Sensibilité aux antibiotiques chez les bacilles gram négatif:

état des lieux en Tunisie

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"Résistance aux Antimicrobiens" LR99ES09

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Deuxième Journée Commune de Réanimation (2ème JCOR)
20 Mai 2017 à l'Hôtel Le Royal Hammamet

Introduction

- **Emergence croissante & dissémination de bactéries multirésistantes (BMR)**
  - → Problème majeur à l'échelle mondiale
  - → Validité de l'arsenal thérapeutique ??
  - → Menace grave (milieu hospitalier +++ , également communautaire)
  - → Augmentation morbidité et mortalité + surcoût (hospitalisations prolongées & surcharge des soins)

Résistance bactérienne aux antibiotiques

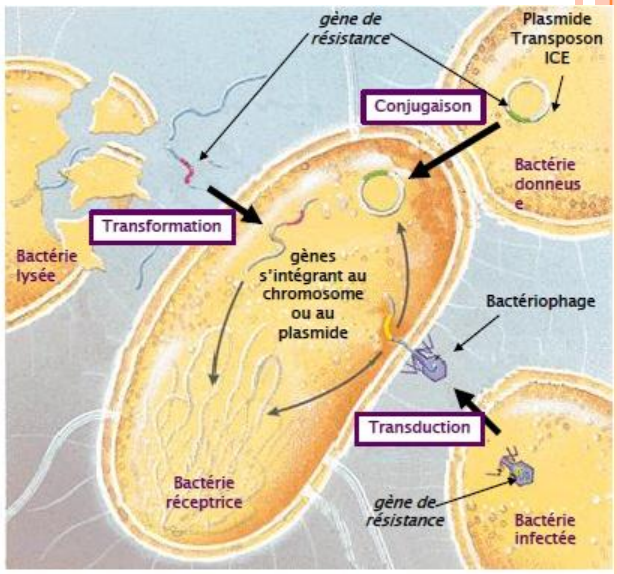
- **Résistance naturelle**
  - Capital génétique à l'état sauvage

- **Résistance acquise**
  - **Chromosomique (mutation):** peu transférable entre bactéries, transmission à descendance

  - **Eléments génétiques mobiles:**

(plasmides, transposons): transférables entre bactéries (espèces différentes),

Affecte souvent plusieurs familles d'antibiotiques



La multirésistance

- **Résistance à plusieurs classes d'antibiotiques**

- **Accumulation de résistances naturelles et acquises:**

  ↳ Sensibilité à un petit nombre d'antibiotiques

  ↳ Arsenal thérapeutique réduit +++

Mondialisation des BMR

- Multiplications des voyages et des échanges
- Multiples vecteurs de résistance
  - Bactéries
  - Eléments génétiques mobiles
    - Plasmides (échanges entre espèces bactériennes différentes)
    - Transposons (changement de support génétique: plasmide → chromosome →plasmide)
- Grande transmissibilité des résistances

Développement de nouveaux antibiotiques

→ **Perspectives très limitées !!!**

Humains contre bactéries

variable	microbes	humains	facteur
Nb sur terre	5×10^{31}	6×10^{9}	10^{22}
Masse(tonne)	5×10^{16}	3×10^{8}	10^{8}
Tps génération	30 mn	30 ans	5×10^{5}
Durée sur terre	3.5×10^{9}	4×10^{6}	10^{3}

Comparées à l'espèce humaine, les bactéries sont

- **plus anciennes**
- **plus nombreuses**
- **mieux adaptées**

D'après S.J. Gould

Prévalence de la résistance bactérienne

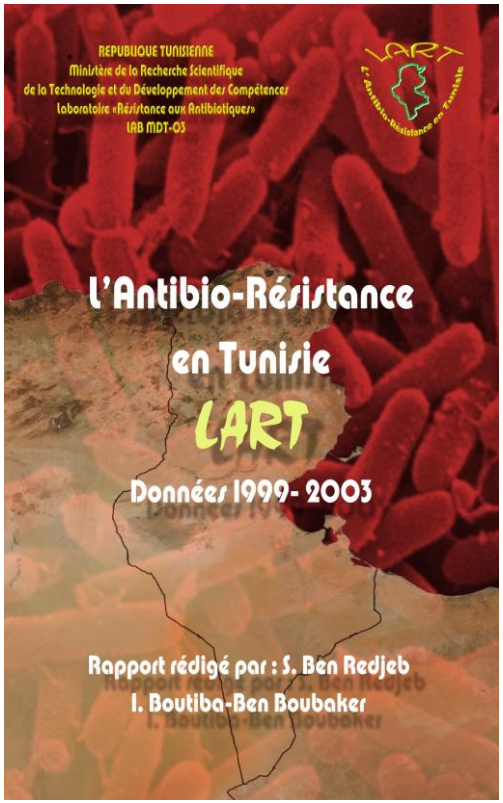
- **Deux facteurs:**
  - **Pression de sélection antibiotique**
    - Flores commensales ++
    - Flores aux sites infectieux
    - Variations en fonction des molécules (fluoroquinolones +++)
  - **Diffusion des souches résistantes**
    - Transmission des souches résistantes = diffusion clonale
    - Transmission du matériel génétique codant pour la résistance

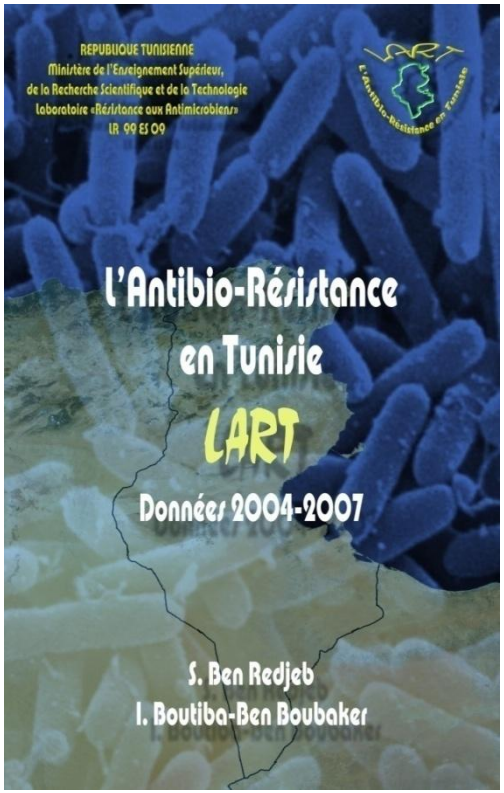
Prévalence de la résistance bactérienne

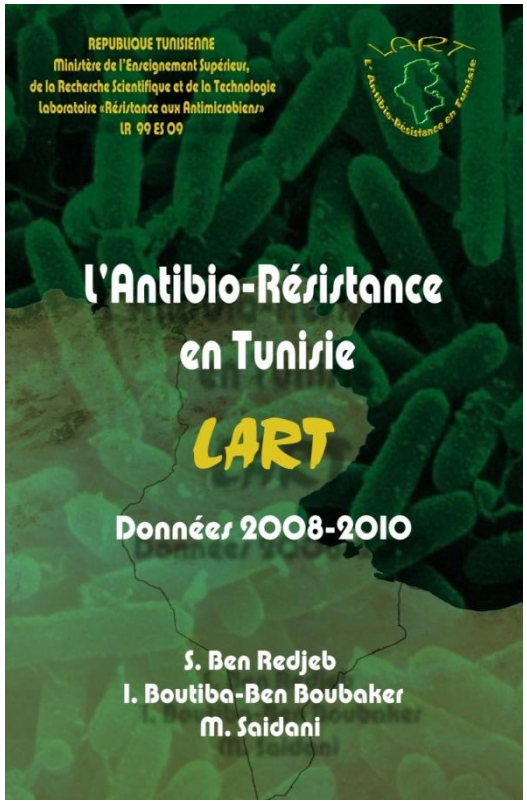
- Tous les pays à degrés variables selon:
  - Espèces pathogènes
  - Habitudes de prescription des antibiotiques
  - Pratiques d'hygiène

- **En Tunisie:**
  - Système de surveillance de R bactérienne aux antibiotiques
  - **L'A**ntibio-**R**ésistance en **T**unisie **= LART**
  - ↳ **Rassembler des données chiffrées et comparatives**

Résultats







Depuis 2011, sur le site de la STPI (www.infectiologie.org.tn)

OBJECTIFS DU LART

- **Base de données** sans cesse réactualisée de R aux ATB des principaux pathogènes & détecter précocement l'émergence de nouveaux phénotypes de R

- Améliorer les **connaissances fondamentales** sur les mécanismes moléculaires & les supports génétiques de R bactérienne

- Prévenir la dissémination des résistances bactériennes par la détection précoce d'épidémies permettant la mise en place des méthodes de contrôle & de **prévention**

- Préserver l'activité des ATB à travers une politique du **bon usage**

Matériel & Méthodes

4 **Centres Hospitalo-Universitaires** totalisant 2839 lits:

- Centre Hospitalo-Universitaire de Sfax regroupant les hôpitaux Hédi Chaker et Habib Bourguiba
- Hôpital Charles Nicolle de Tunis
- Hôpital d'Enfants de Tunis
- Centre National de Greffe de Mœlle Osseuse de Tunis

- **Depuis, 2011** → élargissement du réseau à **8 centres** (5656 lits)
  - Hôpital la Rabta de Tunis
  - Hôpital Militaire de Tunis
  - Institut Mohamed Kassab d'Orthopédie
  - Hôpital Fattouma Bourguiba de Monastir
- Méthodologie comparable:
  - Recueil des données
  - Contrôles de qualité (interne & externe)
  - Critères d'interprétation
  - Doublons épidémiologiques
- **Depuis, 2012 → 2 autres centres** (mais gestion très difficile !!!)

Matériel & Méthodes

- **Surveillance focalisée : 13 espèces**

  Escherichia coli,
  Klebsiella pneumoniae,
  Enterobacter cloacae (depuis, 2011),
  Pseudomonas aeruginosa,
  Acinetobacter baumannii (depuis, 2008),
  Salmonella spp,
  Staphylococcus aureus,
  Enterococcus faecalis,
  Enterococcus faecium (depuis, 2008),
  Streptococcus pyogenes,
  Streptococcus agalactiae (depuis, 2008),
  Streptococcus pneumoniae
  et *Haemophilus influenzae*

- **Identification:** méthodes conventionnelles

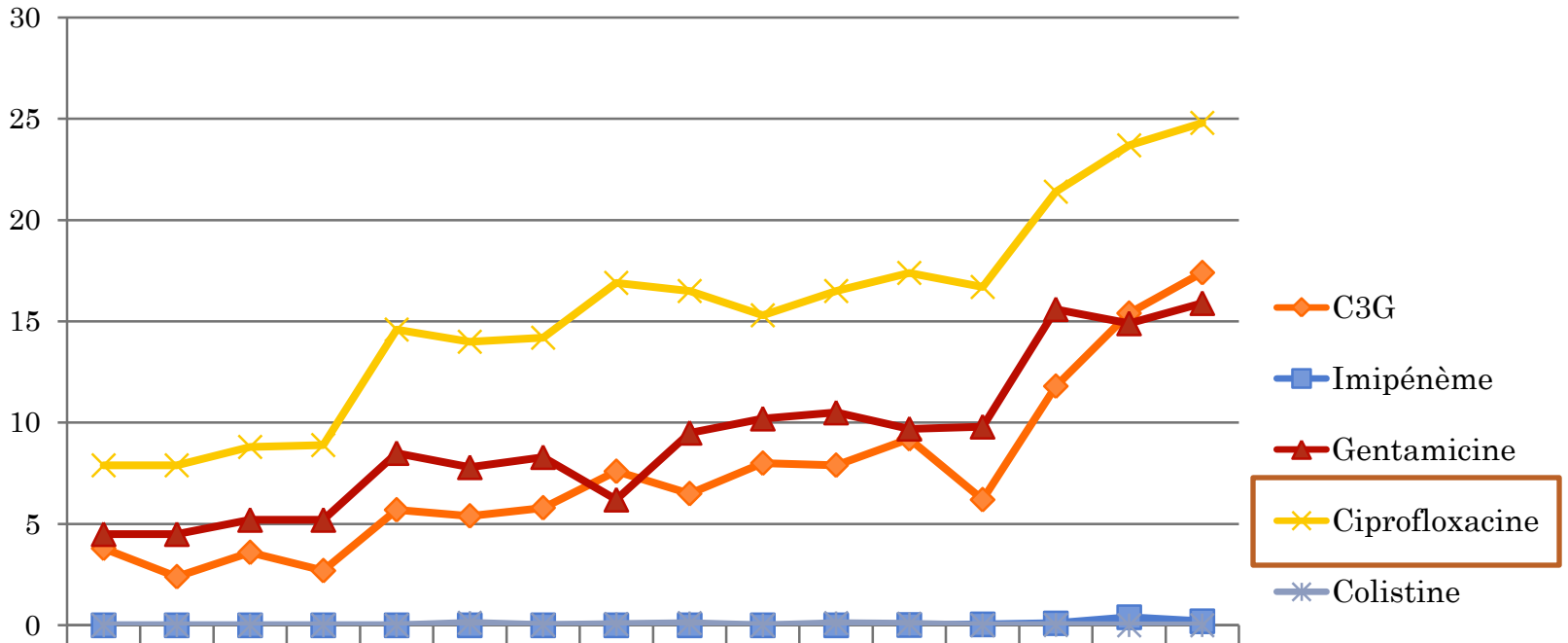
- **Etude de sensibilité aux antibiotiques:** CA-SFM / EUCAST

- **Saisie & analyse statistique données**

Distribution des différentes espèces

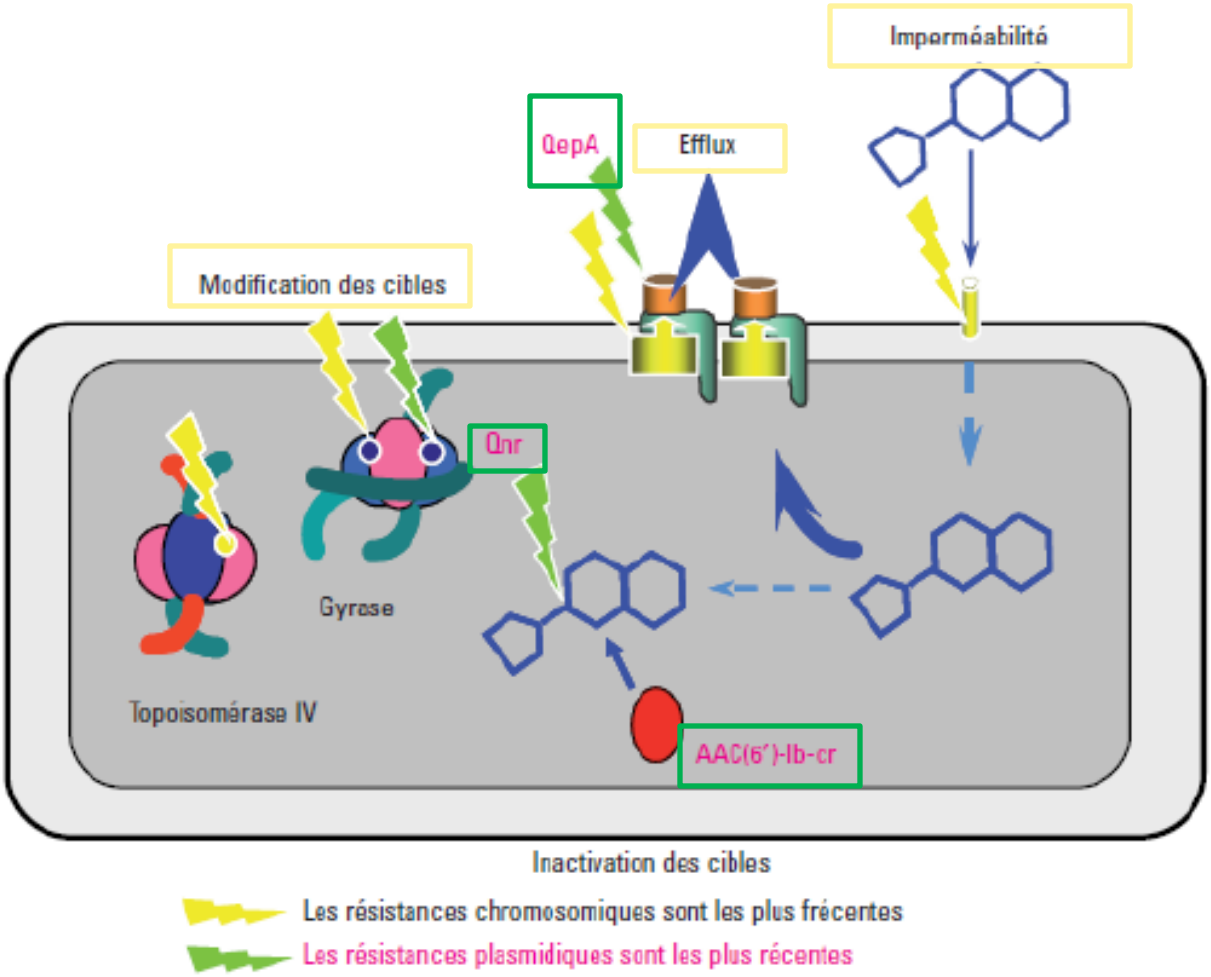
Espèces	Nombre de souches
E. coli	85396
K. pneumoniae	26139
P. aeruginosa	20323
A. baumannii	4995 (depuis 2008)
Salmonella spp.	1280
S. aureus	19891
E. faecium	963
E. faecalis	6861
S. pyogenes	2014
S. pneumoniae	2744
H. influenzae	4714
Total	**175320**

Evolution de la résistance de *E. coli*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C3G	3,8	2,4	3,6	2,7	5,7	5,4	5,8	7,6	6,5	8	7,9	9,2	6,2	11,8	15,4	17,4
Imipénème	0	0	0	0	0	0	0	0	0	0	0	0,02	0,04	0,1	0,4	0,2
Gentamicine	4,5	4,5	5,2	5,2	8,5	7,8	8,3	6,2	9,5	10,2	10,5	9,7	9,8	15,6	14,9	15,9
Ciprofloxacine	7,9	7,9	8,8	8,9	14,6	14	14,2	16,9	16,5	15,3	16,5	17,4	16,7	21,4	23,7	24,8
Colistine	0	0	0	0	0	0,12	0,01	0,06	0,1	0	0,1	0,08	0	0,02	0	0

Résistance aux fluoroquinolones



Résistance aux fluoroquinolones

- **Mutations chromosomiques:**
  - Palliers succéssifs
  - Plusieurs mutations ↳ haut niveau de résistance
- **Plasmidique :**
  - Bas niveau de résistance ↳ facilite la sélection de mutants résistants
  - Transférable horizontalement entre bactéries
  - Portent d'autres marqueurs de résistance

MICROBIAL DRUG RESISTANCE
Volume 00, Number 00, 2014

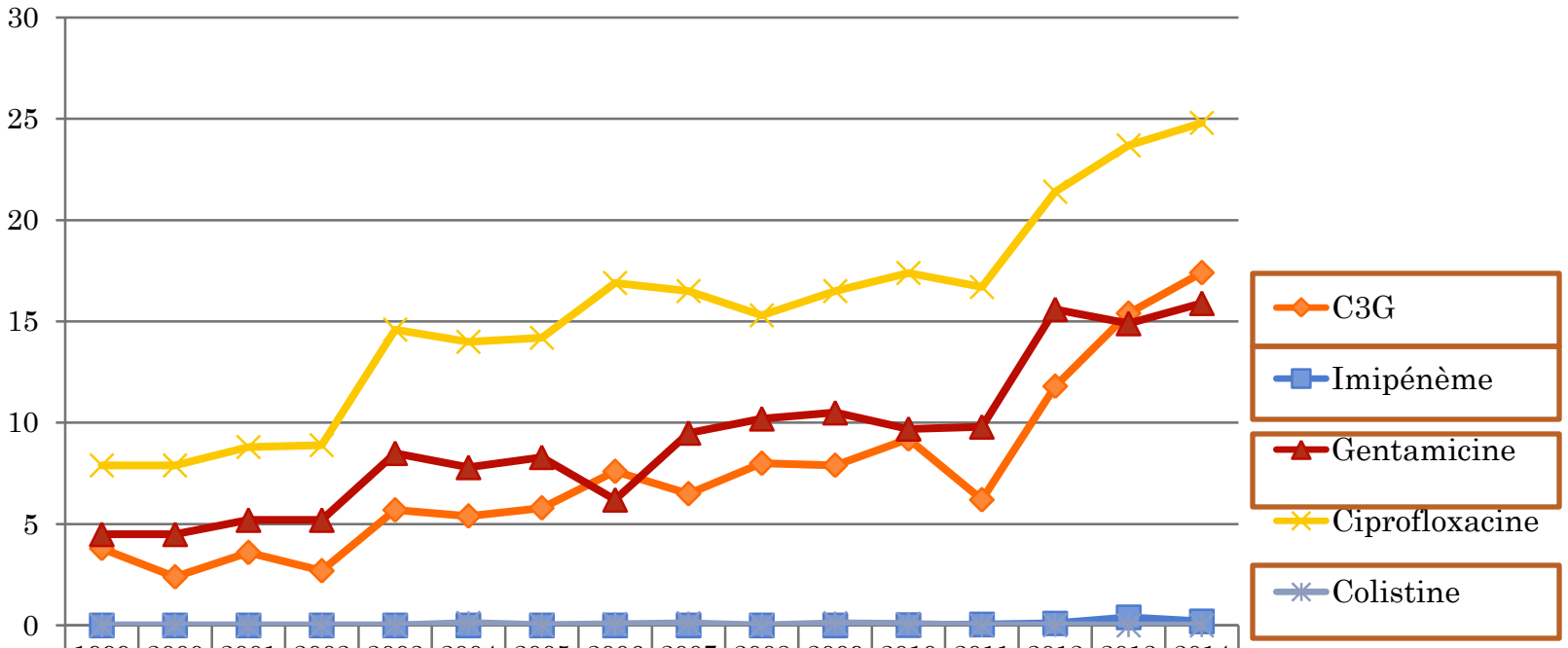
DOI: 10.1089/mdr.2014.0053

Prevalence and Characterization of Plasmid-Mediated Quinolone Resistance Genes in Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae* in a Tunisian Hospital

Sana Ferjani,[1] Mabrouka Saidani,[1,2] Faouzi Slim Amine,[2] and Ilhem Boutiba Ben Boubaker[1,2]

The objective of the study was to assess the prevalence of plasmid-mediated quinolone resistance (PMQR) genes (*qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *aac(6′)-Ib-cr*, *qepA*, and *oqxAB*) in a collection of 120 extended-spectrum β-lactamases (ESBLs)-producing enterobacteria and to characterize them. Overall, PMQR determinants were detected in 72 (60%) isolates (20 *Escherichia coli*, 32 *Klebsiella pneumoniae*, and 20 *Enterobacter cloacae*). PMQR frequencies were as follows: *qnr* genes (25.8%), *oqxAB* (21.6%), and *aac(6′)-Ib-cr* variant (19.2%). Four qnr alleles were identified as *qnrB1* (83.8%), *qnrB4* (6.4%), *qnrB2* (3.2%), and *qnrS1* (6.4%). qnr genes were mainly detected in *E. cloacae* (50%), *aac(6′)-Ib-cr* in *E. coli* (47.5%), and *oqxAB* in *K. pneumoniae* (65%). Overall, blaCTX-M-15 (90.3%) was the most prevalent *blaESBL* type followed by $bla_{SHV\text{-}12}$ (6.4%) and $bla_{SHV\text{-}27}$ (2.7%). Rates of mutations in *gyrA* and *parC* genes were 75% for *E. coli*, 72.8% for *K. pneumoniae*, and 50% for *E. cloacae*. Isolates with mutations in their quinolone resistance-determining regions exhibited high fluoroquinolones resistance levels compared to those with wild ones. Genetic study of PMQR-harboring isolates revealed a great genomic diversity among each *Enterobacteriaceae* species. Our findings indicate the high prevalence of PMQR determinants among ESBL-producing *Enterobacteriaceae* isolates from our hospital and their diffusion in various unrelated CTX-M-15-producing clones.

