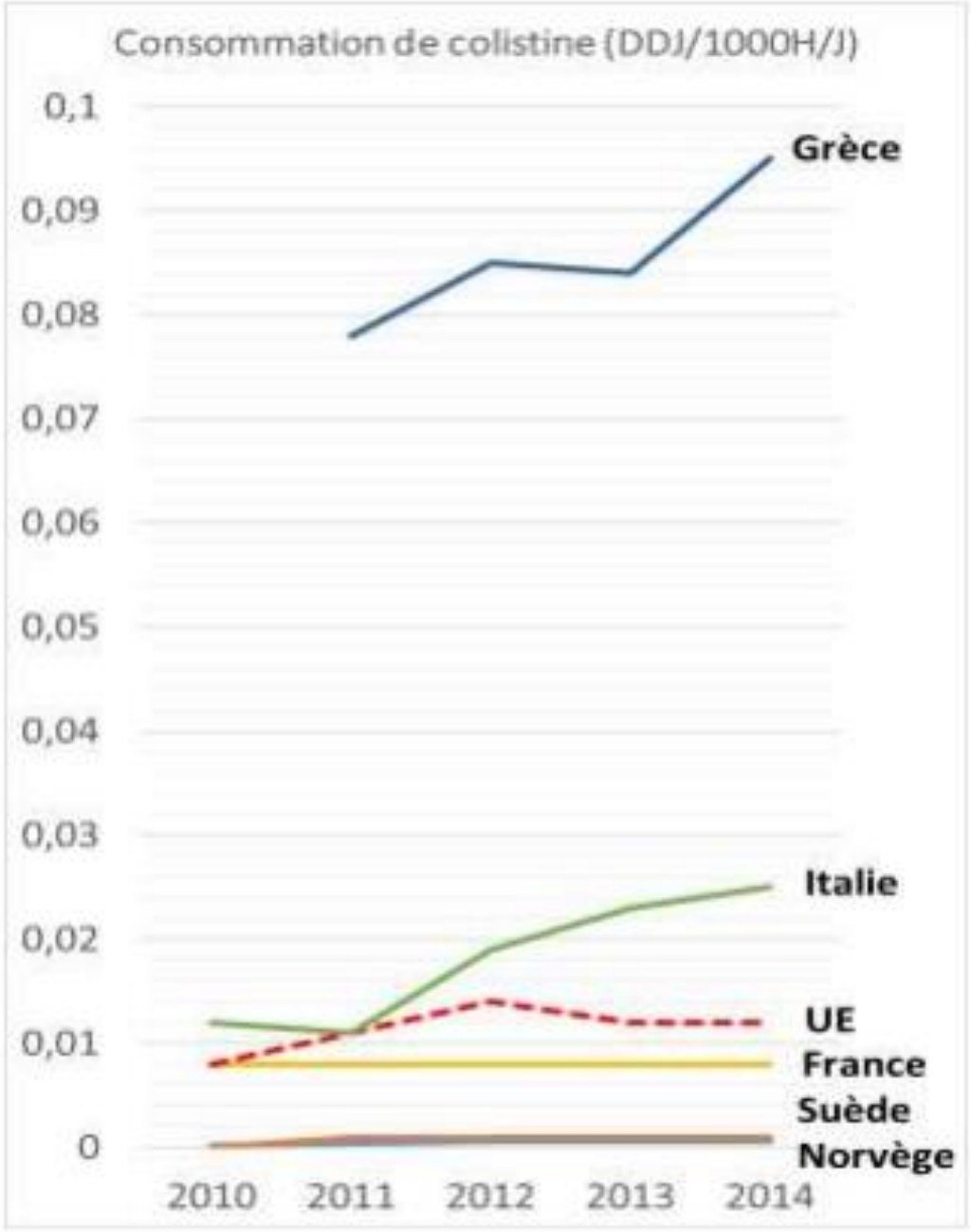
FIG. 2. Killing curves for ATCC 19606 (left panel) and isolate 6 (right panel) by colistin. Symbols: ●, control; ○, 0.5× MIC; ▼, 1× MIC; ▽, 2× MIC; ■, 4× MIC; □, 8× MIC; ◆, 16× MIC; ◇, 32× MIC; ▲, 64× MIC.

- Induction d'une résistance a minima

→ Nécessité de bithérapie

Retour donc de la colistine

- Quel est la posologie optimale ?
  - Les doses initialement recommandées sont-elles valides ?
- Quelle toxicité ?


Consommation de colistine (DDJ/1000H/J)
0,1
0,09
0,08
0,07
0,06
0,05
0,04
0,03
0,02
0,01
0
2010
2011
2012
2013
2014
Grèce
Italie
UE
France
Suède
Norvège

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]

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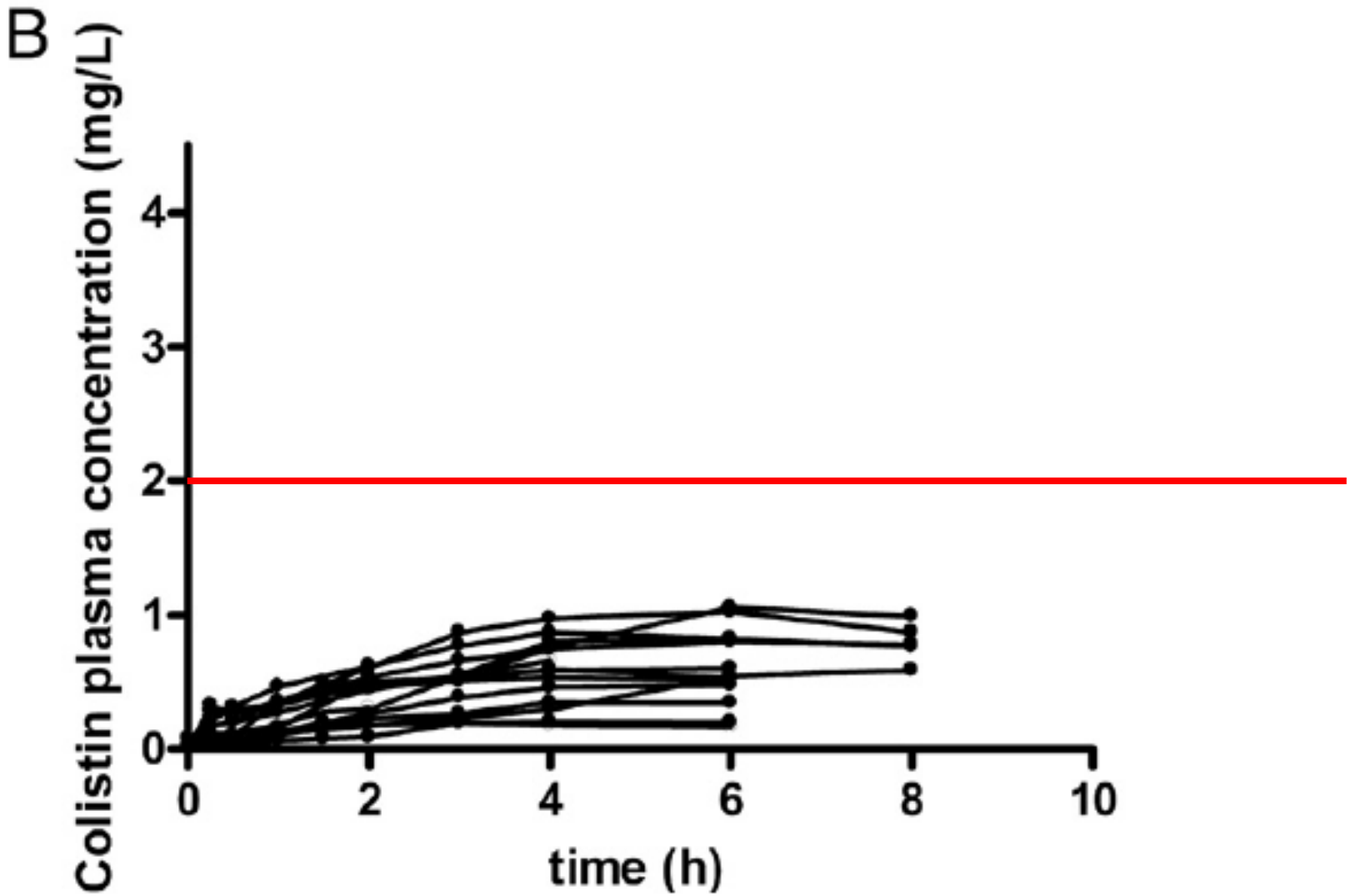
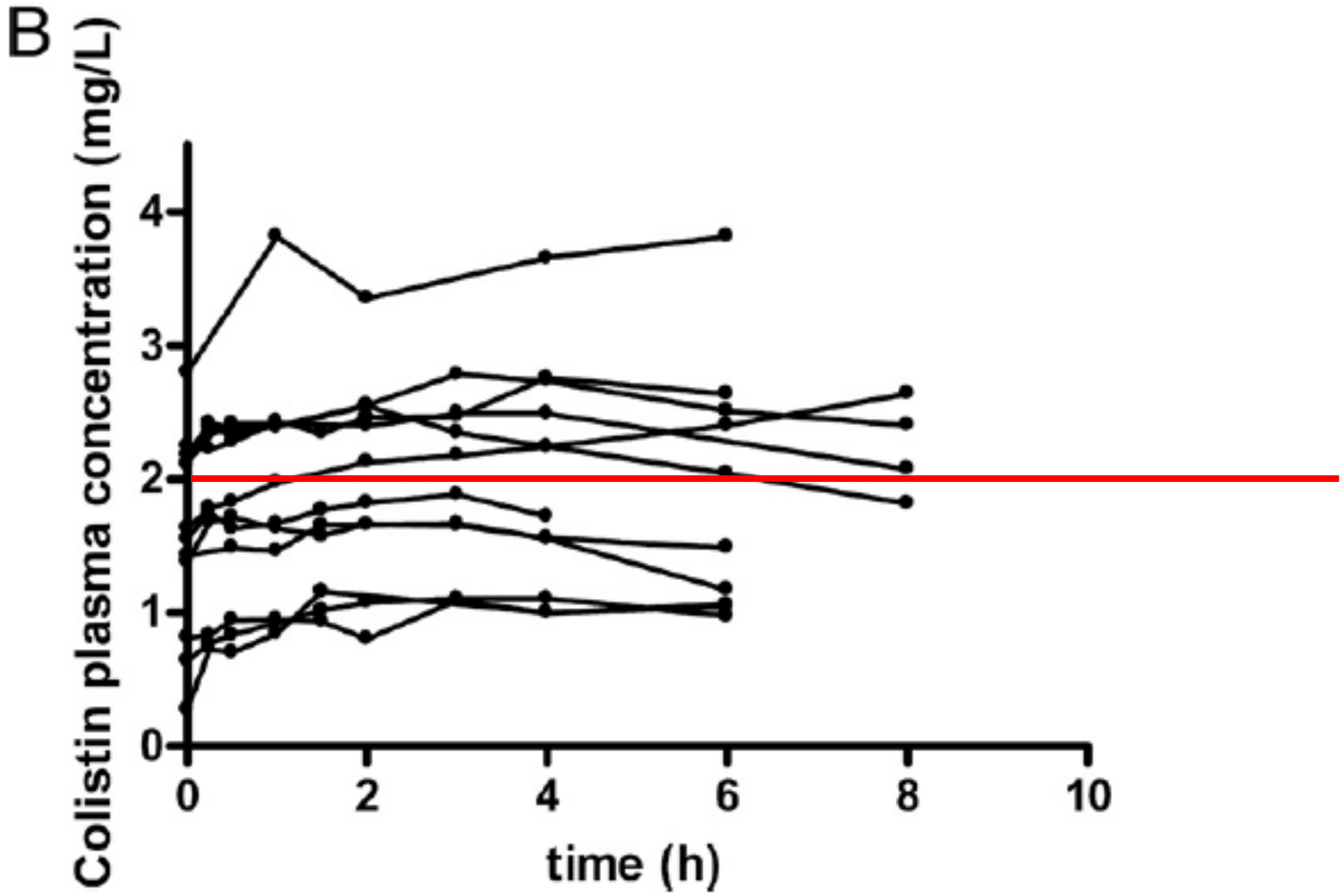
Received 10 October 2008/Returned for modification 8 January 2009/Accepted 4 May 2009



Plachouras 2009
Après la 1ère dose



Plachouras 2009
Après la 4ème dose

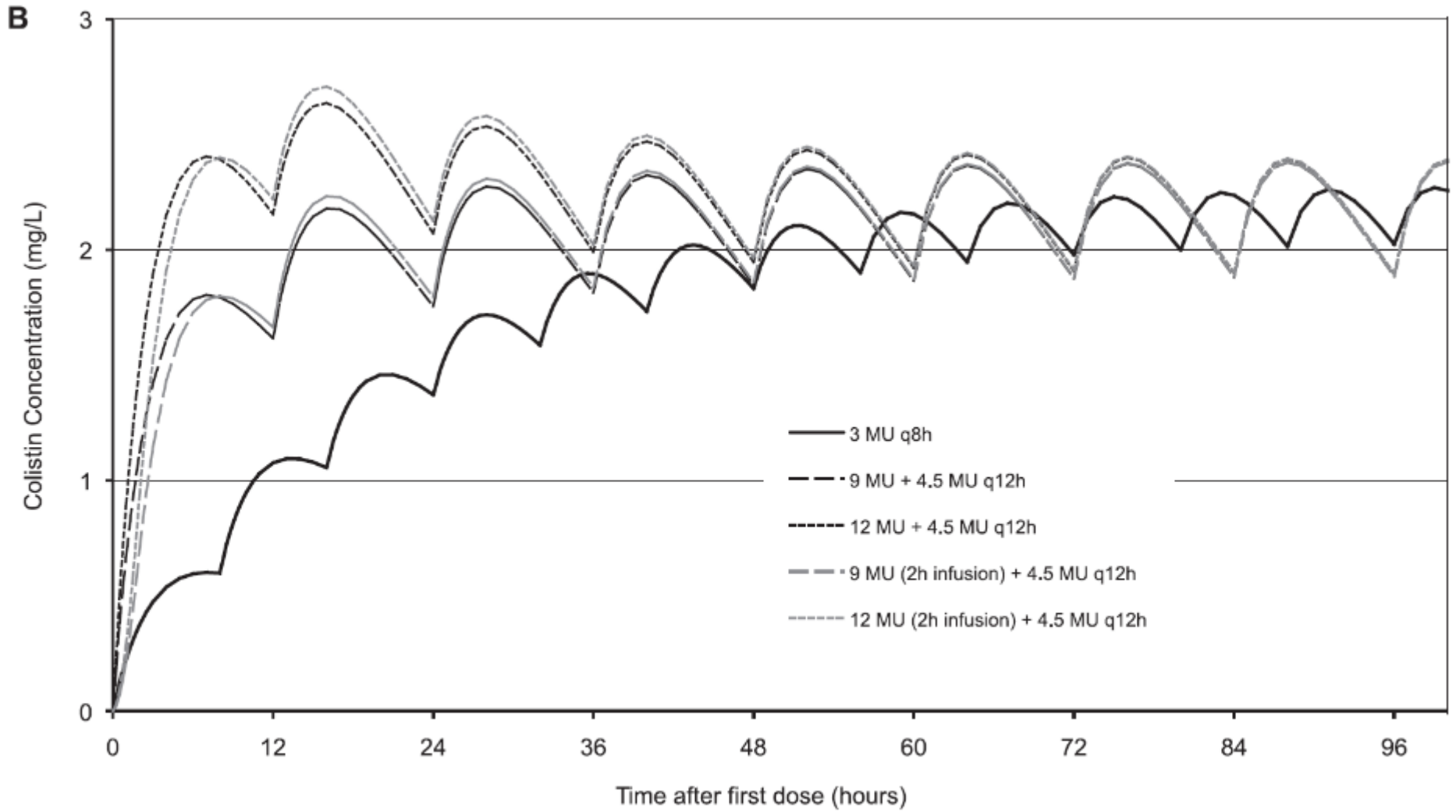


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min o 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).

