DIU « Infection ostéoarticulaire » - Séminaire de Lyon

du mardi 6 et mercredi 7 décembre 2022

Antibiothérapie hors AMM/non conventionnelle

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Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

Président du Comité Scientifique des CRIOAc 2017-2022

Au cours des IOA

- **Peu** d'essai thérapeutique
- **Nombreuses molécules** non évaluées
- **Intérêt de molécules hors AMM** (spectre, profil de tolérance, activité anti-biofilm)
  - Lévofloxacine, moxifloxacine
  - Daptomycine, Dalbavancine
  - Béta-lactamines de dernière génération
  - Linézolide, tédizolide

HORS AMM

HORS AMM

Prescription « hors AMM »

- S’assurer de l’absence d’alternatives
- Connaître les éléments de la littérature permettant de justifier chaque choix
  - Molécule
  - Voie d’administration
  - Dose
  - Interactions médicamenteuses
- Informer le patient
- Exposition à des effets indésirables attendus et non attendus

HORS AMM

HORS AMM

Ertapénème (Invanz®)

AMM
1g/j par voie IV

Infections intra-abdominales.

Pneumonies communautaires.

Infections gynécologiques aiguës.

Infections de la peau et des tissus mous du pied chez le diabétique

- **Large spectre**
  - Gram-positifs
    - Pneumocoques
    - Staphylocoques
    - Streptocoques
    - Inactif sur les entérocoques
  - Gram négatifs
    - *Haemophilus influenzae*
    - **Entérobactéries**
      - **y compris BLSE**
      - **y compris céphalosporinase déréprimée**
    - Inactifs sur :
      - *P. aeruginosa*
      - *Acinetobacter spp.*
      - *Stenotrophomonas maltophilia*
  - Anaérobies

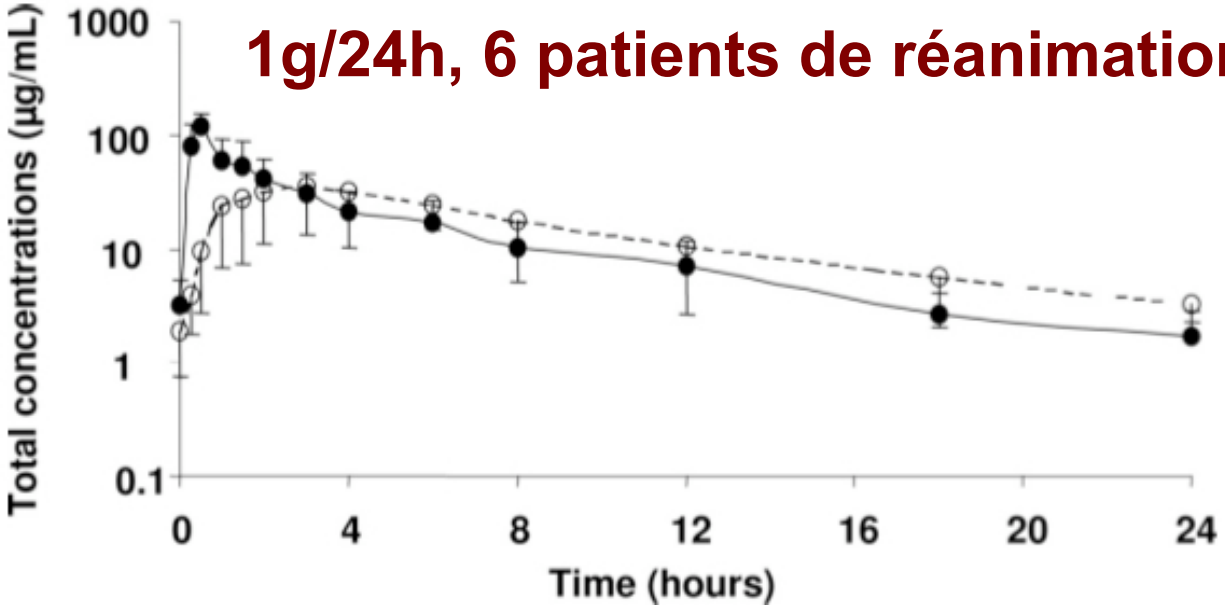
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2010, p. 924–926 Vol. 54, No. 2
0066-4804/10/$12.00 doi:10.1128/AAC.00836-09

Pharmacokinetics of Ertapenem following Intravenous and Subcutaneous Infusions in Patients[▽]

Denis Frasca,[1,3] Sandrine Marchand,[1,2,3] Franck Petitpas,[1,3] Claire Dahyot-Fizelier,[1,2,3] William Couet,[1,2,3]* and Olivier Mimoz[1,2,3]

INSERM, ERI-23, Pôle Biologie Santé, 40 Avenue du Recteur Pineau, Poitiers, France[1]; Université de Poitiers, UFR Médecine-Pharmacie, 6 Rue de la Milétrie, Poitiers, France[2]; and CHU Poitiers, 2 Rue de la Milétrie, Poitiers, France[3]