Evolution de la résistance de *E. coli*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C3G	3,8	2,4	3,6	2,7	5,7	5,4	5,8	7,6	6,5	8	7,9	9,2	6,2	11,8	15,4	17,4
Imipénème	0	0	0	0	0	0	0	0	0	0	0	0,02	0,04	0,1	0,4	0,2
Gentamicine	4,5	4,5	5,2	5,2	8,5	7,8	8,3	6,2	9,5	10,2	10,5	9,7	9,8	15,6	14,9	15,9
Ciprofloxacine	7,9	7,9	8,8	8,9	14,6	14	14,2	16,9	16,5	15,3	16,5	17,4	16,7	21,4	23,7	24,8
Colistine	0	0	0	0	0	0,12	0,01	0,06	0,1	0	0,1	0,08	0	0,02	0	0

Résistance à la colistine

- Mutations chromosomiques +++

- Plus récemment, mécanisme **plasmidique (*mcr-1*)!!!**
  Prévalence mondiale de 20% chez l'animal et autour de 1% chez l'Homme

RAPID COMMUNICATIONS

Impact of food animal trade on the spread of *mcr-1*-mediated colistin resistance, Tunisia, July 2015

R Grami [1,3], W Mansour [2,3], W Mehri [4], O Bouallègue [3], N Boujaâfar [3], J Madec [1], M Haenni [1]
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2. Institut Supérieur des Sciences Appliquées et de Technologie de Mahdia, Tunisia
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4. Commissariat Régional au Développement Agricole, Sousse, Tunisia

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Grami R, Mansour W, Mehri W, Bouallègue O, Boujaâfar N, Madec J, Haenni M. Impact of food animal trade on the spread of mcr-1-mediated colistin resistance, Tunisia, July 2015. Euro Surveill. 2016;21(8):pii=30144. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.8.30144

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- Prévalence élevée de *E. coli* producteur MCR-1 et CTX-M1 volailles

- 2 gènes portés sur le même plasmide (de type IncHI2)

- Réservoir:
  ↳ Risque de dissémination des 2 gènes dans le secteur alimentaire

En Tunisie: Pas de souches cliniques rapportées, en médecine humaine
Les souches tunisiennes: mutations chromosomiques (résultats non publiés)

RÉCENTE ÉTUDE ALLEMANDE: PORTAGE FÉCAL DE SOUCHES PRODUCTRICES DE BLSE ET PORTEUSES DE MCR-1

	Traveller with isolate 1	Traveller with isolate 2	Traveller with isolate 3	Traveller with isolate 4	Traveller with isolate 5
Travel destination	Thailand, Vietnam, Cambodia, Laos	Tunisia	Peru, Bolivia, Colombia	China	China
Travel duration (days)	21	8	40	14	23
Age (years)	56	55	25	54	62
Sex	Female	Female	Female	Male	Female
ESBL gene (ESBL group)	CTX-M-14 (CTX-M group 9)	CTX-M-1 (CTX-M group 1)	CTX-M-15 (CTX-M group 1)	CTX-M-65 (CTX-M group 9)	CTX-M-55 (CTX-M group 1)
Minimum inhibitory concentration of antimicrobial drug (mg/L)*					
Amoxicillin-clavulanic acid	16	8	>16	16	8
Piperacillin-tazobactam	8	≤4	8	≤4	≤4
Cefotaxime	16	8	32	16	>32
Cefoxitin	16	≤4	8	≤4	≤4
Ceftazidime	≤1	≤1	16	≤1	4
Cefepime	2	2	2	≤1	2
Imipenem	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25
Meropenem	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25
Gentamicin	>8	≤1	>8	≤1	>8
Tobramycin	8	≤1	>8	8	8
Nitrofurantoin	256	≤16	128	32	64
Co-trimoxazole	>8	>8	>8	≤1	>8
Norfloxacin	>8	8	>8	2	>8
Ciprofloxacin	>2	>2	>2	1	>2
Colistin	4	4	4	4	4

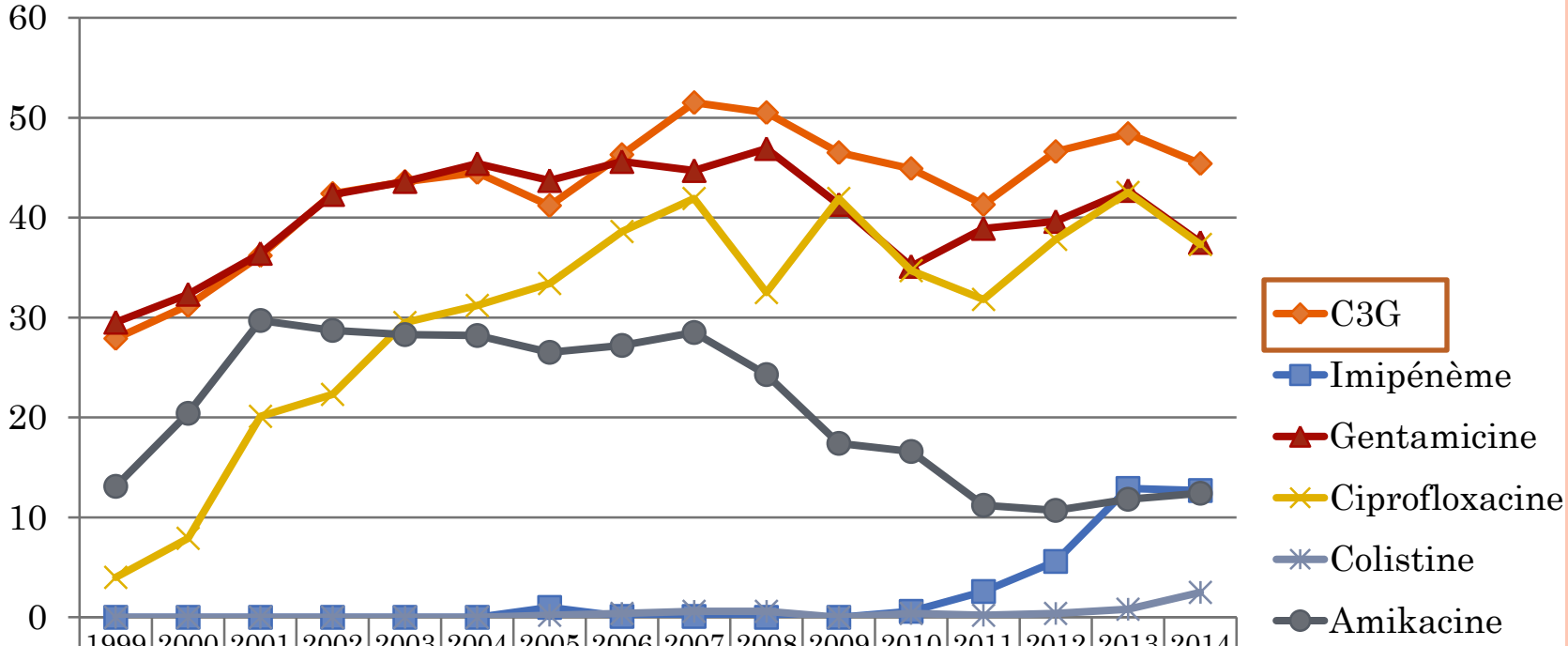
ESBL=extended-spectrum β-lactamase. *Determined using Vitek-2, except for colistin for which E-test results are provided.

Table: Characteristics of travellers and acquired fecal *Escherichia coli* isolates carrying the *mcr-1* gene

ORIGINE TUNISIENNE DE CETTE SOUCHE !!!

(The Lancet, 2016)

Evolution de la résistance de *K. pneumoniae*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C3G	27,9	31,2	36,2	42,4	43,6	44,5	41,2	46,3	51,5	50,5	46,5	44,9	41,3	46,6	48,4	45,4
Imipénème	0	0	0	0	0	0	1	0,1	0,1	0	0,00	0,6	2,6	5,6	12,9	12,7
Gentamicine	29,5	32,3	36,4	42,3	43,6	45,4	43,7	45,6	44,7	46,9	41,3	35,1	38,9	39,6	42,7	37,5
Ciprofloxacine	4	7,9	20,1	22,3	29,5	31,2	33,4	38,6	41,9	32,5	41,9	34,7	31,8	37,8	42,5	37,3
Colistine	0	0	0	0	0	0	0,2	0,4	0,6	0,6	0,00	0,4	0,2	0,4	0,8	2,5
Amikacine	13,1	20,4	29,7	28,7	28,3	28,2	26,5	27,2	28,5	24,3	17,4	16,6	11,2	10,7	11,8	12,4

Fréquence d'isolement des *K. pneumoniae* R aux C_3G selon le type de prélèvement

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Urines	20,2	22,9	25,2	31,6	18,4	39,2	35,7	39,4	40,9	45,3	41,2	36,7	35,3	37	38,7	26,6
Pus	28,6	30	32,5	46,6	44,5	46,2	46,9	36,2	53,6	45,1	40	45,7	44,2	54	47,4	30,4
Hémoc.	**42,4**	**51**	**62,5**	**63,3**	**86,8**	**64,3**	**57,7**	**67,7**	**72,5**	**63,4**	**54,9**	**60**	**63,1**	**69**	**70,2**	**47,8**
Pvts Pulm.	**35**	**34,2**	**57,5**	**39,6**	61,6	**48**	**38,9**	**50**	**68,1**	**54,5**	**60,8**	**57,8**	**48,3**	**44**	**51,2**	**45,1**
Ponct.	**43,7**	**68,7**	**42,1**	**43,5**	**86,2**	**50**	**70**	**85,7**	**60**	**75**	**55**	**52,3**	**51,2**	**48**	**53,8**	**39,4**

USI, pédiatrie et néonatalogie +++ où 2/3 des souches étaient RC3G
50 à 72% des *K pneumoniae* isolées d'hémocultures étaient R aux C3G

Résistance aux céphalosporines de 3ème génération

- Production de bêta-lactamases à spectre étendu (BLSE)
- Céphalosporinases (plasmidiques)
- Carbapénémases plasmidiques
- Souvent, association de malfaiteurs!!!!

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healthcare

REVIEW ARTICLE

Evolution of β-lactams resistance in Gram-negative bacteria in Tunisia

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Abstract

Antimicrobial resistance is a major health problem worldwide, but marked variations in the resistance profiles of bacterial pathogens are found between countries and in different patient settings. In Tunisia, the strikingly high prevalence of resistance of bacteria to penicillins and cephalorosporins drugs including fourth generation in clinical isolates of Gram negative bacteria has been reported. During 30 years, the emerging problem of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates is substantial, and some unique enzymes have been found. Recently, evidence that Gram-negative bacteria are resistant to nearly all available antimicrobial agents, including carbapenems, have emerged.

Keywords: Antibiotic resistance, β-lactamases, Tunisia

Table 1. The incidence of reported beta-lactamases in Tunisian cities.

References	Year	Journal	Species concerned	Enzymes described	Location
Hammami et al.	1991	Eur J Clin Microbiol Infect Dis	Salmonella wien	SHV-2	Sfax
Ben Hassen et al.	1994	Ann Biol Clin	Salmonella typhi	TEM-1	Tunis
Verdet et al.	1998	FEMS Microbiol Lett	Proteus mirabilis; Citrobacter freundii	CMY-2; CMY-4	Tunis
Ben Redjeb et al.	1999	Med Mal Infect	Proteus mirabilis	TEM-1; SHV-2; Amp-C (non identified)	Tunis
Rhimi et al.	2002	Pathol Biol	K. pneumoniae, P. mirabilis, S. enterica	ACC-1	Sfax
Makanera et al.	2003	J. Clin. Microbiol	Salmonella enterica	TEM-4;SHV-2a;ACC-1a	Tunis
Ben-Hamouda et al.	2004	Microb Drug Resist	Klebsiella pneumoniae	SHV-12;SHV-2a	Tunis
Bouallegue et al.	2005	J. Clin. Microbiol	Salmonella enterica	CTX-M-27	Sousse
Chouchani et al.	2006	Antimicrob. Agents Chemother	Salmonella enterica	TEM-138	Tunis
Doloy et al.	2006	Antimicrob. Agents Chemother	Klebsiella pneumoniae; Proteus mirabilis; Salmonella enterica; Escherichia coli	ACC-1	Sfax
Ktari et al.	2006	Antimicrob. Agents Chemother	Klebsiella pneumoniae	VIM-4;CTX-15;CMY-4	Sfax
Mamlouk et al.	2006	J. Clin. Microbiol	Klebsiella pneumoniae; Escherichia coli	CTX-M-15;CTX-M-16	Tunis
Lavollay et al.	2006	Antimicrob. Agents Chemother	Escherichia coli	CTX-M-15	Tunis
Chouchani et al.	2007	Diag Microbiol Infect Dis	Escherichia coli	TEM-15	Tunis
Kalai et al.	2007	Clin Microbiol Infect	Pseudomonas aeruginosa	OXA-18	Tunis
Abbassi et al.	2008	Inter. J. of Antimicrob. Agents	Klebsiella pneumoniae; Escherichia coli	OXA-1;TEM-1;SHV-1;SHV-11;SHV-27;SHV-103;CTX-M-15	Tunis
Mansour et al.	2008	Path. Biol	Acinetobacter baumannii	OXA-69	Sousse
Mansour et al.	2008	Microb. Drug. Resist	Acinetobacter baumannii	OXA-23	Sousse
Poirel et al.	2008	Antimicrob. Agents Chemother	Acinetobacter baumannii	OXA-97	Sousse
Ben Achour et al.	2009	Microb Drug Resist	Klebsiella pneumoniae	TEM-164	Tunis
Ben Achour et al.	2009	Path. Biol	Klebsiella pneumoniae	CTX-M-28	Tunis
Bourouis et al.	2009	Path. Biol	Enterobacter cloacae	CTX-M-9	Tunis
Dahmen et al.	2009	Clin Microbiol Infect	K. pneumoniae; Citrobacter freundii; Proteus mirabilis; Providencia stuartii; E. coli; Enterobacter cloacae; K. oxytoca	CTX-M-15;SHV-2a;SHV-12;SHV-28;TEM-1;LAP-2	Sousse
Kalai et al.	2009	Path. Biol	Pseudomonas aeruginosa	OXA-18;SHV-2a;SHV-5;SHV-12	Tunis
Ktari et al.	2009	Mirob. Drug Resist	Salmonella enterica	TEM-1;SHV-2a;ACC-1	Sfax
Mansour et al.	2009	Microb Drug Resist	Pseudomonas aeruginosa	SHV-2a	Sousse
Mansour et al.	2009	Diagn Microbiol Infect Dis	Pseudomonas aeruginosa	VIM-2	Sousse
Ben Slama et al.	2010	Inter J Food Microbiol	Escherichia coli	CTX-M-1;TEM-1b;TEM-20;CMY-2	Tunis
Dahmen et al.	2010	Microb Drug Resist	Klebsiella pneumoniae; Escherichia coli	CTX-M-15;SHV-12;SHV-2a	Sousse
Elhani et al.	2010	Clin Microbiol Infect	Klebsiella pneumoniae	CTX-M-15;CTX-M-14;CTX-27;SHV-12;SHV-2a	Monastir
Hammami et al.	2010	Clin. Microbiol. Infect	Pseudomonas aeruginosa	VIM-2;SHV-2a	Tunis
Cuzon et al.	2010	Int J Antimicrob Agents	Klebsiella pneumoniae	OXA-48	Djerba

CTX-M15: mode pandémique

JJBS
Jordan Journal of Biolo
ume 7, Number 1, March .2014
ISSN 1995-6673
Pages 1 - 6
Review

The Medi ·M-ESBL-

(Newire *et al.*, 2013). In Tunisia, the initial identification of a CTX-M-producing strain (CTX-M-3) was recovered in 2001. Later on, CTX-M-27 originated a nosocomial outbreak in a Tunisian neonatal center. The first report of CTX-M-15 and CTX-M-16-producing *Enterobacteriaceae* in Tunisia was submitted in 2006 (Mamlouk *et al.*, 2006). Later, Dahmen *et al.* (2010) corroborated the high prevalence of CTX-M-15 with 91% of the isolates producing this enzyme. The majority of CTX-M-15-ESBL-producing *E. coli* belonged to B2 phylogenetic group and to the sequence type 131 and was associated with Qnr-like determinants (Dahmen *et al.*, 2010). It was also found that this CTX-M-15-B2-ST131 *E. coli* clone is also highly disseminating in community-acquired urinary tract infections in Tunisia (Hammami *et al.*, 2013). The molecular analysis of a collection of ESBL producers isolated between 1989 and 2009 confirmed the prominence of *bla*CTX-M-15 gene followed by *bla*CTX-M-14 gene, *bla*SHV-12 gene, *bla*SHV-2a gene and *bla*TEM-26, with the frequent dissemination of CTX-M-15 producing *E. coli* being attributed to the spread of various IncF-type plasmids (Mnif *et al.*,

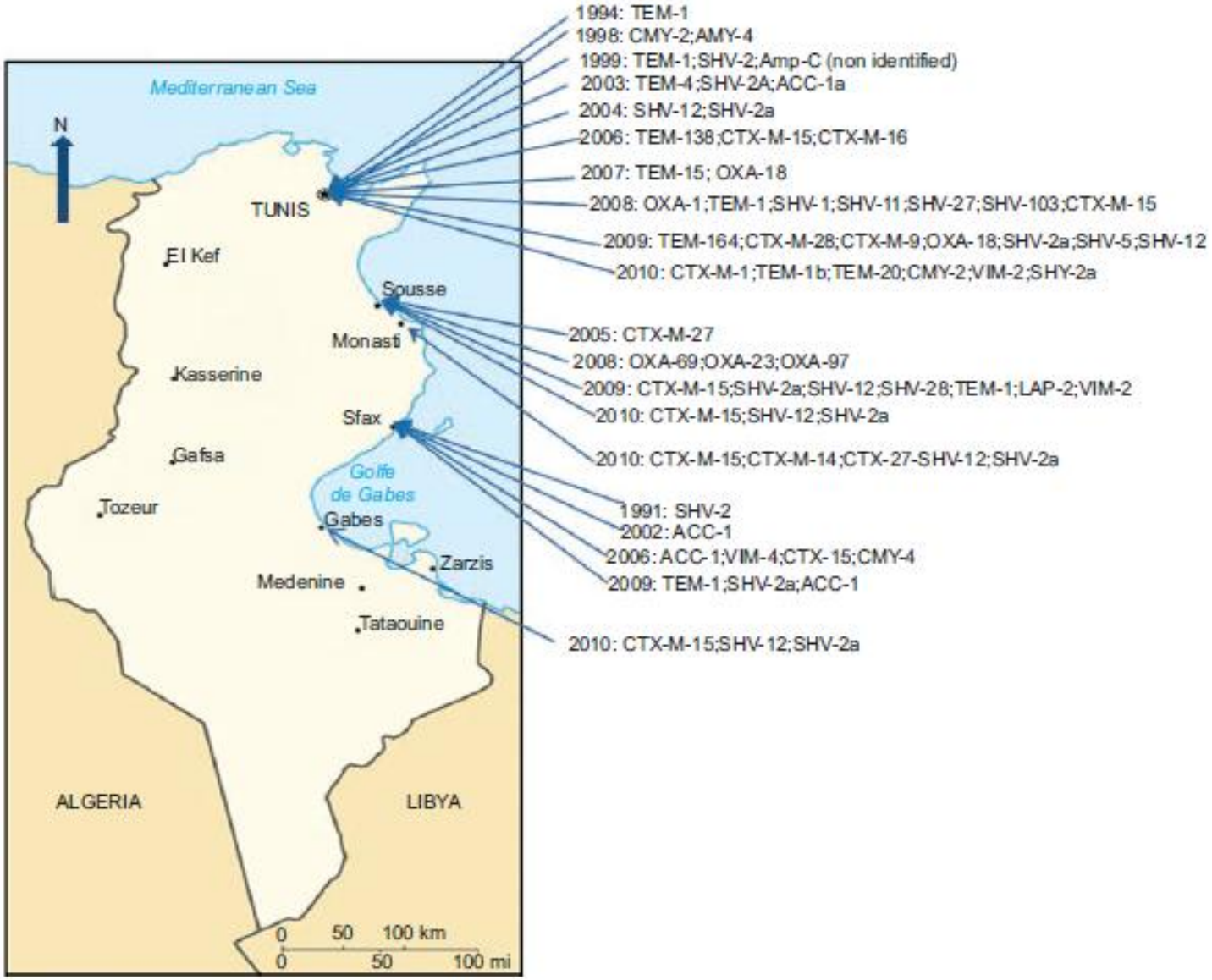


Figure 1. Map shows geographic location of the different beta-lactamases described in Tunisia. Map was obtained from http://www.misterfast.net/guide/tunisie.html

