DIU Infections ostéo-articulaires
Lyon, 28 novembre 2018

Tolérance de l'antibiothérapie au cours des IOA

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Introduction

Antibiothérapie = 1e classe médicamenteuse responsable d'ES

- Rash
- Troubles digestifs
- Troubles hématologiques
- Néphrotoxicité

Traitement des IOA

- Bithérapie
- Prolongée
- Fortes doses
- Patients âgés / comorbidités

→ Risque majoré

Peu d'études spécifiques dans les IOA

Fréquence des effets secondaires

Méta-analyse Cochrane (2013, 4 études, 176 patients) ***5%***

- Traitement IV : 15,5%
- Traitement per os : 4,8%

NS

Pulcini (2008), 129 ostéites chroniques, 29 sem dont 19 sem IV ***16%***

Bouaziz (thèse Lyon 1 2011), 130 IPA SASM-SARM 24 sem ***35%***

Karsenty (thèse Lyon 1 2012), 99 SDI, 33 sem ***49%***

Conterno, Cochrane Database Syst Rev 2013 – Pulcini, Eur J Clin Microbiol Infect Dis 2008

IOA staphylococciques : expérience lyonnaise

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Antimicrobial-Related Severe Adverse Events during Treatment of Bone and Joint Infection Due to Methicillin-Susceptible *Staphylococcus aureus*

Florent Valour,[a,b] Judith Karsenty,[a] Anissa Bouaziz,[a] Florence Ader,[a,b] Michel Tod,[c] Sébastien Lustig,[d] Frédéric Laurent,[b,e,f] René Ecochard,[g] Christian Chidiac,[a,b] Tristan Ferry,[a,b] on behalf of the Lyon BJI Study Group

Etude rétrospective (2001-2011)
CRIOAc Lyon

200 patients traités pour IOA à MSSA

Analyse des ES selon le CTCAE
(NIH – National Cancer Institute)

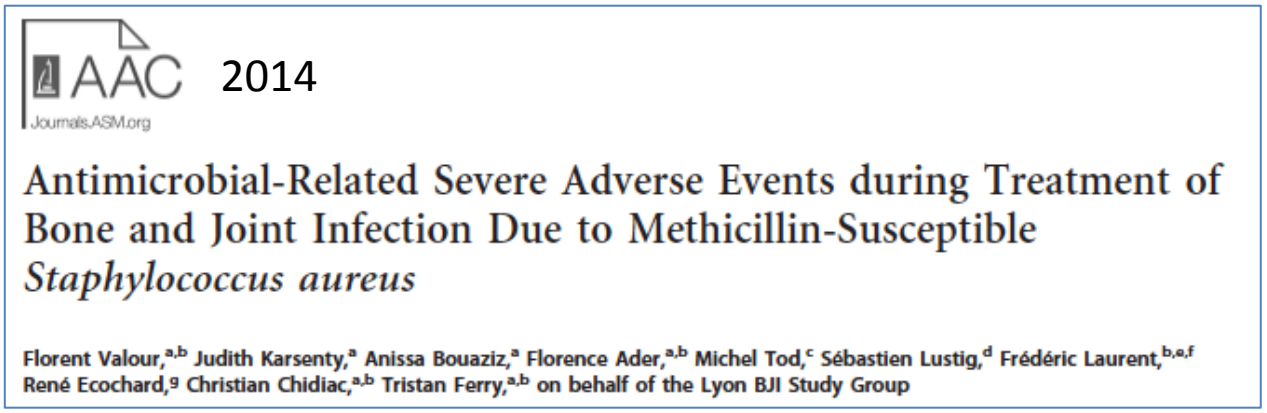
- Grade 1 : léger
- Grade 2 : modéré

ES graves

- Grade 3 : sévère
- Grade 4 : menaçant le pronostic vital
- Grade 5 : décès

Patient data[b]	Total (n = 200)
Sex (male)	124 (62)
Age (median [IQR]) (yr)	60.8 (45.5–74.2)
Comorbidity	
Charlson score (IQR)	0.0 (0.0–2.0)
Obesity (BMI > 30)	39 (20)
Denutrition (BMI < 18)	9 (4.6)
Diabetes	27 (13.5)
Immunodepression	23 (11.5)
Nephropathy	28 (14)
Hepatopathy	5 (2.5)
Chronic pulmonary disease	30 (15)
Chronic heart failure	23 (11.5)
Chronic inflammatory disease	24 (12)
Neoplasm/hemopathy	21 (10.5)
Dementia	7 (3.5)
BJI type	
Arthritis	15 (7.5)
Osteomyelitis	19 (9.5)
Vertebral osteomyelitis	32 (16)
Orthopedic device infection	134 (67)
Joint prosthesis	76 (56.7)
Osteosynthesis	48 (35.8)
Vertebral osteosynthesis	10 (7.5)
BJI mechanism	
Hematogenous (for clinician)	74 (37)
Inoculation	121 (60.5)
Contiguity	5 (2.5)

IOA staphylococciques : expérience lyonnaise



- **Traitement chirurgical :** 164 (82%)
- **Traitement médical**
  - Durée totale : 26.6 semaines (16.8-37.8)
  - Traitement IV initial : 182 (91%) - 7.4 semaines (4.9-14.4)
  - Bithérapie : 200 (100%) - 24.6 semaines (14.1-31.1)

Durée de traitement prolongée

- *S. aureus*
- *Charlson > 2 : 47%*
- *Bactériémie : 60%*
- *Tissus mous endommagés : abcès (39%), fistule (43%)*
- *Chirurgie non conforme aux recommandations (36%)*

97.5%

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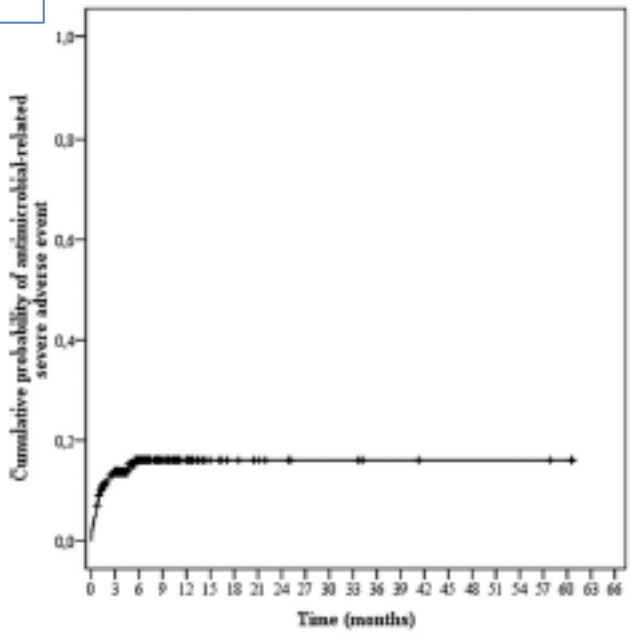