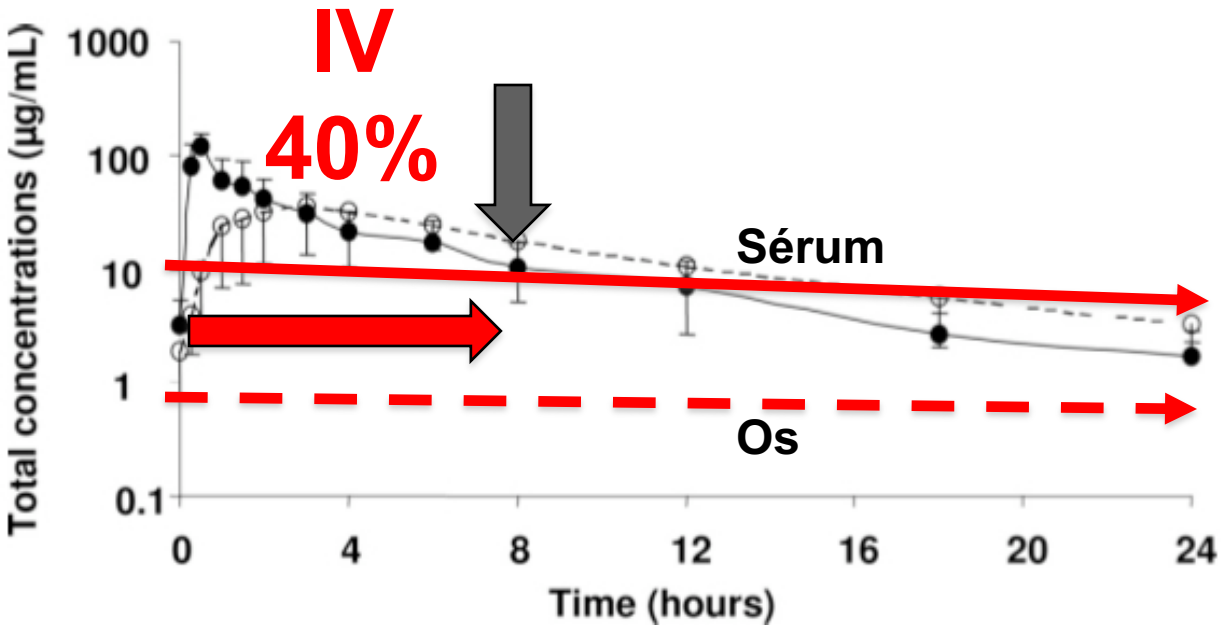
1g/24h, 6 patients de réanimation



Diffusion of ertapenem into bone and synovial tissues

E. Boselli[1]*, D. Breilh[2], S. Djabarouti[2], J. C. Bel[1], M. C. Saux[2] and B. Allaouchiche[1]

[1]*Department of Anaesthesiology and Intensive Care, Édouard Herriot, Lyon, France;*
[2]*Clinical Pharmacokinetics Laboratory, Haut-Lévêque Hospital, Pessac, France*



HORS AMM

Ertapénème (Invanz®) et IOA

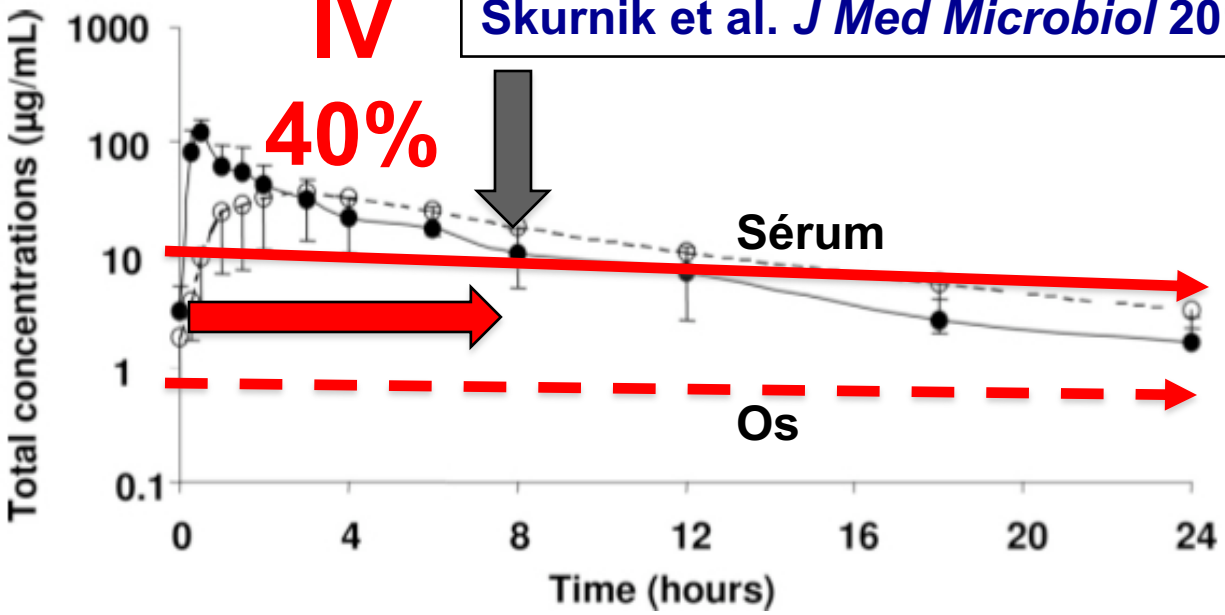
HORS AMM

Echecs !