PORTAGE DIGESTIF DE BLSE

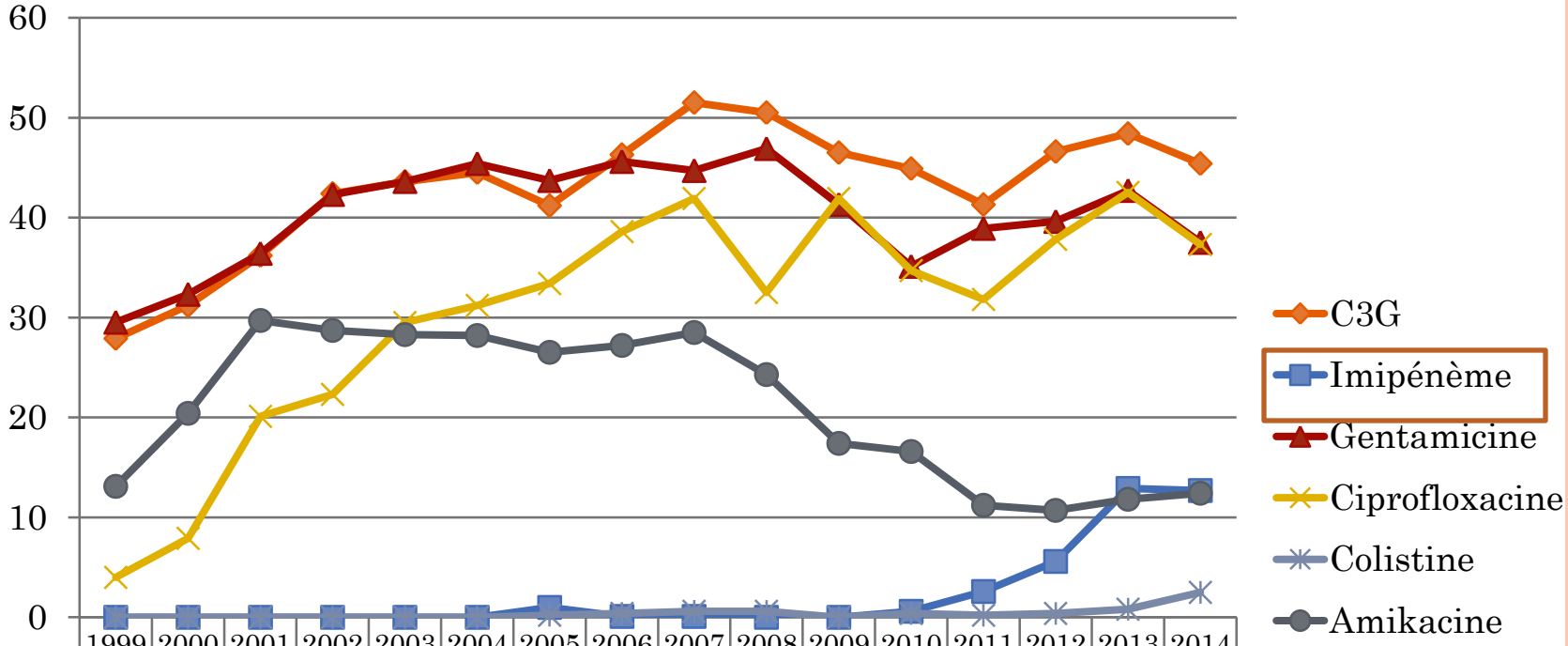
2 études des **populations saines sans facteurs de risque**

Enfant: 6,9% (publication en cours)

Adulte : 7,3%
(Ben Sallem R et al. Eur J Clin Microbiol Infect Dis. 2012;31(7):1511-6)

Adulte avec facteurs de risque : 20,63%
(Maamar A et al. Front Microbiol. 2016; 7: 1859.)

Evolution de la résistance de *K. pneumoniae*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C3G	27,9	31,2	36,2	42,4	43,6	44,5	41,2	46,3	51,5	50,5	46,5	44,9	41,3	46,6	48,4	45,4
Imipénème	0	0	0	0	0	0	1	0,1	0,1	0	0,00	0,6	2,6	5,6	12,9	12,7
Gentamicine	29,5	32,3	36,4	42,3	43,6	45,4	43,7	45,6	44,7	46,9	41,3	35,1	38,9	39,6	42,7	37,5
Ciprofloxacine	4	7,9	20,1	22,3	29,5	31,2	33,4	38,6	41,9	32,5	41,9	34,7	31,8	37,8	42,5	37,3
Colistine	0	0	0	0	0	0	0,2	0,4	0,6	0,6	0,00	0,4	0,2	0,4	0,8	2,5
Amikacine	13,1	20,4	29,7	28,7	28,3	28,2	26,5	27,2	28,5	24,3	17,4	16,6	11,2	10,7	11,8	12,4

CARBAPÉNÉMASES

Journal of Medical Microbiology (2012), **61**, 1746–1749 DOI 10.1099/jmm.0.045229-0

Emergence of carbapenem-resistant OXA-48 carbapenemase-producing *Enterobacteriaceae* in Tunisia

M. Saïdani, S. Hammami, A. Kammoun, A. Slim and I. Boutiba-Ben Boubaker

Laboratoire de Bactériologie Virologie, Hôpital Charles Nicolle, Boulevard 9 Avril, 1006, Tunis, Tunisia

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Received 27 March 2012
Accepted 23 August 2012

We screened 21 extended spectrum β-lactamase-producing *Enterobacteriaceae* with reduced susceptibility to carbapenems for carbapenemase production. Five strains (four *Klebsiella pneumoniae* and one *Citrobacter freundii*) showed carbapenemase production, which was identified as OXA-48. The bla_{OXA-48} gene was detected on ~54 kb plasmids belonging to IncA/C in one case. Two isolates harboured IS*1999*, which is involved in bla_{OXA-48} mobilization. Carbapenem resistance in enterobacteria should be regarded as an emerging clinical problem in our hospital and necessitates rigorous surveillance in order to limit its spread.

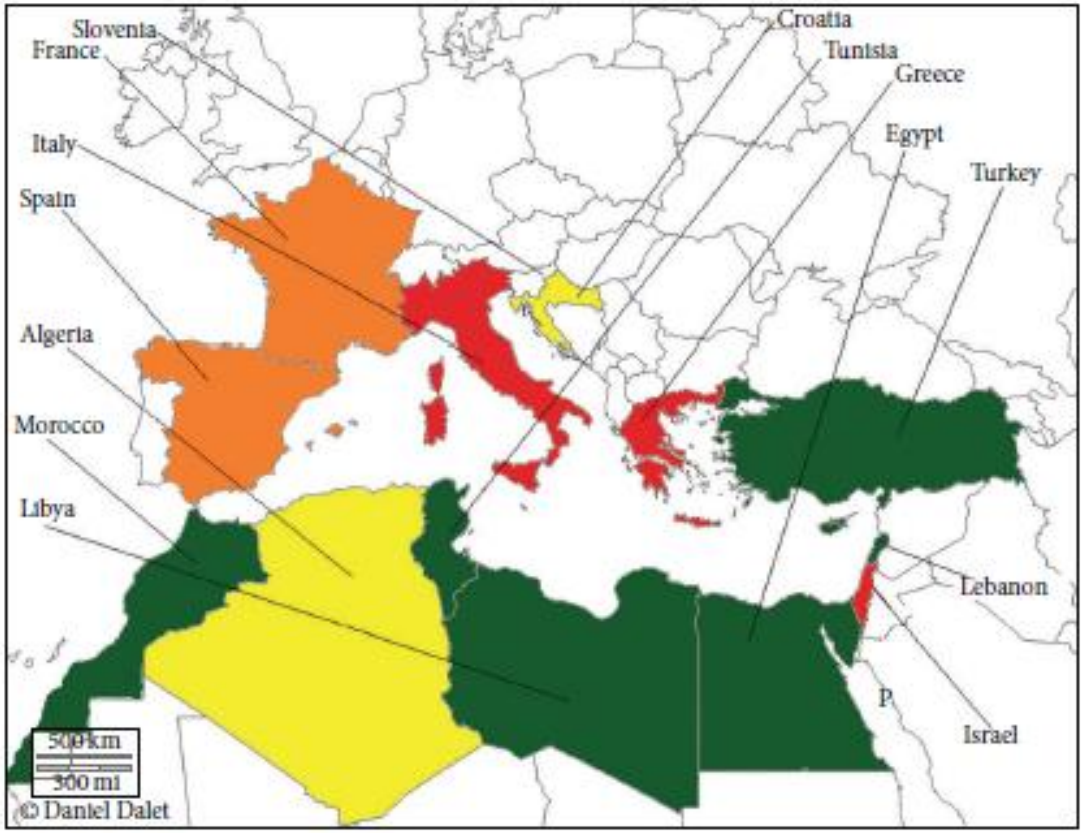


FIGURE 1: Geographic distribution of KPC enzymes in Mediterranean countries. White, no case reported; yellow, single KPC-producing isolates; green, some outbreaks of KPC-producing isolates; orange, several outbreaks of KPC-producing isolates; red, endemicity of KPC-producing isolates.

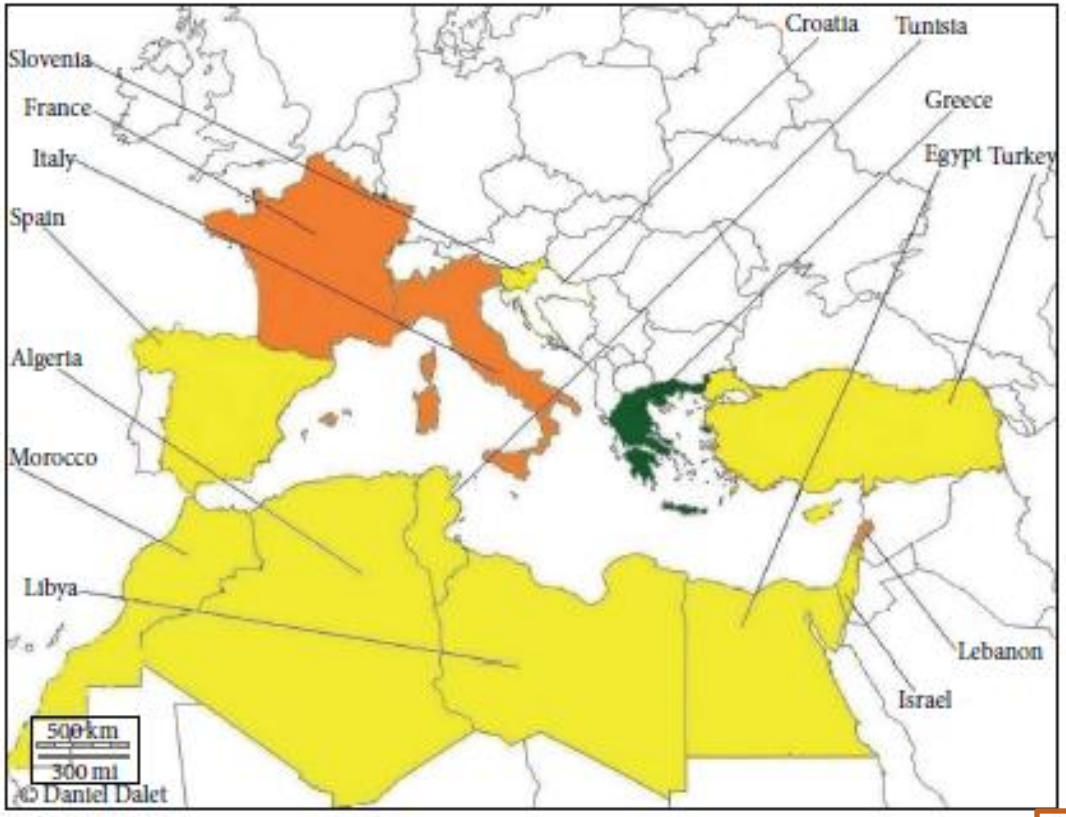


Figure 2: Geographic distribution of NDM type producers in Mediterranean countries. White, no case reported; yellow, sporadic NDM-producing isolates; green, emerging outbreak of NDM-producing isolates; orange, single hospital outbreaks of NDM-producing isolates.

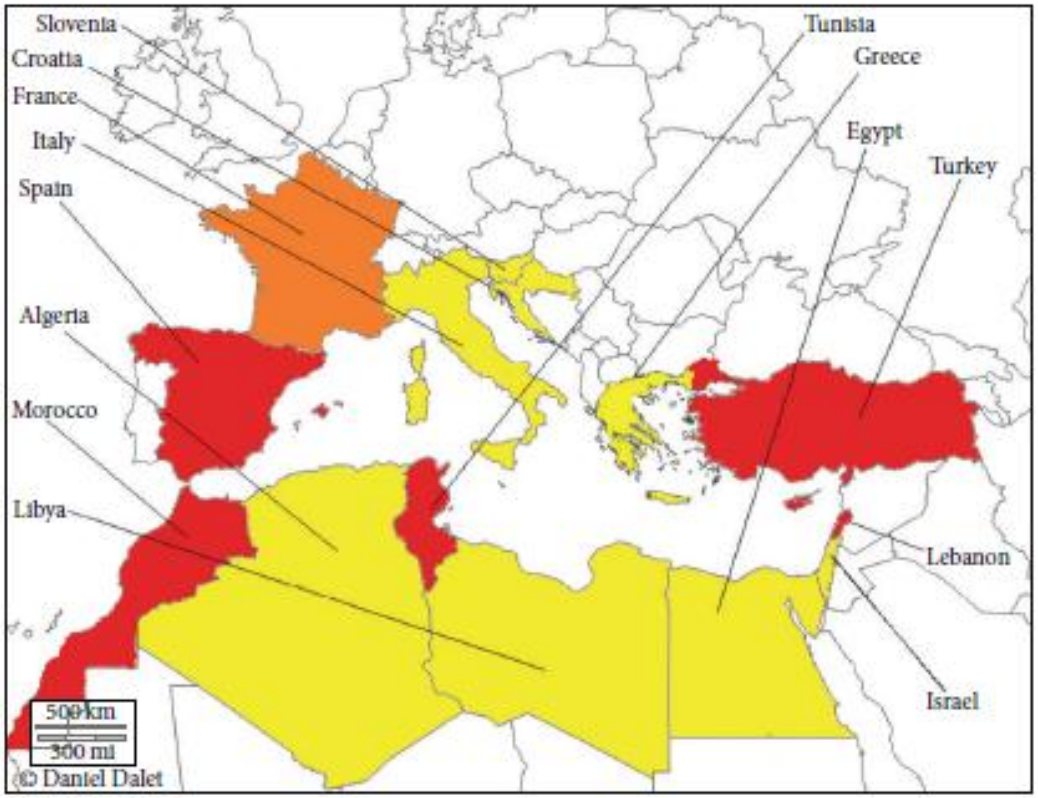


FIGURE 3: Geographic distribution of OXA-48 type producers in Mediterranean countries. White, no case reported; yellow, single OXA-48-producing isolates; orange, several outbreaks of OXA-48-producing isolates; red, nationwide distribution of OXA-48-producing isolates.

CARBAPÉNÉMASES: ENVIROMMENT HOSPITALIER

APMIS 119: 725–732

DOI 10.1111/j.1600-0463.2011.02793.x

VIM and IMP metallo-β-lactamases and other extended-spectrum β-lactamases in *Escherichia coli* and *Klebsiella pneumoniae* from environmental samples in a Tunisian hospital

CHEDLY CHOUCHANI,[1] RIM MARRAKCHI,[1,2] LEILA FERCHICHI,[3] ALLAAEDDIN EL SALABI[4] and TIMOTHY R. WALSH[4]

ASSOCIATION DE MALFAITEURS!!

Indian Journal of Medical Microbiology, (2012) 30(4): 437-41

Original Article

First characterisation of plasmid-mediated quinolone resistance-qnrS1 co-expressed $bla_{CTX\text{-}M\text{-}15}$ and $bla_{DHA\text{-}1}$ genes in clinical strain of *Morganella morganii* recovered from a Tunisian Intensive Care Unit

***S Mahrouki, A Bourouis, H Chihi, R Ouertani, M Ferjani, MB Moussa, F Barguellil, O Belhadj**

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

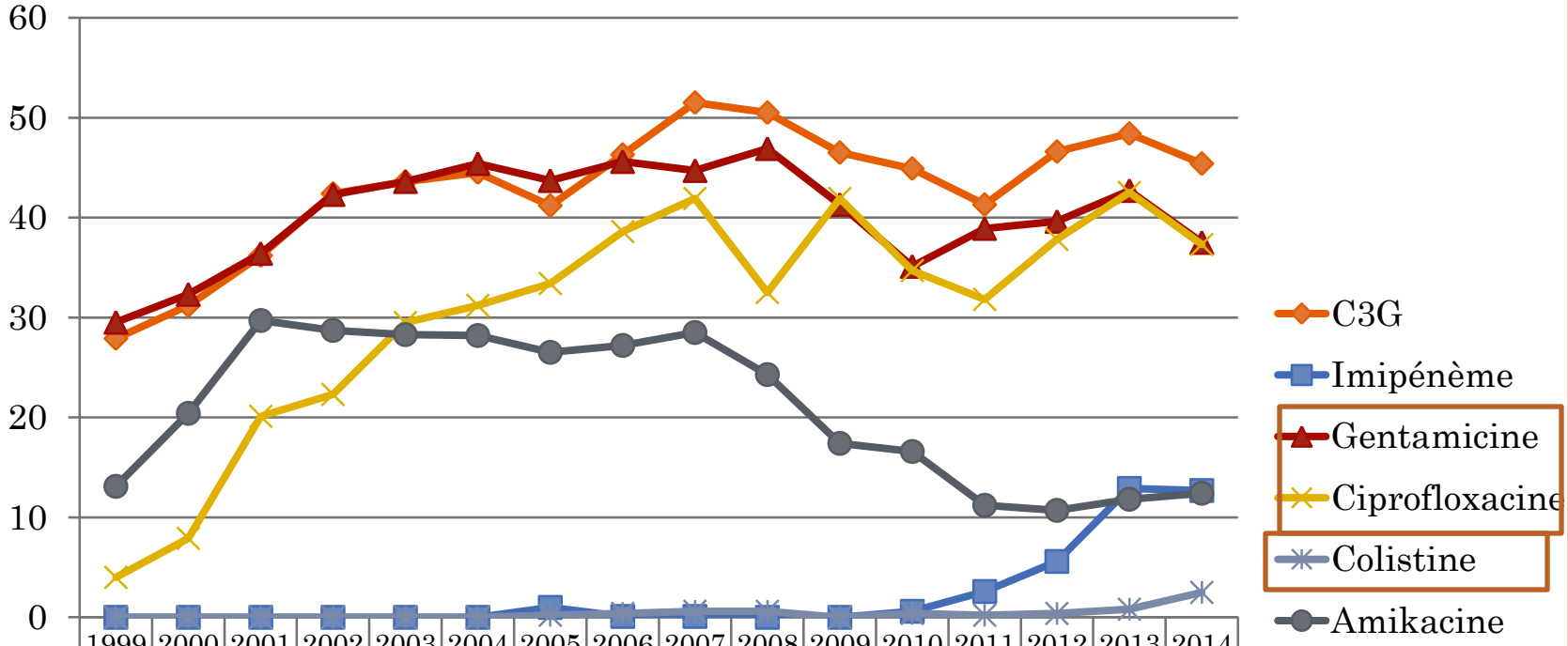
Cooccurrence of Multiple AmpC β-Lactamases in *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* in Tunisia

Thouraya Chérif,[a] Mabrouka Saidani,[a,b] Dominique Decré,[c,d,e] Ilhem Boutiba-Ben Boubaker,[a,b] Guillaume Arlet[c,d,e]

Université de Tunis El Manar, Faculté de Médecine de Tunis, LR99ES09 Laboratoire de Résistance aux Antimicrobiens, Tunis, Tunisia[a]; CHU Charles Nicolle, Service de Microbiologie, Tunis, Tunisia[b]; Sorbonne Université, UPMC Université Paris 06 CR7, Paris, France[c]; INSERM U1135, CIMI, Team E13, Paris, France[d]; AP-HP, Groupe Hospitalier des Hôpitaux Universitaires de l'Est Parisien, Département de Bactériologie, Paris, France[e]

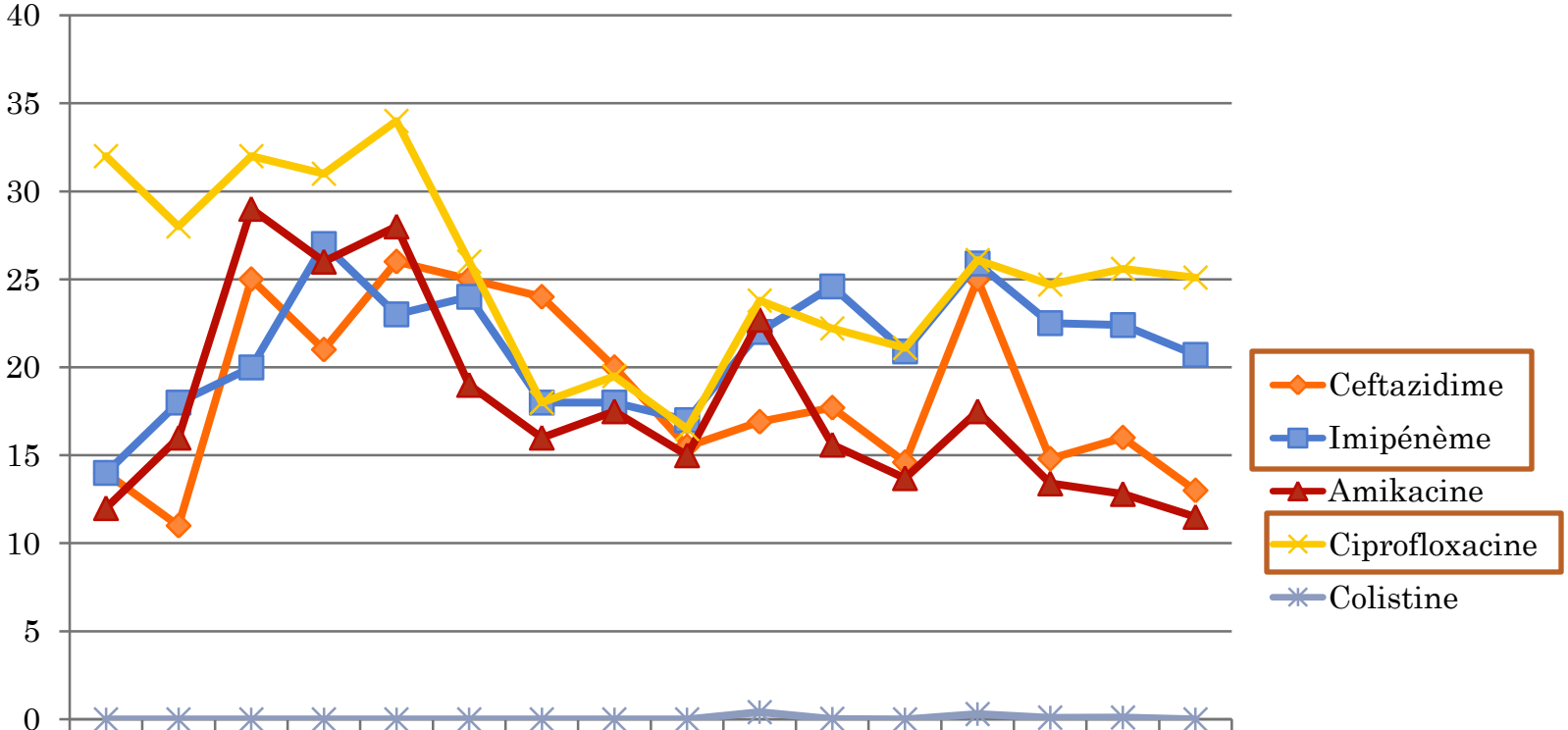
Over a period of 40 months, plasmid-mediated AmpC β-lactamases were detected in Tunis, Tunisia, in 78 isolates (0.59%) of *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. In 67 isolates, only one *ampC* gene was detected, i.e., $bla_{CMY\text{-}2\text{-}type}$ ($n = 33$), bla_{ACC} ($n = 23$), bla_{DHA} ($n = 6$) or bla_{EBC} ($n = 5$). Multiple *ampC* genes were detected in 11 isolates, with the following distribution: $bla_{MOX\text{-}2}$, $bla_{FOX\text{-}3}$, and $bla_{CMY\text{-}4/16}$ ($n = 6$), $bla_{FOX\text{-}3}$ and $bla_{MOX\text{-}2}$ ($n = 3$), and $bla_{CMY\text{-}4}$ and $bla_{MOX\text{-}2}$ ($n = 2$). A great variety of plasmids carrying these genes was found, independently of the species and the *bla* gene. If the genetic context of $bla_{CMY\text{-}2\text{-}type}$ is variable, that of $bla_{MOX\text{-}2}$, reported in part previously, is unique and that of $bla_{FOX\text{-}3}$ is unique and new.