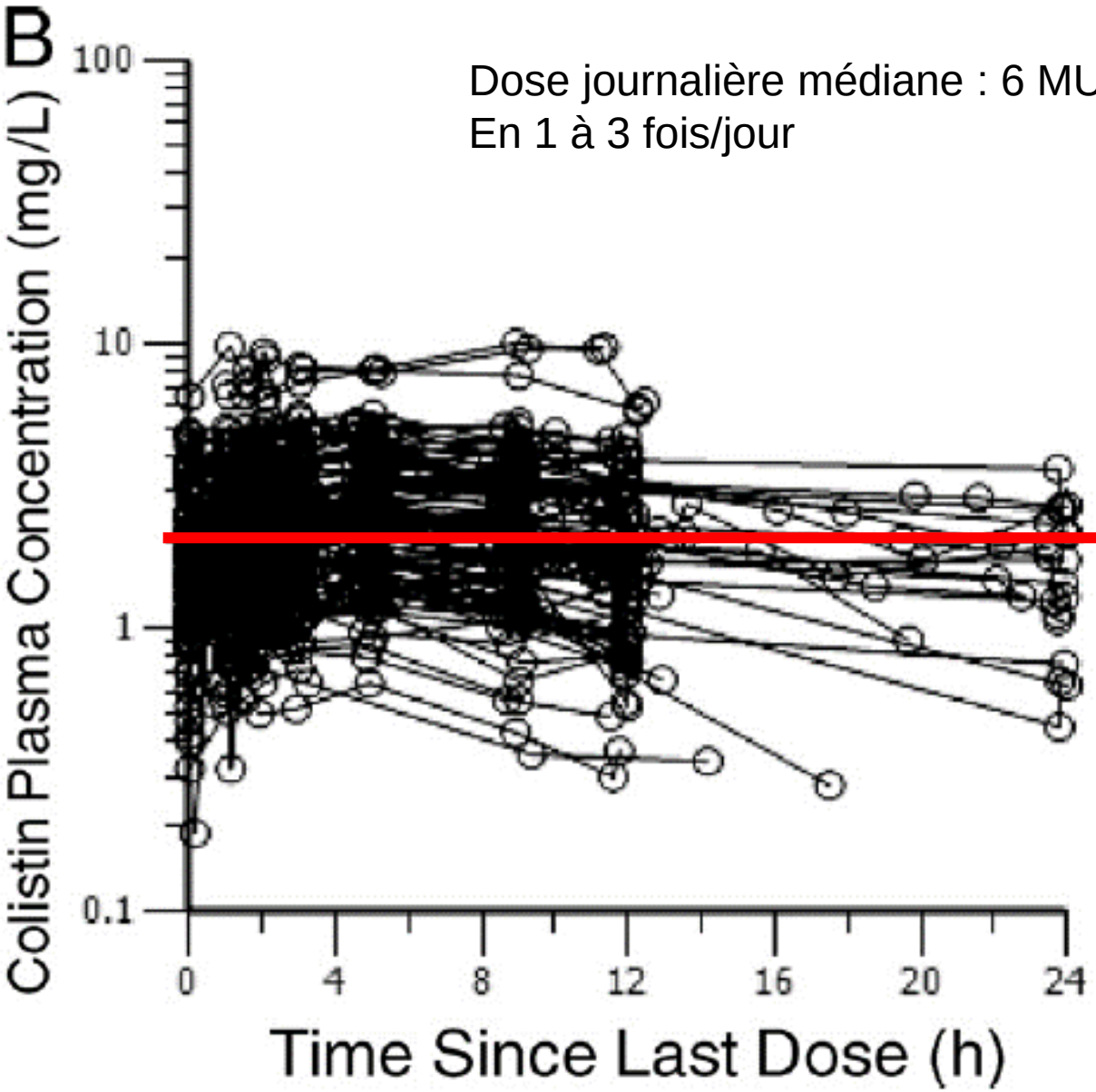
Plachouras 2009

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients▽

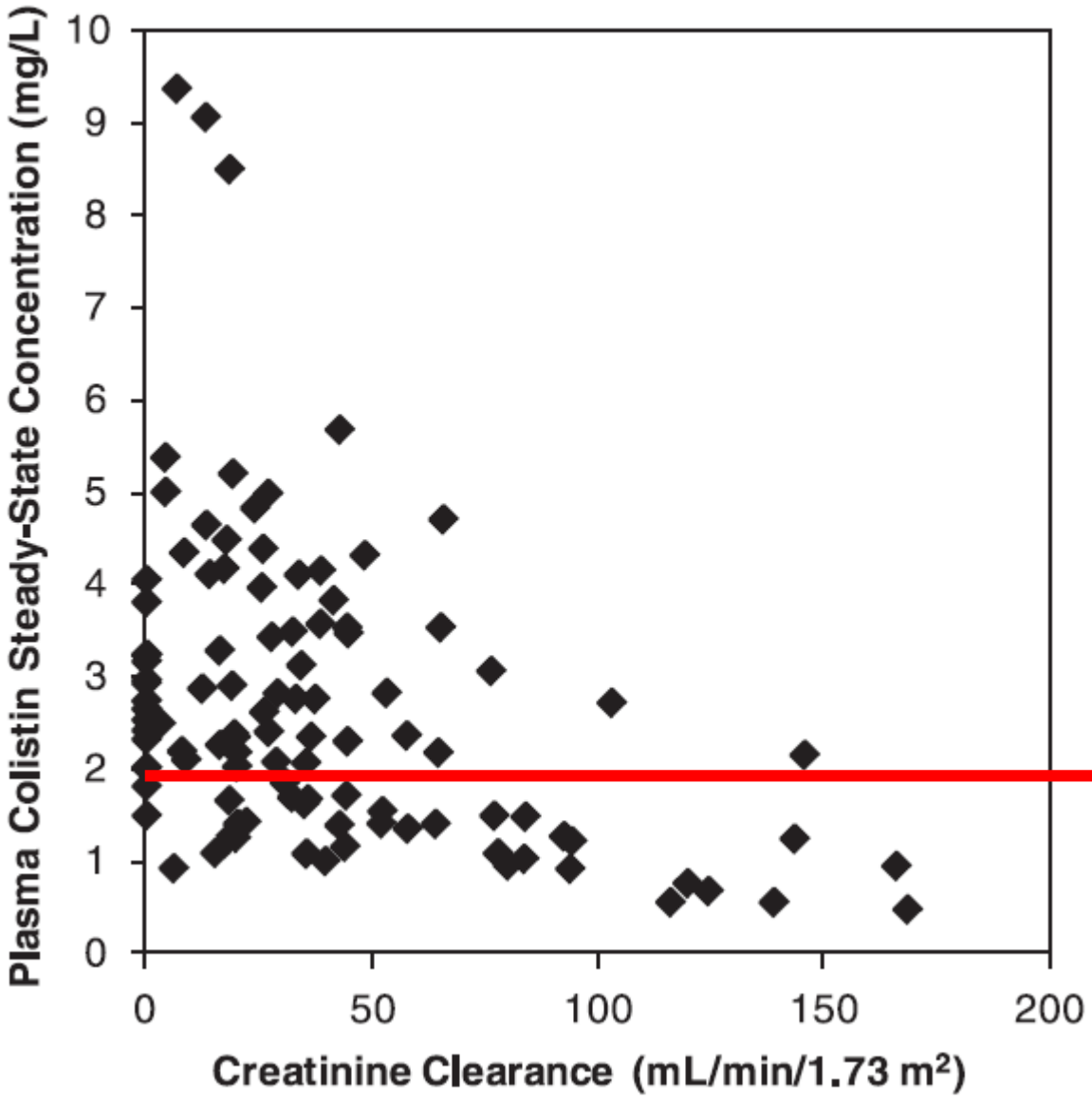
S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York[1]; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia[2]; Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand[3]; The University of Queensland Center for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia[4]; Washington Hospital Center, MedStar Clinical Research Center, Washington, DC[5]; and Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania[6]



Dose journalière médiane : 6 MUI
En 1 à 3 fois/jour

Garonzik 2011



Garonzik 2011

Suggestion des auteurs

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.
	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

Garonzik 2011

MAJOR ARTICLE

2012

Association Between Colistin Dose and Microbiologic Outcomes in Patients With Multidrug-Resistant Gram-Negative Bacteremia

Giulia Vicari,[1] Seth R. Bauer,[2] Elizabeth A. Neuner,[2] and Simon W. Lam[2]

[1]Department of Pharmacy, Community Hospital North, Indianapolis, Indiana; and [2]Department of Pharmacy, Cleveland Clinic, Ohio

Association Between Colistin Dose and Microbiologic Outcomes in Patients With Multidrug-Resistant Gram-Negative Bacteremia

Vicari 2012

76 patients
Dont 60 en ICU

Table 1. Baseline Patient and Bacteremia Characteristics in Patients Treated With Colistin for Carbapenem-Resistant Gram-Negative Bloodstream Infection who Achieved Microbiologic Success vs Failure at Day 7

Characteristic	Microbiological Success at Day 7 (n = 52)	Microbiological Failure at Day 7 (n = 24)	*P*
Gender, male	22 (42.3)	13 (54.2)	.335
Age, years	61.0 (49.3–67.0)	60.0 (52.3–72.3)	.461
DBW, kg	70.7 (60.4–78.0)	76.5 (67.9–95.7)	.080
BMI, kg/m^2	28.6 (23.2–33.2)	33.2 (24.8–39.2)	.154
Pitt bacteremia score	4.0 (2.0–5.0)	6.0 (3.3–7.0)	.002
Serum creatinine, mg/dL	1.1 (0.8–2.0)	1.8 (0.9–2.6)	.263
Charlson comorbidity index	3.0 (2.0–5.0)	3.0 (2.3–5.0)	.302
Duration of hospitalization prior to positive blood culture, days	17.7 (4.68–32.9)	14.6 (9.59–26.5)	.754

Association Between Colistin Dose and Microbiologic Outcomes in Patients With Multidrug-Resistant Gram-Negative Bacteremia

Vicari 2012

76 patients
Dont 60 en ICU

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Duration of hospitalization prior to positive blood culture, days	17.7 (4.68–32.9)	14.6 (9.59–26.5)	.754
Days from index blood culture to first dose of colistin	2.87 (1.10–4.10)	2.80 (1.42–3.72)	.849
Responsible pathogen			.286
P. aeruginosa	19 (37.3)	13 (54.2)	.211
A. baumannii	14 (26.9)	4 (16.7)	.328
K. pneumoniae	19 (37.3)	7 (29.2)	.609
Source of infection[a]			
Catheter-related	22 (42.3)	12 (50.0)	.531
Catheter removal	22/22	11/12	
Abdominal	14 (26.9)	5 (20.8)	.569
Respiratory	9 (17.3)	6 (25.0)	.434
Skin/soft tissue	1 (1.9)	1 (4.2)	.535
Genitourinary	6 (11.5)	1 (4.2)	.421
Endovascular	1 (1.9)	1 (4.2)	.535
Isolates with colistin MIC ≤2 mg/dL	41/43	15/15	1.0
Colistin dose (in CBA) in mg/kg/day (DBW)	2.90 (1.70–3.68)	1.50 (1.10–2.0)	.011

=90.10^3 UI/kg

=45.10^3 UI/kg

Table 2. Multivariate Logistic Regression Analysis of Independent Risk Factors Associated With Day-7 Microbiological Success in Patients Treated With Colistin for Carbapenem-Resistant Gram-Negative Bloodstream Infection

Variables	Adjusted OR	95% CI	*P*
Colistin dose in mg/kg/day (DBW)	1.74	1.11–2.71	.015
Pitt bacteremia score	0.64	.49–.85	.001
Concomitant tigecycline	0.23	.07–.79	.019

All factors entered into the multivariate logistic regression model are presented. Hosmer–Lemeshow goodness of fit test, $\chi^2 = 10.97$; $P = .14$.

Abbreviations: CI, confidence interval; DBW, dosing body weight; OR, odds ratio.

Vicari 2012

MAJOR ARTICLE

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

[1]Anesthesia and Intensive Care Unit, Department of Emergeny and Organ Transplantion; and [2]Microbiology Section, Department of Interdisciplinary Medicine, University of Bari, Italy

(See the Editorial Commentary by Roberts and Lipman, on pages 1727–9.)

2012

Dalfino 2012

- 25 patients, 28 traitements
- Loading dose 9MUI
- Puis 4,5MUI/12h

- 23 succès

Table 1. Patients' Characteristics and Clinical Features of Infectious Episodes Among 23 Infectious Episodes With and 5 Without a Favorable Response to Colistimethate Sodium Therapy

Variable	CMS Response[a]	No CMS Response
Age (years), mean ± SD	62 ± 18	76 ± 3
Charlson comorbidity index, mean ± SD	2 (1.5)	3.2 (2.2)[b]
Surgical admission, No. (%) of patients	8/20 (40)	4/5 (80)
APACHE II score, mean ± SD	18 ± 6	25 ± 7[b]
SOFA score, mean ± SD	7.6 ± 2	9.1 ± 2
ICU LOS (days)	56 (30–85)	75 (52–86)
ICU mortality, No. (%) of patients	5/20 (25)	5/5 (100)[b]
Infectious episodes, No. (%) of cases	23/28 (82.1)	5/28 (17.9)
Onset time of infection (days)	22 (12–47)	42 (23–54)
BSI, No. (%) of cases	13/23 (56.5)	5/5 (100)
BSI-associated pathogens, No. of isolates		
Acinetobacter baumannii	6	2
Klebsiella pneumoniae	6	3
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	13/13 (100)	0/5[b]
VAP, No. (%) of cases	10/23 (43.5)	0/5
VAP-associated pathogens, No. of isolates		
Acinetobacter baumannii	5	0
Klebsiella pneumoniae	4	0
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	4/10 (40)	0/5 (0)
Clinical presentation, No. (%) of cases		
Severe sepsis	16/23 (69.5)	0/5 (0)[b]
Septic shock	7/23 (30.5)	5/5 (100)[b]
Daily CMS dose (MU/d)	8.5 (7.3–9)	7.7 (5–8.5)
Cumulative CMS dose (MU/course)	91 (61–122)	105 (17–142)
CMS monotherapy, No. (%) of courses	12/23 (52.2)	2/5 (40)
CMS treatment duration (days)	11 (10–14.5)	15.5 (7–21)

Data are median value (interquartile range), unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CMS, colistimethate sodium; ICU, intensive care unit; LOS, length of stay; MU, million units; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

[a] Three patients developed 2 infectious episodes due to different species of pathogens susceptible only to colistin. Each infection was considered to be a second case and was treated with CMS separately.

[b] $P < .05$ versus patients with response.

AAC
Journals.ASM.org

Décembre 2015

Colistin Population Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in Critically Ill Patients

Ilias Karaiskos,[a] Lena E. Friberg,[b] Konstantinos Pontikis,[c] Konstantinos Ioannidis,[d] Vasiliki Tsagkari,[c] Lamprini Galani,[a] Eirini Kostakou,[c] Fotini Baziaka,[a] Charalambos Paskalis,[e] Antonia Koutsoukou,[c] Helen Giamarellou[a]

6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece[a]; Department of Pharmaceutical Biosciences, Uppsala University, Sweden[b]; 1st Department of Respiratory Diseases–Intensive Care Unit, Sotiria Hospital, Greece[c]; Clinical Pharmacist, Hygeia General Hospital, Athens, Greece[d]; Intensive Care Unit, Hygeia General Hospital, Athens, Greece[e]

- 9 MUI en dose de charge
- Puis 4,5 MUI / 12h

MAJOR ARTICLE

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

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(See the Editorial Commentary by Roberts and Lipman, on pages 1727–9.)

2012

Risque d'insuffisance rénale

Factor	No AKI (n = 23)	AKI (n = 5)
Septic shock	10 (43.5)	2 (40)
Concomitant nephrotoxic agents	20 (86.9)	4 (80)
Antibiotics	7 (30.4)	3 (60)
Diuretics	15 (65.2)	3 (60)
Radiocontrast agents	1 (4.3)	4 (80)[a]
Mannitol	4 (17.4)	1 (20)
Daily CMS dose (MU/day)	8.3 (6.5–9)	7.1 (6–8.5)
CMS treatment duration (days)	11 (9.5–17.5)	12 (10–15)
Cumulative CMS dose	92 (56–126)	81 (64–92)

Data are No. (%) of infectious episodes or median (interquartile range).

Abbreviations: CMS, colistimethate sodium; MU, million units.

[a] $P < .05$ between groups.