Lee et al. *Int J Infect Dis* 2010

Elliott et al. *Clin Infect Dis* 2006

Skurnik et al. *J Med Microbiol* 2010



HORS AMM

Ertapénème (Invanz®) et IOA

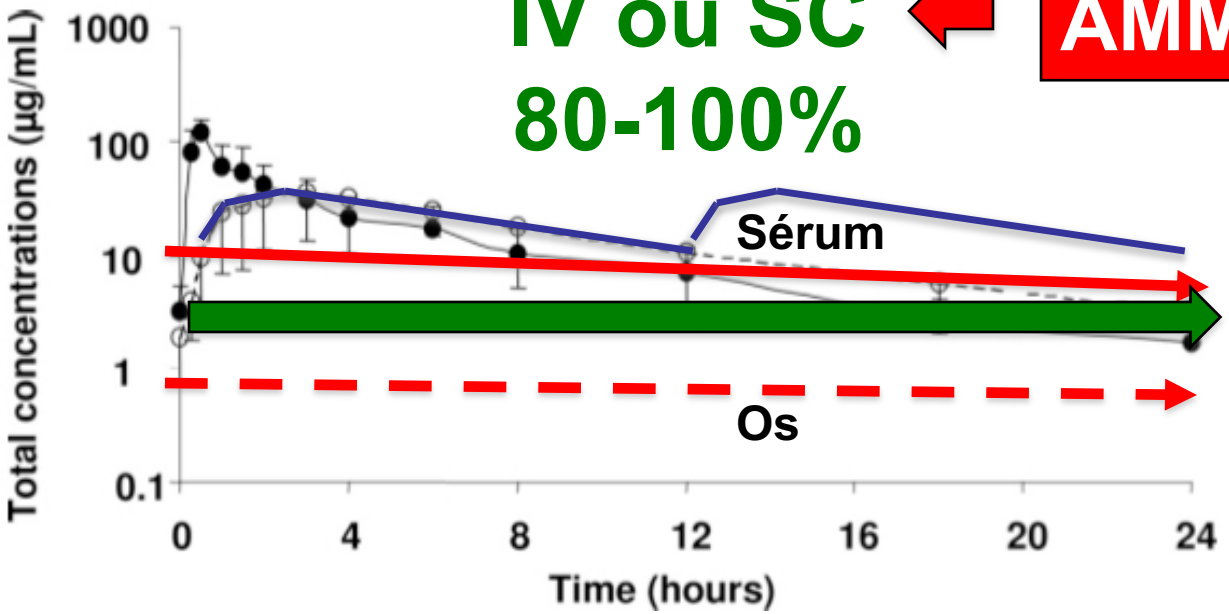
HORS AMM

1g 2x/j

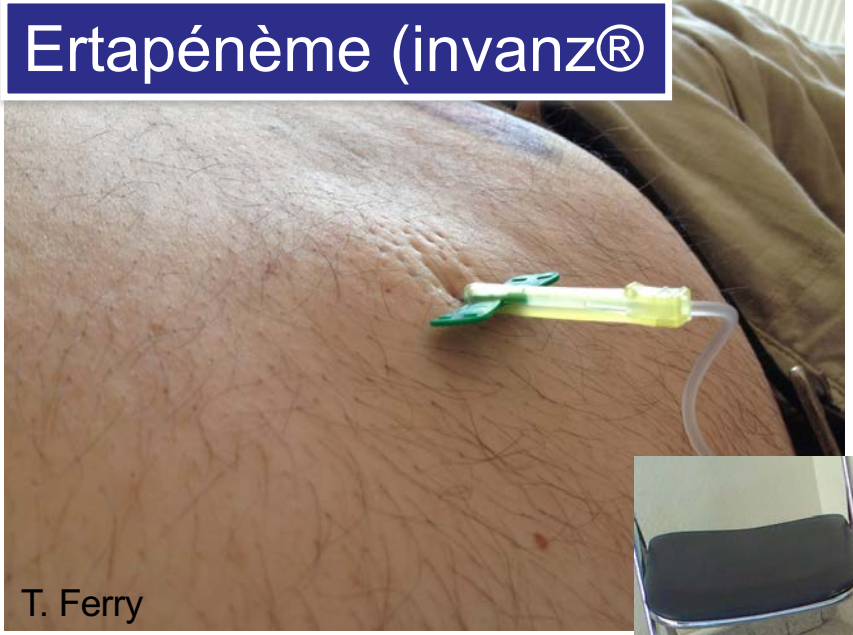
IV ou SC

80-100%

Hors AMM



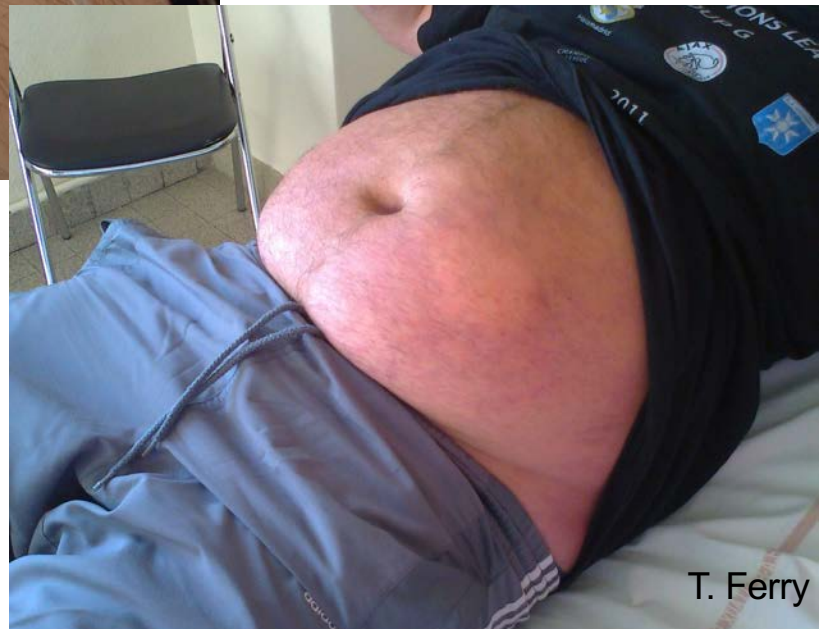
Ertapénème (invanz®



50cc sérum physiologique

Injection SC lente

chez un patient n'ayant pas d'anticoagulation curative



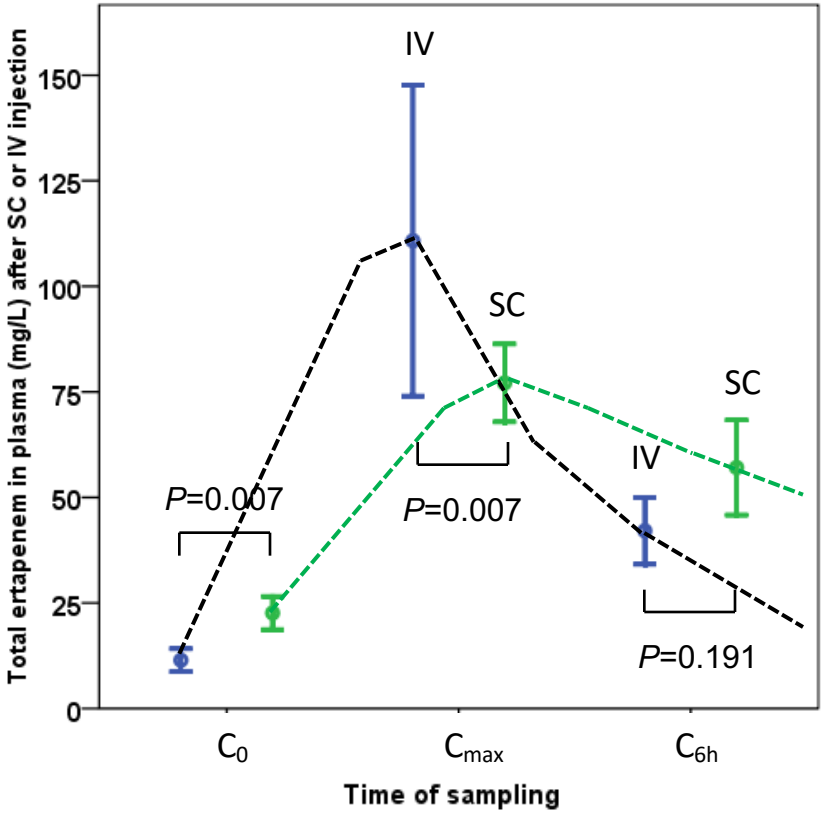
Hors AMM

Pas d'injection SC directe

J Infect. 2012 Dec;65(6):579-82. doi: 10.1016/j.jinf.2012.09.004. Epub 2012 Sep 12.

Prolonged subcutaneous high dose (1 g bid) of Ertapenem as salvage therapy in patients with difficult-to-treat bone and joint infection.

Ferry T, Sénéchal A, Gagnieu MC, Boibieux A, Laurent F, Perpoint T, Tod M, Chidiac C.