Evolution de la résistance de *K. pneumoniae*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
C3G	27,9	31,2	36,2	42,4	43,6	44,5	41,2	46,3	51,5	50,5	46,5	44,9	41,3	46,6	48,4	45,4
Imipénème	0	0	0	0	0	0	1	0,1	0,1	0	0,00	0,6	2,6	5,6	12,9	12,7
Gentamicine	29,5	32,3	36,4	42,3	43,6	45,4	43,7	45,6	44,7	46,9	41,3	35,1	38,9	39,6	42,7	37,5
Ciprofloxacine	4	7,9	20,1	22,3	29,5	31,2	33,4	38,6	41,9	32,5	41,9	34,7	31,8	37,8	42,5	37,3
Colistine	0	0	0	0	0	0	0,2	0,4	0,6	0,6	0,00	0,4	0,2	0,4	0,8	2,5
Amikacine	13,1	20,4	29,7	28,7	28,3	28,2	26,5	27,2	28,5	24,3	17,4	16,6	11,2	10,7	11,8	12,4

EVOLUTION DE LA RÉSISTANCE DE *P. AERUGINOSA*



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Ceftazidime	14	11	25	21	26	25	24	20	15,5	16,9	17,7	14,6	25	14,8	16	13
Imipénème	14	18	20	27	23	24	18	18	17	22	24,6	20,9	25,9	22,5	22,4	20,7
Amikacine	12	16	29	26	28	19	16	17,5	15	22,7	15,6	13,7	17,5	13,4	12,8	11,5
Ciprofloxacine	32	28	32	31	34	26	18	19,5	16,5	23,8	22,2	21,1	26,1	24,7	25,6	25,1
Colistine	0	0	0	0	0	0	0	0	0	0,4	0,02	0	0,3	0,09	0,1	0

- **46%** des souches de *P. aeruginosa* isolées en **USI** étaient R à imipénème
- **1/3** des souches responsables de **bactériémies** ou **infections pulmonaires** basses
- chez des malades sous ventilation mécanique étaient R à imipénème
- Près de 42% de ces souches étaient R à tous les antibiotiques testés, sauf la colistine

Epidémie nosocomiale à P. aeruginosa producteur de BLSE type oxa-18 au CNGMO

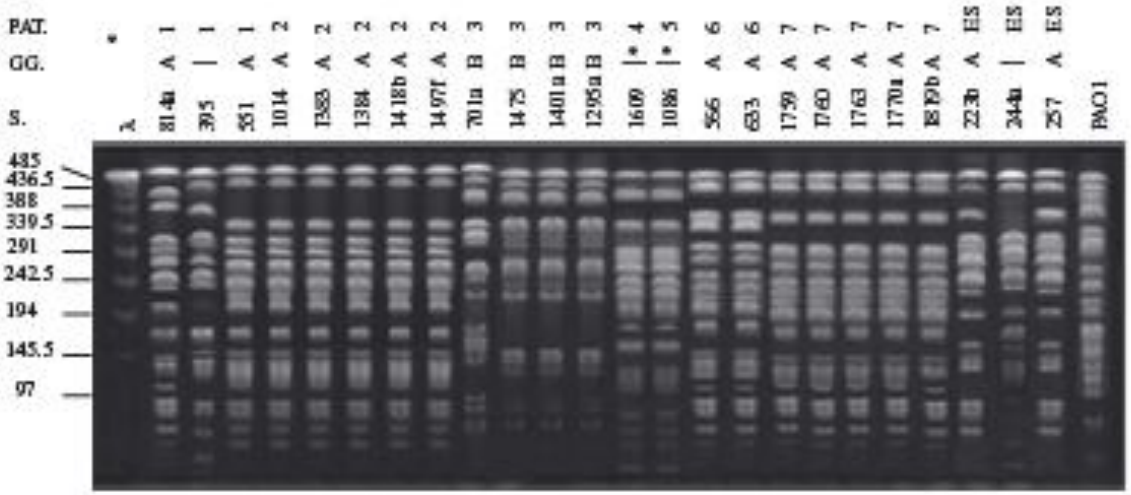


Fig. 1. Pulsed-field gel electrophoresis profiles of *Pseudomonas aeruginosa* isolates producing OXA-18. Size markers are shown in the left-hand lane. PAT, patient; GG, genogroup; S, strain.

Hammami et al. Diagnostic Pathology 2011, 6:106
http://www.diagnosticpathology.org/content/6/1/106

DIAGNOSTIC PATHOLOGY

RESEARCH Open Access

Nosocomial outbreak of imipenem-resistant *Pseudomonas aeruginosa* producing VIM-2 metallo-β-lactamase in a kidney transplantation unit

S Hammami[1*], I Boutiba-Ben Boubaker[1,2], R Ghozzi[1,2], M Saidani[1,2], S Amine[1,2] and S Ben Redjeb[1]

Abstract

Background: Twenty four non replicate imipenem resistant *P. aeruginosa* were isolated between January and November 2008, in the kidney transplantation unit of Charles Nicolle Hospital of Tunis (Tunisia). This study was conducted in order to establish epidemiological relationship among them and to identify the enzymatic mechanism involved in imipenem resistance.

Methods: Analysis included antimicrobial susceptibility profile, phenotypic (imipenem-EDTA synergy test) and genotypic detection of metallo-β-lactamase (MBL) (PCR), O-serotyping and pulsed-field gel electrophoresis.

Results: All strains showed a high level of resistance to all antimicrobials tested except to colistin. The presence of MBL showed concordance between phenotypic and genotypic methods. Sixteen isolates were identified as VIM-2 MBL-producers and 13 of them were serotype O4 and belonged to a single pulsotype (A).

Conclusions: This study describes an outbreak of VIM-2-producing *P. aeruginosa* in a kidney transplantation unit. Clinical spread of bla_{VIM-2} gene is a matter of great concern for carbapenem resistance in Tunisia.

Keywords: pulsed-field gel electrophoresis, carbapenem, *P. aeruginosa*, epidemiology

J Antimicrob Chemother 2015; 70: 23–40
doi:10.1093/jac/dku356 Advance Access publication 26 September 2014

Journal of Antimicrobial Chemotherapy

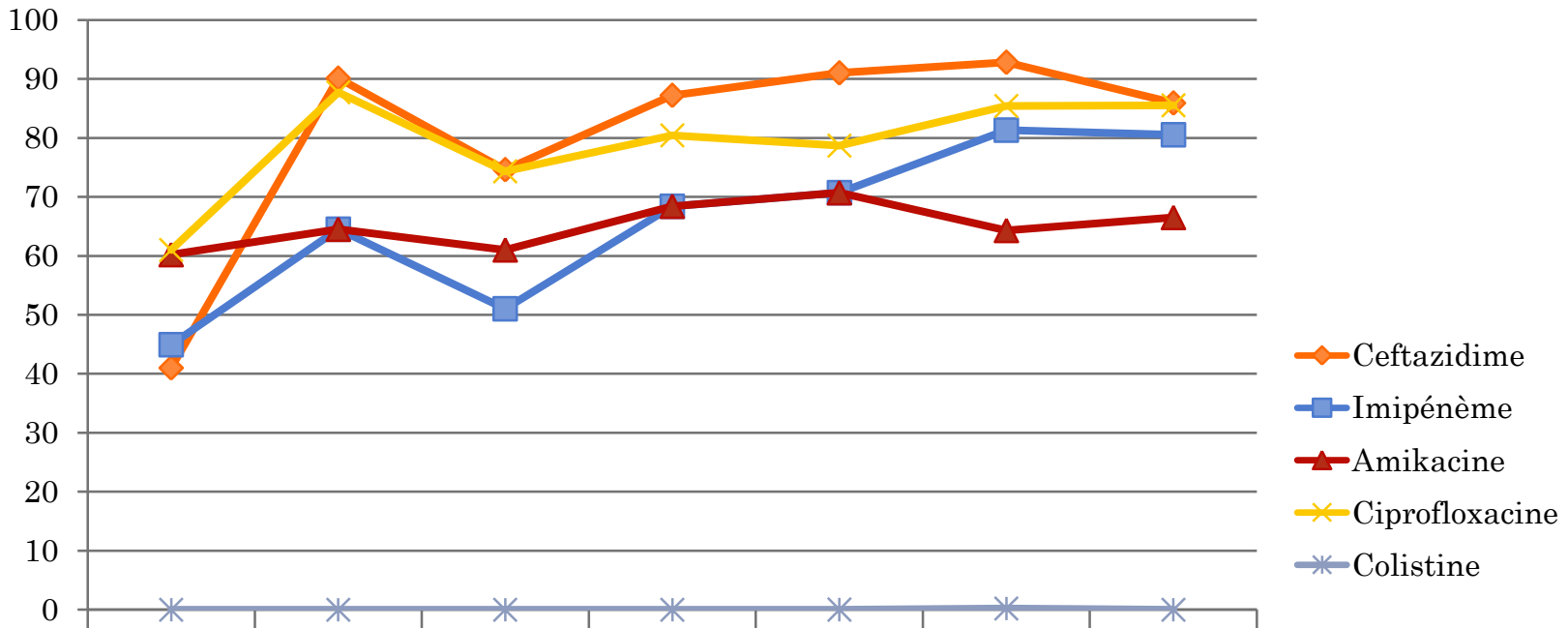
The spread of carbapenemase-producing bacteria in Africa: a systematic review

Rendani I. Manenzhe[1], Heather J. Zar[2,3], Mark P. Nicol[1,4,5] and Mamadou Kaba[1,4]*

								IMP (3)			
Tunisia	2008	laboratory-based surveillance[a]	urine, cutaneous pus, blood	*P. aeruginosa*	16/24 (67)		VIM-2 (16)		H	A	52
Tunisia	2001–05	laboratory-based surveillance	blood, pus	*A. baumannii*	19/39 (49)	OXA-97 (19)			H	NA	34
Tunisia	2003–07	laboratory-based surveillance[a]	blood, urine, catheter	*P. aeruginosa*	5/75 (6.7)		VIM-2 (5)		H	A	55
Tunisia	2002–06	laboratory-based surveillance	pus, blood, urine, catheter, bronchial secretions	*P. aeruginosa*	35/73 (48)		VIM-2 (35)		H	Ch & A	51
Tunisia	2007	laboratory-based surveillance[a]	blood, pus, urine, pulmonary specimens, materials	*A. baumannii*	41/50 (82)	OXA-23 (41)			H	NA	72
Tunisia	2007	case report	tracheal protection culture	*A. baumannii*	NA	OXA-23 (1)			H	A	154
Tunisia	2007	laboratory-based surveillance	NA	*P. aeruginosa*	30/30 (100)		VIM-2 (30)		H	NA	155
Tunisia	2005–07	laboratory-based surveillance[a]	blood, pus, urine, tracheal aspirate	*A. baumannii*	13/99 (13)	OXA-23 (13)			H	A	73

BAL, bronchoalveolar lavage; Ch, children; A, adult; H, hospital; C, community; NA, not available.
For the 'Carbapenemase described' columns, blanks mean 'not detected'.
[a]Identified outbreak.
[b]Transferred or travel patient.
[c]Three isolates from human head lice.

Evolution de la résistance d'*A. baumannii*



	2008	2009	2010	2011	2012	2013	2014
Ceftazidime	41	90,1	74,6	87,2	91	92,8	85,9
Imipénème	44,9	64,5	51	68,4	70,7	81,3	80,5
Amikacine	60,2	64,5	61	68,4	70,7	64,3	66,5
Ciprofloxacine	61	87,7	74,3	80,4	78,7	85,4	85,5
Colistine	0	0	0	0	0,02	0,2	0

- Infections graves (respiratoires et bactériémies) +++
- Multirésistance, voire tous les antibiotiques testés, sauf la colistine

J Antimicrob Chemother 2015; 70: 23–40
doi:10.1093/jac/dku356 Advance Access publication 26 September 2014

Journal of Antimicrobial Chemotherapy

The spread of carbapenemase-producing bacteria in Africa: a systematic review

Rendani I. Manenzhe[1], Heather J. Zar[2,3], Mark P. Nicol[1,4,5] and Mamadou Kaba[1,4]*

								IMP (3)			
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Tunisia	2001–05	laboratory-based surveillance	blood, pus	*A. baumannii*	19/39 (49)	OXA-97 (19)			H	NA	34
Tunisia	2003–07	laboratory-based surveillance[a]	blood, urine, catheter	*P. aeruginosa*	5/75 (6.7)		VIM-2 (5)		H	A	55
Tunisia	2002–06	laboratory-based surveillance	pus, blood, urine, catheter, bronchial secretions	*P. aeruginosa*	35/73 (48)		VIM-2 (35)		H	Ch & A	51
Tunisia	2007	laboratory-based surveillance[a]	blood, pus, urine, pulmonary specimens, materials	*A. baumannii*	41/50 (82)	OXA-23 (41)			H	NA	72
Tunisia	2007	case report	tracheal protection culture	*A. baumannii*	NA	OXA-23 (1)			H	A	154
Tunisia	2007	laboratory-based surveillance	NA	*P. aeruginosa*	30/30 (100)		VIM-2 (30)		H	NA	155
Tunisia	2005–07	laboratory-based surveillance[a]	blood, pus, urine, tracheal aspirate	*A. baumannii*	13/99 (13)	OXA-23 (13)			H	A	73

BAL, bronchoalveolar lavage; Ch, children; A, adult; H, hospital; C, community; NA, not available.
For the 'Carbapenemase described' columns, blanks mean 'not detected'.
[a]Identified outbreak.
[b]Transferred or travel patient.
[c]Three isolates from human head lice.

Microbial Pathogenesis 74 (2014) 20–24

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

Multidrug-resistant *Acinetobacter baumannii* strains carrying the bla_{OxA-23} and the bla_{GES-11} genes in a neonatology center in Tunisia

Karama Charfi-Kessis [a, b], Wejdene Mansour [b, *], Anis Ben Haj Khalifa [c], Maha Mastouri [b], Patrice Nordmann [a, d], Mahjoub Aouni [b], Laurent Poirel [a, d]

Conclusion

- Etudes multicentriques standardisées, effectuées régulièrement depuis 1999 → Données fiables de la résistance aux antibiotiques
- Mécanismes moléculaires: identifiés

- **Cependant,**
  - **Données non représentatives de l'ensemble du pays !!**
  - **Données communautaires manquantes (BGN)!!**

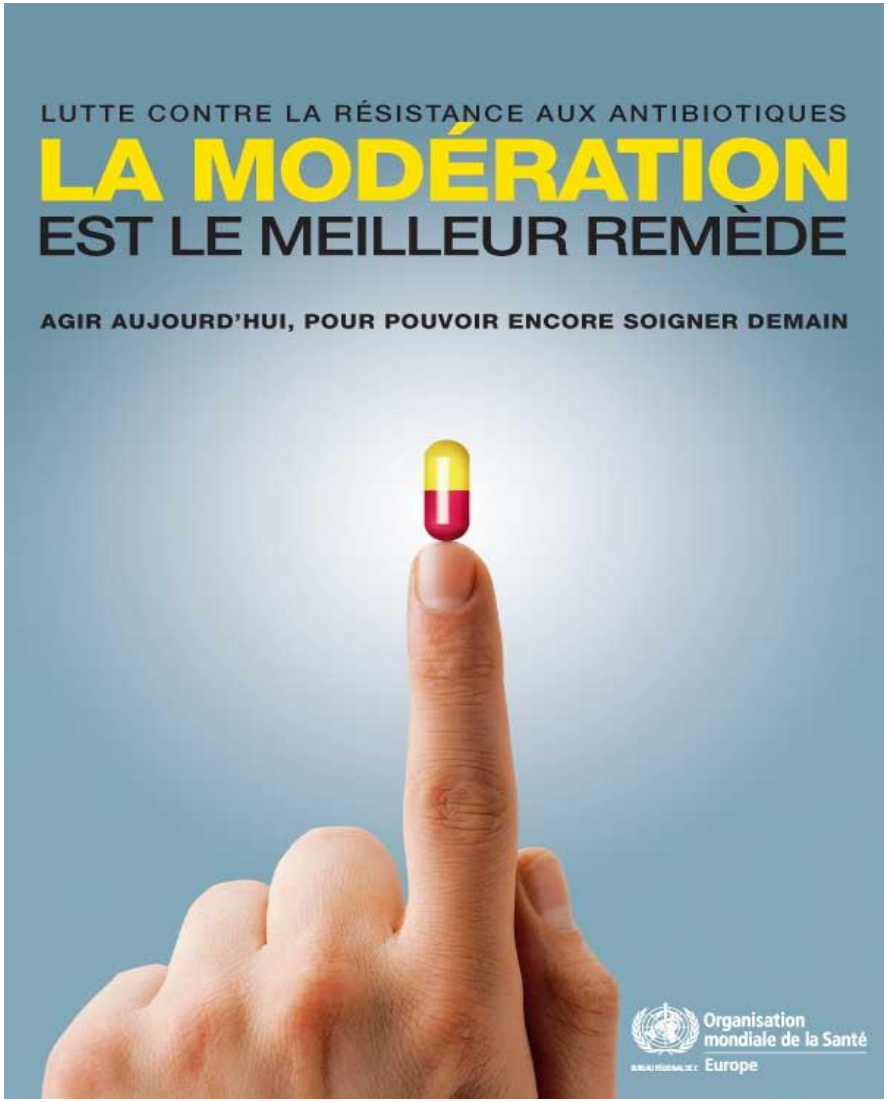
- **Mise en place urgente d'un plan d'action national** (Retarder au maximum la diffusion de ces BMR)

Plan d'action national de lutte contre l'antibiorésistance

- Hygiène, prévention et vaccination
- Rationalisation de l'utilisation des antibiotiques
- Suivi de la résistance et recherche
- Sensibilisation et formation

Remerciements
a tout le groupe de travail

MERCI POUR VOTRE ATTENTION …


LUTTE CONTRE LA RÉSISTANCE AUX ANTIBIOTIQUES
LA MODÉRATION
EST LE MEILLEUR REMÈDE
AGIR AUJOURD'HUI, POUR POUVOIR ENCORE SOIGNER DEMAIN
Organisation mondiale de la Santé
Europe