Dalfino 2012

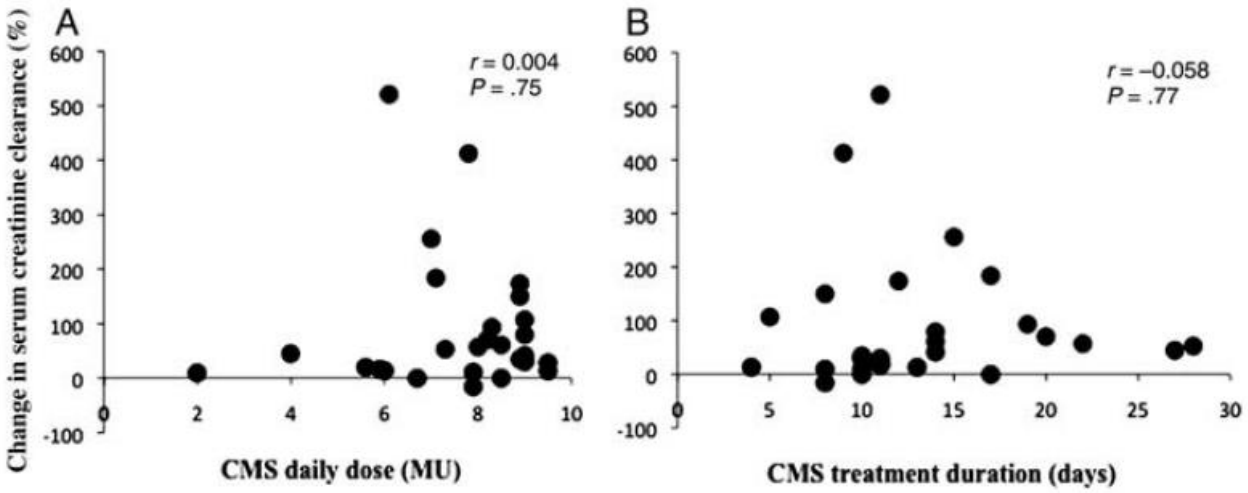
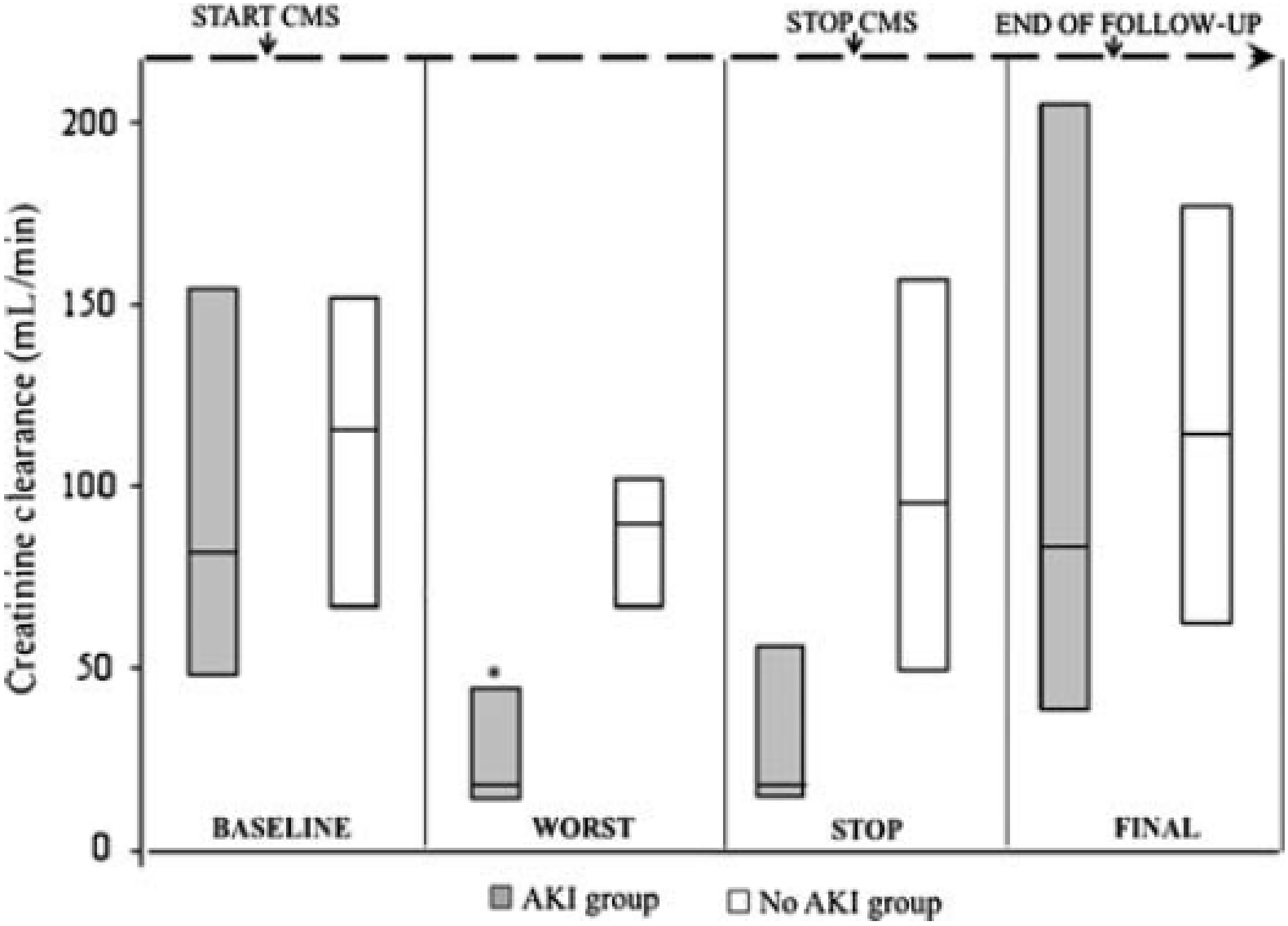


Figure 2. Correlation between serum creatinine variation (from baseline to peak values) and daily colistimethate sodium doses (*A*) and between serum creatinine variation (from baseline to peak values) and treatment duration (*B*). Abbreviation: CMS, colistimethate sodium.

Dalfino 2012



Dalfino 2012

International Journal of Antimicrobial Agents 35 (2010) 473–477

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

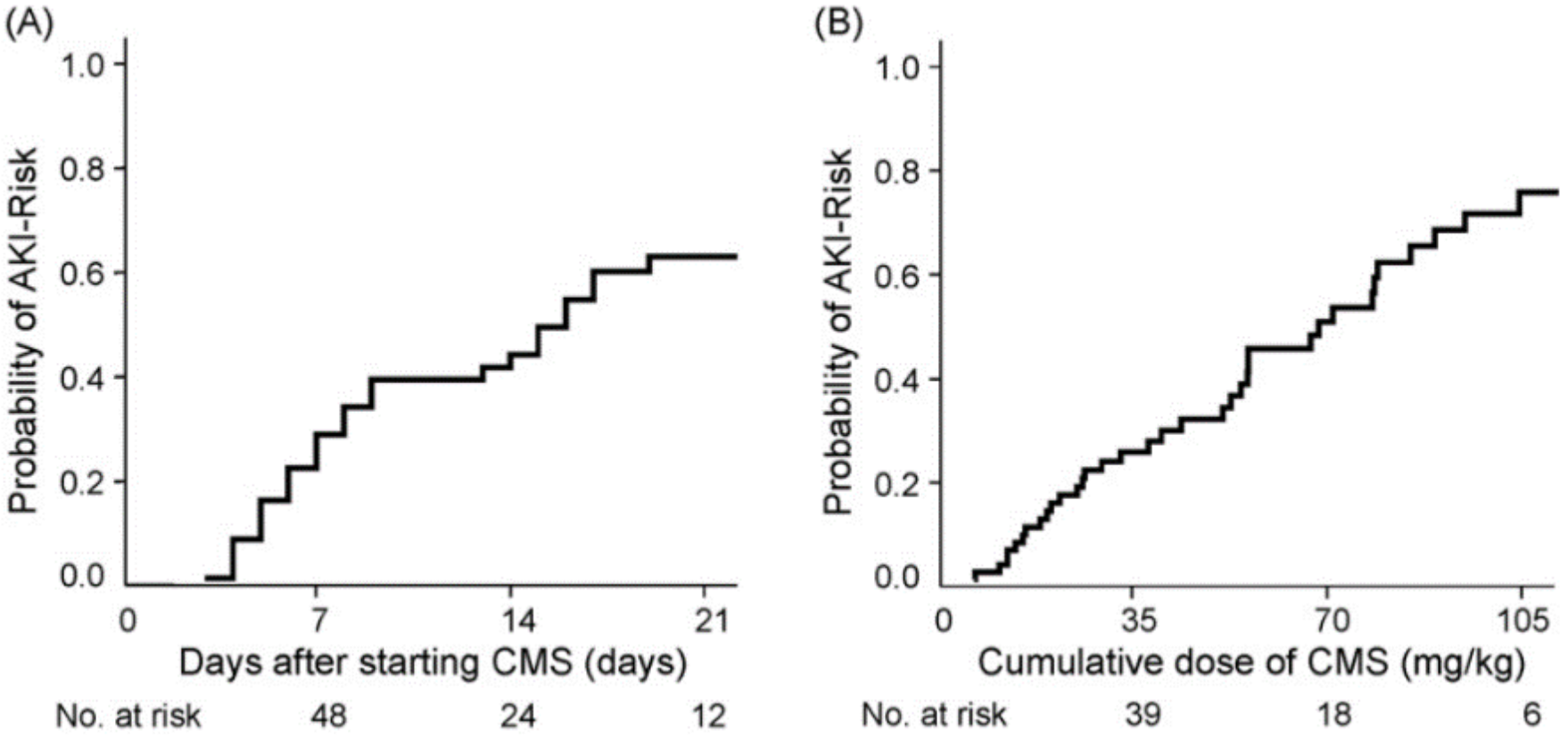
Predictors of acute kidney injury associated with intravenous colistin treatment

Jeong-Ah Kwon[a], Jung Eun Lee[a,*], Wooseong Huh[a], Kyong Ran Peck[b], Yoon-Goo Kim[a], Dae Joong Kim[a], Ha Young Oh[a]

[a] Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea
[b] Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

- 71 patients
- Dose médiane : 6.10^4 UI/kg/j
- 38 AKI :
  - 11 : créat x1,5
  - 10 : créat x2
  - 27 : créat x3 ou >400µM

AKI = Créat x 1,5



Kwon 2012

Table 3
Cox proportional hazard models of acute kidney injury Risk based on cumulative colistimethate sodium dose (mg/kg).

Variable	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)[a]
Age	1.02 (1.00–1.04)	0.12	
Sex (male vs. female)	1.71 (0.80–3.64)	0.16	3.55 (1.47–8.55)
Hypertension	1.89 (0.98–3.64)	0.058	
Diabetes mellitus	1.92 (0.98–3.77)	0.057	
Sepsis	0.54 (0.24–1.21)	0.13	
Radiocontrast	0.85 (0.42–1.73)	0.66	
Diuretics	1.55 (0.82–2.95)	0.18	
NSAIDs	0.49 (0.17–1.38)	0.17	
Calcineurin inhibitor	3.76 (1.80–7.89)	<0.001	6.74 (2.49–18.24)
Vancomycin	1.75 (0.90–3.40)	0.098	
GFR <60 mL/min/1.73 m^2	1.06 (0.46–2.45)	0.89	
Serum albumin <2.0 g/dL	2.84 (1.08–7.47)	0.035	6.29 (2.04–19.39)
Total bilirubin >5 mg/dL	2.54 (0.95–6.78)	0.064	3.53 (1.17–10.71)

HR, hazard ratio; 95% CI, 95% confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; GFR, glomerular filtration rate.

[a] The multivariate model also included age, hypertension, diabetes mellitus and concomitant use of vancomycin.

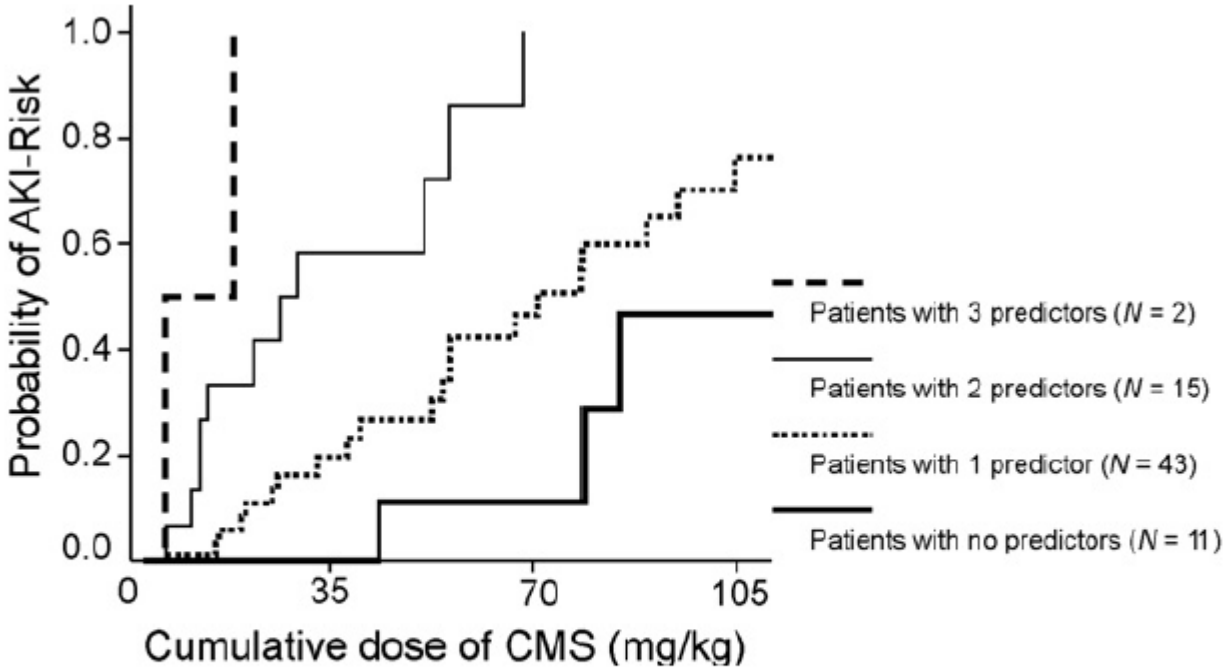


Fig. 3. Probability of acute kidney injury (AKI) Risk according to the number of predictors present as identified in a Cox regression model ($P < 0.001$ by log-rank test). CMS, colistimethate sodium.

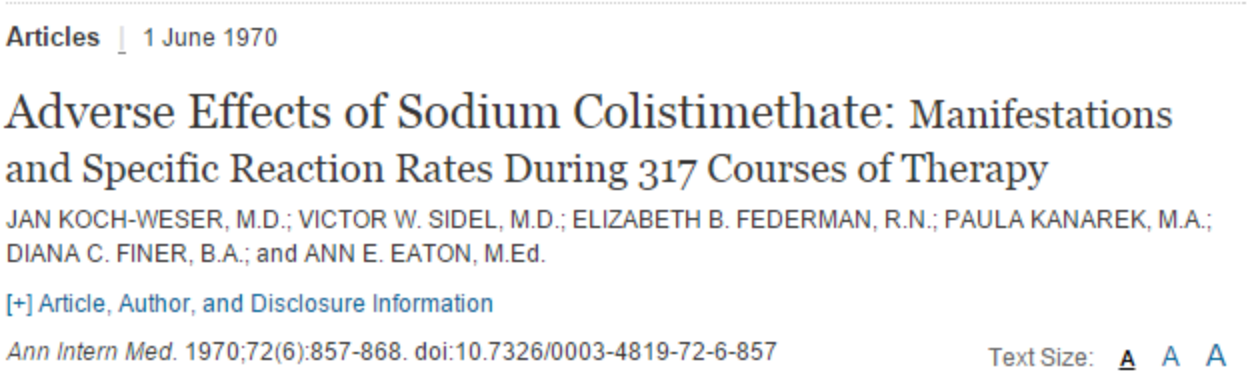
70mg/kg = 60 MUI pour 70 kg

Predictors:

- *male*
- *calcineurine Inh*
- *hypoprotidemia*
- *hyperbilirubinemia*

Kwon 2010

Neurotoxicité



Articles | 1 June 1970

Adverse Effects of Sodium Colistimethate: Manifestations and Specific Reaction Rates During 317 Courses of Therapy

JAN KOCH-WESER, M.D.; VICTOR W. SIDEL, M.D.; ELIZABETH B. FEDERMAN, R.N.; PAULA KANAREK, M.A.; DIANA C. FINER, B.A.; and ANN E. EATON, M.Ed.