17 patients

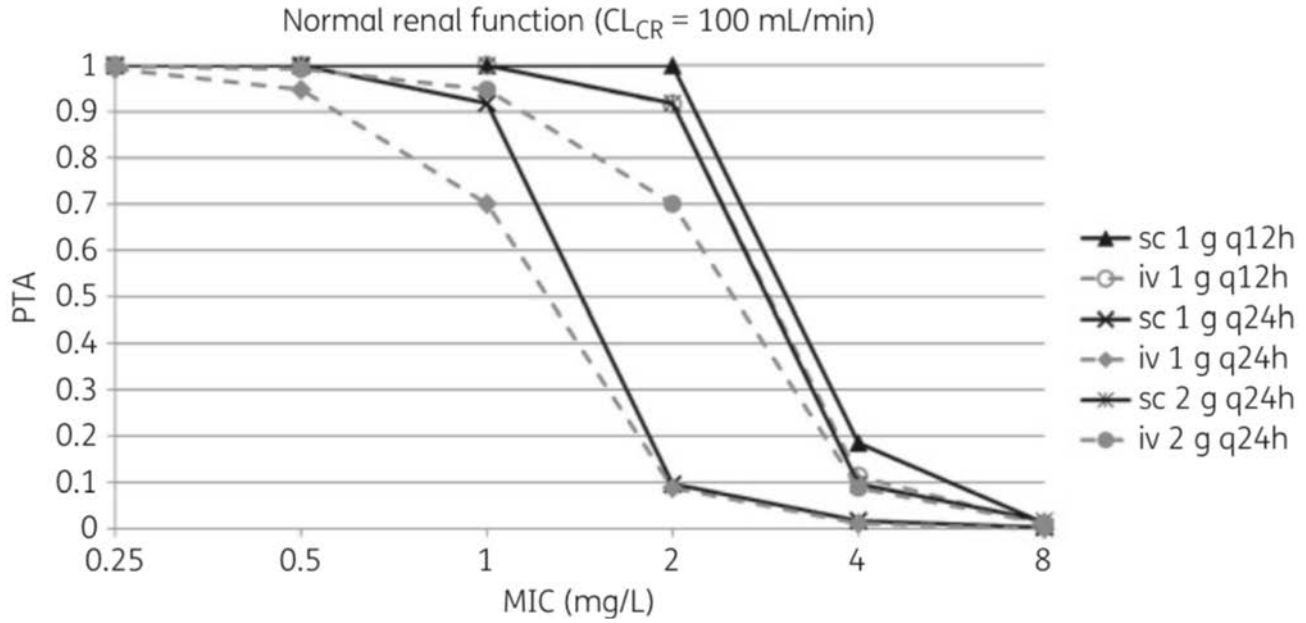
Durée moyenne de 3 mois

Plus de 1000 injections SC

***t*1/2 estimée à 5,9h (IQR 5,1-7,6)**
3,8 h pour 1g IV 1x/j

Population pharmacokinetics and probability of target attainment of ertapenem administered by subcutaneous or intravenous route in patients with bone and joint infection

Sylvain Goutelle[1–3]*, Florent Valour[2,4,5], Marie-Claude Gagnieu[6], Frédéric Laurent[2,5], Christian Chidiac[2,4,5] and Tristan Ferry[2,4,5] on behalf of the Lyon Bone and Joint Infection Study Group†



Journal of Antimicrobial Therapy 2017

Daptomycine et os

Données PK

- Forte liaison protéique (90%)
- Seule la forme libre pénètre dans l'intertitium du tissu osseux
- Faible pénétration ratio os/sérum 0.1

Landersdorfer *Clin Pharmacokinet* 2009

13 volontaires sains

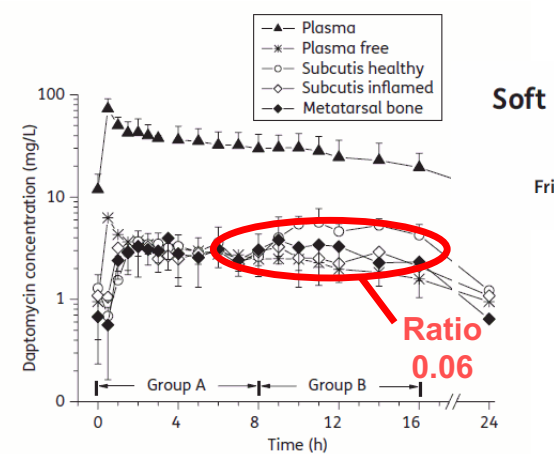
	C_{max} plasmatique	Concentration osseuse	Concentration synoviale
Médiane [extrèmes], mg/l	71,3 [39,4-110,3]	3,1 [1,4-5,7]	22,4 [13,1-35,0]

8 mg/kg
1 injection

H+7

Ratio
0.04

Chirouze et al. *ICAAC* 2011 A1-1745



Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections

Friederike Traunmüller[1,2]†, Michael V. Schintler[1]†, Julia Metzler[1], Stephan Spendel[1], Oliver Mauric[2], Martin Popovic[2,3], Karl Heinz Konz[4], Erwin Scharnagl[1] and Christian Joukhadar[1,2,5,6]*

J Antimicrob Chemother 2010

6 mg/kg
Au plateau

RESEARCH ARTICLE Open Access

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

BMC Infectious Diseases 2016

Patient characteristics

43 patients (61±17 years) received daptomycin

- Mean dose of **8 ±0.9 mg/kg/d (⅓ received > 8 mg/kg/d)**
- Mean duration of **81 ±59 days**

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- Most patients had **chronic implant-associated BJI**
- Criteria for **complexity**:
  - Intolerance to a first line antimicrobial therapy in 42 patients (98%)
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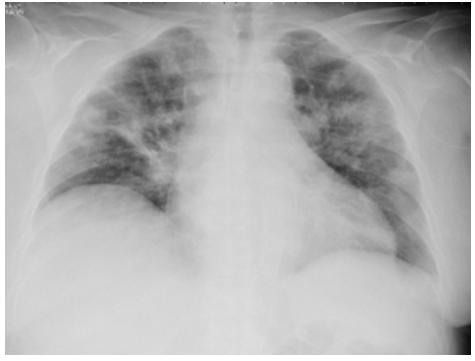
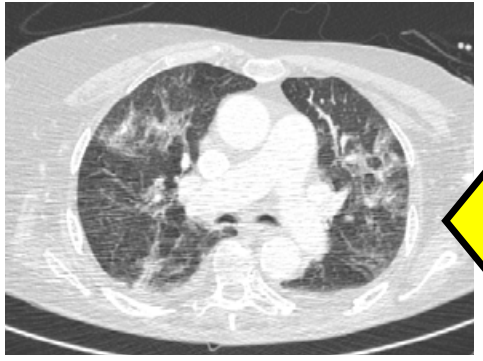
- **Microbiology**:
  - Coagulase-negative staphylococci in 32 patients (74%)
  - *S. aureus* in 11 patients (26%)
  - *P. acnes* in 8 patients (19%)
- Daptomycin was mainly **used in combination** for targeting the Gram-positive isolate
  - Fosfomycin in 15 patients [35%]
  - Rifampin in 9 patients [21%]
  - Clindamycin in 5 patients [12%])

Serious adverse events leading to daptomycin discontinuation

Patient	Dose (mg/kg/d)	Associated antibiotic	Serious adverse event	SAE onset (days)	C_{min} at SAE onset (mg/L)
1	9	Rifampin	Neutropenia	73	-
2	7	Rifampin	Pneumonia Hypereosinophilia	92	-
3	8	Rifampin	**Eosinophilic pneumonia**, **Hypereosinophilia**, **Rhabdomyolysis**	**6**	**134**
4	9	None	**Eosinophilic pneumonia**, **Hypereosinophilia**	**23**	**38**
5	8	Linezolid	Acute renal failure	8	-





Overdose ???