Au moins 90 patients avec au moins 1 ES (45%)
38 ES graves (CTCAE 3-5) chez 30 patients (15%)

Délai de survenue : 34 jours (15-61)

18 hospitalisations / prolongement d'hospitalisation – 8 jours (4-29)
30 arrêt / switch d'antibiothérapie (79%)

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Type of SAE (*n*)	Subtype of SAE (*n*)	CTCAE[b] grade	Antimicrobial(s) involved (*n*)	Time from treatment initiation to SAE (median [IQR]) (days)
Hematologic disorders (10)	Neutrophil count decrease (5), febrile neutropenia (3), anemia (1), pancytopenia (1)	Grade 3 (5), grade 4 (5)	β-Lactams (7), fluoroquinolones (1), glycopeptides (1), fosfomycin (1), linezolid (1)	26.0 (13.25–35.0)
Allergic reactions (9)	Maculopapular rash (5), Stevens-Johnson syndrome (3), anaphylactic shock (1)	Grade 3 (5), grade 4 (4)	Glycopeptides (5), fluoroquinolones (6), rifampin (4), β-lactams (3), macrolide group (1)	20.0 (11.0–22.0)
Renal disorders (6)	Acute kidney injury (6)	Grade 3 (4), grade 4 (1), grade 5 (1)	β-Lactams (4), aminoglycosides (4), fluoroquinolones (4), glycopeptides (3), macrolide group (1)	2.0 (1.25–7.25)
Metabolic disorders (4)	Hypokalemia (4)	Grade 3 (4)	Fosfomycin (4)	21.0 (15.75–21.0)
Hepatobiliary disorders (4)	Blood bilirubin increase (2), blood GGT[c] increase (1), hepatic failure (1)	Grade 3 (4)	β-Lactams (3), rifampin (1), fluoroquinolones (1), fusidic acid (1), cotrimoxazole (1)	43.5 (18.0–65.75
Gastrointestinal disorders (3)	Vomiting (2), duodenal ulcer (1)	Grade 3 (3)	Rifampin (2), macrolide group (1)	7.0 (4.0–86.0)
Nervous system disorders (2)	Cognitive disturbance (1), ototoxicity (1)	Grade 3 (2)	β-Lactams (1), fosfomycin (1)	7.0 (4.5–9.5)

Facteurs de risque d'effets secondaires

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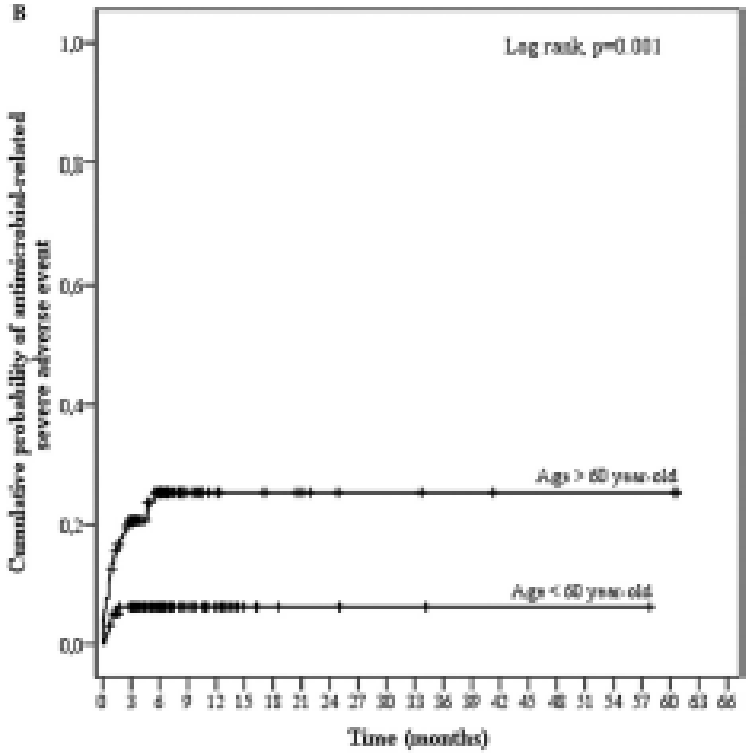
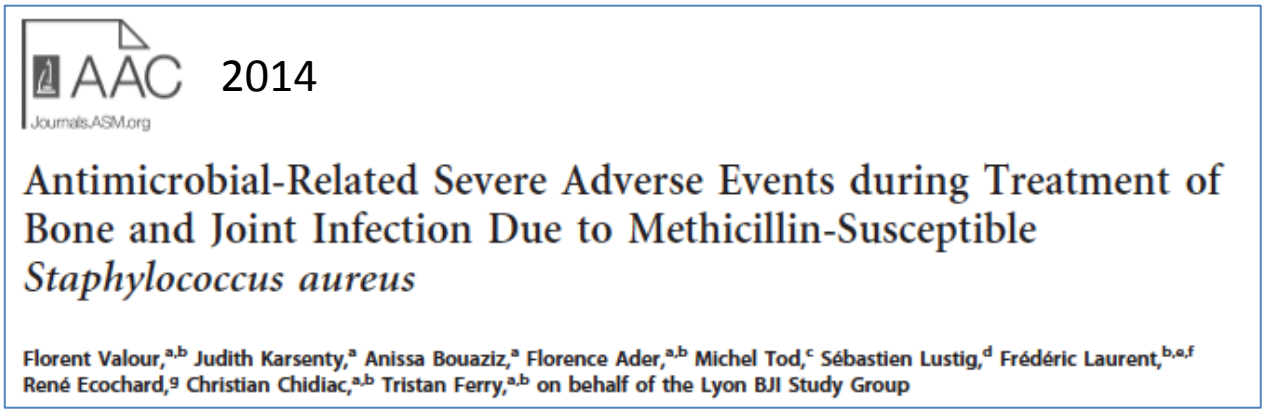
Seul facteur de risque indépendant : AGE

OR = 1,4 / 10 ans (95%CI 1,1-1,8), *p*=0.011



Facteurs de risque d'effets secondaires



Autres facteurs de risque connus :

- APA : durée de traitement, béta-lactamines ou glycopeptides
- SDI : sexe féminin, maladie de système, C3G ou clindamycine
- Facteur protecteur : prescription selon protocole standardisé informatisé

Karsenty, Thèse Lyon 1 2012 – Hoffman-Terry 1999 Am J Med – Pestonik 1996 Ann Intern Med