[+] Article, Author, and Disclosure Information

Ann Intern Med. 1970;72(6):857-868. doi:10.7326/0003-4819-72-6-857

Text Size: A A A

- 7% des cas (série de 1970) :
  - Paresthésies orofaciales
  - Comitialité
  - Confusion
  - Bloc neuromusculaire myasthéniforme
- Études plus récentes : quasi-absent

CASE REPORT

Colistin-mediated neurotoxicity

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Accepted 18 August 2014

SUMMARY

We describe a 51-year-old man who developed renal and neural toxicity after the administration of colistin. He developed respiratory apnoea, neuromuscular blockade and severe comatose encephalopathy with the lack of brainstem reflexes. After discontinuation of the antibiotic, he made a prompt recovery to his baseline neurological function. The case illustrates the importance of recognising the toxicities associated with colistin. Although recent literature details its nephrotoxicity, current data have been discordant with the rare cases of respiratory apnoea or neuromuscular blockade once cited over 30 years ago. Additionally, no cases have ever described the profound encephalopathy with lack of

CASE REPORT

Colistin neurotoxicity: revisited

Aruna Nigam,[1] Archana Kumari,[1] Reena Jain,[2] Swaraj Batra[1]

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Accepted 12 July 2015

SUMMARY

The revival of polymyxin antibiotics with the advent of multidrug resistant gram–negative bacteria in the recent decade has led to renewed interest in toxicity of this indispensable drug. We report a postoperative case of burst abdomen where colistin was started in view of *Pseudomonas* organism sensitive to colistin. Subsequently, the patient went into respiratory depression and encephalopathy after starting the treatment. She recovered promptly after stopping the drug.

Recommandations ?

- Dose de charge 9 MUI
- Puis 4,5 MUI / 12h
- Si insuffisance rénale : ?

Dear doctor letter, fev 2013

La rubrique « Posologie et Mode d'administration » a été revue.
La spécialité doit désormais être utilisée selon les modalités suivantes chez l'adulte et chez l'enfant :
COLIMYCINE® 1 000 000 U.I., poudre et solvant pour solution injectable doit être administré **par voie intraveineuse en perfusion lente, d'une durée de 1 heure**. L'utilisation par voie intrathécale ou par voie intraventriculaire peut éventuellement être envisagée. L'administration par voie intramusculaire n'est pas recommandée.

La dose à administrer est exprimée en colistiméthate sodique.
Pour la voie intraveineuse
Adulte, adolescent :

Pour 70kg : 5-10 MUI

75 000 à 150 000 UI/kg/j, en 1 à 3 administrations journalières, sans dépasser 12 MUI/j.
Une utilisation de COLIMYCINE® 1 000 000 U.I., poudre et solvant pour solution injectable chez un patient avec une fonction rénale altérée doit s'accompagner, dans tous les cas, d'une surveillance de la fonction rénale.
Si la clairance de la créatinine est > 30 ml/min, se référer à la posologie du sujet normo-rénal.
Si la clairance de la créatinine est ≤ 30 ml/min, voir le tableau ci-dessous :

Clairance de la créatinine (ml/min)	Dose	Fréquence d'administration
10 - 30	30 000 à 50 000 UI/kg/dose	Toutes les 12 à 18 h
< 10	30 000 à 50 000 UI/kg/dose	Toutes les 18 à 24 h

2015

The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

Antonis Valachis, MD, PhD[1]; George Samonis, MD, PhD[2]; Diamantis P. Kofteridis, MD, PhD[2]

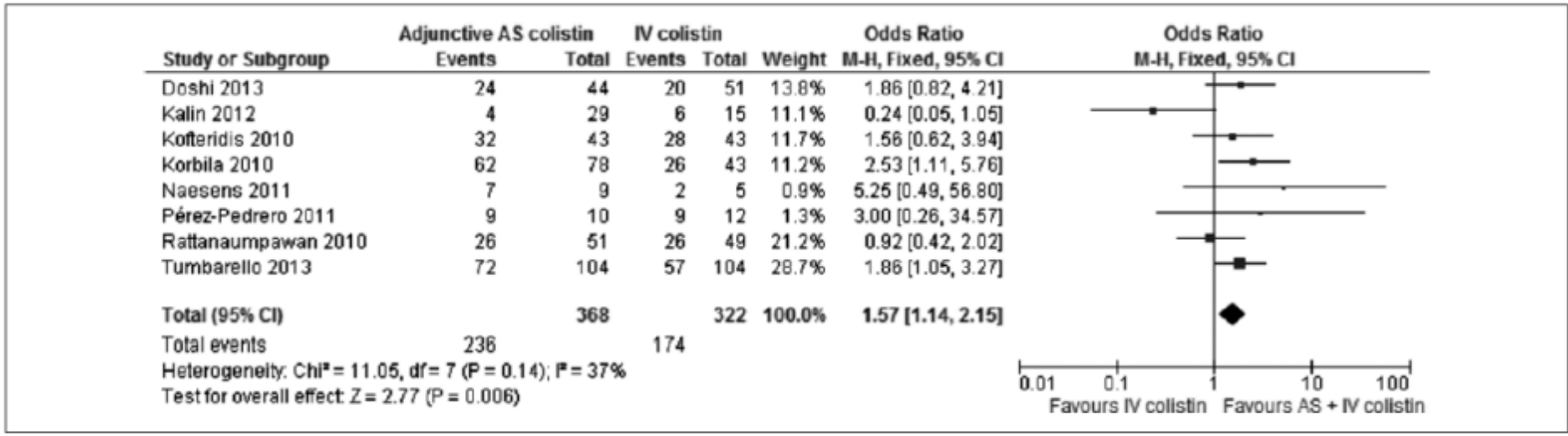


Figure 2. Forest plot of clinical response between patients who received aerosolized (AS) + IV colistin and those who received IV colistin. M-H = Mantel-Haenszel.

Clinical response

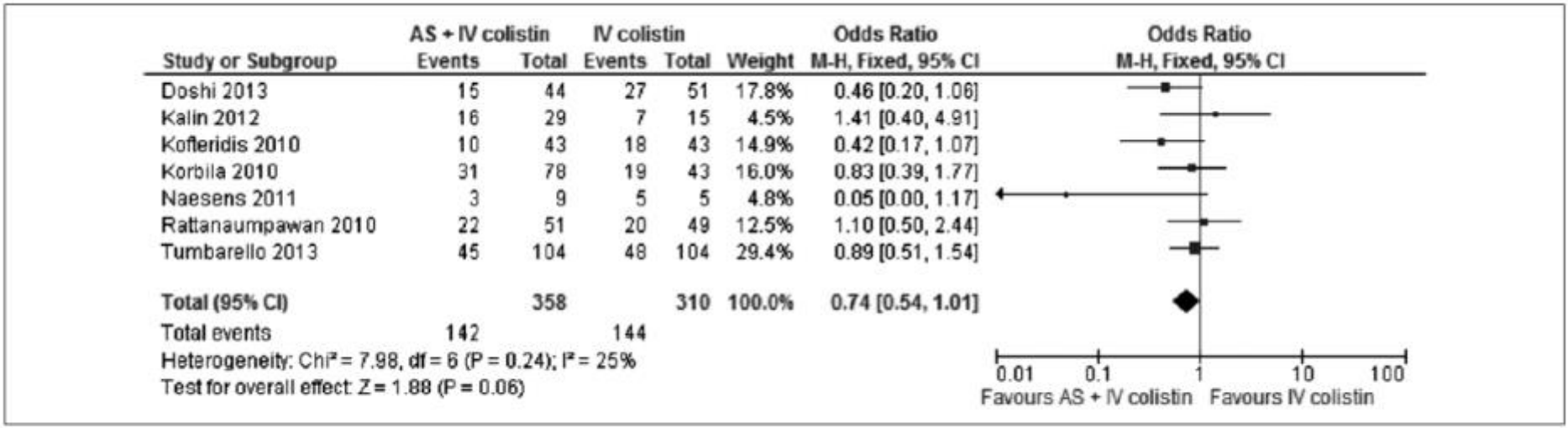


Figure 3. Forest plot of overall mortality between patients who received aerosolized (AS) + IV colistin and those who received IV colistin. M-H = Mantel-Haenszel.

Mortality

International Journal of Antimicrobial Agents 46 (2015) 603–609

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis

Dong Liu[a], Jing Zhang[b], Hai-Xia Liu[a], Ying-Gang Zhu[a], Jie-Ming Qu[a,c,*]

[a] Department of Pulmonary Medicine, Huadong Hospital, Shanghai Medical College, Fudan University, Shanghai, China
[b] Department of Pulmonary Medicine, Zhongshan Hospital, Shanghai Medical College, Fudan University, Shanghai, China
[c] Ruijin Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, China

Study or Subgroup	IV-AS Events	IV-AS Total	IV Events	IV Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Doshi, N. M 2013	24	44	20	51	16.5%	1.86 [0.82, 4.21]
Kalin, G 2012	4	29	6	15	13.3%	0.24 [0.05, 1.05]
Kofteridis, D. P 2010	32	43	26	43	13.0%	1.90 [0.76, 4.76]
Korbila, I. P 2010	62	78	26	43	13.4%	2.53 [1.11, 5.76]
Mohamed, A 2013	22	28	7	12	4.1%	2.62 [0.61, 11.28]
Naesens, R 2011	7	9	2	5	1.1%	5.25 [0.49, 56.80]
Perez-Pedrero, M. J 2011	12	15	12	18	4.3%	2.00 [0.40, 9.91]
Tumbarello, M 2013	72	104	57	104	34.3%	1.86 [1.05, 3.27]
Total (95% CI)		**350**		**291**	**100.0%**	**1.81 [1.30, 2.53]**
Total events	235		156			

Heterogeneity: $Chi^2 = 8.88$, df = 7 (P = 0.26); $I^2 = 21\%$

Test for overall effect: Z = 3.49 (P = 0.0005)

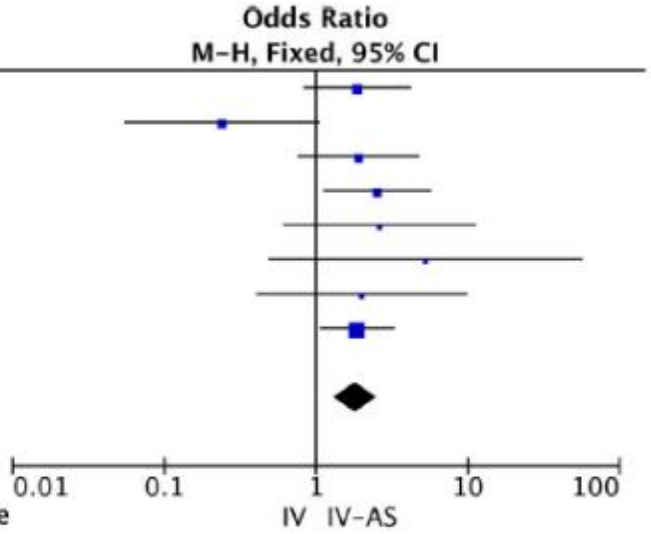


Fig. 2. Clinical response rates (improvement and cure) with aerosolised and intravenous (IV-AS) colistin compared with intravenous (IV) colistin alone. Clinical cure was defined as resolution of presenting symptoms and signs of infection by the end of colistin treatment, and clinical improvement was defined as partial resolution of presenting symptoms and signs of infection. Patients receiving IV-AS colistin treatment showed a higher clinical response rate (improvement and cure) compared with those treated with IV colistin alone (eight studies; 641 patients).

Clinical response

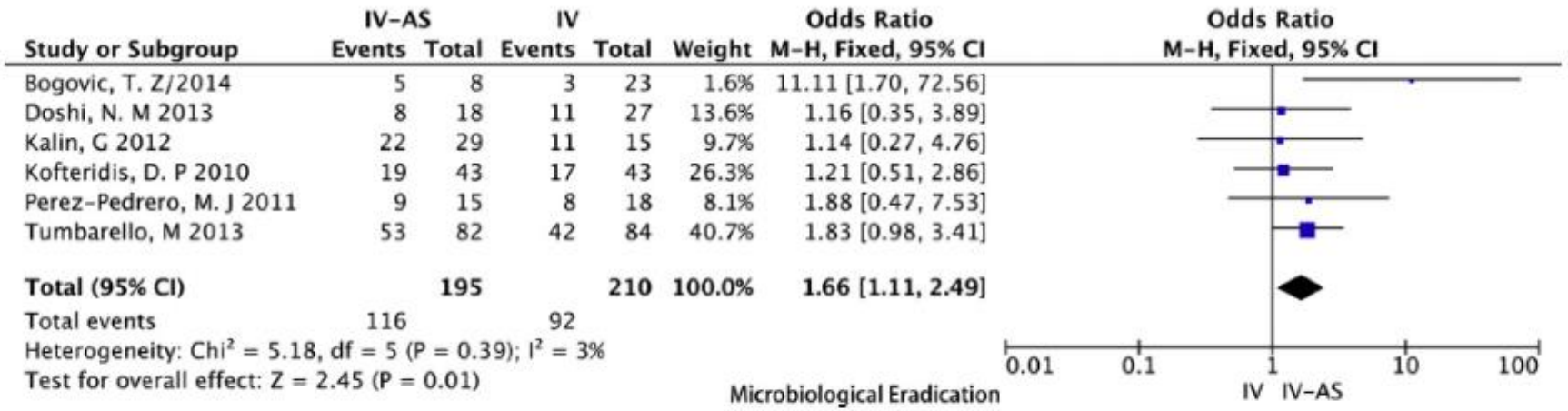


Fig. 4. Microbiological eradication with aerosolised and intravenous (IV-AS) colistin compared with intravenous (IV) colistin alone. Microbiological eradication was defined as eradication of the pathogen in the final culture of specimens during the entire hospitalisation. Patients receiving IV-AS colistin treatment achieved a higher rate of pathogen eradication compared with those treated with IV colistin alone (six studies; 405 patients).

Microbiological eradication

Spyros D. Mentzelopoulos
Maria Pratikaki
Evangelia Platsouka
Helen Kraniotaki
Dimitris Zervakis
Antonia Koutsoukou
Serafim Nanas
Olga Paniara
Charis Roussos
Evangelos Giamarellos-Bourboulis
Christina Routsi
Spyros G. Zakynthinos

Prolonged use of carbapenems and colistin predisposes to ventilator-associated pneumonia by pandrug-resistant *Pseudomonas aeruginosa*

Juin 2007

Table 3 Factors significantly associated with infection due to pandrug-resistant *P. aeruginosa* in pandrug-resistant *P. aeruginosa* cases and controls (univariate analysis) (*PDR* pandrug-resistant, *CI* confidence interval)

	Cases ($n=5$)	Controls ($n=20$)	Odds ratio	95% CI	p
Carbapenem use > 20 days and colistin use > 13 days[a]	4 (80%)	1 (5%)	76.0	3.9–1487.5	0.004
> 78 open suction procedures 6–26 Sept. 2005	4 (80%)	4 (20%)	16.0	1.4–185.4	0.03
Carbapenem use > 20 days[b]	4 (80%)	5 (25%)	12.0	1.1–134.1	0.04

[a] Also identified as the sole independent predictor of PDR *P. aeruginosa* infection by binary, stepwise logistic regression results, with an identical odds ratio, 95% CI, and p value

[b] Considered a confounder

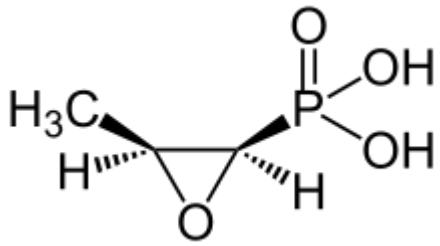
En conclusion pour la colistine

- Médicament de réserve pour les BMR
  - *Klebsiella* / carbapénémase
  - *Acinetobacter* multi-R
  - *Pseudomonas* multi-R
- En association
- Dose de charge (9MUI)
- Puis toutes les 12h (4,5MUI)
- Association avec aérosol si pneumonie

Fosfomycine

Fosfomycine

- Isolée d'un *Paecilomyces* en 1969
- Action : inhibiteur enzymatique
  - UDP-N-acetyglucosamine enolpyruvyl transferase
  - Inhibe la formation de l'acide N-acétylmuramique
  - Donc la synthèse du peptidoglycane
- Petite molécule, haute diffusion
- Large spectre
- Effets indésirables :
  - Veinite/thrombophlébite
  - Tubulopathie



Fosfomycine

- Principales indications jusqu'à récemment :
  - Cystites
    - PO
    - Dose unique (voire en prophylaxie) voire 3 jours
  - Infections tissulaires graves à staphylocoque
    - En particulier neuroméningées / épidurales
    - 12g/j
  - Travaux anciens suggérant une synergie sur les SAMR avec la cefotaxime
    - Mais pertinence clinique discutable

2010

Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review

Matthew E Falagas, Antonia C Kastoris, Anastasios M Kapaskelis, Drosos E Karageorgopoulos

- Sensibilité des EB-BLSE
  - 95 à 100% selon les études

  - Sauf pour certaines, minoritaires
    - Espagne, 2007 : 51%
    - Japon, 2006 : 73%
    - Thaïlande, 2006 : 75-80%
    - France, 1996 : 4% (clone épidémique)

Sensibilité des souches urinaires d'*E. coli*

Tableau 3
Prévalence de l'antibiorésistance en France en 2016 chez les isolats de *Escherichia coli* responsables d'IU communautaires de l'adulte.