#HandHygiene #AntibioticResistance
LUTTEZ CONTRE
LA RÉSISTANCE
AUX ANTIBIOTIQUES
C'EST ENTRE VOS MAINS
World Health Organization
HANDLE ANTIBIOTICS WITH CARE
SAVE LIVES
CLEAN YOUR HANDS

université PARIS DIDEROT PARIS 7

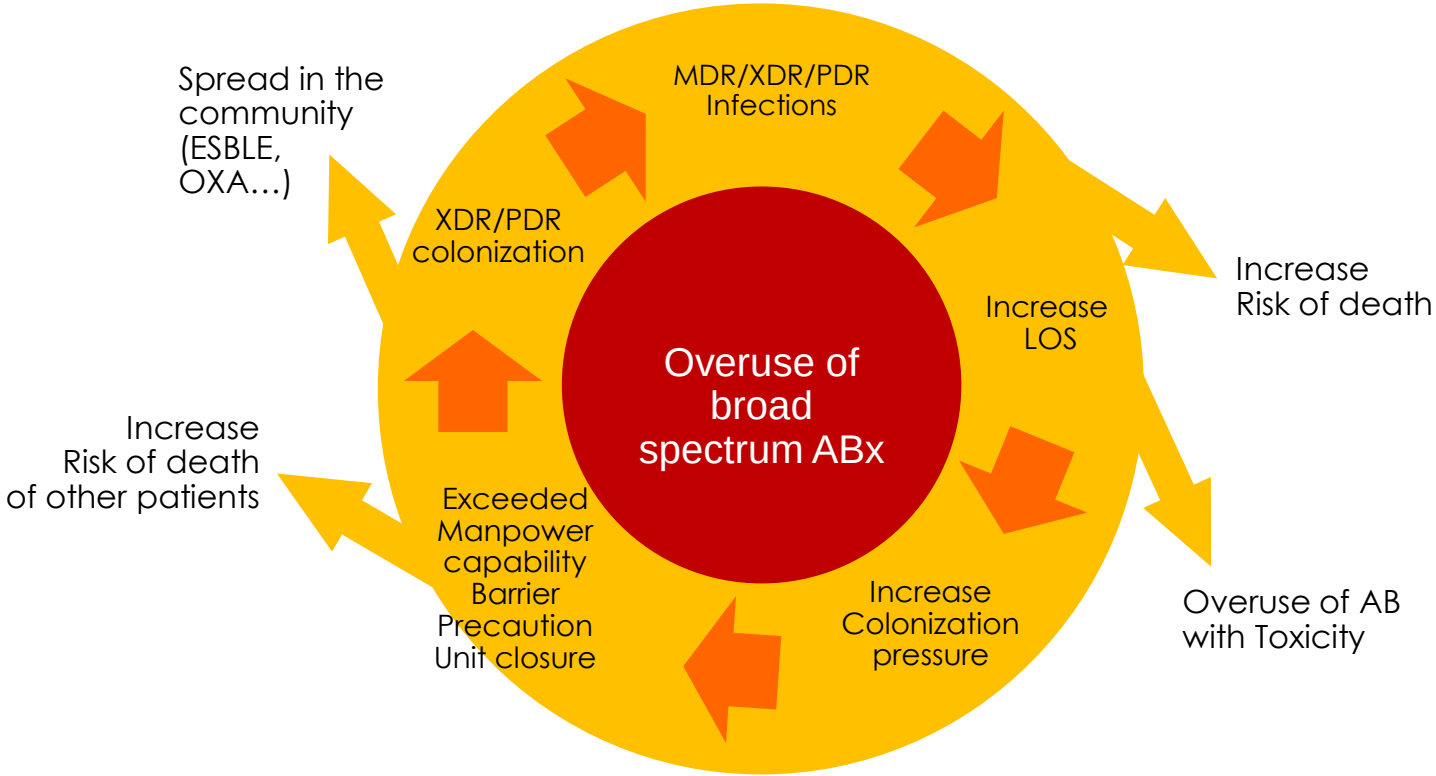
Optimisation du traitement des baciles gram negatifs résistants à l'aire des carbapénémases

Jean-François Timsit MD PhD
Medical and Infectious Diseases ICU
Bichat Hospital
Inserm UMR 1137 IAME
Paris-Diderot University
Paris FRANCE

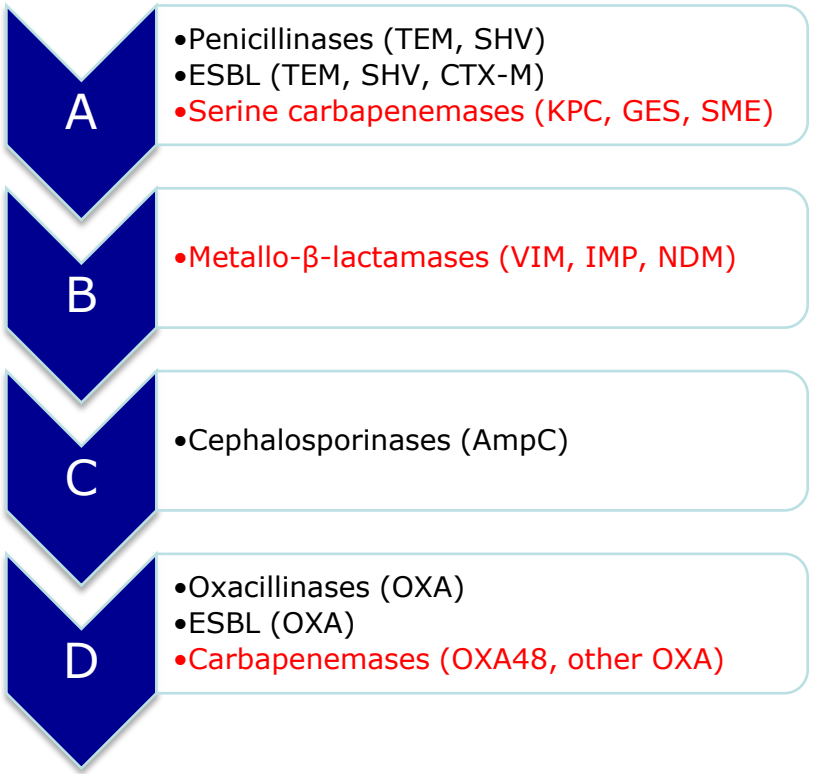
iame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution

Hammamet; May 20th 2017

The vicious circle



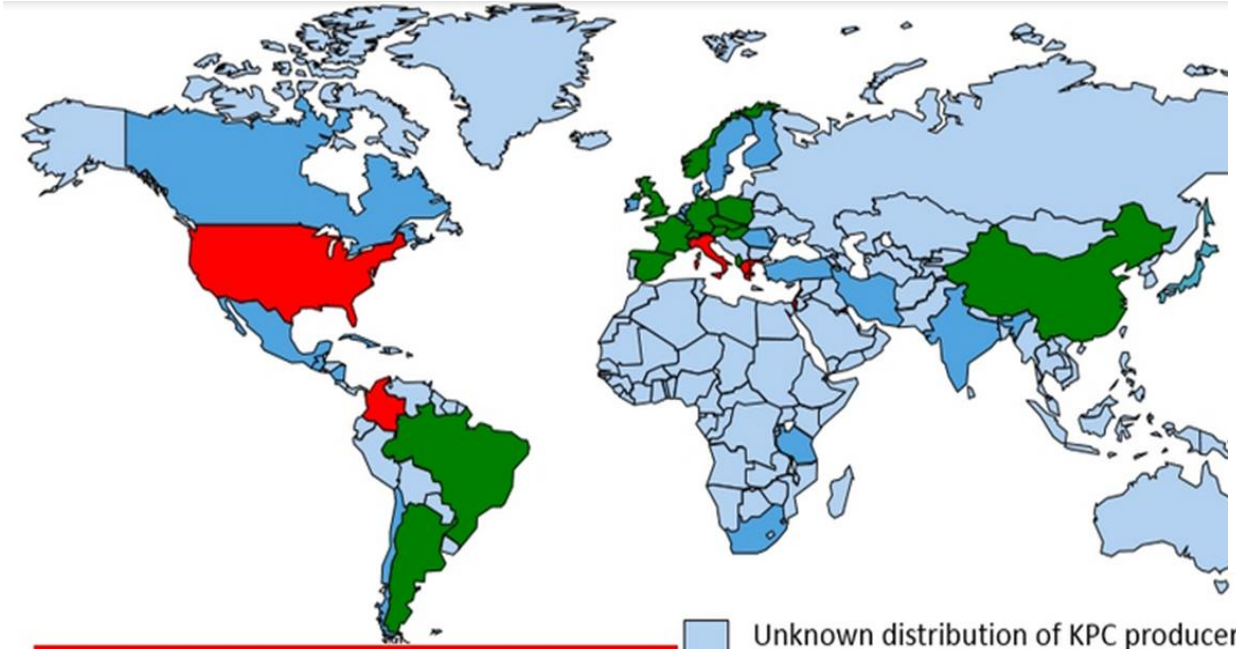
Classification of β-lactamases

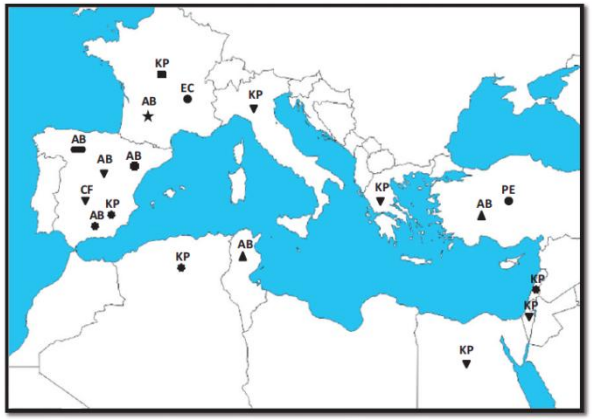


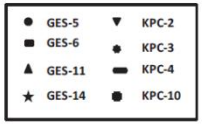
Ambler classification

Hall BG JAC 2005 ; 55 : 1050

KPC producers enterobacteriaceae 2016







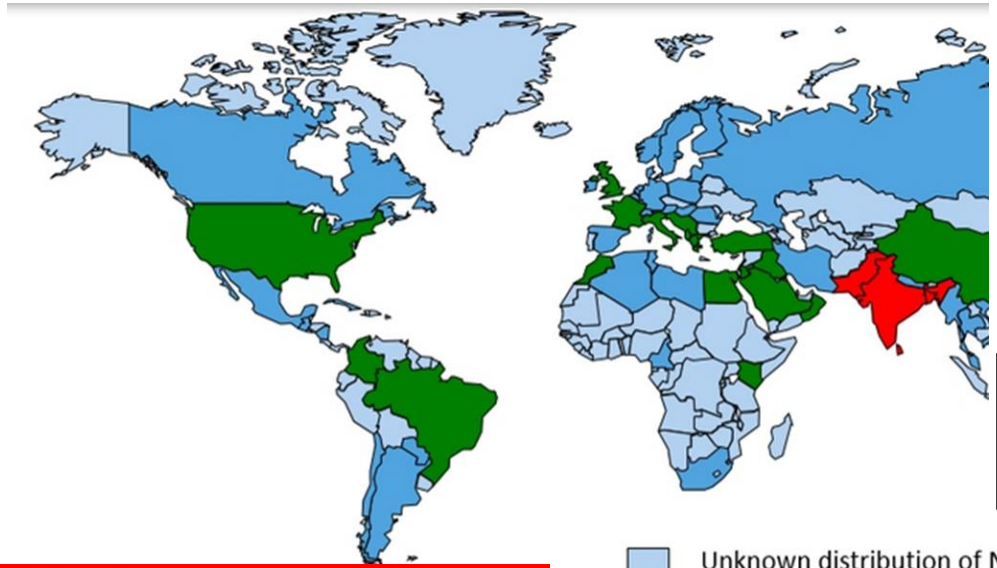
AB: *Acinetobacter baumannii*
PE: *Pseudomonas aeruginosa*
KP: *Klebsiella pneumoniae*
EC: *Escherichia coli*
CF: *Citrobacter freundii*

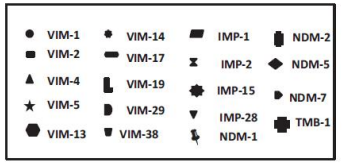
Unknown distribution of KPC producers
Sporadic spread of KPC producers
Outbreaks due to KPC producers
Endemicity of KPC producers

Key points:
-High level resistance to carbapenems
-Still mostly in *K. pneumoniae, rarely in E. coli*
- Several South American countries
Italy and Greece are now endemic countries

Mathlouthi Critical Reviews in Microbiology (2017), 43:1, 43-61

NDM producing enterobacteriaceae 2016





AB: *Acinetobacter baumannii*
PE: *Pseudomonas aeruginosa*
KP: *Klebsiella pneumoniae*
EC: *Escherichia coli*
EN: *Enterobacter cloacae*
PM: *Proteus mirabilis*
AX: *Achromobacter xylosoxidans*
KO: *Klebsiella oxytoca*
PM: *Pseudomonas mosselii*
PS: *Pseudomonas monteilii*
PR: *Providencia stuartii*
PP: *Pseudomonas putida*
PR : *Providencia rettgeri*
MM: *Morganella morganii*

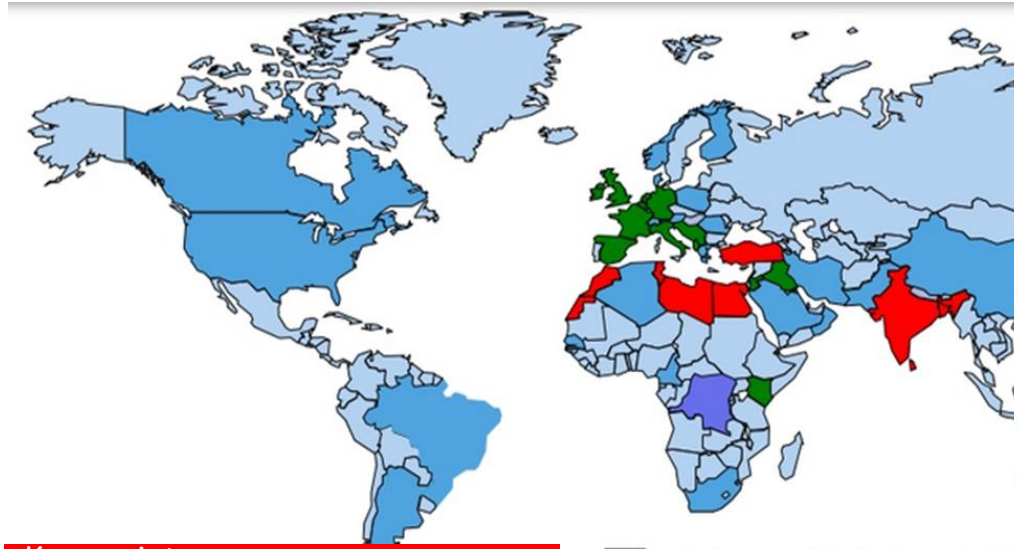
Unknown distribution of NDM producers
Sporadic spread of NDM producers
Outbreaks due to NDM producers
Endemicity of NDM producers

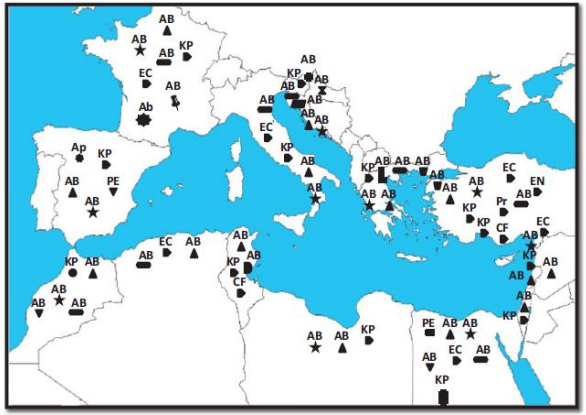
Keys points

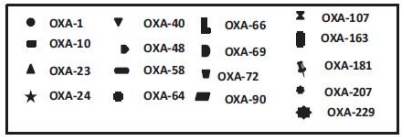
Variable resistance to carbapenems
Secondary reservoirs: Balkans and Middle east
K pneumoniae, E coli, E cloacae

Mathlouthi Critical Reviews in Microbiology (2017), 43:1, 43-61

OXA-48 like producers







AB: *Acinetobacter baumannii*
PE: *Pseudomonas aeruginosa*
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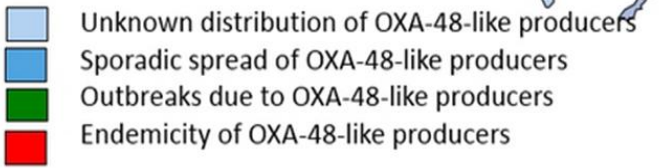
EC: *Escherichia coli*
CF: *Citrobacter freundii*
EN: *Enterobacter cloacae*
PR: *Providencia rettgeri*
Ab: *Acinetobacter bereziniae*
Ap: *Acinetobacter pittii*



Keys points
Variable resistance to carbapenems
North africa, Middle east, turkey, India
Community acquisition tranfer ++
E coli ++, *K pneumoniae*, *E cloacae*
Acinetobacter (Oxa 23, 24, 58)

Mathlouthi- Critical Reviews in Microbiology (2017), 43:1, 43-61

Carbapenemases: Winter is coming

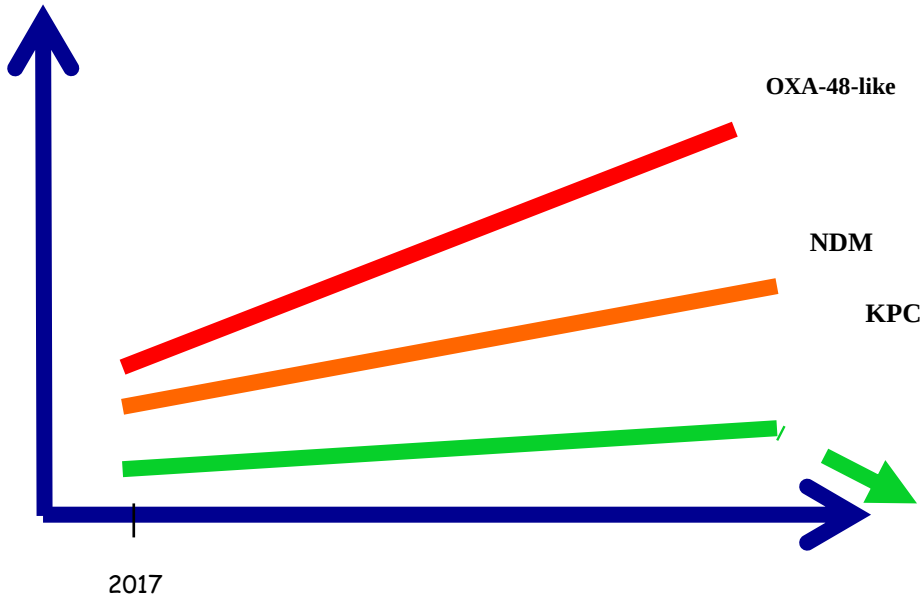
Carbapenemases story mimick ESBL story

- We found it in :
  - Sewage and sewage treatment
  - community : *Salmonella sp*
  - Pets, birds
  - Animal farming
  - food: animal feeding
  - Bathing waters

South east asia
Latin america
Europe

Feasey NA PLoS Negl Trop Dis. 2015
Day MR JAC 2015
Guerra B Vet Micobiology 2014
Fischer J JAC 2013
Montezzi LF Int J Antimicob Agents 2015

Future spread of carbapenemases in *Enterobacteriaceae*

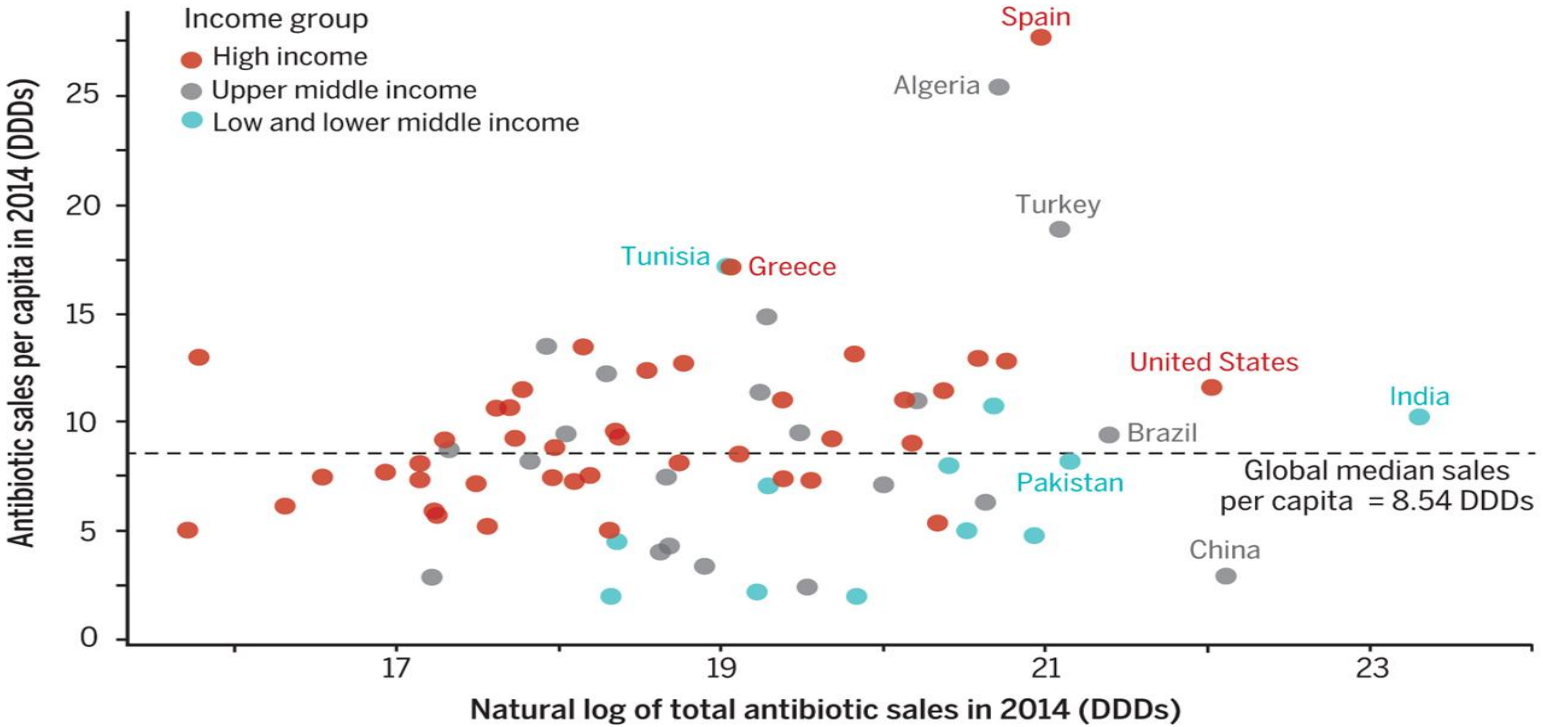


OXA-48: *E. coli* ++, community-acquired, highly transferable plasmid
NDM: *Enterobacteriaceae*, community- and hospital-acquired
KPC; *K. pneumoniae*, hospital-acquired

Adapted from Nordmann P- SRLF 2017

Antimicrobial sales vary by country

Data from 75 countries. The five countries with highest total antibiotic sales for human use and the five with highest per capita sales are identified. See SM.