Principales molécules utilisées

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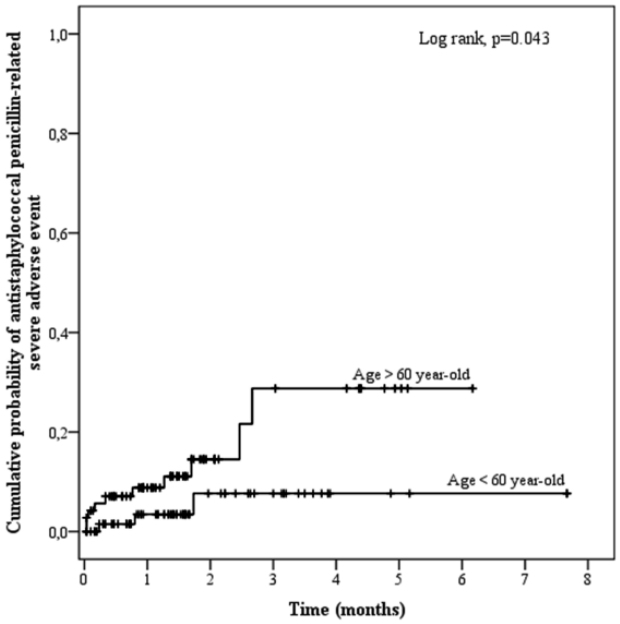
Antimicrobial(s) (*n*)	Type of SAE[a] (*n*)	CTCAE[b] grade (*n*)	Time from treatment initiation to SAE (median [IQR]) (days)
β-Lactams (17): ASP[c] (13), others (4)	Hematologic disorders (7), acute kidney injuries (4), allergic reactions (3), hepatobiliary disorders (2), cognitive disturbance (1)	Grade 3 (13), grade 4 (4)	28.0 (7.0–63.0)
Fluoroquinolones (10)	Allergic reactions (6), acute kidney injuries (2), hematologic disorders (1), hepatobiliary disorders (1)	Grade 3 (3), grade 4 (6), grade 5 (1)	20.0 (12.5–49.25)
Glycopeptides (9)	Allergic reactions (5), acute kidney injuries (3), hematologic disorders (1)	Grade 3 (5), grade 4 (3)	20.0 (2.0–20.0)
Rifampin (7)	Allergic reactions (4), vomiting (2), blood bilirubin increase (1)	Grade 4 (3), grade 3 (4)	20.0 (20.0–24.5)

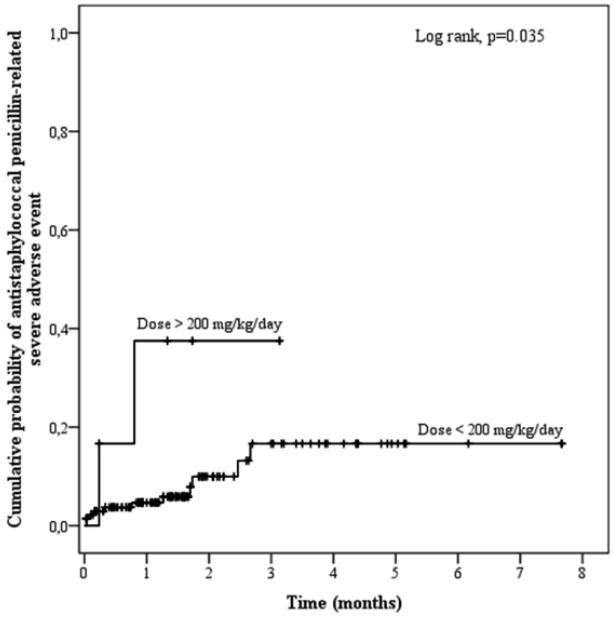
Principales molécules utilisées : pénicilline M

- 145 patients
- 146.3 mg/kg/j (132-171) – 44 jours

- **13 EIG (9%)**
  - Hématologiques (n=7)
  - IRA (n=4)
  - Allergiques (n=3)
  - Hépatobiliaires (n=2)
  - Syndrome confusionnel (n=1)

- Facteurs de risque (an. multivariée)
  - **Age : OR 1.8** (1.2-2.8), p=0.008
  - **IOA hématogène : OR 5.9** (1.0-33.8), p=0.045
  - **Dose : OR 1.02** (1.01-1.05), p=0.014





Principales molécules utilisées : rifampicine

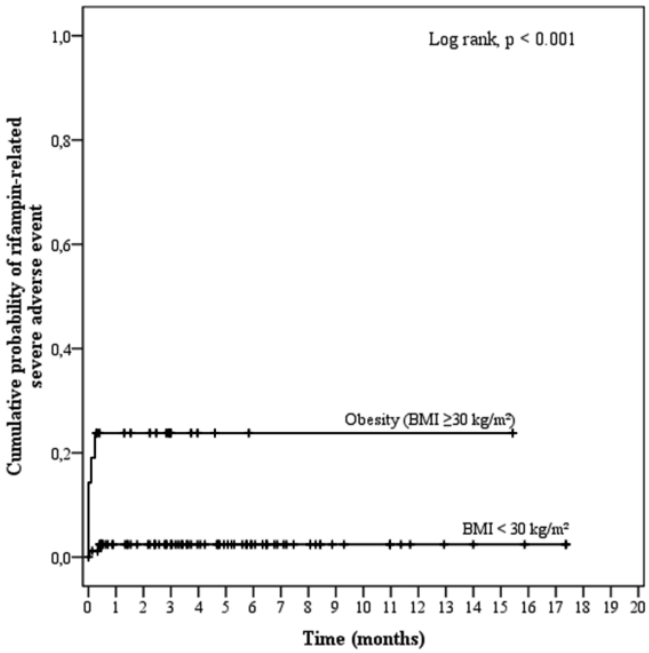
- 107 patients
- 18.8 mg/kg/j (16.2-21.2) - 101 jours (39.5-187.5)

- **7 EIG (6.5%)**
  - Rash / Allergie (n=4)
  - Vomissements (n=2)
  - Hépatite cholestatique (n=1)

- Facteurs de risque (an. multivariée)