< 5 %	Fosfomycine trométamol	Population générale
	Nitrofurantoïne	Population générale
	Aminosides	Population générale
≈ 5 %	C3G et aztréonam	Population générale
< 10 %	Ciprofloxacine, levofloxacine	IU simples et non récidivantes, en l'absence de FQ dans les 6 mois
	Pivmécillinam	Cystites simples
10 à 20 %	Amoxicilline-acide clavulanique	Population générale, selon les concentrations adaptées aux cystites
	Pivmécillinam	Cystite à risque de complication
	Ciprofloxacine, lévofloxacine	IU à risque de complication
	TMP et SMX-TMP	Cystites simples
> 20 %	Amoxicilline	Population générale
	Amoxicilline-acide clavulanique	Population générale, selon les concentrations adaptées aux PNA et IU masculines
	TMP et SMX-TMP	IU à risque de complication

Caron 2018

Journal of Global Antimicrobial Resistance 8 (2017) 164–168

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Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Fosfomycin: In vitro efficacy against multidrug-resistant isolates beyond urinary isolates

Tulin Demir[a,b,*], Tuncay Buyukguclu[c]

[a] Ahi Evran University Research and Training Hospital, Microbiology Department, Kirsehir, Turkey
[b] Public Health Institution of Turkey, National Reference Laboratory of Microbiology, Ankara, Turkey
[c] Ministry of Health, Public Healthcare Center, Karabük, Turkey

Étude en Turquie

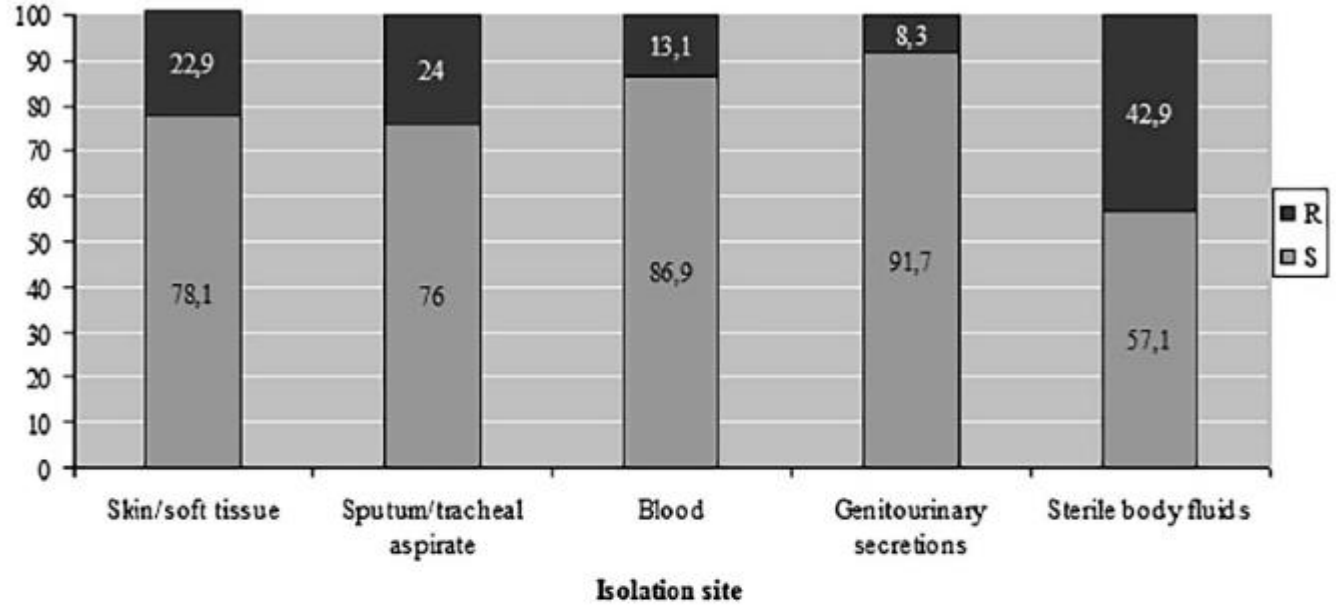


Fig. 1. Distribution of fosfomycin susceptibility rates of bacterial isolates by isolation site.

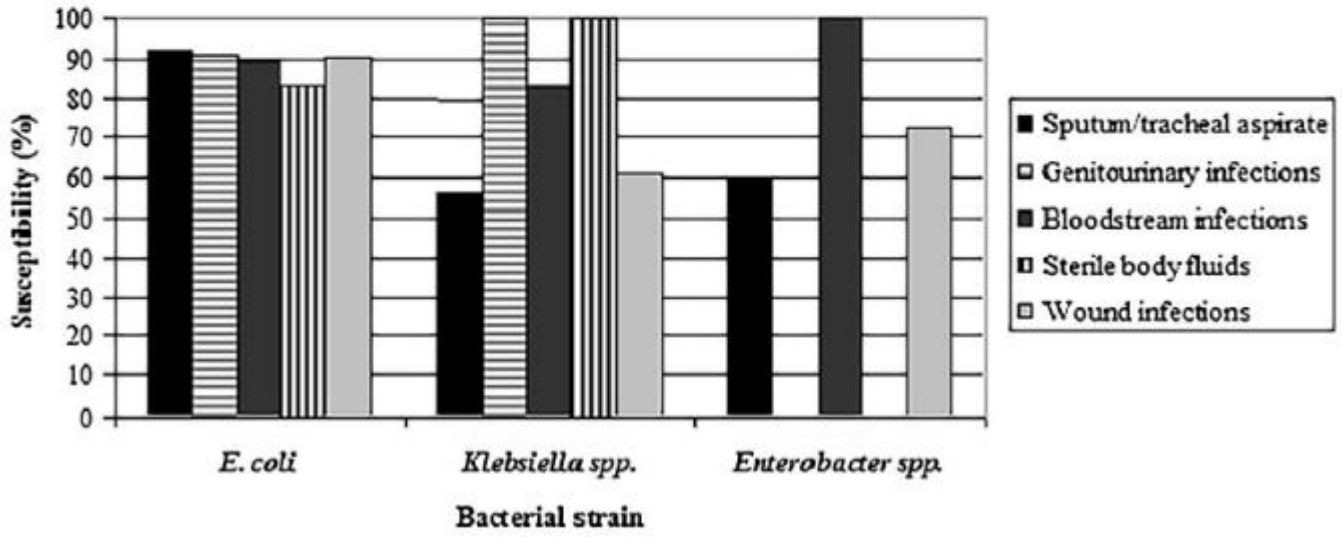


Fig. 2. Distribution of fosfomycin susceptibility rates of bacterial isolates by isolate type and isolation site.

Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation

A. Michalopoulos[1,2], S. Virtzili[1], P. Rafailidis[2,3], G. Chalevelakis[2], M. Damala[4] and M. E. Falagas[2,3,5]

1) *Intensive Care Unit, 'Henry Dunant' Hospital, Athens, Greece,* 2) *Department of Medicine, Tufts University School of Medicine, Boston, MA, USA,* 3) *Department of Medicine, 'Henry Dunant' Hospital, Athens,* 4) *Department of Microbiology, 'Henry Dunant' Hospital, Athens, Greece and* 5) *Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece*

2010

TABLE I. Demographic and clinical characteristics for the patients studied (*n* = 11)

General features	Entire group
Female gender, *n* (%)	6 (54.5)
Mean ± SD age, years	67.5 ± 14.5
Previous surgery, *n* (%)	5 (45.4)
Underlying disease	
Diabetes mellitus	3 (27.2)
Chronic obstructive pulmonary disease	3 (27.2)
Transfer from another institution, *n* (%)	3 (27.2)
APACHE II score on ICU admission (mean ± SD)	23.4 ± 4.9
Previous antibiotic courses during the same hospitalization period, median (range)	3 (2–7)
Number of organ dysfunctions, median (range)	3 (2–5)
Length of hospital stay before isolation of multiresistant *Klebsiella pneumoniae* (sensitive to fosfomycin)–associated infection, median (range) (days)	27 (7–208)
Mechanical ventilation for >48 h, *n* (%)	11 (100)
Total length of ICU stay, median (range) (days)	31 (4–107)
Total length of hospital stay, median (range) (days)	86 (20–330)

APACHE, Acute Physiology and Chronic Health Evaluation score; ICU, intensive care unit.

- 16g/j en 4 fois

- **Fosfomycine**-colimycine : 6 patients
- **Fosfomycine**-gentamycine : 3 patients
- **Fosfomycine**-pipéracilline/tazobactam : 1
- Durée 14+/-5 jours
- Succès thérapeutique chez tous
- Pas d'EI rapporté

… Étude typique des « vieux » ATB

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

Konstantinos Pontikis[a,*], Ilias Karaiskos[b], Styliani Bastani[c], George Dimopoulos[d], Michalis Kalogirou[e], Maria Katsiari[f], Angelos Oikonomou[g], Garyphallia Poulakou[g], Emmanuel Roilides[h], Helen Giamarellou[b]

[a] *First Department of Respiratory Medicine – Intensive Care Unit, University of Athens, Sotiria Chest Diseases and General Hospital, 152 Mesogeion Avenue, 115 27 Athens, Greece*

2014

- **Fofosmycine** co-administrée avec …
  - Colimycine (32 patients)
  - Tigecycline (19)
  - Gentamicine (15)
  - Méropénème (12)
  - Pipéracilline/tazobactam (4)

- Durée médiane 14 jours
- **16 à 24g/24h** (24g chez >50% des patients)
  - Si épuration extrarénale (14) : 12-24g/24h

Table 1
Description of the effectiveness population ($n = 48$).

Characteristic	n (%)[a]
Age (years) (mean ± S.D.)	56.7 ± 17.2
Male	37 (77.1)
Medical admission	32 (66.7)
Organ failures at admission	
Respiratory failure	40 (83.3)
Cardiovascular failure	22 (45.8)
GCS score <6	17 (35.4)
Renal failure	6 (12.5)
Co-morbidities	
Renal disease	14 (29.2)
Diabetes	10 (20.8)
Coronary heart disease	9 (18.8)
Use of immunosuppressants	8 (16.7)
Malignant solid tumour	7 (14.6)
Chronic heart failure	6 (12.5)
Chronic lung disease	6 (12.5)
Fosfomycin initiation	
APACHE II score at fosfomycin initiation (mean ± S.D.)	20.5 ± 7.6
SOFA score at fosfomycin initiation (mean ± S.D.)	9.0 ± 4.0
ICU LoS before fosfomycin initiation [median (IQR)]	34 (23–51)
Severe sepsis/septic shock at fosfomycin initiation[b]	30 (65.2)
Types of infection[c]	
Primary bacteraemia	18 (37.5)
CR-BSI[d]	7 (14.6)
VAP	14 (29.2)
IAI[e]	7 (14.6)
UTI	1 (2.1)
Meningitis	1 (2.1)
Pleural empyema[d]	1 (2.1)
Lung abscess[d]	1 (2.1)

S.D., standard deviation; GCS, Glasgow Coma Scale; APACHE, Acute Physiology and

Clinical outcome

Table 4
Patient outcomes in the effectiveness population ($n = 48$).[a]

Infection	Clinical outcome at Day 14			
	Successful	Failure	Superinfection	Indeterminate
Primary bacteraemia ($n = 18$)	11 (61.1)	6 (33.3)	0	1 (5.6)
CR-BSI ($n = 7$)	1 (14.3)	3 (42.9)	2 (28.6)	1 (14.3)
VAP ($n = 12$)	8 (66.7)	3 (25.0)	1 (8.3)	0
VAP + IAI ($n = 1$)	1 (100)	0	0	0
VAP + pleural empyema ($n = 1$)	1 (100)	0	0	0
UTI ($n = 1$)	1 (100)	0	0	0
IAI ($n = 6$)	3 (50.0)	2 (33.3)	0	1 (16.7)
Lung abscess ($n = 1$)	0	1 (100)	0	0
Meningitis ($n = 1$)	0	1 (100)	0	0
Total ($n = 48$)	26 (54.2)	16 (33.3)	3 (6.3)	3 (6.3)

Microbiological outcome

Infection	Microbiological outcome at Day 14		
	Eradication	Persistence	Indeterminate
Primary bacteraemia ($n=18$)	13 (72.2)	4 (22.2)	1 (5.6)
CR-BSI ($n=7$)	3 (42.9)	1 (14.3)	3 (42.9)
VAP ($n=12$)	5 (41.7)	4 (33.3)	3 (25.0)
VAP + IAI ($n=1$)	1 (100)	0	0
VAP + pleural empyema ($n=1$)	0	1 (100)	0
UTI ($n=1$)	0	0	1 (100)
IAI ($n=6$)	3 (50.0)	3 (50.0)	0
Lung abscess ($n=1$)	1 (100)	0	0
Meningitis ($n=1$)	1 (100)	0	0
Total ($n=48$)	27 (56.3)	13 (27.1)	8 (16.7)

Description of safety population ($n = 66$) and reported adverse events (AEs).

Duration of fosfomycin administration [median (IQR)]	12 (7–15)
Severe hypokalaemia [n (%)]	10 (15.2)
Lowest K^+ value (mEquiv./L) (mean ± S.D.)	2.7 ± 0.3
Renal toxicity [n (%)]	3 (4.5)
Thrombocytopenia [n (%)]	4 (6.1)
Diarrhoea/CDI [n (%)]	2 (3.0)
Rash [n (%)]	1 (1.5)
Neutropenia [n (%)]	1 (1.5)
Withdrawal of fosfomycin treatment owing to AEs [n (%)]	4 (6.1)[a]

Efficacy and Safety of Fosfomycin Plus Imipenem as Rescue Therapy for Complicated Bacteremia and Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus*: A Multicenter Clinical Trial

Ana del Río,[1,a] Oriol Gasch,[2,3,a] Asunción Moreno,[1] Carmen Peña,[2] Jordi Cuquet,[4] Dolors Soy,[1] Carlos A. Mestres,[1] Cristina Suárez,[2] Juan C. Pare,[1] Fe Tubau,[2,5] Cristina Garcia de la Mària,[1] Francesc Marco,[1,6] Jordi Carratalà,[2] José M. Gatell,[1] Francisco Gudiol,[2] José M. Miró[1], and the FOSIMI Investigators[b]

- 2g/6h

- 12 endocardites,
  1 infection sur greffe vasculaire,
  1 infection sur TIPS,
  2 bactériémies prolongées

- Traitement pendant 28 jours en médiane

- Négativation des hémocultures en 48h

- 5 décès, dont 4 non reliés à l'infection
- 1 décès lié à une acidose tubulaire

Scandinavian Journal of Infectious Diseases, 2012; 44: 182–189

informa
healthcare

ORIGINAL ARTICLE

Fosfomycin: Efficacy against infections caused by multidrug-resistant bacteria

AURÉLIEN DINH[1], JÉRÔME SALOMON[1], JEAN PIERRE BRU[2] & LOUIS BERNARD[1,3]

From the [1]Division of Infectious Diseases, AP-HP, Raymond Poincaré University Hospital, Garches, [2]Division of Infectious Diseases, Annecy General Hospital, Annecy, and [3]Division of Infectious Diseases, University Hospital of Tours, Tours, France

- Ostéoarthrites, pneumonies, infections urinaires et bactériémies
- Toujours en association
  - 4g 3 ou 4 fois par jour

- Principaux germes :
  - *Pa* (43)
  - Entérobactéries (29)
  - SCNMR (23)
  - SAMR (15)
  - 71% de BMR