Efficacy

- **<u>Treatment failure:</u>**
  - Occurred in 9 patients (23%, all with implant-associated BJI)
  - during a prolonged follow-up (mean 387 days)

Risk-factors for treatment failure

Variable	N (%)	unadjusted HR (95% CI)	*p* value
Age (per 10 years)	-	**1.89 (1.03-3.47)**	**0.041**
Male sex	23 (59)	1.48 (0.25-1.48)	0.245
Obesity	12 (31)	1.06 (0.93-1.06)	0.932
ASA score	-	1.11 (0.79-1.11)	0.787
Smoking	13 (33)	0.91 (0.23-3.65)	0.896
Implant associated BJI	33 (85)	27.8 (0.02-40422.69)	0.371
Chronic BJI	5 (13)	1.15 (0.14-9.22)	0.894
Fistula	14 (36)	2.94 (0.60-14.43)	0.185
Relapsing BJI	15 (63)	5.50 (0.69-44.02)	0.108
S. aureus	11 (28)	0.59 (0.12-2.89)	0.517
No or non-optimal surgery	**15 (38)**	**3.63 (0.91-14.73)**	**0.068**
Previous treatment with glycopeptides	34 (87)	25.47 (0.01-142518.48)	0.462
Glycopeptide-resistant isolate	20 (51)	2.965 (0.70-12.58)	0.141
Daptomycin ≤ 8 mg/kg/d	26 (67)	0.676 (0.18-2.55)	0.563
Daptomycin discontinuation for SAE	**5 (12)**	**4.680 (1.14-19.17)**	**0.032**

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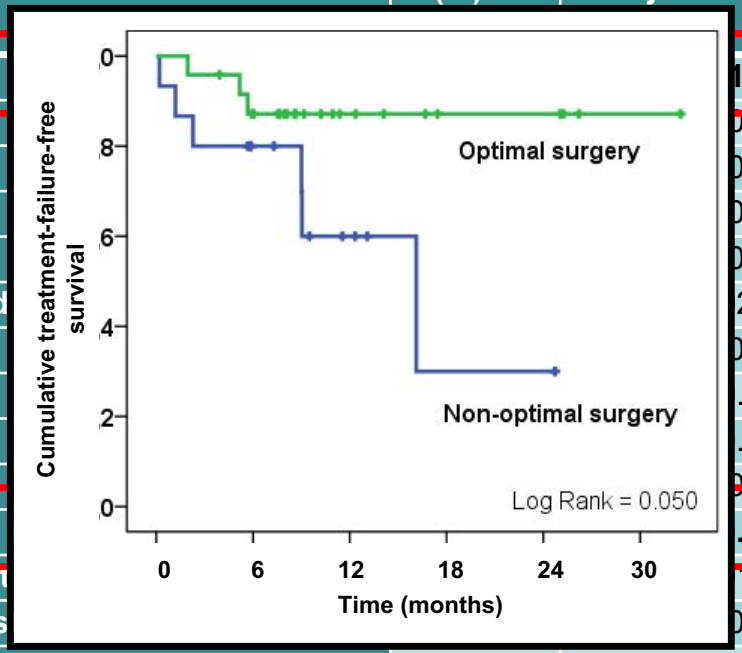

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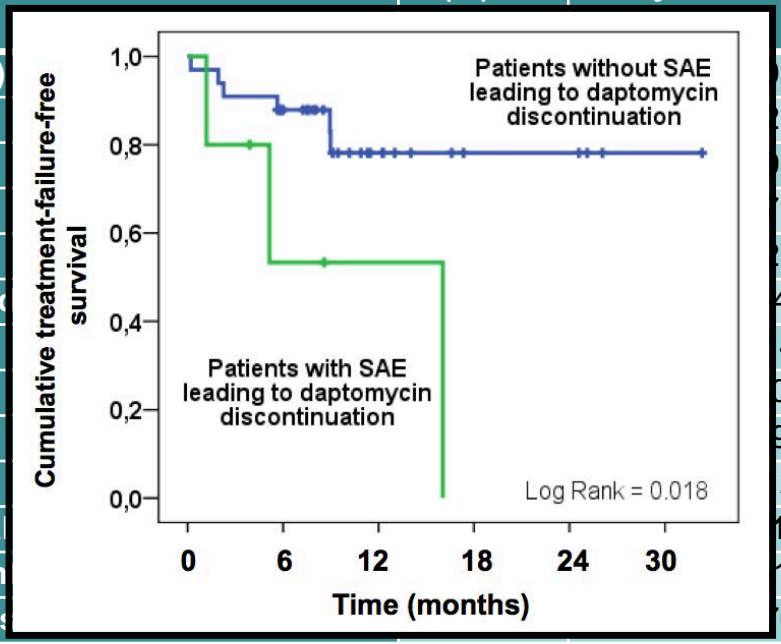
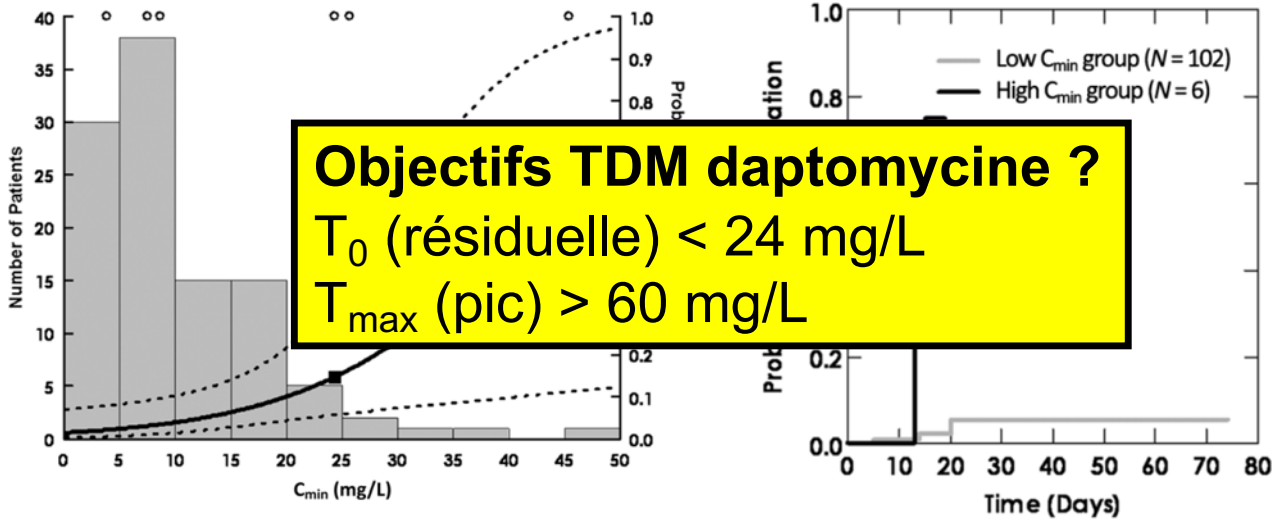