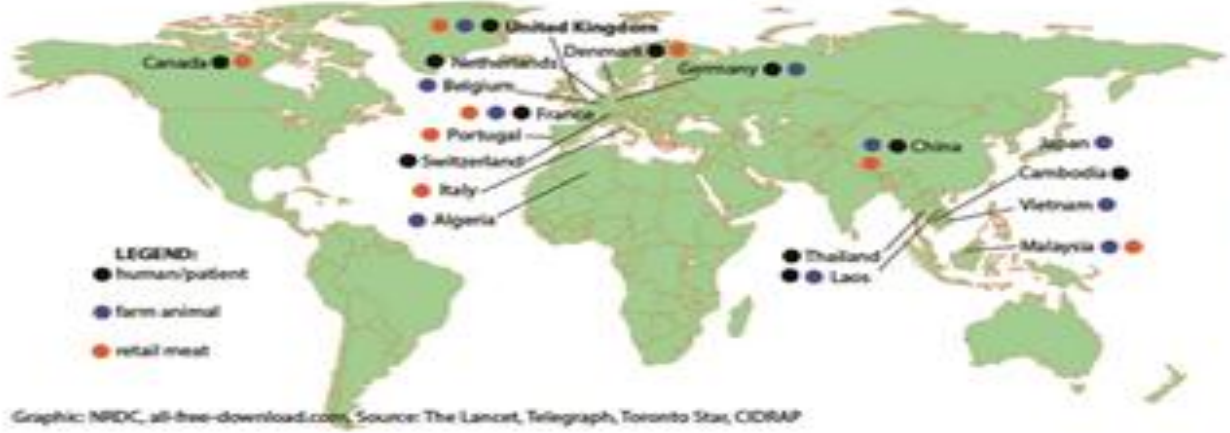
Published by AAAS

Ramanan Laxminarayan et al. Science 2016;353:874-875

STOP ANTIBIOTIC SELECTION PRESSURE

Picture From: Intensive care medicine

Colistin resistance:
Spread of Plasmid MCR-1



1: Liu YY et al . Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China - Lancet Infect Dis. 2016 Feb;16(2):161-8.

Hand Hygiene is key+++++

Universal precautions

<u>If one case:</u>
Screening
CHG bath
Isolation
Limiting spread / cohorting in isolation units

Agenda

- **Ne traiter que les patients réellement infectés**
- Commencer vite: quand suspecter un BGN potentiellement résistant
- Traiter avec les bons antibiotiques aux bonnes doses en utilisant la bonne voie d’administration
- Contrôler la source de l’infection
- Arrêter précocement les traitements inutiles

Systematic antimicrobial prescription may be deleterious

	Aggressive (n=247)	Conservative (n=237)	p value
Time from blood culture to start of treatment (h)			
Median (IQR)	12 (3–30)	22 (7–58)	<0·0001
Time from fever to start of treatment (h)			
Median (IQR)	6 (3–14)	24 (9–44)	<0·0001
Duration of antimicrobial treatment (days)			
Median (IQR)	11 (7–8)	10 (7–14)	0·015
Appropriate antimicrobials (number [%])			
Initial*	144 (62%)	158 (74%)	0·0095
Switched	64 (28%)	48 (23·5%)	0·17
Overall	208 (90%)	206 (96%)	0·010

Before after study comparing early aggressive empirical therapy vs conservative strategy in case of SICU acquired sepsis

Hranjec et al, Lancet Inf Dis 2012

Systematic antimicrobial prescription may be deleterious

Lower all cause mortality:

27/101 [27%] vs 13/100 [13%]; p=0·015

	Aggressive (n=27)	Conservative (n=13)	p value
Death while receiving antimicrobials	20 (74%)	8 (62%)	0·66
Death due to infection	14 (52%)	7 (54%)	1·00
Death due to underlying pathology	10 (37%)	6 (46%)	0·84
Death due to new onset, non-infectious disorder	2 (7%)	0 (0%)	0·82
Multifactorial death	1 (4%)	0 (0%)	1·00

Table 6: Causes of death while receiving antimicrobials

Before after study comparing early aggressive empirical therapy

vs

conservative strategy in case of SICU-acquired sepsis

Hranjec et al, Lancet Inf Dis 2012

Agenda

- Ne traiter que les patients réellement infectés
- **Commencer vite: quand suspecter un BGN potentiellement résistant?**
- Traiter avec les bons antibiotiques aux bonnes doses en utilisant la bonne voie d'administration
- Contrôler la source de l'infection
- Arrêter précocement les traitements inutiles

Antibiotic resistance in French ICUs

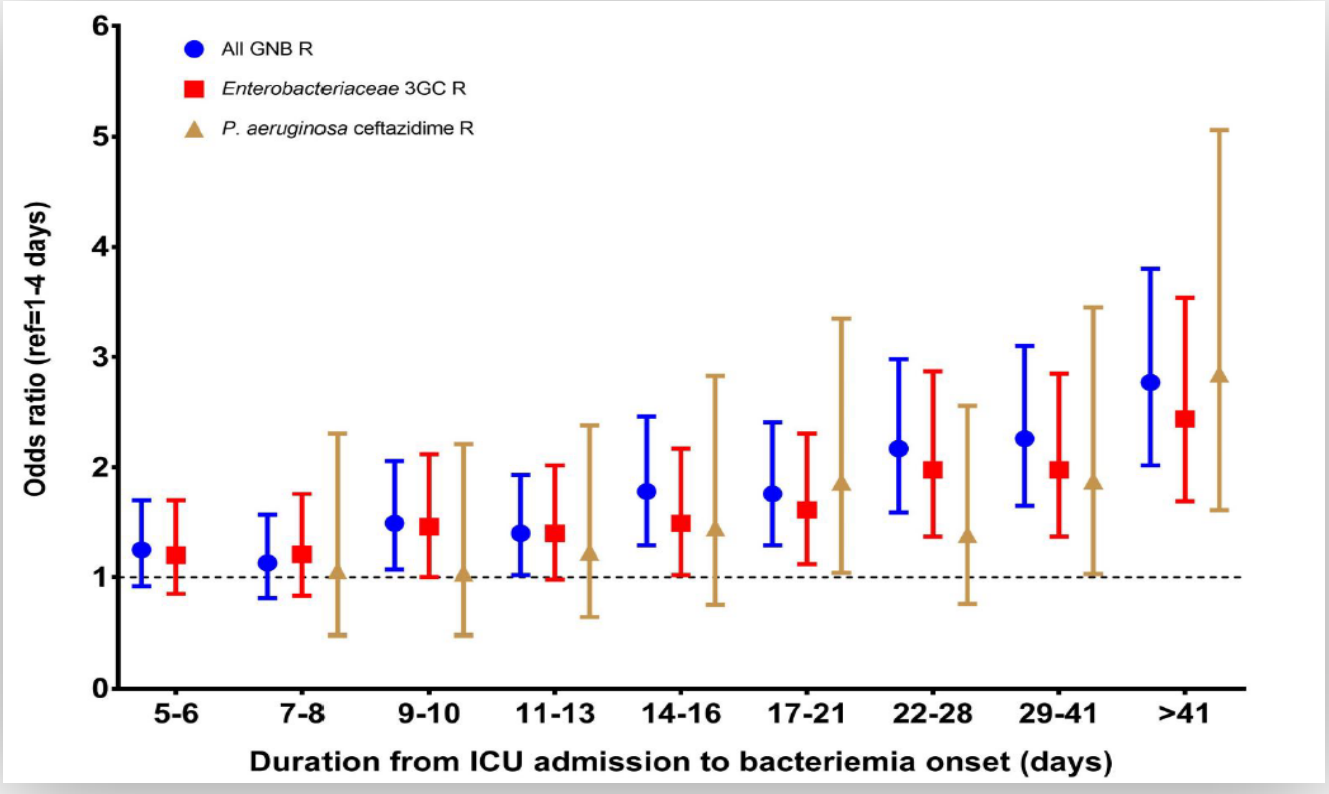
REA-RAISIN
212 ICUs/ 2548 ICU beds
(50.4% of French ICUs)/ 54226 patients

	2004-2007	2014	Evolution
MRSA	48.7%	19.3%	↓↓↓
VRE-GRE	2.6%	3.2%	→
3rdGC R-EB	7.4%	18.3%	↑↑
IMI-R EB	2.4% (2011)	1.6%	→↑
IMI R A. baumannii		37.5%	(↑↑)
CAZ-R PA		20.8%	(→↑)
IMI-R PA		19.7%	(→↑)

Geographic variation++++

Réa-RAISIN 2014

Influence du délai depuis l'hospitalisation en réanimation sur le risque de bactériémie à BGN résistants (4547 épisodes)



Réseau national de prévention des infections associées aux soins

INSTITUT DE VEILLE SANITAIRE

lame UMR 1137

Infection • Antimicrobiens • Modélisation • Evolution

ESBL more frequent if *(Univariate analysis)*

1- **Asian or middle east ethnicity**

2- **Chronic diseases**: Chemotherapy<6 months; Structural lung diseases

3- **Invasive procedures**: Gastrointestinal tube, Nephrostomy, foley catheter,Chronic vascular hardware

4- **Previous colonization** with ESBLE or Carbapenemases

5- Total **previous** nb of day of **hospitalization**

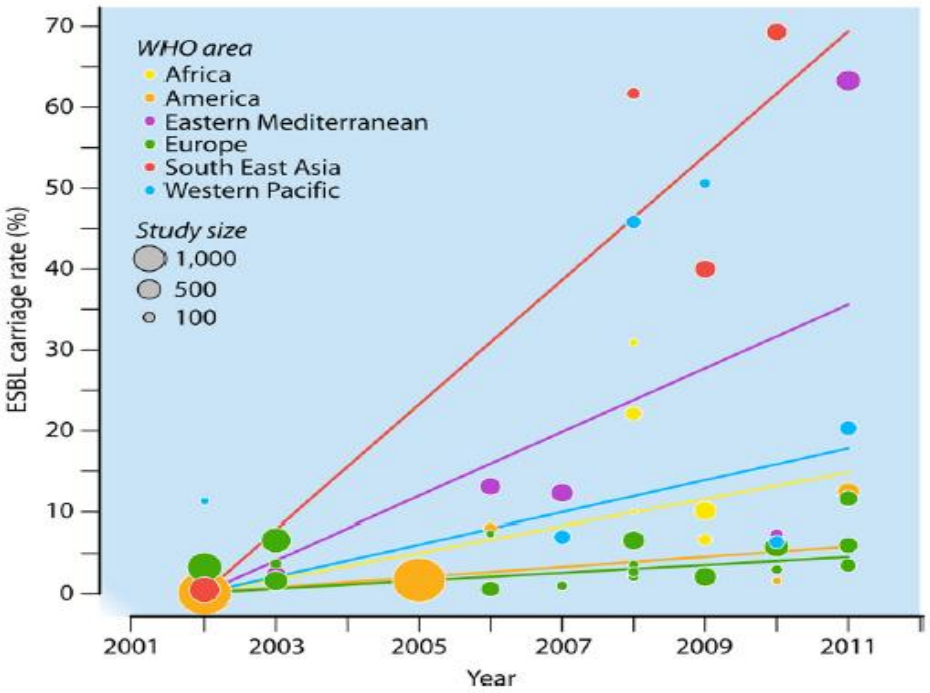
6- Number of days of **broad spectrum** penicilin, carbapenems, 4gen cephalosporin, aminoglycosides

7- At least **one day of hospitalization in a high burden country**

8- **Long-term acute care facility** residences

Goodman KE et al CID 2016

ESBL *E. coli* in general population



South-East Asia

East. Medit.

America

Europe

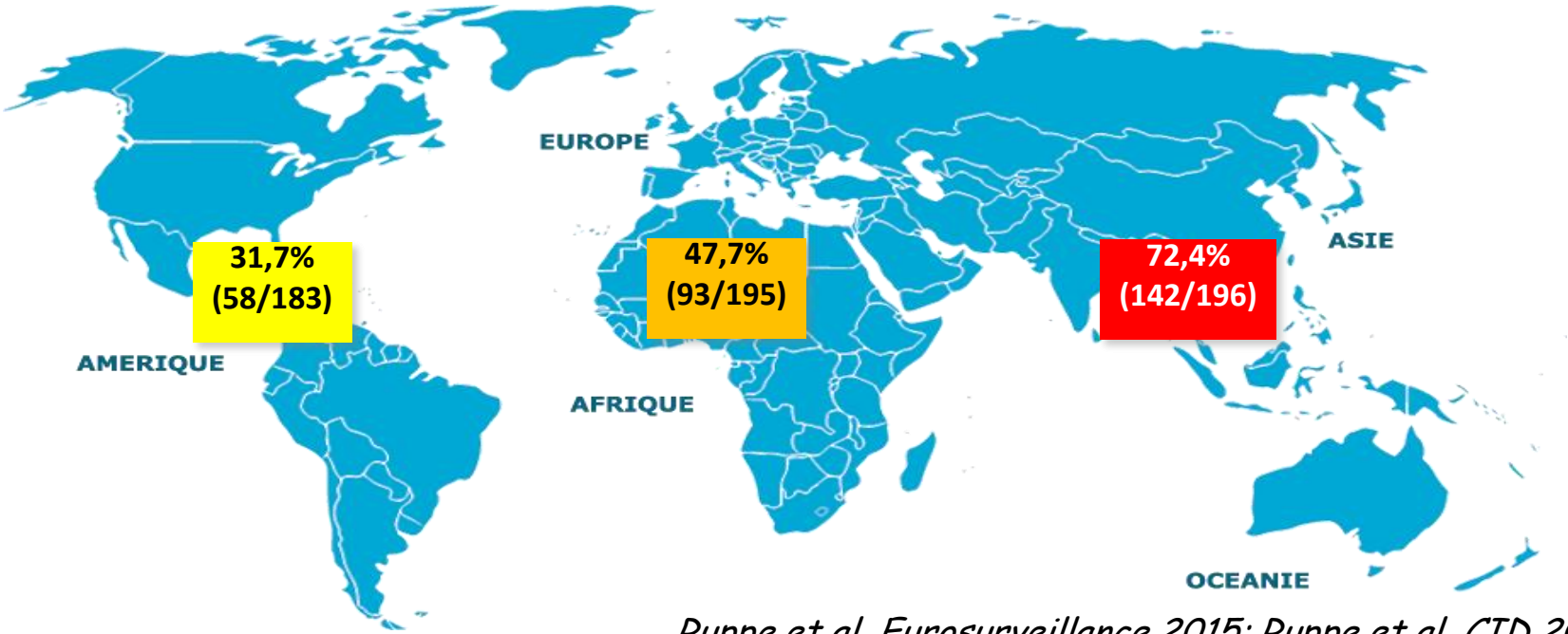
Woerther PL & Andremont A- Clinical Microb Reviews 2013

Acquisition de EBLSE au cours d'un voyage

VOYAG-R
Voyage en zone intertropicale
et acquisition de bactéries multirésistantes aux antibiotiques

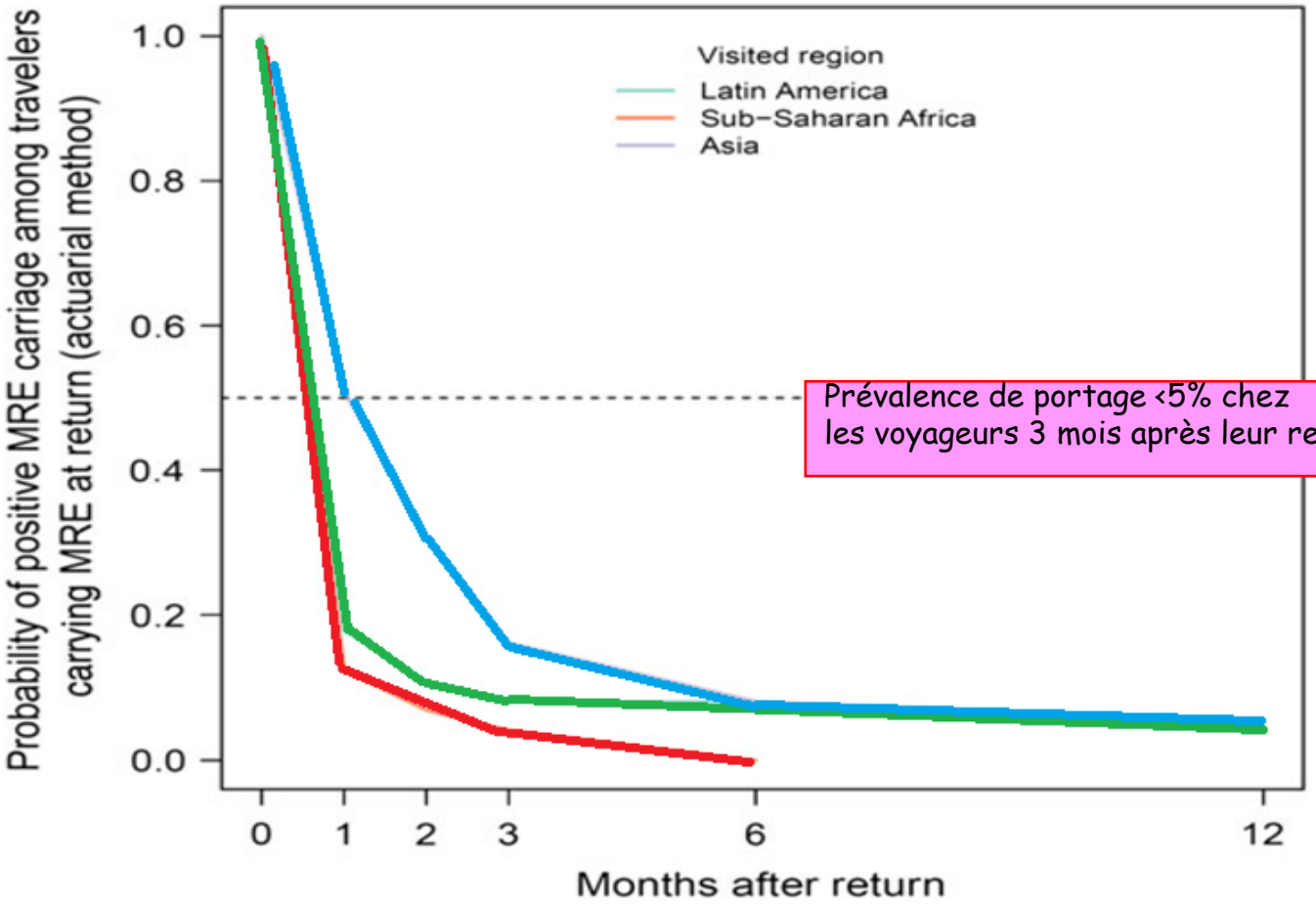
574 voyageurs en zone intertropicale
(dépistage négatif avant le départ)

Taux d'acquisition global : 50,9% (n=292)



Ruppe et al, Eurosurveillance 2015; Ruppe et al, CID 2015

VOYAG-R
Voyage en zone intertropicale
et acquisition de bactéries multirésistantes aux antibiotiques

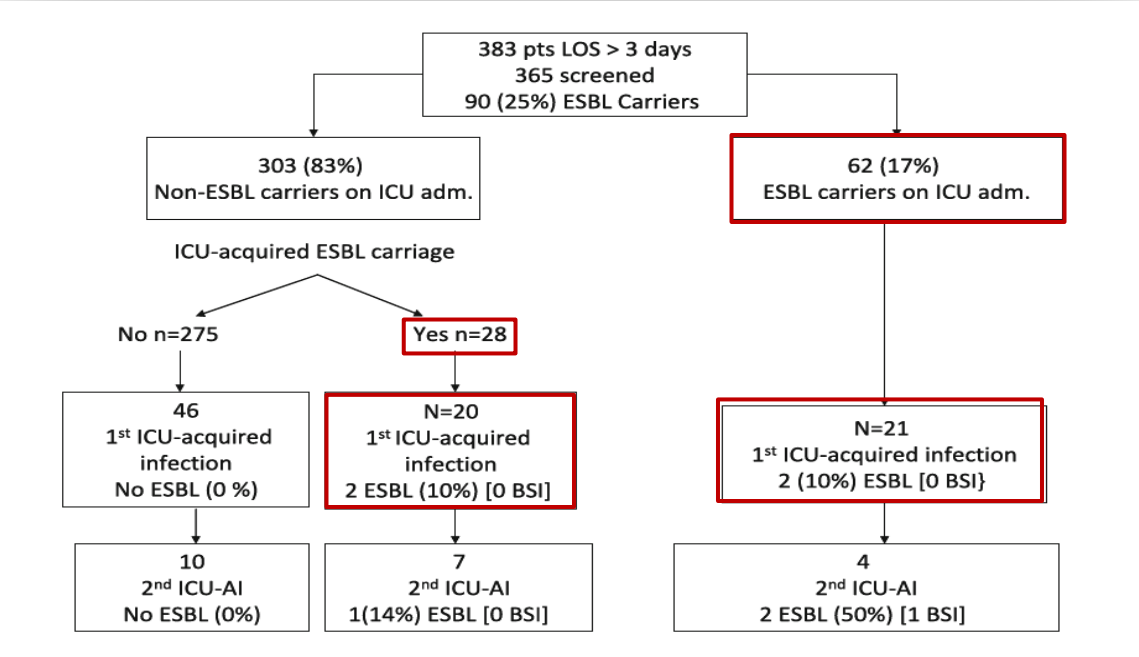


Prévalence de portage <5% chez les voyageurs 3 mois après leur retour

Ruppe et al, Eurosurveillance 2015; Ruppe et al, CID 2015

When ESBLE VAP should be suspected?

Previous digestive colonization



PPV 10%
NPV 100%

Razazi K et al – Intens care med 2012; 38:1769

Think quantitatively: relative abundance?