- 44% en USI, 22% de choc septique

- Évolution favorable : 76% des cas

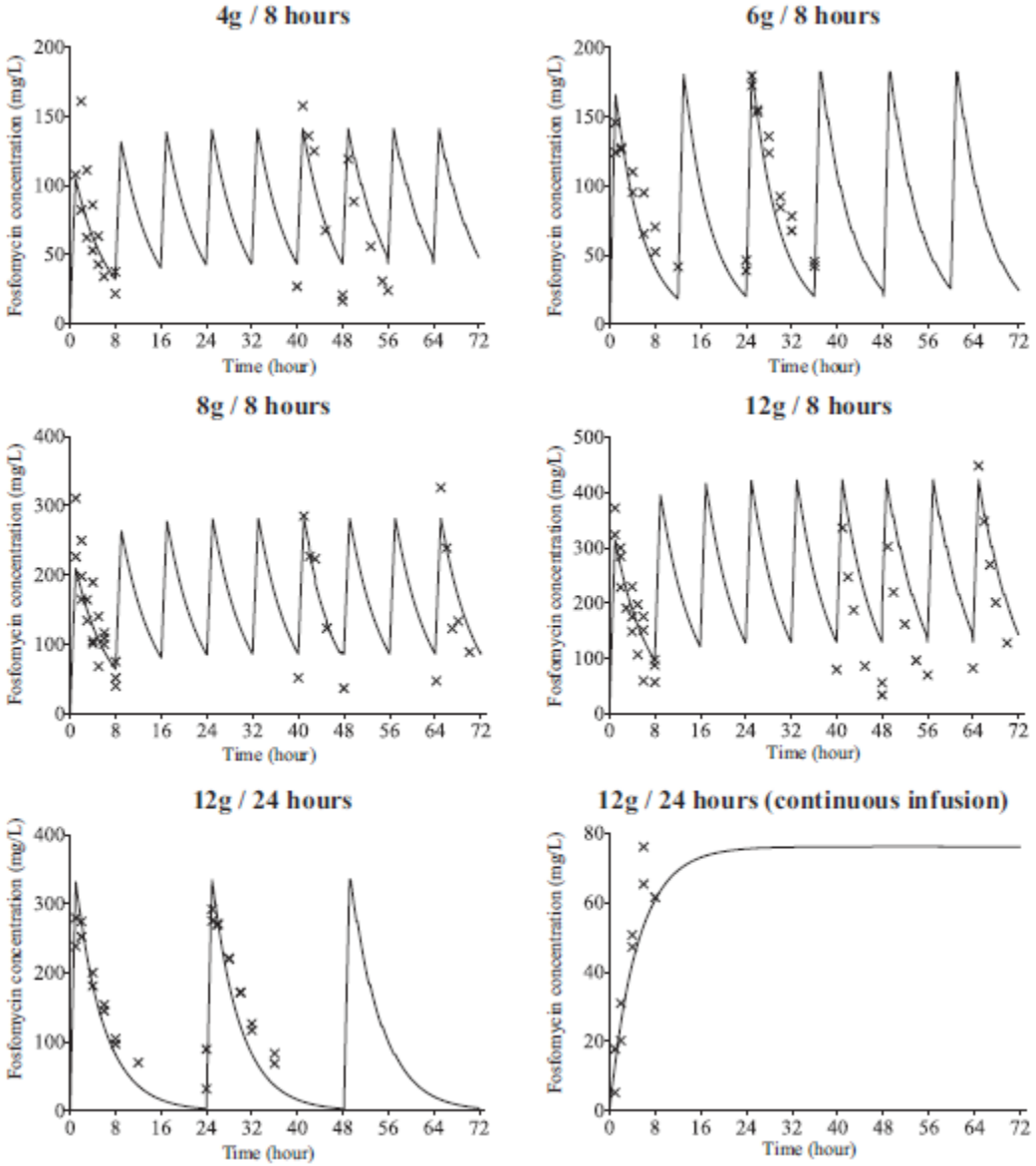
AAC
Journals.ASM.org

2015

Pharmacodynamics of Fosfomycin: Insights into Clinical Use for Antimicrobial Resistance

F. Docobo-Pérez,[a] G. L. Drusano,[b] A. Johnson,[c] J. Goodwin,[c] S. Whalley,[c] V. Ramos-Martín,[c] M. Ballestero-Tellez,[a] J. M. Rodriguez-Martinez,[d] M. C. Conejo,[d] M. van Guilder,[e] J. Rodríguez-Baño,[a,f] A. Pascual,[a,d] W. W. Hope[c]

Unidad Intercentros de Enfermedades Infecciosas, Microbiología Clínica y Medicina Preventiva, Hospital Universitario Virgen de Macarena, Seville, Spain[a]; Institute for Therapeutic Innovation, College of Medicine, University of Florida, Lake Nona, Florida, USA[b]; Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom[c]; Departmento de Microbiología, Universidad de Sevilla, Seville, Spain[d]; Laboratory of Applied Pharmacokinetics, School of Medicine, University of Southern California, Los Angeles, California, USA[e]; Departamento de Medicina, Universidad de Sevilla, Seville, Spain[f]



nacokinetic profiles of the fosfomycin dosages used in the hollow fiber infection model. Solid lines, predicted concentrations; crosses, observed
ns.

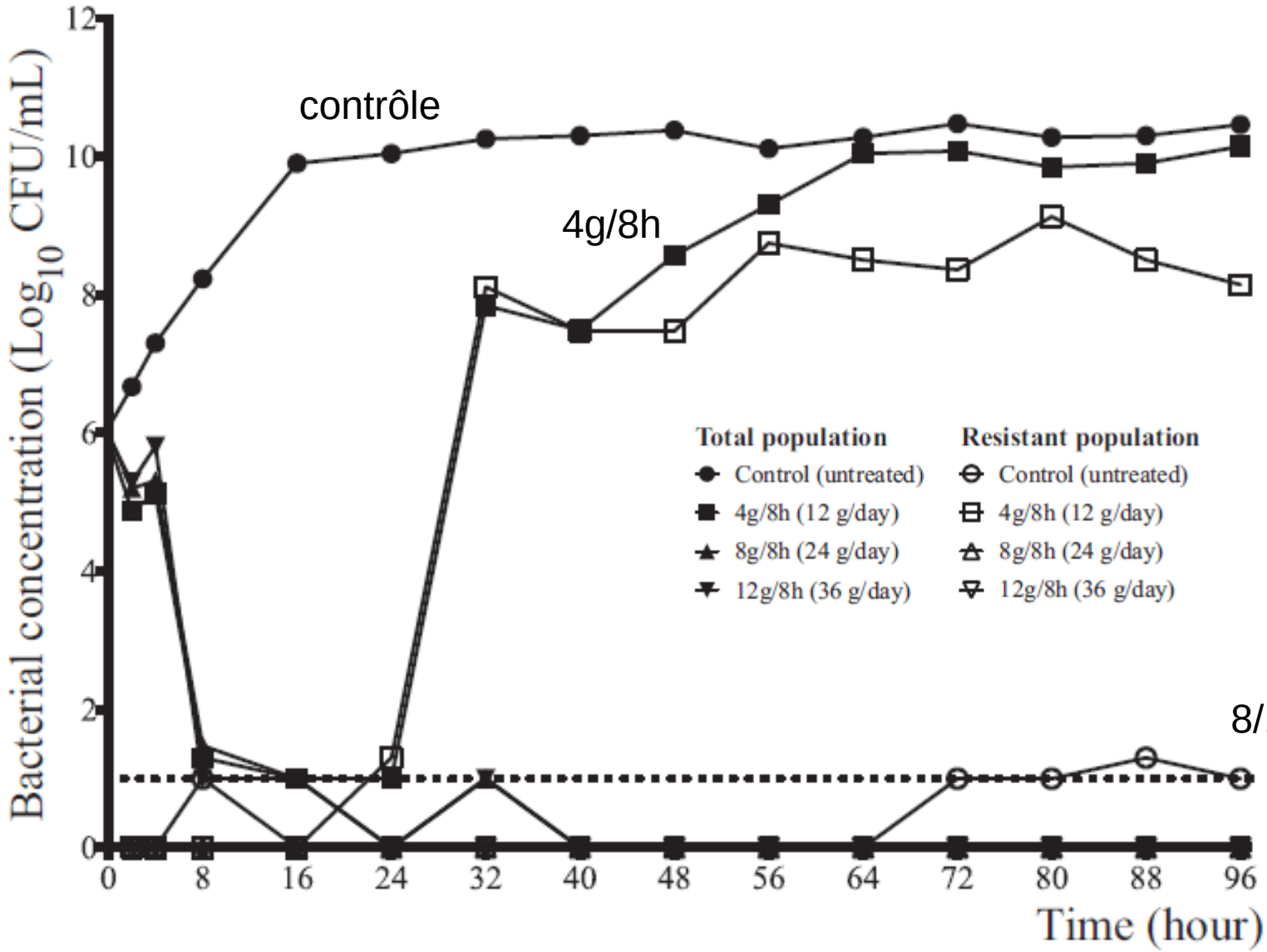
Docobo-perez 2015

Résultats des différents schémas

- Peu efficace sur souches à CMI>64
- Efficacité des doses d'au moins 16g/j
  - Mais à moins de 24g/j : émergence rapide de mutants
- Paramètre corrélé à la bactéricidie :
  - AUC / CMI

Docobo-perez 2015

Pour une souche d'*E. coli* avec une CMI de 1 mg/l



Docobo-perez 2015

J Antimicrob Chemother 2012
doi:10.1093/jac/dks270
Advance Access publication 10 July 2012

Emergence of resistance to fosfomycin used as adjunct therapy in KPC *Klebsiella pneumoniae* bacteraemia: report of three cases

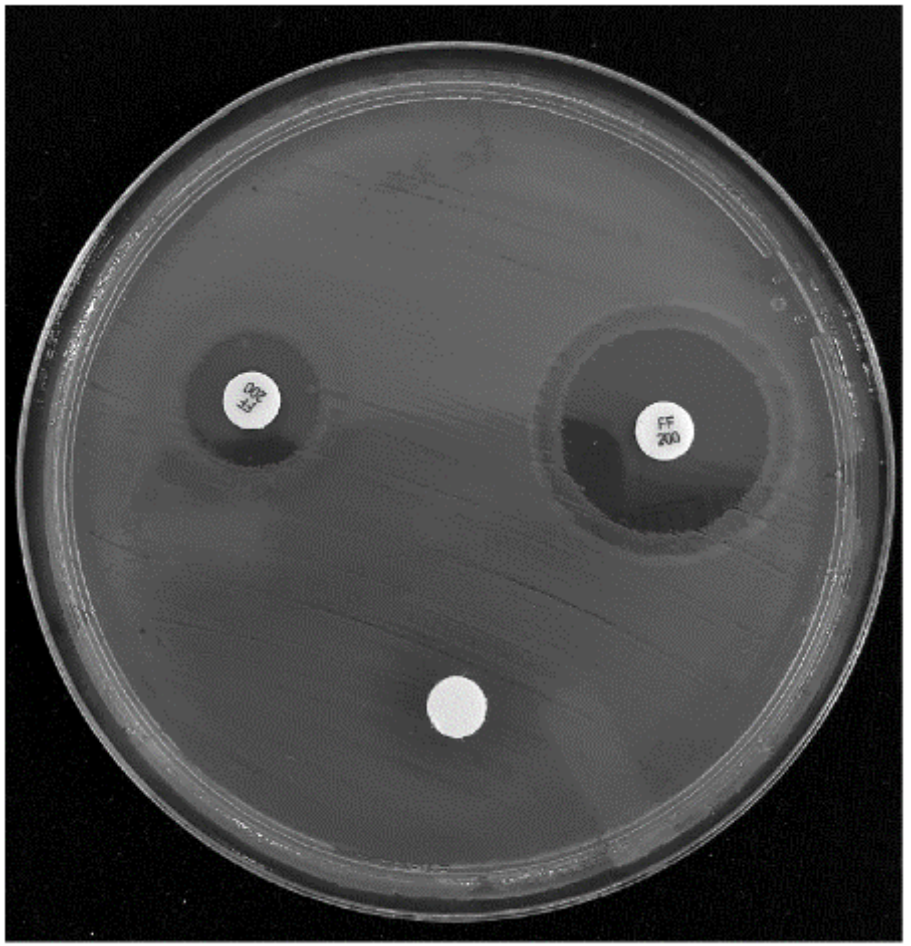
Drosos E. Karageorgopoulos[1], Vivi Miriagou[2], Leonidas S. Tzouvelekis[3], Kalliopi Spyridopoulou[1] and George L. Daikos[1]*

[1]First Department of Propaedeutic Medicine, University of Athens, Laikon General Hospital, Athens, Greece; [2]Laboratory of Bacteriology, Hellenic Pasteur Institute, Athens, Greece; [3]Department of Microbiology, University of Athens, Athens, Greece

2017

Emergence of Plasmid-Mediated Fosfomycin-Resistance Genes among *Escherichia coli* Isolates, France

Yahia Benzerara, Salah Gallah, Baptiste Hommeril, Nathalie Genel, Dominique Decré, Martin Rottman, Guillaume Arlet



- Circulation de quelques souches … émergence ?

En conclusion pour la fosfomycine

- En association
- Sur antibiogramme
- Dose : 12 ?16 ? 24g/24h ?
  - Probablement 24g pour les BGN
  - En 3 ou 4 fois … voire en continu
- Toxicité : tubulopathie
  - Mais traitement a priori sur durée <8jours

Rupture de stock fosfomycine IV

Jeudi 21 Janvier 2016

Le seul fournisseur mondial de la matière première nécessaire pour la fabrication de fosfomycine injectable rencontre actuellement un problème majeur qui empêche la production de fosfomycine injectable.

L'ANSM a sollicité une concertation avec la SPILF et la SFP/GPIP pour gérer la situation de pénurie (les stocks actuellement disponibles ne permettent de couvrir que quelques semaines de consommation) en définissant des situations cliniques pour lesquelles l'utilisation de la fosfomycine est jugée indispensable".

Cet antibiotique bactéricide naturel à large spectre inhibe les premiers stades de la synthèse de la paroi bactérienne, et n'a aucune parenté structurale avec les autres classes d'antibiotiques existantes. Elle est active à la fois vis-à-vis des Cocci à gram + et de certains bacilles à Gram -.

Compte tenu de l'évolution des résistances bactériennes, de l'arsenal thérapeutique actuellement disponible, et de stocks très limités de produit, la **fosfomycine injectable doit être réservée aux infections documentées à bacilles à Gram négatif multi résistants, en particulier non fermentants, quand il n'existe pas d'alternative**.

La fosfomycine ne doit pas être utilisée en monothérapie (risque important d'émergence de résistance). Son utilisation en association permet de limiter l'émergence des résistances au partenaire de l'association (colistine, fluoroquinolones…).

Pour les infections à cocci Gram positif, y compris les staphylocoques dorés multirésistants, y compris dans les localisations neuroméningées et oséto-articulaires, il y a des alternatives:

- D'autres molécules actuellement disponibles (ceftaroline, ceftobiprole, linezolide, tedizolide, daptomycine) ont une bonne diffusion dans le LCS et/ou l'os.
- Des molécules plus anciennes combinent une activité restant élevée contre les SARM et une bonne diffusion cérébrale et/ou osseuse (cotrimoxazole, rifampicine)

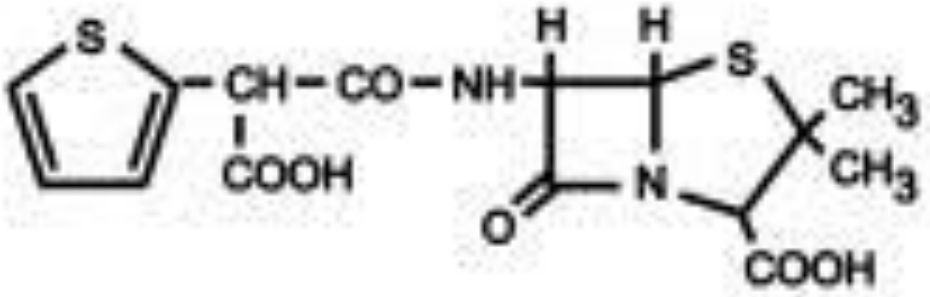
Le groupe de travail SPILF/GPIP

Témocilline

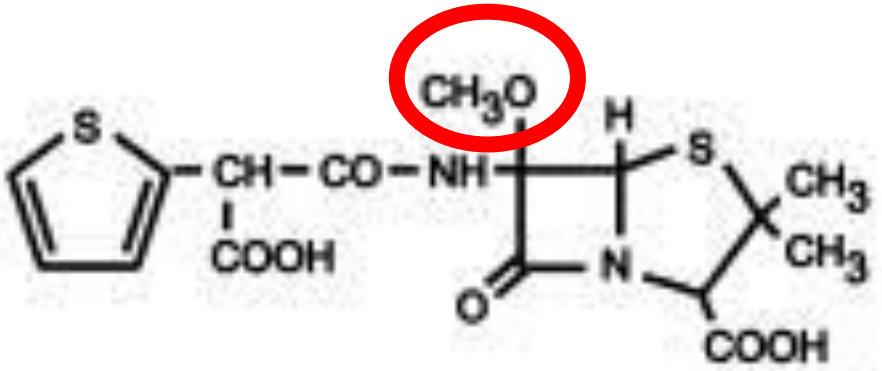
Contexte

- Montée des BLSE et des céphalosporinases déréprimées
  - Entérobactéries
    - Céphalosporinase AmpC
    - BLSE
  - *Acinetobacter*