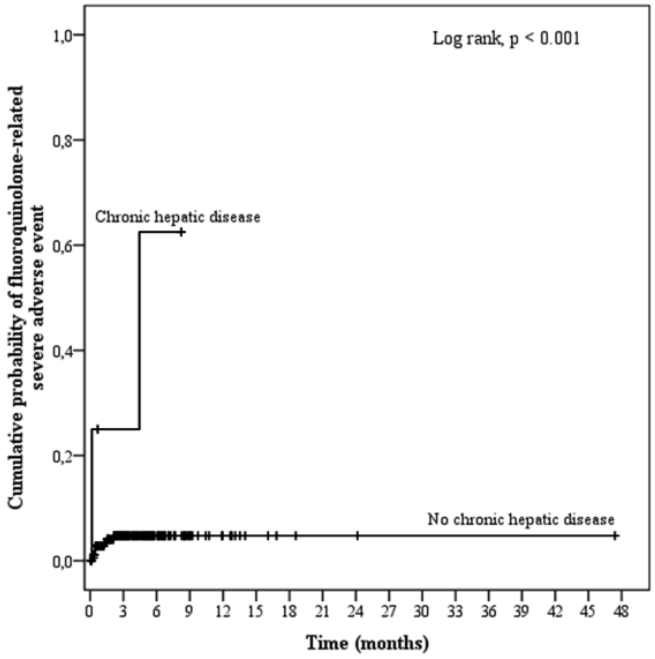
Obésité : OR 9.0 (1.5-55.6), p=0.018

Dose : 1.5 g (1.2-1.8) vs 1.2 (1.2-1.5), p=0.021



Principales molécules utilisées : fluoroquinolones

- 187 patients – 112.5 jours (65.8-184.5)
- Ofloxacine (89.3%) : 400 mg/j (57.5%), 600 mg/j (34.7%)
- **10 EIG (5.3%)**
  - Rash / Allergie (n=6)
  - Insuffisance rénale aiguë (n=2)
  - Hématologique (n=1)
  - Hépato-biliaire (n=1)
- Facteurs de risque (an. univariée)
  - Age : OR 1.4 (1.0-2.2), p=0.078
  - Charlson score > 2 : OR 2.8 (0.8-10.5), p=0.126
  - **Hépatopathie : OR 14.5** (2.1-99.3), p=0.006



Principales molécules utilisées : glycopeptides

- 102 patients - 19.8 jours (6.3-48.3)

- Téicoplanine (61.8%) : 5.6 mg/kg (4.7-6.7)
- Vancomycine (38.2%) : 25.6 mg/kg (23-32)

- **9 EIG (8.8%)**
  - Rash / Allergie (n=5)
  - Insuffisance rénale aiguë (n=3)
  - Hématologique (n=1)

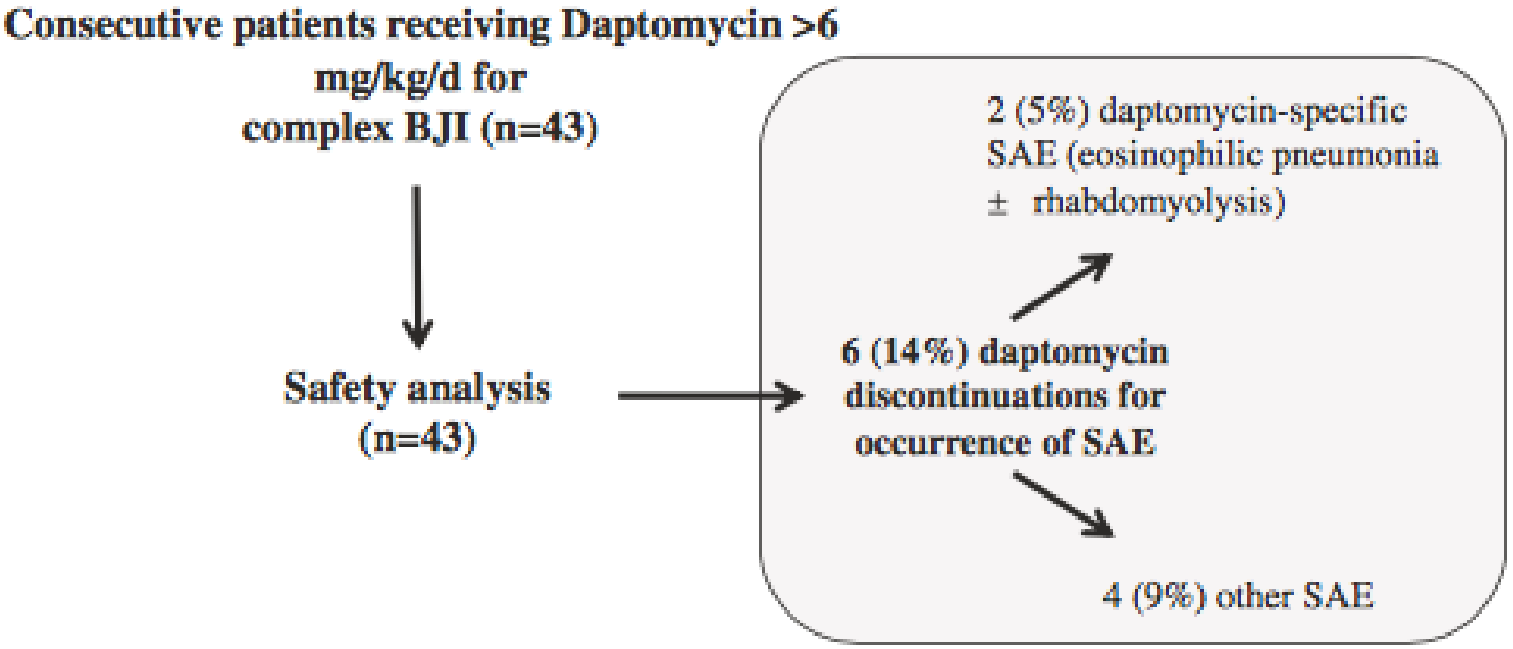
- Facteurs de risque : 0

Principales molécules utilisées : ATB hors AMM

- **Daptomycine**
  - 43 patients
  - 8 +/- 0.9 mg/kg/j pdt 81+/- 59 jours
  - 17 ES, dont 9 ES graves

Daptomycin > 6 mg/kg/day as salvage therapy in patients with complex bone and joint infection: cohort study in a regional reference center

Sandrine Roux[1,2], Florent Valour[1,2,3], Judith Karsenty[1,2,4], Marie-Claude Gagnieu[5], Thomas Perpoint[1], Sébastien Lustig[2,6], Florence Ader[1,2,3], Benoit Martha[4], Frédéric Laurent[2,3,7], Christian Chidiac[1,2,3], Tristan Ferry[1,2,3*] and on behalf of the Lyon BJI Study group