Daptomycin Exposure and the Probability of Elevations in the Creatine Phosphokinase Level: Data from a Randomized Trial of Patients with Bacteremia and Endocarditis

Sujata M. Bhavnani, Christopher M. Rubino, Paul G. Ambrose, and George L. Drusano

Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York



Objectifs TDM daptomycine ?

T_0 (résiduelle) < 24 mg/L

T_{max} (pic) > 60 mg/L

Clinical Infectious Diseases 2010;50(12):1568–1574

IOA complexe

Dosage plasmatique de la DAPTOMYCINE

Méthode : chromatographie liquide couplée à un détecteur à barrette de diodes (LC-DAD)

Posologie : 500 mg
Poids du patient 52 kg
Soit : 9.61 mg/kg/jour
Durée de la perfusion :
Date de début de traitem
Date et heu

Faut-il faire du TDM de la daptomycine
Tolérance / efficacité ?

	Temps	Daptomycine
Concentrations	T0	21.6 mg/L
Concentrations	T37'	99.1 mg/L
Concentrations	T5H27	36.4 mg/L

Valeurs estimées & Interprétation

Estimation ASC de 0 à 24 h : 1217 mg.h/L
Estimation t1/2 terminal : 11.4 h

Estimation C maximale (fin de perf) = 104 mg/L (Potentiel d'efficacité > 60 mg/L)
Estimation C résiduelle à T+24h = 22 mg/L (Potentiel de toxicité > 24 mg/L)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Généricué en 2018

Pharmacokinetic Variability of Daptomycin during Prolonged Therapy for Bone and Joint Infections

Sylvain Goutelle,[a,b,c] Sandrine Roux,[d] Marie-Claude Gagnieu,[g] Florent Valour,[d] Sébastien Lustig,[e] Florence Ader,[d,e,f] Frédéric Laurent,[b,e,f] Christian Chidiac,[d,e,f] Tristan Ferry,[d,e,f] on behalf of the Lyon Bone and Joint Infections Study Group

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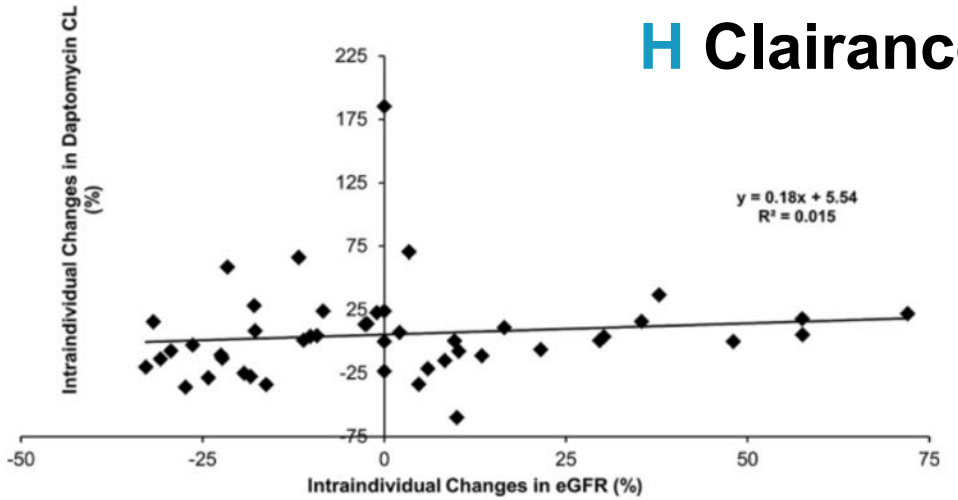
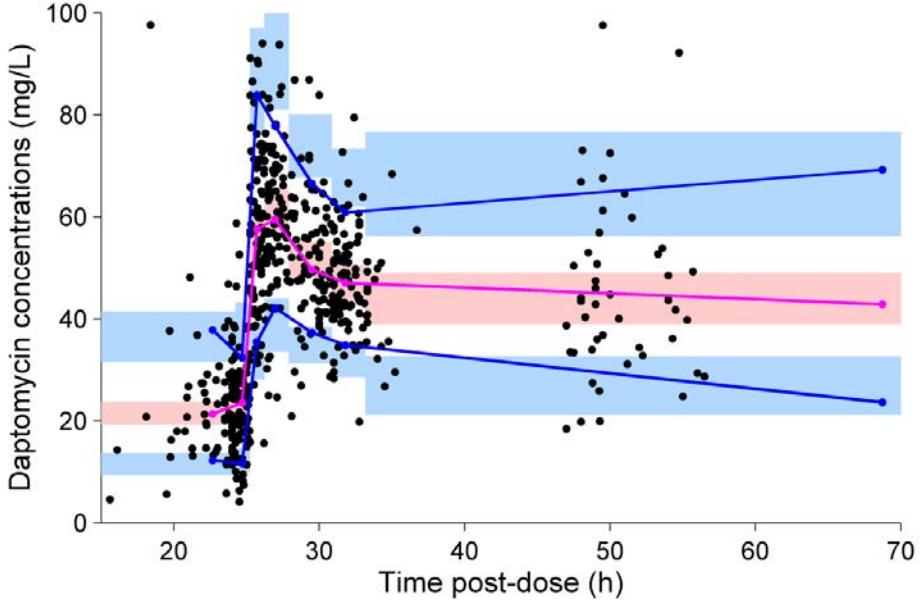


FIG 2 Plot of individual changes in daptomycin clearance over the therapeutic drug monitoring period versus corresponding changes in renal function ($n = 46$ pairs).