- Montée de la consommation des carbapénèmes
  - Et montées des carbapénémases



Ticarcilline



Temocilline

Stabilité face

- **aux BLSE**
- **aux céphalosporinases AmpC**

Historique

- AMM belge en 1984
- AMM Luxembourg en 1986
- AMM UK en 2006
- AMM française en 2014
  - Après une longue période d'ATU pour les infections à *Burkholderia cepacia* en contexte de mucoviscidose

Eur J Clin Microbiol Infect Dis (2007) 26:777–783
DOI 10.1007/s10096-007-0370-9

ARTICLE

In vitro activity of temocillin against prevalent extended-spectrum beta-lactamases producing *Enterobacteriaceae* from Belgian intensive care units

Y. Glupczynski · T.-D. Huang · C. Berhin · G. Claeys · M. Delmée · L. Ide · G. Ieven · D. Pierard · H. Rodriguez-Villalobos · M. Struelens · J. Vaneldere

Table 1 Number and percentage of non-susceptible isolates to the tested antimicrobials, classified by species

Species[a] (No. isolates)	Number of non-susceptible isolates (%)				
	Ceftazidime	Meropenem	Temocillin	Amikacin	Ciprofloxacin
Escherichia coli (186)	10 (5.4)	0	4 (2.2)	2 (1.2)	32 (17.2)
Enterobacter cloacae (115)	38 (33)	0	7 (6.1)	3 (2.6)	5 (4.3)
K. pneumoniae (75)	24 (32.0)	0	9 (12)	11 (14.7)	16 (21.3)
Enterobacter aerogenes (72)	48 (66.7)	2 (2.8)	18 (25)	11 (15.3)	41 (57)
K. oxytoca (62)	3 (4.8)	0	3 (4.8)	1 (1.6)	18 (29)
S. marcescens (39)	1 (2.6)	0	10 (25.6)	2 (5.1)	8 (20.5)
Proteus mirabilis (35)	0	0	1 (2.9)	0	5 (14.3)
M. morganii (27)	5 (18.5)	0	0	0	2 (7.4)
Citrobacter freundii (15)	4 (26.7)	0	0	1 (6.7)	2 (13.3)
Total[a] (652)	134 (20.5)	2 (0.4)	53 (8.1)	31 (4.8)	131 (20.1)

[a] In addition to the species groups detailed, this total also includes: *Proteus vulgaris* (9); *Hafnia* spp. (6), *Citrobacter diversus* (5); *Providencia* spp (3); *Serratia liquefaciens* (2), *Proteus penneri* (1)

These isolates were all susceptible to the tested agents with the single exception of one ESBL-producing *Providencia rettgeri* (resistant to ceftazidime (MIC≥32 μg/ml) and to ciprofloxacin (MIC≥256 μg/ml)

J Antimicrob Chemother 2011; **66**: 2628–2631
doi:10.1093/jac/dkr317 Advance Access publication 2 August 2011

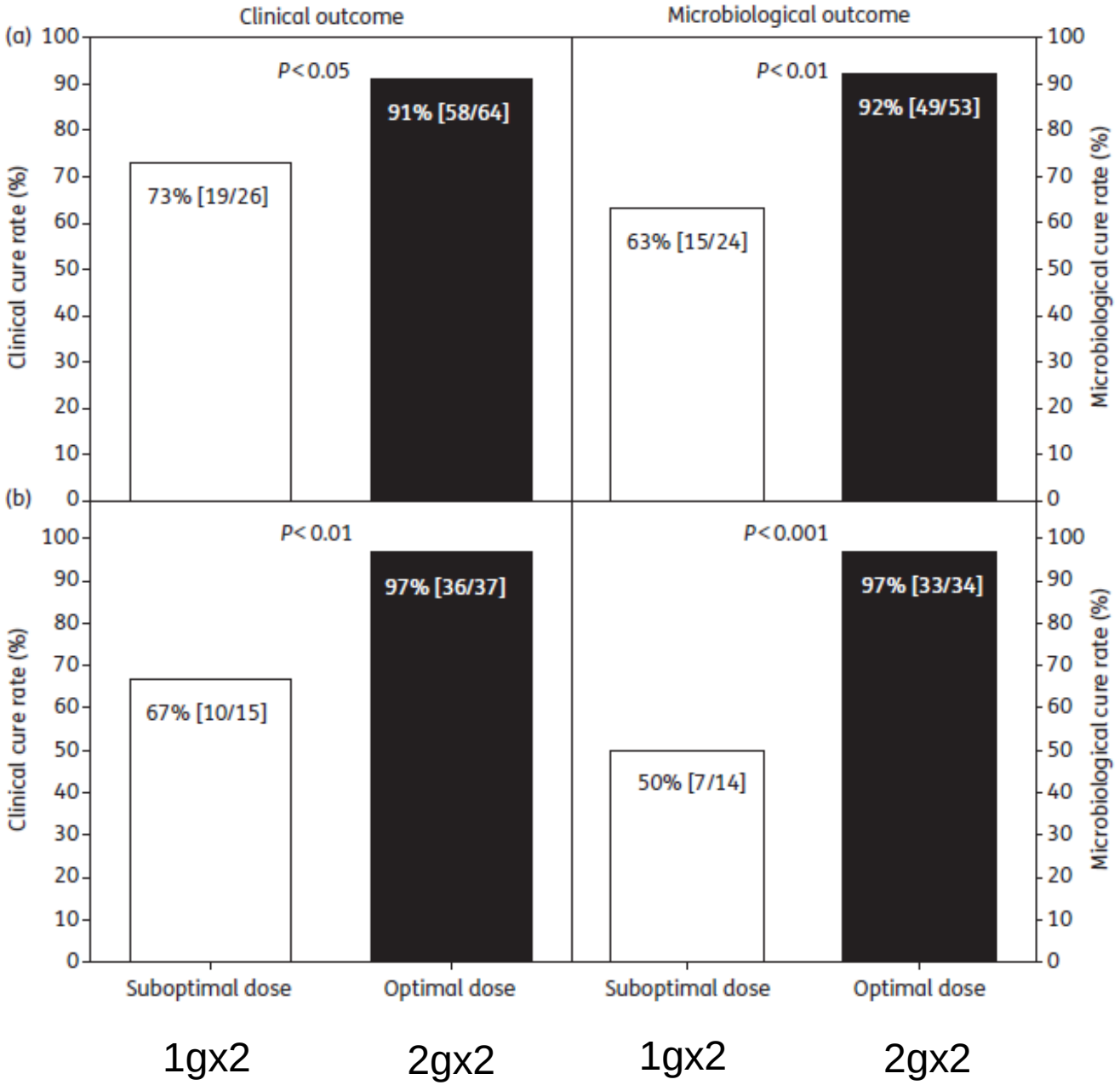
Journal of Antimicrobial Chemotherapy

Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae

Indran Balakrishnan[1]*, F. Mustafa Awad-El-Kariem[2], Adnan Aali[3], Prasanna Kumari[4], Rohinton Mulla[5], Benny Tan[6], Daniel Brudney[1], David Ladenheim[2], Anan Ghazy[3], Imran Khan[5], Nilangi Virgincar[6], Shabnam Iyer[6], Stephane Carryn[7] and Sebastien Van de Velde[7]

All patients

ESBL / AmpC

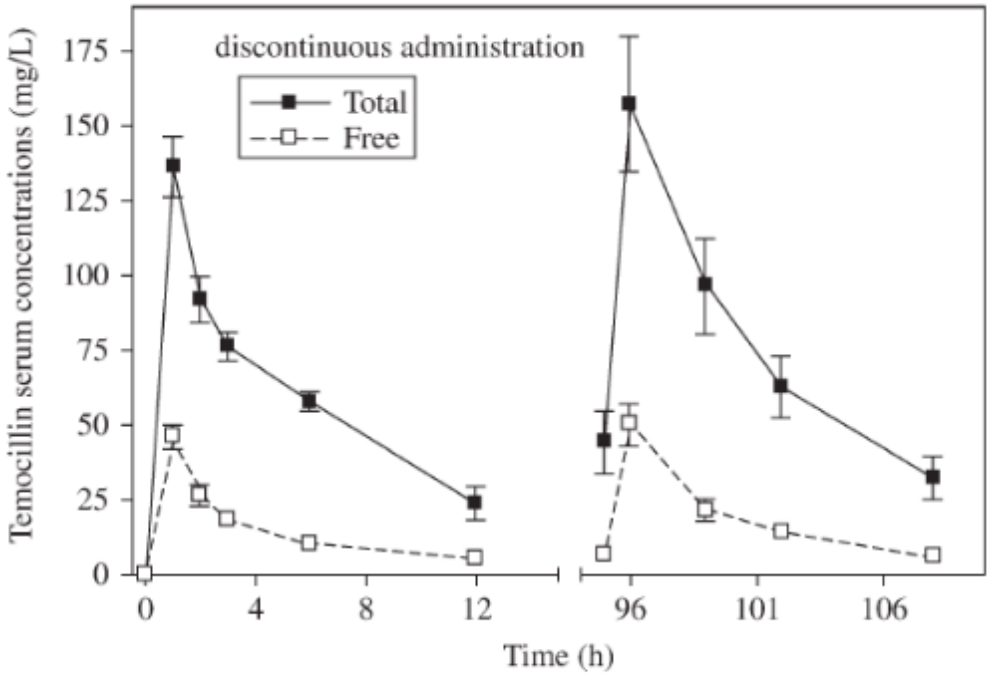


Journal of Antimicrobial Chemotherapy (2008) **61**, 382–388
doi:10.1093/jac/dkm467
Advance Access publication 10 December 2007

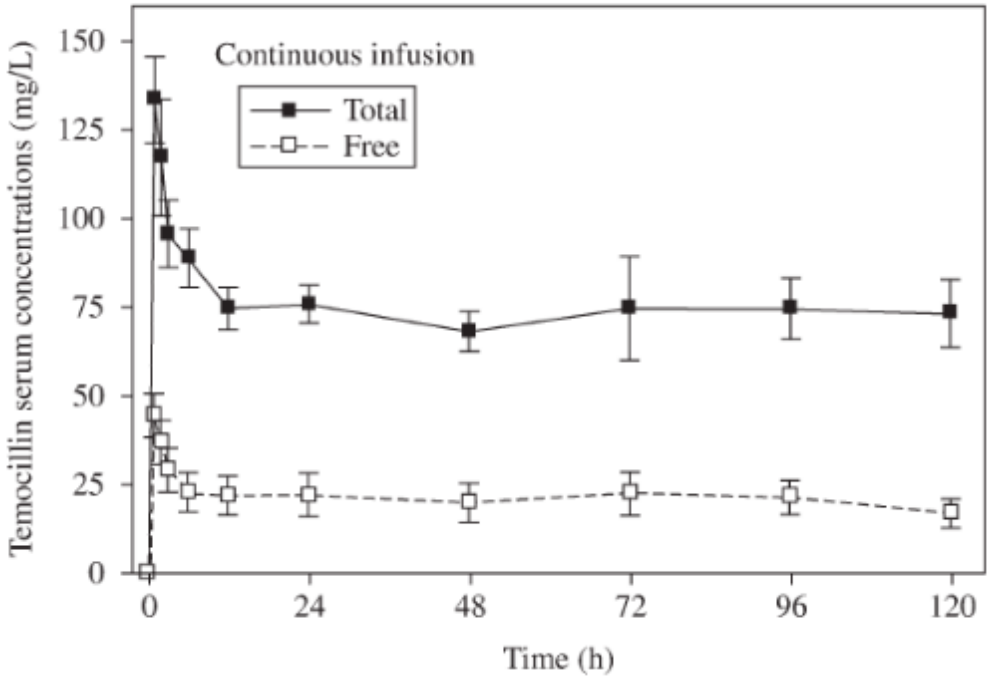
JAC

Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

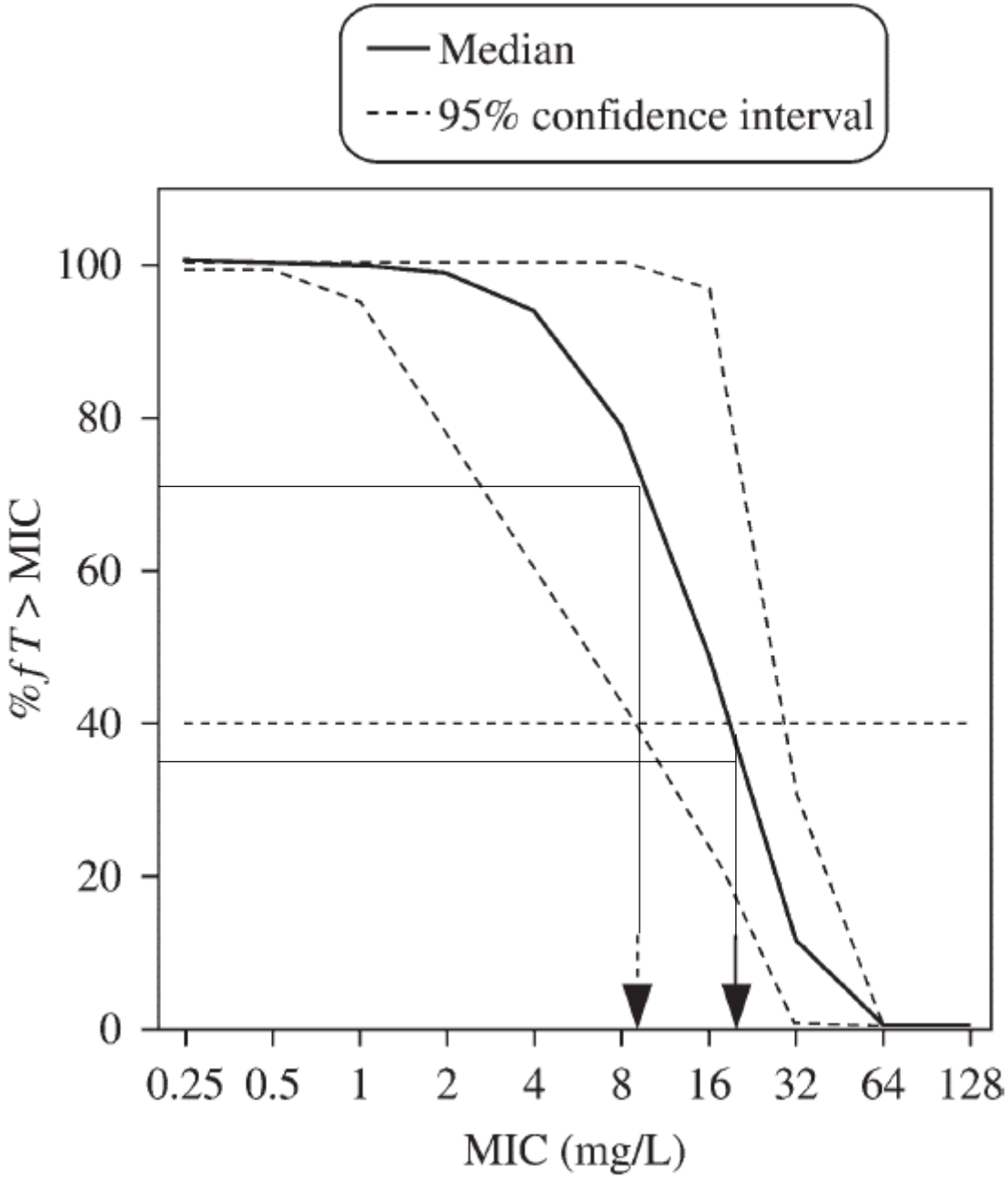
Raf De Jongh[1], Ria Hens[1], Violetta Basma[2], Johan W. Mouton[3], Paul M. Tulkens[2]* and Stéphane Carryn[2]



2gx2



2gx1 puis
4g/24h


Median
95% confidence interval
100
80
60
40
20
0
%fT > MIC
0.25
0.5
1
2
4
8
16
32
64
128
MIC (mg/L)

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

Avis
1er avril 2015

NEGABAN 1 g, poudre pour solution injectable

B/1 flacon (CIP : 34009 300 045 2 4)

NEGABAN 2 g, poudre pour solution injectable ou perfusion

B/1 flacon (CIP : 34009 300 045 3 1)

DCI	Témocilline
Code ATC (2013)	J01CA17 (pénicillines à spectre étendu)
Motif de l'examen	**Inscription**
Liste concernée	**Collectivités** (CSP L.5123-2)
Indications concernées	**« Chez les adultes et chez les enfants, pour le traitement des infections suivantes :** **des voies urinaires compliquées (incluant les pyélonéphrites);** **des voies respiratoires basses, des bactériémies et des infections des plaies.** **Il convient de tenir compte des recommandations officielles concernant l'utilisation appropriée des antibactériens ».**

Adultes (y compris les personnes âgées)

1 à 2 g par jour, à répartir en 2 administrations. Cette posologie peut être doublée en cas d'infections sévères.