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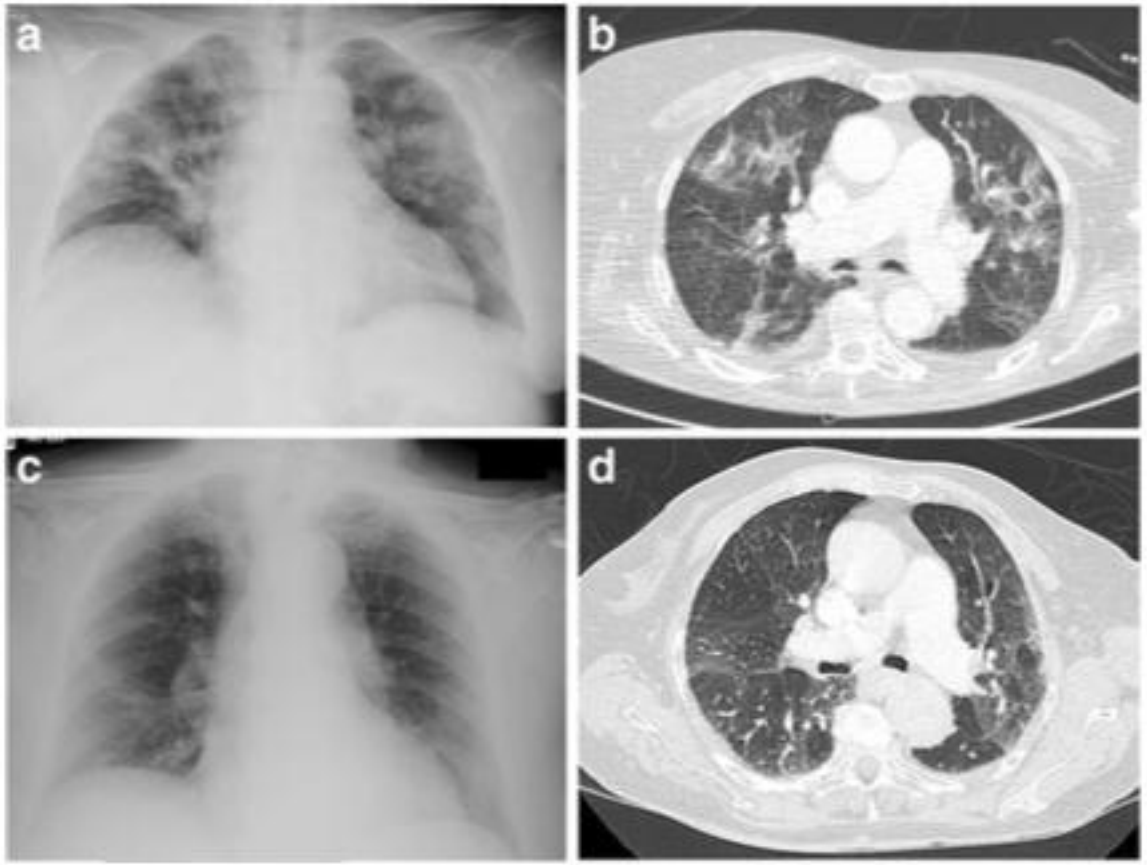

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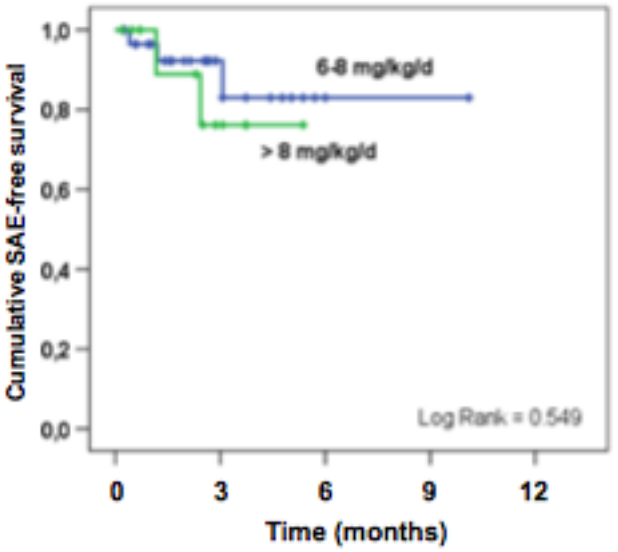
Adverse events	*n* (%)	Daptomycin dose (mean, range)	AE onset (mean, range)	Daptomycin withdrawal	Companion drug withdrawal
Hematologic disorders	12 (28)	7,8 (7–9)	44 (7–92)	4/12	3/12
Hypereosinophilia	6 (14)	7,8 (7–9)	43 (10–92)	3/6	1/6
Neutropenia	4 (9)	7,8 (7–9)	73 (49–88)	1/4	2/4
Increased blood CPK	4 (9)	7,5 (7–8)	49 (9–92)		
PICC thrombosis	3 (7)	8,3 (7–9)	39 (12–79)		
Hepatic disorders	3 (7)	8,2 (7,5–9)	71 (13–112)		
Eosinophilic pneumonia	2 (5)	8,5 (8–9)	17 (6–23)		
Increased blood creatinine	1 (2)	8	8		
Pancreatitis	1 (2)	8	180		



Daptomycine Cmin > 24 mg/L (FR ES modérés à sévères)

Principales molécules utilisées : ATB hors AMM

- **Téicoplanine**
  - 60 patients
  - 5.7 mg/kg/j (4;7-6;5) après charge
  - IV et/ou SC (n=14)
  - 7 ES chez 6 patients (10%)
  - Pas de facteur prédictif

Teicoplanin-based antimicrobial therapy in *Staphylococcus aureus* bone and joint infection: tolerance, efficacy and experience with subcutaneous administration

Olivier Peeters[1,2,3], Tristan Ferry[1,2,4], Florence Ader[1,2,4], André Boibieux[1,2], Evelyne Braun[1,2], Anissa Bouaziz[5], Judith Karsenty[6], Emmanuel Forestier[7], Frédéric Laurent[1,4,8], Sébastien Lustig[1,4,9], Christian Chidiac[1,2,4], Florent Valour[1,2,4*] and on behalf of the Lyon BJI study group

Table 2 Description of the seven teicoplanin-related adverse events observed in 6 of the 60 included patients

Case	Modified CCI	BJI type	AE subtype	CTCAE grade	Route	Dosage	Delay	Companion drug	Stop	Hospitalization (duration)	Resolution
1	5	Acute osteomyelitis	Rash maculo-papular	2	IV	12 mg/L	7 days	None	Yes	Yes (3 days)	Yes
2	4	Acute PJI	Rash maculo-papular	2	IV	No	10 days	Oxacillin Clindamycin	Yes	No (17 days)	Yes
3	0	Acute VO	Rash maculo-papular Pancytopenia	3	SC	No	11 days	Rifampicin	Yes	No	Yes
4	5	Chronic osteomyelitis	Headache	1	IV	27.8 mg/L	20 days	Rifampicin	Yes	No	Yes
5	2	Chronic VO	Rash maculo-papular	3	SC	No	22 days	Ofloxacin	Yes	Yes (4 days)	Yes
6	2	Acute VO	Rash maculo-papular	2	IV	No	14 days	Ofloxacin	Yes	No	Yes