- Previous ESBL colonization is poorly related to ESBLE infection risk

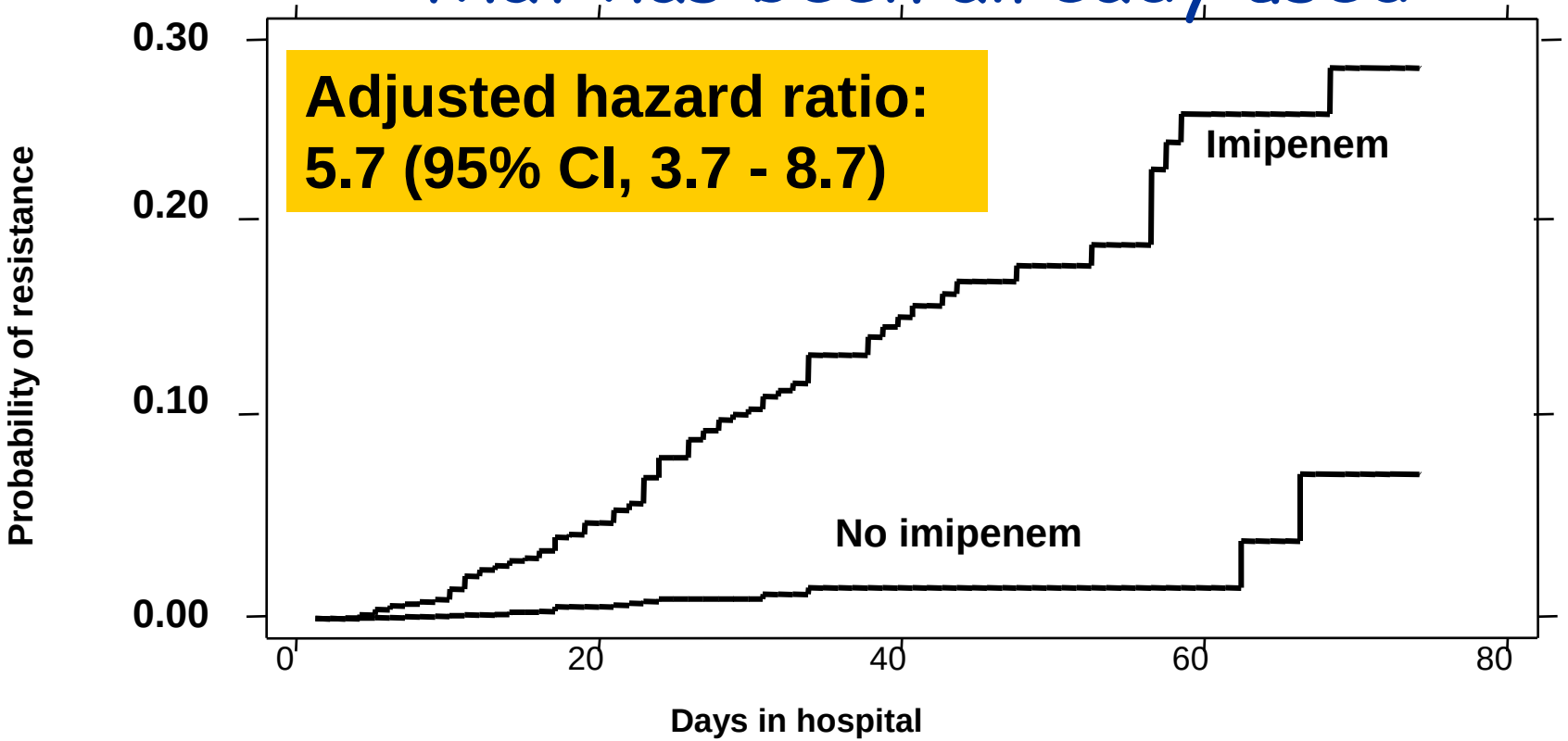
- ESBL *E coli* UTI more frequent if high relative abundance in the stool Ruppe E et al – AAC 2013; 57: 4512

But

- The relative abundance increased among hospitalized patients

- and is more important in case of previous antimicrobial exposure De Lastours V AAC 2016;60: 6941

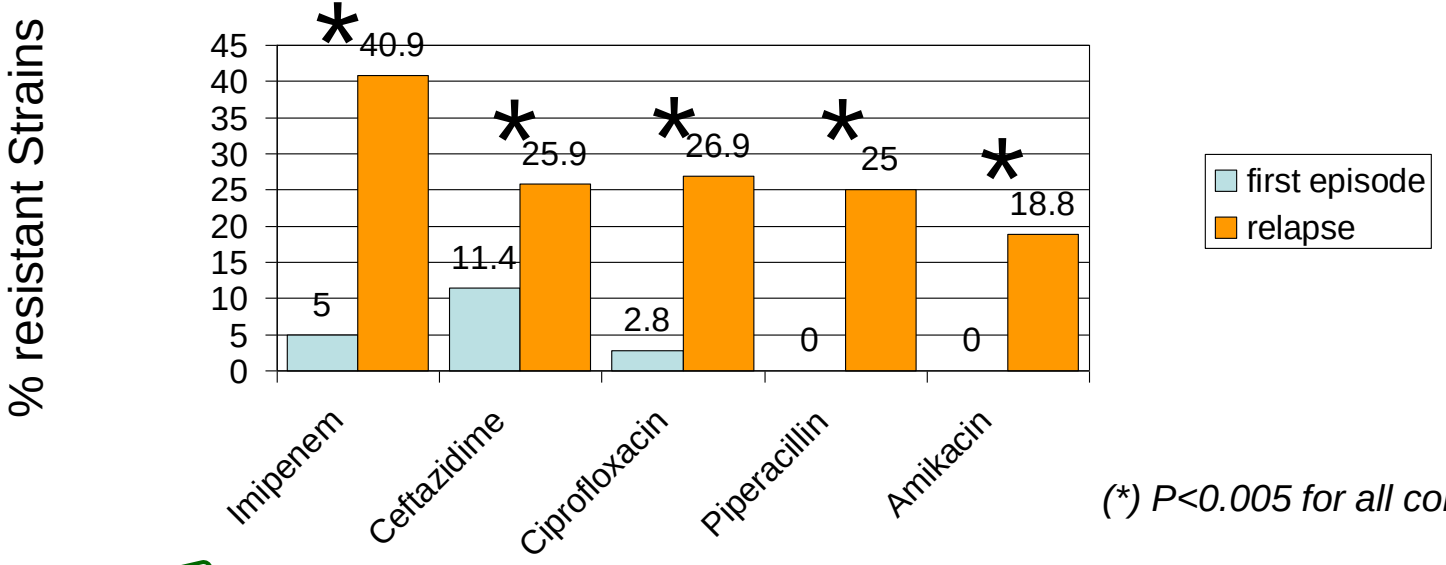
In pratice: do not use antimicrobial that has been already used



Harbarth, et al. Clin Infect Dis 2001; 33: 1462-68

In pratice: do not use antimicrobial that has been already used

62 recurrences in 314 patients with *P. aeruginosa* VAP



(*) P<0.005 for all comparisons

OUTCOMEREA

Planquette B et al – Am J Respir crit care Med 2012

New (already available) tests

- Maldi TOF alone → Identification 24 hours
- Rapid Antibiotic susceptibility test combined with Maldi-TOF[1,2,3,4] → 24 hours
- PCR (S. aureus[5]; KPC; (VRE)) → 2- 3 hours
- Multiplex rtPCR (13 pathogens; 24 resistance mechanisms (Penicillinase, ESBL, Carbapenemase, *mec gene))*[6] → *6 hours*
- Polymerase chain reaction followed by electrospray ionization-mass spectrometry[7] (PCR/ESI-MS) (800 microorganisms, 4 resistance mechanisms) → 6 hours

The near future

1-Cercenado E et al – DMID 2007
2- Bouza E et al - Clin infect Dis 2007
3- Boyer A et al – DMID 2012
4- Le Dorze M et al – CMI 2015
5- Leone M et al - Crit Care 2013
6- Bogaerts P et al - JAC. 2013
7- Vincent JL Crit Care Med 2015

Agenda

- Ne traiter que les patients réellement infectés
- Commencer vite: quand suspecter un BGN potentiellement resistant
- **Traiter avec les bons antibiotiques aux bonnes doses en utilisant la bonne voie d'administration**
- Contrôler la source de l'infection
- Arrêter précocement les traitements inutiles

For MDR EB and *P. aeruginosa*, No magic bullets high MICs for all the traditional antimicrobials

EUCAST breakpoints

	Species related breakpoints (S≤/R>)	
	Enterobacteriaceae	*Pseudomonas*
Piperacillin-tazobactam	8/16	16/16
Ceftazidime	1/8	8/8
Cefepime	1/8	8/8
Meropenem	2/8	2/8
Amikacin	8/16	8/16
Ceftolozane-tazobactam	1/1	4/4
Ceftazidime-avibactam	8/8	8/8

Le positionnement des beta-lactamines traditionelles

Risque de	CTZ	CPM	AZT	TAZ	ERT	IMI/MER
Pyo R	++	+	-	+	-	-
BLSE	-	-	-	+-	++	++
HCase	-	++	-	-	+	+
Carb ases	- (Oxa)	-	+- (MBL)	-	-	+-

Ceftazidime /Avibactam

Active in Vitro:

- Against ESBLs
- Most KPC producers
- Strains with AmpC
- Strains with OXA-48

Breakpoints EUCAST		
	CMI (mg/l)	
	S	R
Enterobacteriaceae	≤ 8	>8
P. aeruginosa	≤ 8	> 8

- Strains which are carbapenem resistant due to porin loss plus production of an ESBL or AmpC

Not active in vitro

- *Poorly against Acinetobacter* spp, S maltophilia and Gram-negative anaerobic spp
- **NOT active on MBL (VIM,NDM) (role for Aztreonam-avibactam?)**

Livermore AAC 2011;55:390-394

Ceftazidime/avibactam

- 76% of P. aeruginosa isolates nonsusceptible to CAZ, CPM, PIP/TAZ and MERO
- Animal models
  - Potential interest in VAP (ratio 4/1 between components reached in the ELF)
  - Discordance between in vitro and in vivo efficacy for some enterobacteriaceae (NDM1)
- Phase III study on VÄP finished (n=878)
- Already KPC Resistant mutants
- C dif colonization

Berkhout J AAC 2015; 59 : 2299
Housman ST AAC 2014; 58 : 1365
MacVane SH AAC 2014; 58 : 7007
Humphries RH AAC 2015; 59 : 6605
Rashid MU IJAA 2015; 46 : 60
Sader et al AAC 2017; e02083-16
Shields et al – CID Sept 13rd 2016, online

REPROVE: CAZ-AVI vs MERO in HAP/VAP

	CAZ-AVI 2g/0.5g X3	MERO 1g X 3	Différence % IC95%
Guérison clinique au TOC cMITT	245/356 69%	270/370 73%	- 4,2 (-10,76,2,46)
Guérison clinique au TOC CE	199/257 77%	211/270 78%	-0,7 (-7,86,6,39)
Ceftazidime R	35/45 78%	40/54 74%	3,7 (-13,73,20,38)
Ceftazidime S	80/119 67%	96/126 76%	-9 (-20,17,2,33)

Torres A et al - ECCMID 2017

Intensive Care Med (2015) 41:2057–2075
DOI 10.1007/s00134-015-4079-4

José Garnacho-Montero
George Dimopoulos
Garyphallia Poulakou
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Harald Seifert
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Jean-Ralph Zahar
Matteo Bassetti

Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU

Table 2 Recommended doses of antimicrobials for *A. baumannii* infections in patients with normal renal function

Antibiotic	Loading dose[a]	Daily dose	Observations
Imipenem[b]	Not required	0.5–1 g/6 h	Extended infusion is not possible due to drug instability High doses are associated with seizures
Meropenem[b]	Not required	2 g/8 h	Extended infusion (3–4 h) is recommended, In this case, first dose (2 g) should be administered in 30-min
Sulbactam[b]	Not required	9–12 g/day (in 3 or 4 doses)	4-h infusion is recommended
Polymyxin E[b] (Colistin)	6–9 million IU[c]	9 million IU/day in 2 or 3 doses	One million IU of colistin is equivalent to 80 mg of CMS. See text for doses on intermittent hemodyalisis and CRRT[d]
Polymyxin B	2–2.5 mg/kg	1.5–3 mg/kg/day in 2 doses.	Continuous infusion may be suitable. Same dose in patients on CRRT[d]
Tigecycline	100 mg	50 mg/12 h	May be adequate in secondary bacteremia for approved indications (abdominal infections and SSTI[e])
	200 mg	100 mg/12 h	For other sources including pneumonia and primary bloodstream infection (consider combination with another active antimicrobial). Without approval by regulatory agencies
Rifampicin	Not required	600 mg/day or 600 mg/12 h	Always in combination therapy
Fosfomycin[b]	Not required	12–24 g/day (in 3 or 4 doses)	Always in combination therapy

[a] The loading dose should be administered in all patients including those with renal dysfunction
[b] Dose adjustment is necessary in case of renal dysfunction
[c] *IU* International Units
[d] *CRRT* continuous renal replacement therapy
[e] *SSTI* skin and soft tissue infection

Tigecycline for XDR *(A baumannii)..*

- Bacteriostatic, not active againt *P aeruginosa*
- *Inconstant activity on S maltophilia*
- ↑ Resistance (Enterobacteriaceae)
- Good tissue difusion and ELF/serum ratio >1
- **100mg/d Dose is not sufficient** for Acinetobacter with MIC of 1 or 2 mg/l

  Scheetz AAC 2007;
- Largely insufficient to kill extracellular Ab

  Burkhardt et al - IJAA 2009:99
- Combining with CTZ it Failed to be as effective as imipenem-vancomycin in HAP

  Freire AT et al Diag Microbiol Infec Dis 2010

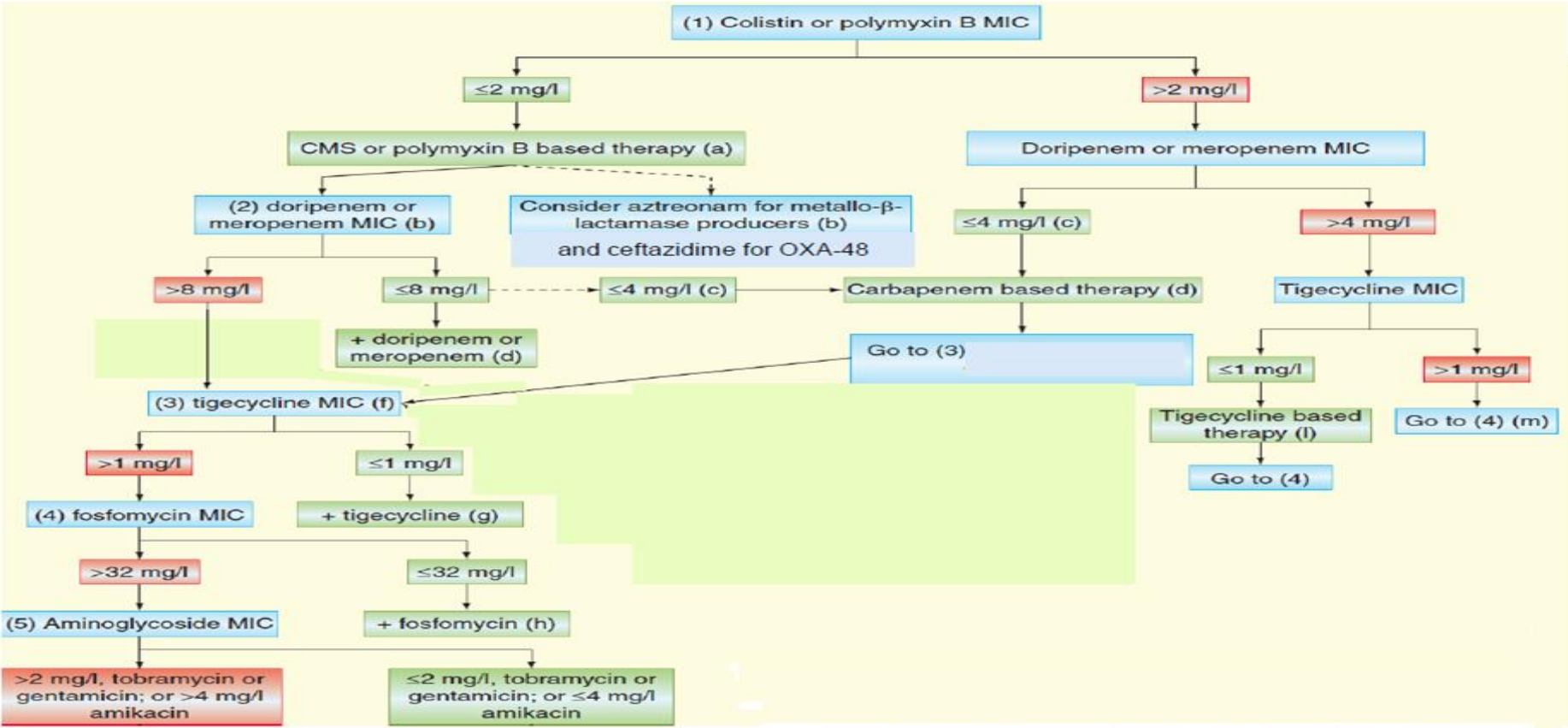
→ HIGH DOSE:

- **200mg Loading dose and 100mg X 2** effective and safe in HAP

  Ramirez et al - AAC 2013;57:1756
- Tige + COL or TIG + AG for KPCs

  Daikos GL. Clin Microbiol Rev 2012;25:682

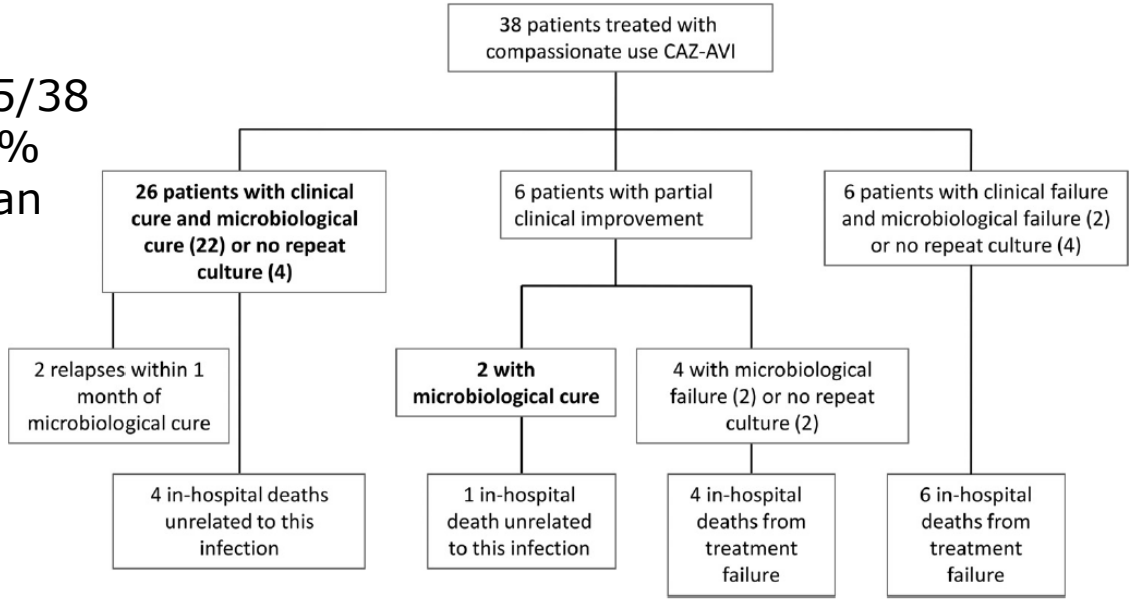
Antibiothérapie pour les CPE



Zavascki et al. Expert Rev Anti Infect Ther 2013, 11:1333-53.

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

- 36 CRE/ 2 PA
- Bacteremia 68.4%/ IAI 15/38
- MV 37%/ Vasopressor 45%
- AB before 13 dys in median
- Extended infusion 95%
- Standard dose 63%



Clinical cure 68.4%
Documented microbiological cure 63%
In hospital death 39.5%

Temkin et al- AAC February 2017 Volume 61 Issue 2 e01964-16

Clinical outcomes, drug toxicity and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections

Ryan K. Shields et al – Clinical infectious diseases Sept 13rd 2016, online

April 2015-Feb 2016 Pittsburg university

Clinical success 59% (22/37)

30-d Survival 76% (28/37)

Recurrence; 23% (5/22) of clinical successes within 90-days

Microbiologic failure rate 27% (10/37).

Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures after 10, 15 and 19 days.