Population pédiatrique

25 à 50 mg par kg par jour, à répartir en 2 administrations, avec un maximum de 4 g/jour.

NEGABAN	POSOLOGIE PAR 24 HEURES	
	Posologie habituelle	Infections sévères
Adultes	2 g en 2 administrations (injections I.M., I.V. ou perfusion)	4 g en 2 administrations (injections I.V. ou perfusion)
	avec antibiothérapie complémentaire éventuelle	
Enfants	25 mg/kg/24 h en 2 administrations (injections I.M., I.V. ou perfusion)	50 mg/kg/24 h en 2 administrations (injections I.V. ou perfusion)

- En fait, 6g/J ? Tant qu'on n'a pas la CMI …

Essai français en cours

- Témocilline dans les infections urinaires à BLSE
- Essai ouvert sans comparateur
- Inclusions en cours

Phénicolés

Phénicolés

- Isolement du chloramphénicol de *Streptomyces venezuelae* en 1947
- Puis synthèse chimique exclusive
- Inhibition de la synthèse protéique
  - Par interaction avec la ss-U ribosomale 70s

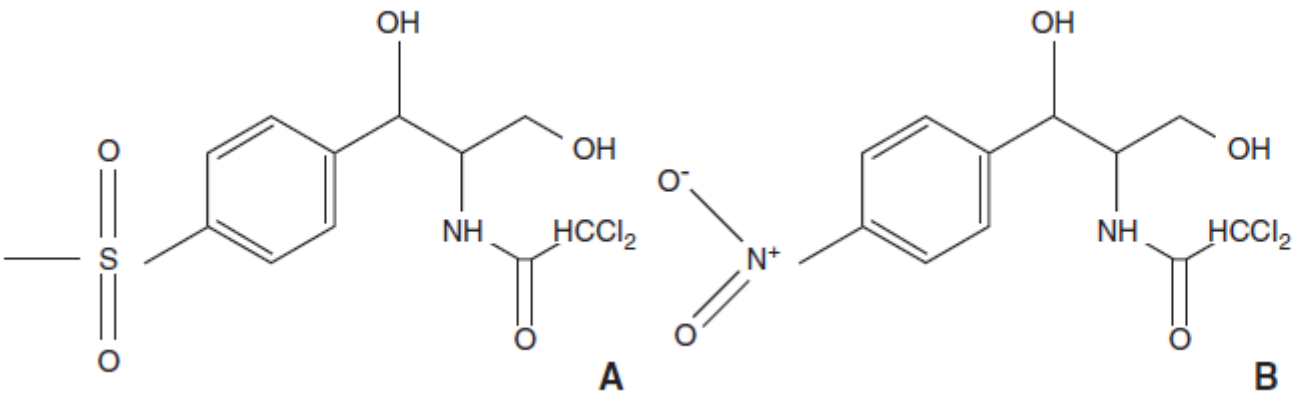


Figure 1.
A. Chloramphénicol.
B. Thiamphénicol.

- Spectre très large
  - CG+, CG-, BG+
  - Entérobactéries
  - Anaérobies
  - Résistance naturelle :
    - *P. aeruginosa*
    - *A. baumanii*
    - *Serratia marcescens*
    - Mycobactéries
- Diffusion importante
  - En particulier cérébrale : 50% des concentrations sériques

Deux molécules

- Chloramphénicol (plus disponible en France*)
  - Toxicité principale : anémie aplasique irréversible
    - Mécanisme mal connu
    - Survenue parfois à distance du traitement
    - 1/20000 traitement
  - Largement utilisé en traitement des méningites bactériennes en afrique subsaharienne
    - Forme retard huileuse : 1 injection
- Thiampénicol
  - Spectre idem
  - Risque d'aplasie : fréquente (30%) et réversible

*Sauf en collyre

Regain d’intérêt pour le thiampénicol

- … regain modeste cependant

- Abcès cérébraux non documentés, pour le relai oral
- Intracellulaires

J Antimicrob Chemother 2015; **70**: 979–996
doi:10.1093/jac/dku530 Advance Access publication 11 January 2015

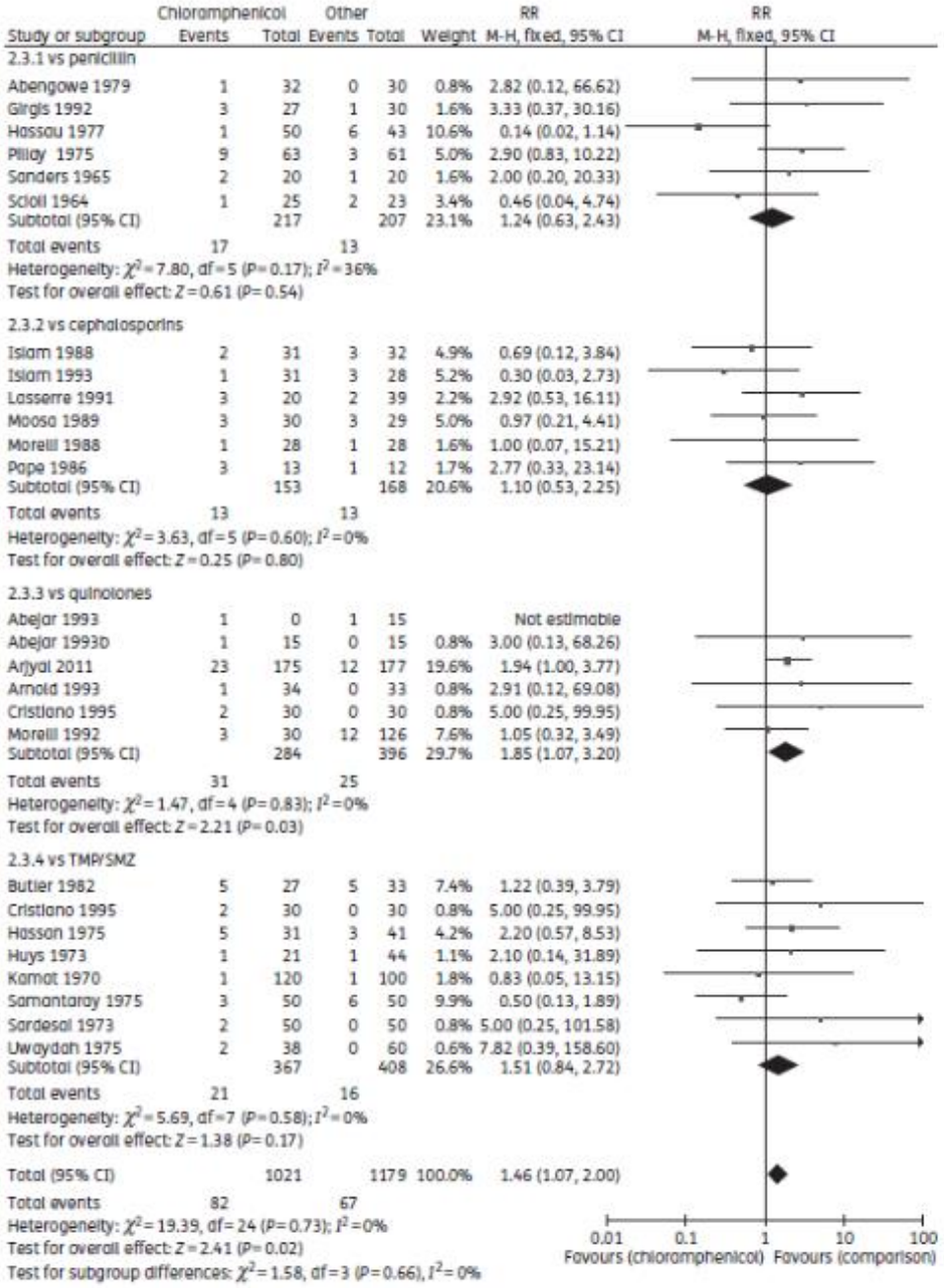
Journal of Antimicrobial Chemotherapy

Efficacy and safety of chloramphenicol: joining the revival of old antibiotics? Systematic review and meta-analysis of randomized controlled trials

Noa Eliakim-Raz[1–3]*†, Adi Lador[1,2]†, Yaara Leibovici-Weissman[2,4], Michal Elbaz[1,2], Mical Paul[2,5] and Leonard Leibovici[1,2]

[1]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel; [3]Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel; [4]Department of Medicine D, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel; [5]Unit of Infectious Diseases, Rambam Hospital, Haifa, Israel

Typhoïde



Vs pénicillines

Vs céphalosporines

Vs FQ

Vs cotrimoxazole

Figure 8. Failure at EOF for enteric fever. Chloramphenicol versus penicillins, cephalosporins, fluoroquinolones or trimethoprim/sulfamethoxazole and the total comparison. Studies are identified by the name of the first author and the year of publication. FE meta-analysis was used for estimating the combined RR (95% CI). The diamond indicates the overall summary estimate for the analysis. M-H, Mantel–Haenszel.

Study or subgroup	Chloramphenicol Events	Total	Other Events	Total	Weight	RR M-H, fixed, 95% CI
Nathan 2005	12	256	14	247	14.0%	0.83 (0.39, 1.75)
Nelson 1972	7	129	5	177	4.1%	1.92 (0.62, 5.92)
Pecoul 1991	93	254	82	274	77.5%	1.22 (0.96, 1.56)
Peltola 1989	3	53	5	101	3.4%	1.14 (0.28, 4.60)
Whittle 1973	2	65	1	58	1.0%	1.78 (0.17, 19.17)
Total (95% CI)		757		857	100.0%	1.20 (0.96, 1.50)
Total events	117		107			

Heterogeneity: $\chi^2 = 1.75$, df = 4 ($P = 0.78$); $I^2 = 0\%$

Test for overall effect: $Z = 1.59$ ($P = 0.11$)

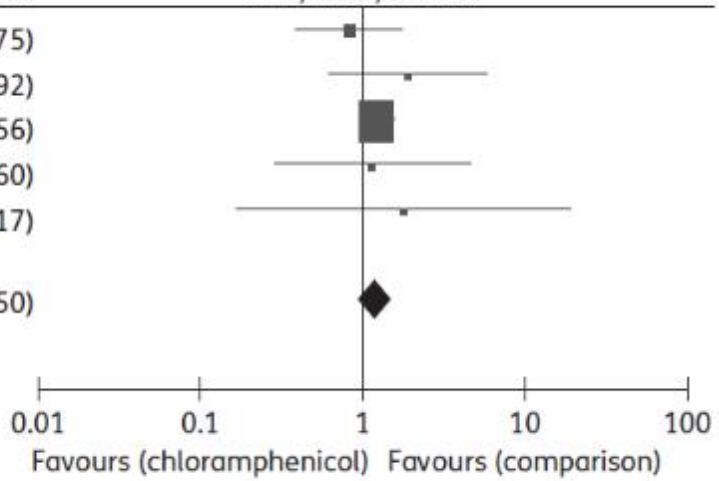


Figure 4. Mortality at EOF for meningitis. Chloramphenicol versus β-lactams. Studies are identified by the name of the first author and the year of publication. FE meta-analysis was used for estimating the combined RR (95% CI). The diamond indicates the overall summary estimate for the analysis. M-H, Mantel-Haenszel.

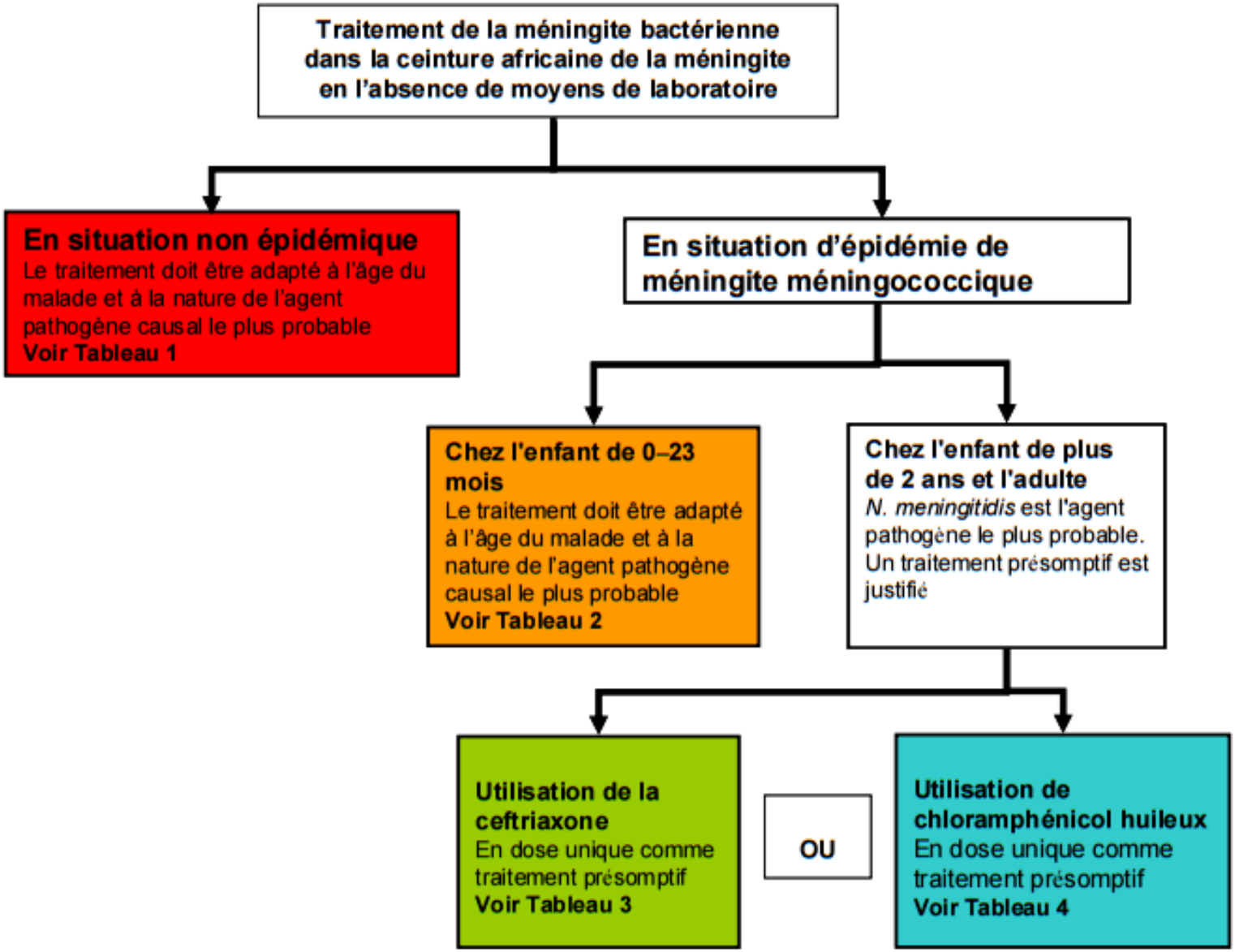
Mortalité / méningites

Vs béta-lactamines

Organisation mondiale de la Santé

WHO/CDS/EPR/2007.3

Traitement normalisé de la méningite en Afrique en situation épidémique ou non épidémique


Traitement de la méningite bactérienne dans la ceinture africaine de la méningite en l'absence de moyens de laboratoire
En situation non épidémique
Le traitement doit être adapté à l'âge du malade et à la nature de l'agent pathogène causal le plus probable
Voir Tableau 1
En situation d'épidémie de méningite méningococcique
Chez l'enfant de 0–23 mois
Le traitement doit être adapté à l'âge du malade et à la nature de l'agent pathogène causal le plus probable
Voir Tableau 2
Chez l'enfant de plus de 2 ans et l'adulte
N. meningitidis est l'agent pathogène le plus probable. Un traitement présomptif est justifié
Utilisation de la ceftriaxone
En dose unique comme traitement présomptif
Voir Tableau 3
OU
Utilisation de chloramphénicol huileux
En dose unique comme traitement présomptif
Voir Tableau 4

En conclusion

- Connaitre les « vieilles » molécules
- Savoir les utiliser en cas d'impasse
  - surtout lors d'infections graves
- En général en association
- En gardant à l'esprit le moindre niveau de preuve