Genetic polymorphisms of ABCB1 (P-glycoprotein) as a covariate influencing daptomycin pharmacokinetics: a population analysis in patients with bone and joint infection

Romain Bricca[1], Sylvain Goutelle[2,3,4*], Sandrine Roux[1], Marie-Claude Gagnieu[5], Agathe Becker[1], Anne Conrad,[1,3,6] Florent Valour[1,3,6], Frederic Laurent,[3,6] Claire Triffault-Fillit[1], Christian Chidiac[1,3,6] and Tristan Ferry[1,3,6], on behalf of the Lyon BJI study group†



JAC 2018

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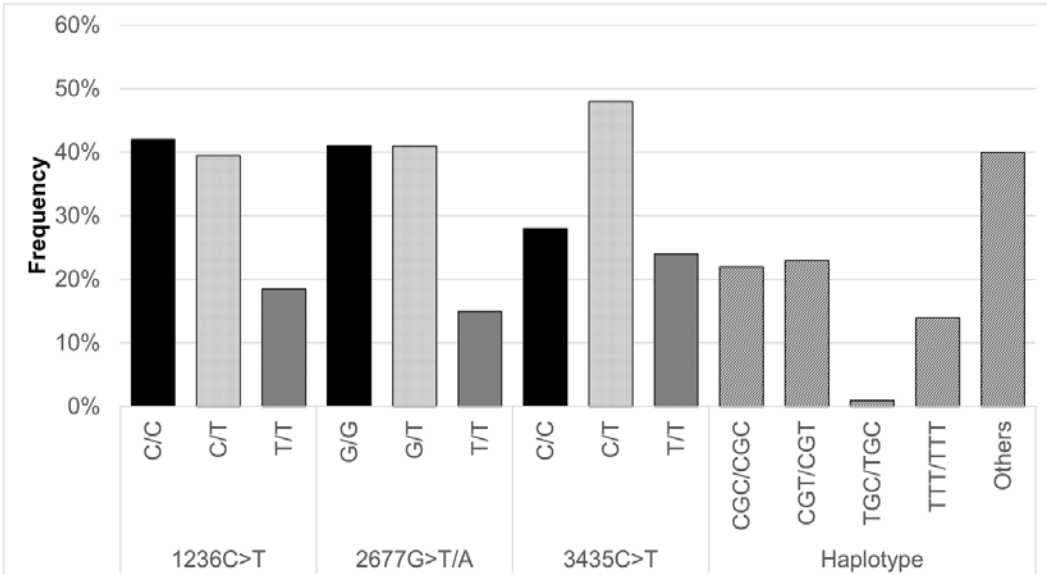

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- Daptomycin central volume of distribution (V1) was allometrically scaled to body weight and **was 25% lower in patients with homozygous CGC ABCB1** haplotype than in patients with any other genotype

- Simulations performed with the model showed that **sex** and **P-gp haplotype** may influence the probability of target attainment for high MIC values,

JAC 2018

Daptomycin dosage	Sex / ABCB1 haplotype	Cmax (mg/L)	Cmin (mg/L)	AUC (mg.h/L)	PTA *f*AUC/CMI ≥ 66	PTA fC_{max}/CMI ≥ 12	PTA C_{min} ≥ 24.3 mg/L
6 mg/kg	F / other	55.1 ± 8.5	16.9 ± 5.9	735 ± 159	0.626	0	0.11
	M / other	49.9 ± 7.7	12.1 ± 4.9	601 ± 133	0.278	0	0.017
	F / CGC	63.0 ± 9.5	14.9 ± 5.9	740 ± 164	0.63	0	0.079
	M / CGC	57.7 ± 8.7	10.3 ± 4.7	603 ± 135	0.281	0	0.012
8 mg/kg	F / other	73.4 ± 11.4	22.5 ± 7.9	980 ± 212	0.967	0.002	0.365
	M / other	66.6 ± 10.3	16.1 ± 6.5	801 ± 178	0.761	0.001	0.112
	F / CGC	83.9 ± 12.6	19.9 ± 7.9	987 ± 219	0.968	0.016	0.256
	M / CGC	76.9 ± 11.6	13.8 ± 6.2	804 ± 181	0.763	0.006	0.063
10 mg/kg	F / other	91.8 ± 14.2	28.1 ± 9.9	1225 ± 265	0.998	0.03	0.611
	M / other	83.2 ± 12.9	20.1 ± 8.1	1001 ± 222	0.972	0.01	0.264
	F / CGC	104.9 ± 15.8	24.9 ± 9.9	1233 ± 273	0.998	0.239	0.465
	M / CGC	96.2 ± 14.5	17.2 ± 7.8	1005 ± 226	0.972	0.142	0.17

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MAJOR ARTICLE

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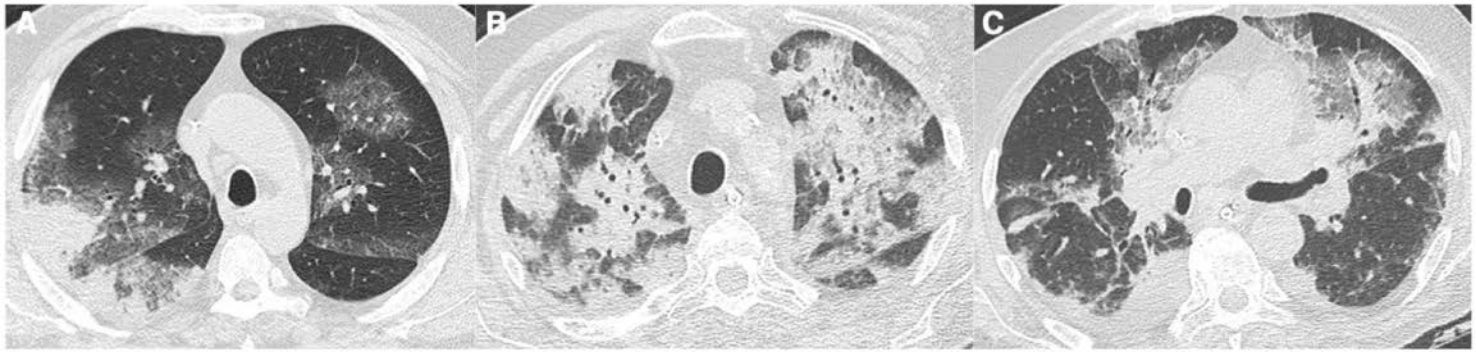

Figure 1. Different computed tomography (CT) patterns of daptomycin-induced eosinophilic pneumonia, with specific signs on CT scan based on criteria by Jeong et al [15]. *A*, Diffuse ground glass opacities and air-space consolidations compatible with chronic eosinophilic pneumonia. *B* and *C*, Same patient with multiple bilateral infiltrates compatible with chronic eosinophilic pneumonia (*B*) and central ground glass opacities with interlobular septal lines suggestive of acute eosinophilic pneumonia (*C*).