Principales molécules utilisées : ATB hors AMM

- **Pristinamycine**
  - 98 patients
  - 47.6 (45.5–52.6) mg/kg/j
  - 9.3 (1.4–20.4) semaines

Pristinamycin in the treatment of MSSA bone and joint infection

Florent Valour[1–3]*, André Boibieux[1,2], Judith Karsenty[4], Marie-Paule Vallat[1,2], Evelyne Braun[1,2], Thomas Perpoint[1,2], François Biron[1,2], Frédéric Laurent[2,3,5], Sébastien Lustig[2,3,6], Christian Chidiac[1–3] and Tristan Ferry[1–3] on behalf of the Lyon Bone and Joint Infection Study Group†

  - 15 ES chez 14 patients (13.3%), 2 ES graves
  - Délai médian de 21 jours (7-55)
  - Troubles digestifs (n=10), réactions allergiques (n=3)
  - Facteur de risque : dose journalière OR 2.7 pour 10 mg/kg supplémentaires

Principales molécules utilisées : ATB hors AMM

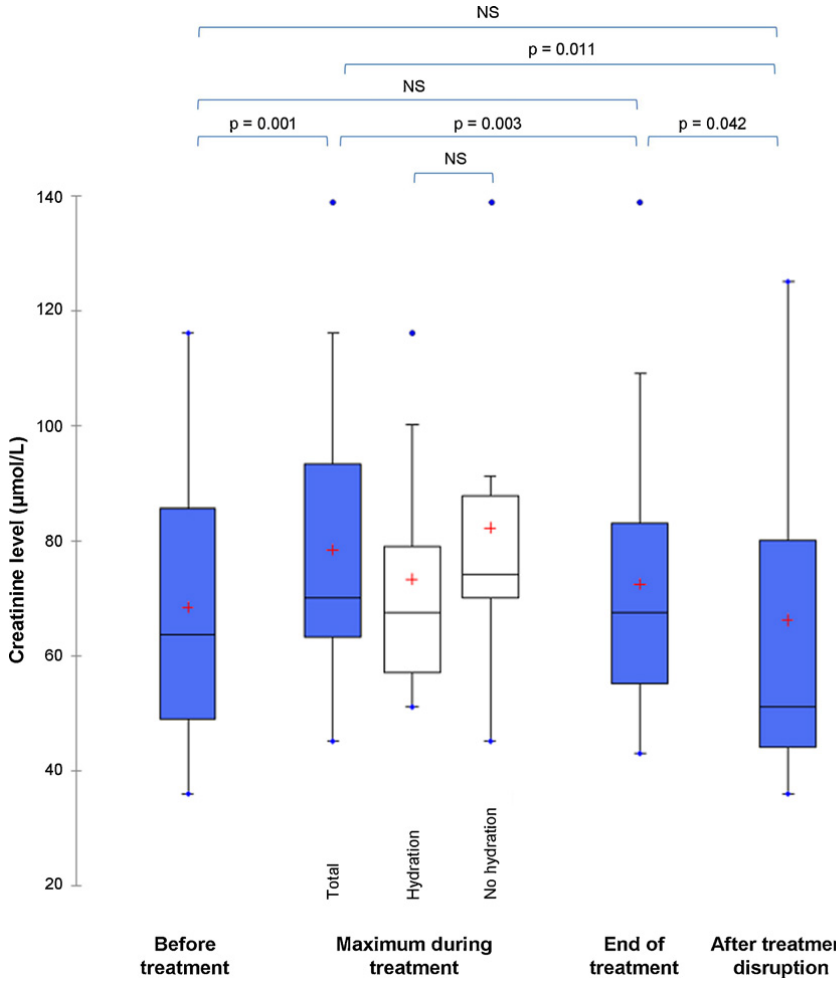
- **Colimycine**
  - 19 patients
  - 50 000 UI/kg/j (40-55)
  - 81 jours (37-149)

  - 8 ES de grade 1-2, pas d'ES graves
  - 5 insuffisances rénales modérées
  - Délai 20 jours (17-93)

Difficult-to-treat Gram-negative bone and joint infections: efficacy and safety of prolonged intravenous **colistin**.

Valour F, Dutronc H, Dinh A, Cazorla C, Pavèse P, Lesens O, Uçkay I, Chidiac C, Ferry T; **Colistin** BJIs Study Group.

Int J Antimicrob Agents. 2013 Feb;41(2):197-9. doi: 10.1016/j.ijantimicag.2012.09.016.



Principales molécules utilisées : ATB hors AMM

- **Tigécycline**
  - 36 patients
  - 50 mg x 2/j
    après dose de charge (100 mg J1)
  - 8.4 +/- 7.1 sem

  - 18 ES chez 13 patients (36.1%)
  - 7 ES graves

Tigecycline-based prolonged salvage therapy in patients presenting with complex bone and joint infection☆

Antibiothérapie de sauvetage à base de tigécycline chez des patients présentant une infection ostéoarticulaire complexe

J. Wach[a], A. Dinh[b], H. Dutronc[c], O.R. Sipahi[d], A. Candevir[e], F. Valour[f,g,h,i], V. Zeller[j], S. Lustig[g,h,k], F. Laurent[g,h,l], C. Chidiac[f,g,h,i], T. Ferry[f,g,h,i,*], on behalf of the Lyon BJI study group[l]

	All AEs ($n=13$)	CTCAE grade ≥ 3 ($n=7$)	AEs requiring discontinuation ($n=4$)
Nausea/vomiting	9	4	2
Diarrhea	2	0	0
Increased asymptomatic lipase	1	0	1
Clinical pancreatitis	1	1	1
Drug fever	1	0	0
Renal failure	0	/	/
Allergy	0	/	/
Neutropenia	2	1	0
Increased aminotransferase	1	0	0
Decreased fibrinogene	1	1	1[a]

Antibiothérapie probabiliste

Prospective Cohort Study of the Tolerability of Prosthetic Joint Infection Empirical Antimicrobial Therapy

Claire Triffault-Fillit,[a,b] Florent Valour,[a,b,c] Ronan Guillo,[a,b] Michel Tod,[a,d,e] Sylvain Goutelle,[a,d,e] Sébastien Lustig,[a,e,f] Michel-Henry Fessy,[a,e,g] Christian Chidiac,[a,b,c] Tristan Ferry,[a,b,c] on behalf of the Lyon BJI Study Group