Bla KPC3 mutation confers CAZ/AVI resistance *(Haidar et al - AAC 2017)*

PK/PD optimization/ COMBO++++

Les beta-lactamines

- Temps au dessus de la CMI++++
- Grande variabilité inter et intra individuelle

Intérêt de la perfusion prolongée ou continue

Après DOSE DE CHARGE

Intensive Care Med
DOI 10.1007/s00134-015-4188-0

ORIGINAL

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Jason A. Roberts

Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

Table 2 Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

Primary endpoint	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, n (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
Meropenem	14 (67)	8 (38)	29 (−0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (−0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, n (%)[d]				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, n (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, n (%)[f]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

Secondary endpoints	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
PK/PD target attainment, n (%)[g]				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (−0.4 to −0.1)	**<0.001**
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (−0.4 to −0.1)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	21 (19–23)	21 (14–24)	0 (−3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (−2 to 18)	**0.043**
ICU survivors[i]	23 (21–25)	21 (0–25)	2 (−3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (−0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (−0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	**<0.001**

CI better If :
Monotherapy
Lung infections
MDRO

Warning: LOADING DOSE++++/ Glomerular hyperfiltration

Association

- Pour
  - Elargissement du spectre
  - ↓Emergence de résistance dans le site infecté
  - Données cliniques pour les patients les plus graves pour les bactéries « peu » sensibles

- Contre
  - ✓ Aucune preuve dans des essais contrôlés
  - ✓ Cumul des pressions de sélection → résistance dans le microbiote?
  - ✓ Cumul des toxicités
  - ✓ Synergie in vitro non démontrée en clinique

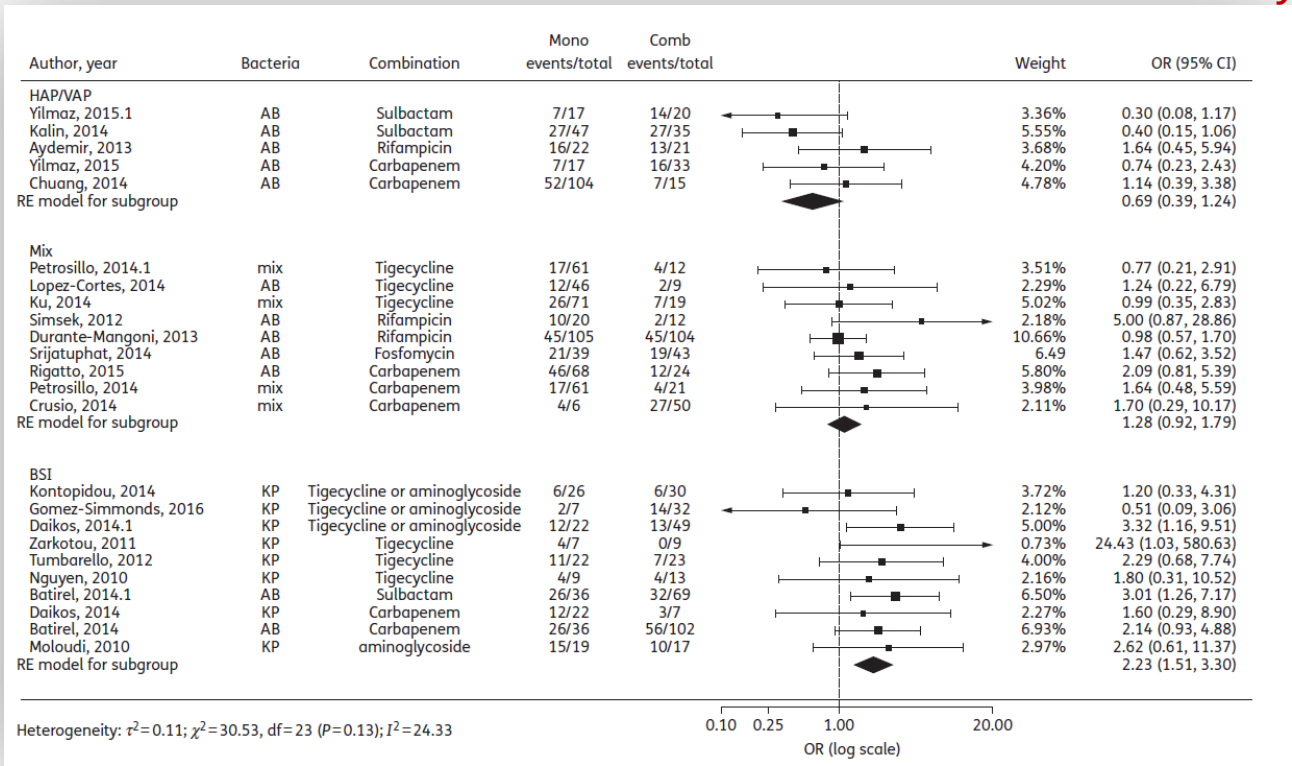
J Antimicrob Chemother 2017; **72**: 29–39
doi:10.1093/jac/dkw377 Advance Access publication 13 September 2016

Journal of Antimicrobial Chemotherapy

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Oren Zusman[1]*, Sergey Altunin[2,3]†, Fidi Koppel[2], Yael Dishon Benattar[2,4], Habip Gedik[5] and Mical Paul[2,3]

All cause mortality



Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Belén Gutiérrez-Gutiérrez, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†*

INCREMENT cohort: 2004-2013

26 tertiary hospitals in ten countries.

Exclusion criteria were

- **Missing key data**
- **Death sooner than 24 h after the index date**
- **Therapy with an active antibiotic for at least 2 days when blood cultures were taken**
- **Subsequent episodes in the same patient.**

www.thelancet.com/infection **Published online April 22, 2017** http://dx.doi.org/10.1016/ S1473-3099(17)30228-1

MAYO CLINIC

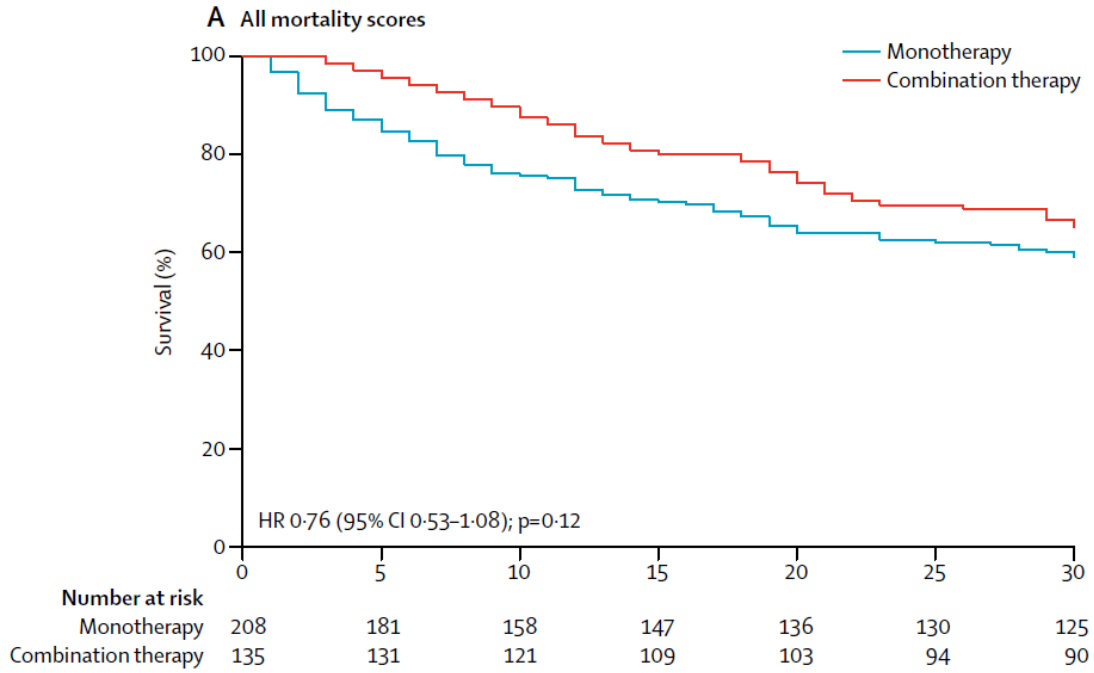
A Predictive Model of Mortality in Patients With Bloodstream Infections due to Carbapenemase-Producing Enterobacteriaceae

TABLE 3. Assignment of Scores on the Basis of the Regression Coefficients Obtained for the Selected Variables Using Hierarchical Logistic Regression

Variable	Regression coefficient (95% CI)	Score
Severe sepsis or septic shock	1.76 (1.01-2.50)	5
Pitt score ≥6	1.39 (0.54-2.25)	4
Charlson comorbidity index ≥2	0.93 (0.09-1.78)	3
Source of BSI other than urinary or biliary tract	0.92 (0-1.85)	3
Inappropriate early targeted therapy	0.69 (0.07-1.31)	2
Total points		*17*

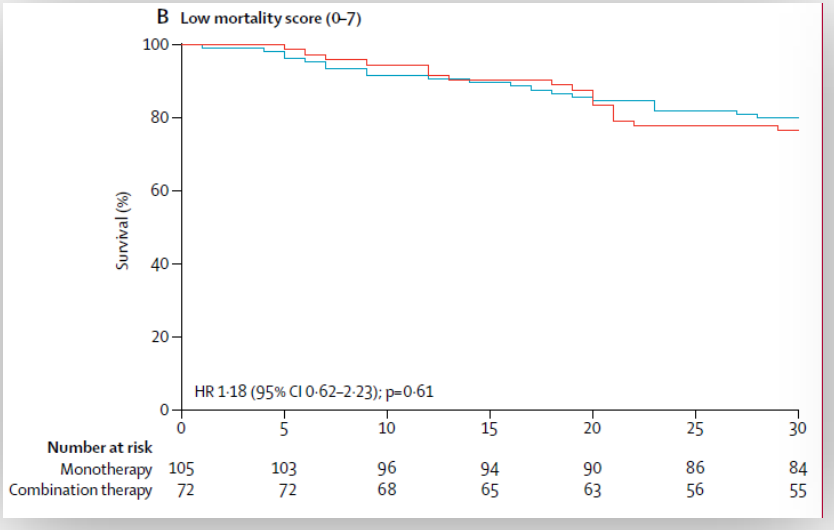
BSI = bloodstream infection.

343 received appropriate therapy

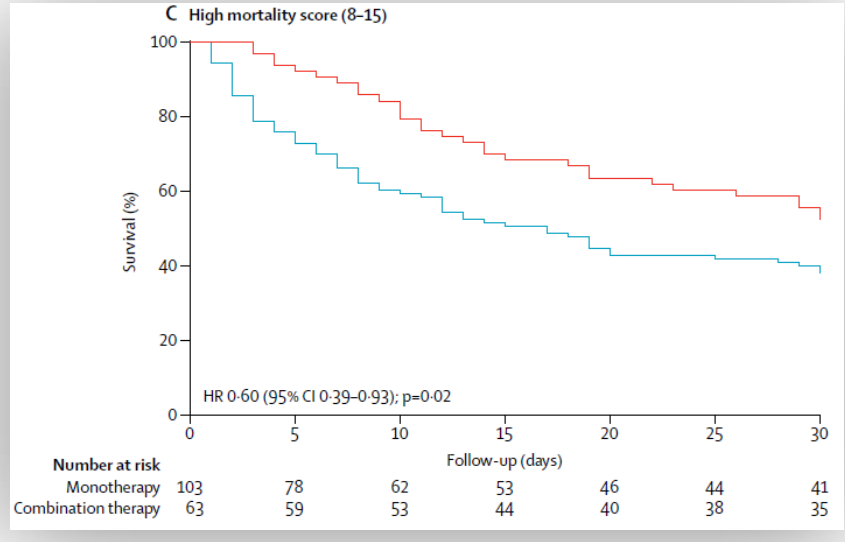


	Adjusted analysis*	
	HR (95% CI)	p value
INCREMENT-CPE mortality score (per unit)	1·23 (1·16–1·31)	<0·0001
Combination therapy	1·63 (0·67–3·91)	0·28
Delay to first active treatment (per day)	..	..
High-mortality-risk centre	2·00 (1·40–2·85)	0·0001
Study period 2004–11 (reference 2012–13)	1·46 (0·98–2·18)	0·06
Propensity score†	1·20 (0·61–2·35)	0·60
Interaction of INCREMENT-CPE mortality score (per unit) with combination therapy	0·92 (0·84–0·99)	0·04

Mortality stratified by level of increment CPE score



Death: 20 vs 24%



Death: 62 vs 48%

Adjusted HR 0.56 (0.34-0.91, p=0.02

Outcomes with ceftazidime/avibactam in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections: a multi-center study

60 patients
Pitt score 2
ICU 59%
BSI 38%
KPC 83%
Mono n=33
Combo n=27

	Patients, n/N (%)		
Parameter	**In-hospital mortality**	**Microbiologic Cure**	**Clinical Success**
Overall population	19/60 (32)	39/60 (65)	32/60 (53)
Concomitant therapy	9/27 (33)	17/27 (63)	17/27 (63)
Monotherapy	10/33 (30)	22/33 (67)	15/33 (45)
	P=1.0	P= 0.2	P=0.79
ICU	16/35 (46)	18/35 (51)	16/35 (46)
Non-ICU	3/25 (12)	21/25 (84)	16/25 (64)
	P=0.01	P=0.013	P=0.196
Renal dose adjustment	14/33 (42)	18/33 (55)	19/33 (58)
No renal dose adjustment	5/27 (19)	21/27 (78)	13/27 (48)
	P=0.057	P=0.1	P=0.604
Infection Type			
Bacteremia	9/23 (39)	19/23 (82)	14/23 (61)
Urinary tract	2/17 (12)	7/17 (41)	15/17 (88)
Pneumonia	9/16 (56)	7/16 (44)	9/16 (56)
Wound	2/8 (25)	3/8 (38)	5/8 (63)
Intra-abdominal	1/4 (25)	3/4 (75)	3/4 (75)
Bone/joint	1/2 (50)	1/2 (50)	0/2 (0)

King et al – AAC online 8 May 2017 doi:10.1128/AAC.00449-17

Le partenaire

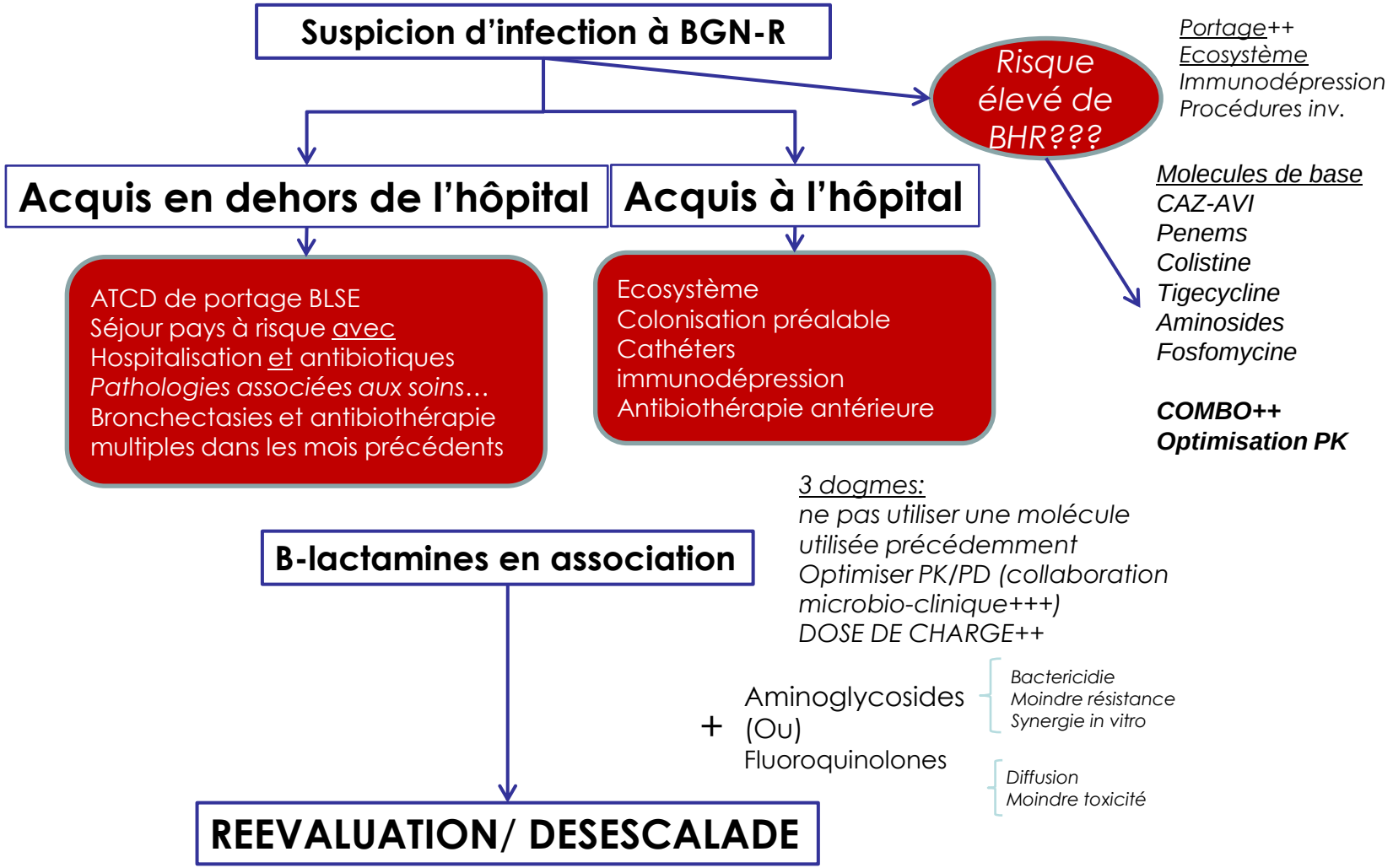
- **Aminosides:**
  - activité concentration dépendante (Pic/CMI)
  - doses initiales élevées
- **Fluoroquinolones:**
  - activité concentration dependante (AUC/CMI),
  - doses initiales élevées, difficile à atteindre pour certaines CMI limites
- **Colymicine:**
  - Concentration dependante/ Dose de charge 9-12MUI
- **Tigecycline:**
  - Double dose

…en fonction de ce qui est possible….

Antibiothérapie des infections à germes résistants
Mécanique de précision

- Collaboration avec les microbiologistes
  - Diagnostic précoce d'espèce et de résistance
  - CMI

- DOSAGES
  - Aminosides++++
  - à améliorer pour les autres molécules

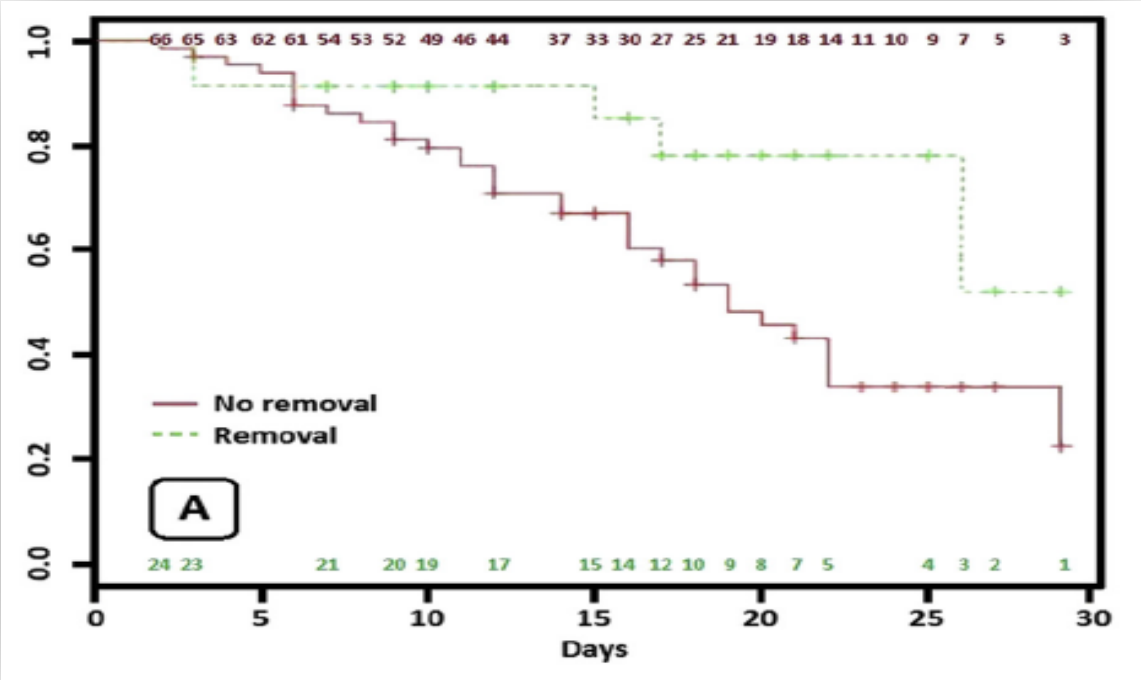

Suspicion d'infection à BGN-R
Risque élevé de BHR???
Portage++
Ecosystème
Immunodépression
Procédures inv.
Acquis en dehors de l'hôpital
Acquis à l'hôpital
ATCD de portage BLSE
Séjour pays à risque avec
Hospitalisation et antibiotiques
Pathologies associées aux soins…
Bronchectasies et antibiothérapie
multiples dans les mois précédents
Ecosystème
Colonisation préalable
Cathéters
immunodépression
Antibiothérapie antérieure
Molecules de base
CAZ-AVI
Penems
Colistine
Tigecycline
Aminosides
Fosfomycine
COMBO++
Optimisation PK
3 dogmes:
ne pas utiliser une molécule
utilisée précédemment
Optimiser PK/PD (collaboration
microbio-clinique+++)
DOSE DE CHARGE++
B-lactamines en association
+
Aminoglycosides
(Ou)
Fluoroquinolones
Bactericidie
Moindre résistance
Synergie in vitro
Diffusion
Moindre toxicité
REEVALUATION/ DESESCALADE

Agenda

- Ne traiter que les patients réellement infectés
- Commencer vite: quand suspecter un BGN potentiellement resistant
- Traiter avec les bons antibiotiques aux bonnes doses en utilisant la bonne voie d'administration
- **Contrôler la source de l'infection**
- Arrêter précocement les traitements inutiles

In XDR infection, control of the source is key

111 KPC septic shock – *Falcone et al CMI 2016; 22:444*



Agenda

- Ne traiter que les patients réellement infectés
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- **Arrêter précocement les traitements inutiles**

Désecalade et arrêt précoce

- Si les prélèvements microbiologiques sont effectués AVANT antibiothérapie
- Bi-thérapie à haute dose de durée limitée
- Durée de traitement : si contrôle clinique toute anibiothérapie > 7 jours doit être rediscutée
- Rôle de la Procalcitonine

Conclusion

Reconnaitre précocemment les facteur de risque de EBLSE

- Séjour en zone d'endémie + hospitalisation+antibiotiques
- Antibiothérapie antérieure
- Colonisation préalable/ écosystèmes
- Dépistage
- Immunodépression/ procédure invasives/ durée de séjour

Risque de BHR à évaluer:

- colonisation préalable
- antibiothérapies préalables
- pression de colonisation

Promouvoir le diagnostic rapide

Traitement précoce:

- Bithérapie (tri?)
- Dose de charge et optimisation PK
- Evacuation du foyer infectieux

Désescalade si Souche sensible+++

Politique globale

Maitrise de la transmission croisée ET Maitrise de la prescription des antibiotiques

	ESBL	AmpC	Carbapenemases			Pseudomonas spp.	Acinetobacter	Phase
			Serine (KPC)	Oxa48-like	MBL			
Ceftolozane-tazobactam*	+	-	-	-	-	++	-	FDA approved
Ceftazidime-avibactam*	++	++	++	+	-	++	-	FDA approved
Aztreonam-avibactam	++	++	++	+	++	+	-	2
Imipenem-relebactam (MK7655)	++	++	++		-	+	-	3
Meropenem-vaborbactam (RPX7009)	++	++	++		-	+	-	3
Cefepime-zidebactam (WCK 5222)	++	++	++	++	++	++	-	2
Cefiderocol (S49266)	++	++	++	++	++	++	+	3
Eravacycline	++	++	++	++	++	-	++	3
Plazomicin	++	++	++	++	++/-	++	+	3
Murepavadin (POL7080)						+++		2