AAC 2018

Etude de cohorte prospective (2011-2016)
CRIOAc Lyon

333 PJI recevant un traitement probabiliste

Analyse des ES selon le CTCAE
(NIH – National Cancer Institute)

- Grade 1 : léger
- Grade 2 : modéré
- Grade 3 : sévère
- Grade 4 : menaçant le pronostic vital
- Grade 5 : décès

ES graves

Parameter or therapy	Total population (n = 333)
Demographics and comorbidities	
Sex, no. male	168 (50.5%)
Mean age, yrs	69.8 (59.3–79.1)
Mean BMI, kg/m² (range)	28.0 (24.7–33.0)
Obesity, BMI > 30 kg/m²	89 (39.4%)
ASA score	2 (2–3)
ASA score > 2	143 (43.5%)
Empirical antimicrobial therapy	
Glycopeptide	262 (78.7%)
Vancomycin	229 (68.8%)
Vancomycin trough concn (mg/liter)	NA
Vancomycin overexposure (>30 mg/liter)	NA
Teicoplanin	33 (9.9%)
Daptomycin	4 (1.2%)
Beta-lactam	
PT	131 (39.3%)
3rdGC	50 (15.0%)
ASP	30 (9.0%)
Carbapenem	8 (2.4%)
Aminoglycoside	72 (21.6%)
Plus glycopeptide	46 (13.8%)
Others	
Clindamycin	49 (14.7%)
Pristinamycin	21 (6.3%)
Fluoroquinolone	52 (15.6%)
Rifampin	10 (3.0%)
Main combinations	
Vancomycin + PT	123 (36.9%)
Vancomycin + 3rdGC	33 (9.9%)

Antibiothérapie probabiliste

Prospective Cohort Study of the Tolerability of Prosthetic Joint Infection Empirical Antimicrobial Therapy

Claire Triffault-Fillit,[a,b] Florent Valour,[a,b,c] Ronan Guillo,[a,b] Michel Tod,[a,d,e] Sylvain Goutelle,[a,d,e] Sébastien Lustig,[a,e,f] Michel-Henry Fessy,[a,e,g] Christian Chidiac,[a,b,c] Tristan Ferry,[a,b,c] on behalf of the Lyon BJI Study Group

AAC 2018

42 (12.6%) patients avec au moins 1 ES, dont 10 ES graves
Médiane de survenue : 8 jours (5-13)

Type of adverse event (*n*)	Subtype of adverse event (*n*)	CTCAE grade (*n*)	Antimicrobial therapy (*n*)
Renal and urinary disorders (25)	Acute kidney injury (25)	Grade 1 (5) Grade 2 (17) Grade 3 (3)	Vancomycin (25) Piperacillin-tazobactam (20) Gentamicin (4) Ceftriaxone (2) Others: clindamycin, ofloxacin, metronidazole, rifampin (1 each)
Skin and subcutaneus tissue disorders (8)	Pruritus (4) Rash, maculopapular (4)	Grade 1 (4) Grade 2 (3) Grade 3 (1)	Vancomycin (7) Piperacillin-tazobactam (4) Ceftriaxone (2) Others: clindamycin, fosfomycin, gentamicin, imipenem, linezolid, metronidazole (1 each)
General disorders and administration site conditions (5)	Fever (4) Injection site reaction (1)	Grade 1 (2) Grade 2 (2) Grade 3 (1)	Vancomycin (5) Piperacillin-tazobactam (4) Pristinamycin (1)
Blood and lymphatic system disorders (4)	Febrile neutropenia (1) Other, hypereosinophilia (3)	Grade 2 (3) Grade 3 (1)	Vancomycin (3) Piperacillin-tazobactam (2) Gentamicin (2) Ceftriaxone (1) Oxacillin (1)
Immune system disorders (4)	Allergic reaction, DRESS (4)	Grade 4 (4)	Vancomycin (3) Others: ceftriaxone, cloxacillin, fosfomycin, ofloxacin, piperacillin-tazobactam (1)
Hepatobiliary disorders (2)	Cytolytic hepatitis (2)	Grade 2 (2)	Vancomycin (2) Others: gentamicin, piperacillin-tazobactam, rifampin (1 each)
Gastrointestinal disorders (1)	Vomiting (1)	Grade 2 (1)	Gentamicin, oxacillin, rifampin (1)

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AAC 2018

42 (12.6%) patients avec au moins 1 ES, dont 10 ES graves
Médiane de survenue : 8 jours (5-13)

Prolongement de l'hospitalisation / réhospitalisation : 10 (25%)
Changement de traitement : 38 (95%)

Antibiothérapie probabiliste

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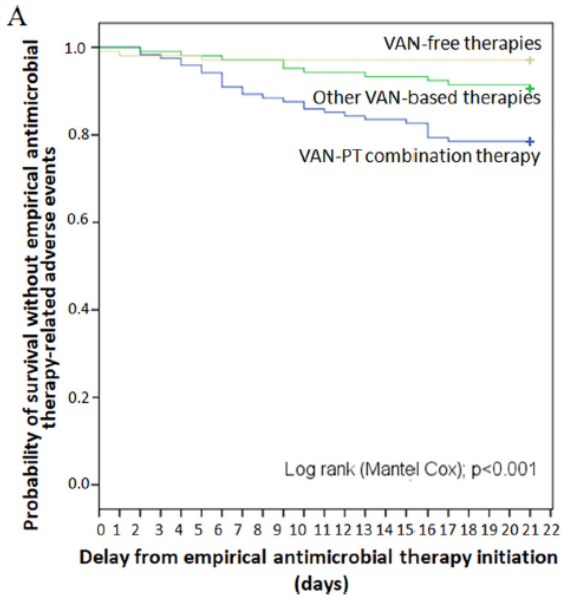
Facteurs de risque d'ES (analyse univariée) :

- Vancomycine : OR = 6.9 (95%CI, 2.1-22.9; p=0.002)
- Pipéracilline/tazobactam : OR = 3.7 (95%CI, 1.8-7.2; p<0.001)
- Association vanco – pipé/tazo : OR = 4.1 (95%CI, 2.1-3.5; p<0.001)



Antibiothérapie probabiliste

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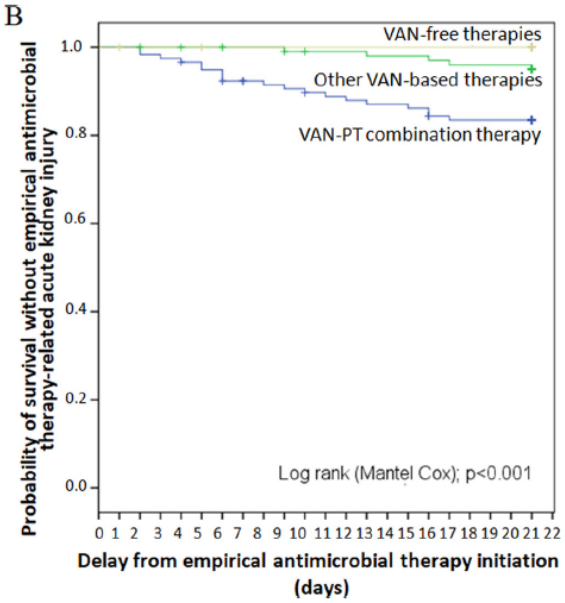
Facteurs de risque d'insuffisance rénale (analyse univariée) :

- Pipéracilline/tazobactam : OR = 6.0 (95%CI, 2.3-15.4); p<0.001)
- Association vanco – pipé/tazo : OR = 6.7 (95%CI, 2.6-17.3); p<0.001)



25 insuffisances rénales
Tous les patients sous vancomycine
Surdosage (> 30 mg/L) : 9 patients seulement

Antibiothérapie probabiliste

Prospective Cohort Study of the Tolerability of Prosthetic Joint Infection Empirical Antimicrobial Therapy

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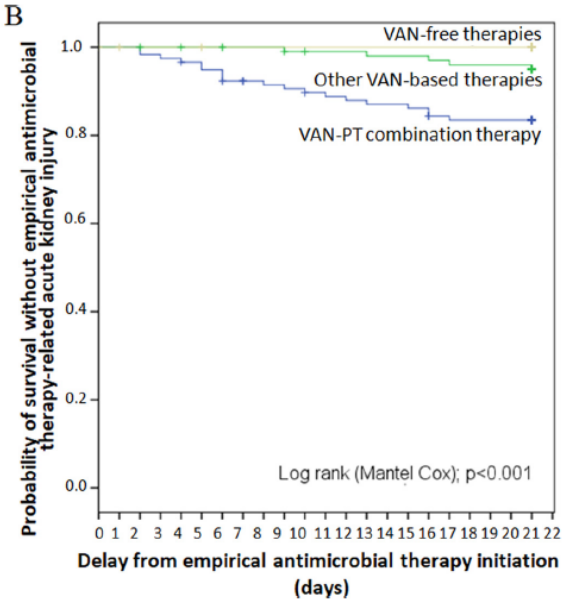


25 insuffisances rénales
Tous les patients sous vancomycine
Surdosage (> 30 mg/L) : 9 patients seulement

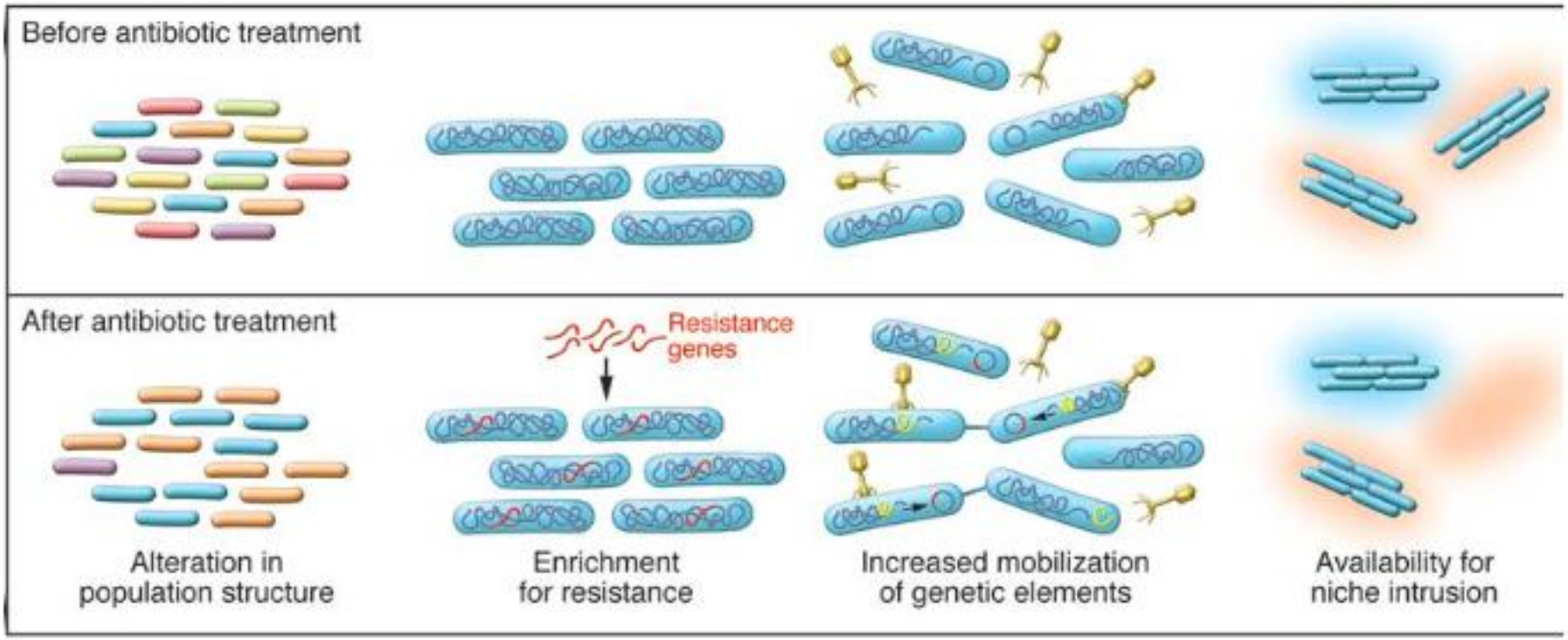
TIME to SWITCH ?!

Vancomycine – Céfépime +/- métronidazole ?

Impact écologique, microbiote

Effet secondaire constant : impact sur la flore commensale

- Appauvrissement des espèces « indigènes » (*Lactobacillus*, *Eubacterium* …)
- Favorise l'implantation des espèces pathogènes (*Salmonella*, *C. difficile*)
- Favorise l'échange de matériel génétique (virulence et/ou résistance)



Modi et al, J Clin Invest 2014

Take-home messages

Synthèse

Antibiothérapie des IOA à risque d'effets secondaires : 15-20%

- Bithérapie
- Prolongée
- Forte dose

Se méfier

- Des patients à risque : âge, obésité, comorbidités
- De l'antibiothérapie probabiliste
- De l'antibiothérapie hors AMM (information, monitoring)

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Hospices Civils de Lyon

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