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Table 3. Number of Positive Criteria by Definitions of Daptomycin-Induced Eosinophilic Pneumonia, Depending on the Previous Published Criteria, and Depending on the French Referral Centre for Complex Bone and Joint Infections (CRIOAc) Lyon Criteria Proposed Here

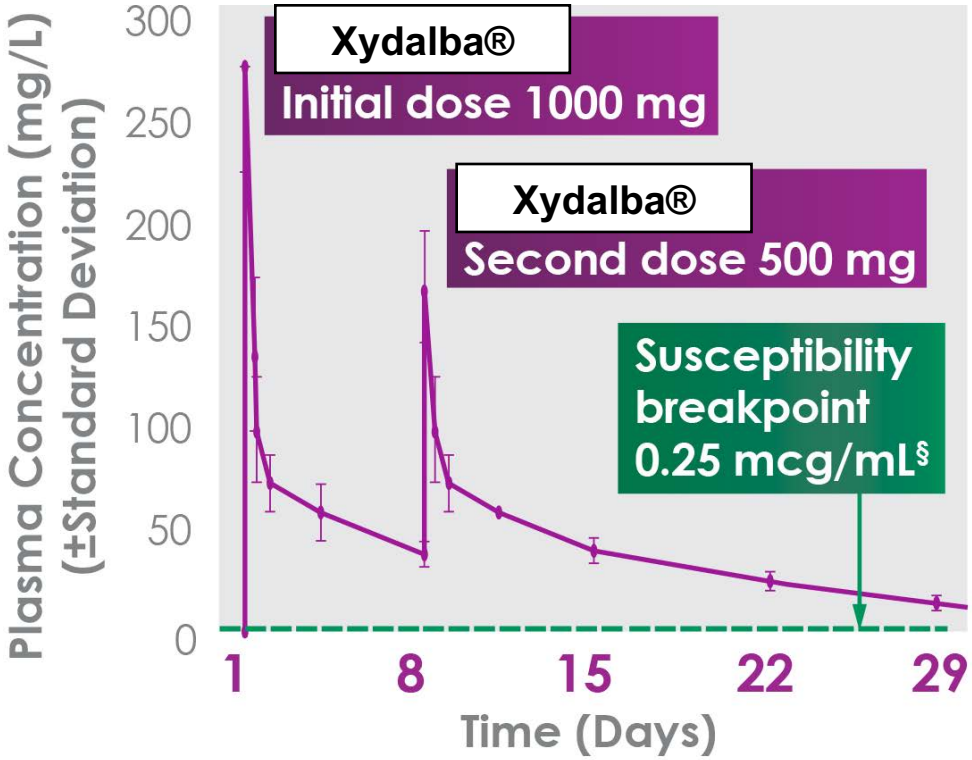
Patient ID	FDA [16] No. of Criteria in a Total of 6; Final Diagnosis of DIEP	Solomon and Schwarz [17] No. of Criteria in a Total of 5; Final Diagnosis of DIEP	Phillips et al [18] No. of Criteria in a Total of 6; Final Diagnosis of DIEP	Kim et al [19] Final Diagnosis of DIEP[a]	Lyon Algorithm Final Diagnosis of DIEP[a]
1	5; No	4; No	6; Yes	Probable	Yes, definite
2	4; No	3; No	6; Yes	Probable	Yes, definite
3	4; No	3; No	4; No	Probable	Probable
4	5; No	3; No	6; Yes	Probable	Yes, definite
5	3; No	3; No	4; No	Possible	Probable
6	5; No	3; No	5; No	Probable	Yes, definite
7	5; No	3; No	6; Yes	Probable	Yes, definite
8	4; No	3; No	6; Yes	Probable	Yes, definite
9	3; No	3; No	4; No	Possible	Yes, definite
10	5; No	3; No	5; No	Probable	Yes, definite
11	4; No	3; No	5; No	Probable	Probable
12	5; No	3; No	6; Yes	Probable	Yes, definite
13	5; No	3; No	6; Yes	Probable	Yes, definite
14	4; No	3; No	4; No	Possible	Yes, definite
15	4; No	3; No	5; No	Probable	Yes, definite
16	5; No	3; No	6; Yes	Probable	Yes, definite
17	4; No	3; No	4; No	Possible	Yes, definite

Red color indicates patients without the diagnosis of DIEP; orange color indicates patients with probable or possible diagnosis of DIEP; green indicates patients with a final diagnosis of DIEP.

Abbreviations: DIEP, daptomycin-induced eosinophilic pneumonia; FDA, United States Food and Drug Administration.

[a]Definite, probable, possible, or unlikely.

Dalbavancine (Xydalba®)



Tédizolide (Sivextro®)

- Comprimé à 200 mg/j
- « La dose recommandée est de 200 mg une fois par jour pendant 6 jours »
- Indication : infection peau et des tissus mous

J. Bone Joint Infect., 6, 337–346, 2021
https://doi.org/10.5194/jbji-6-337-2021

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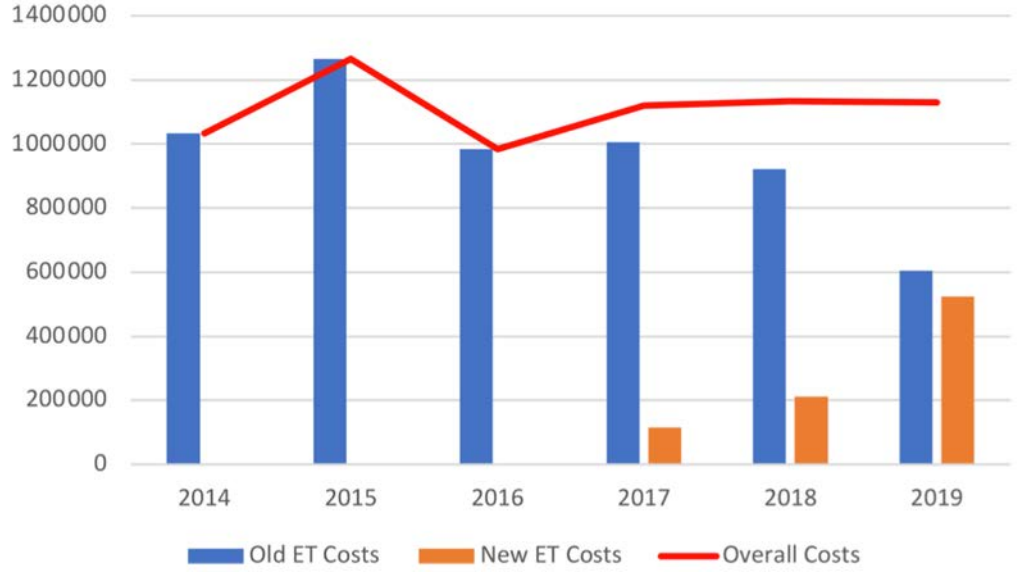

Figure 2. Costs (EUR) related to old and new expensive treatments and total costs. ET – expensive treatment.

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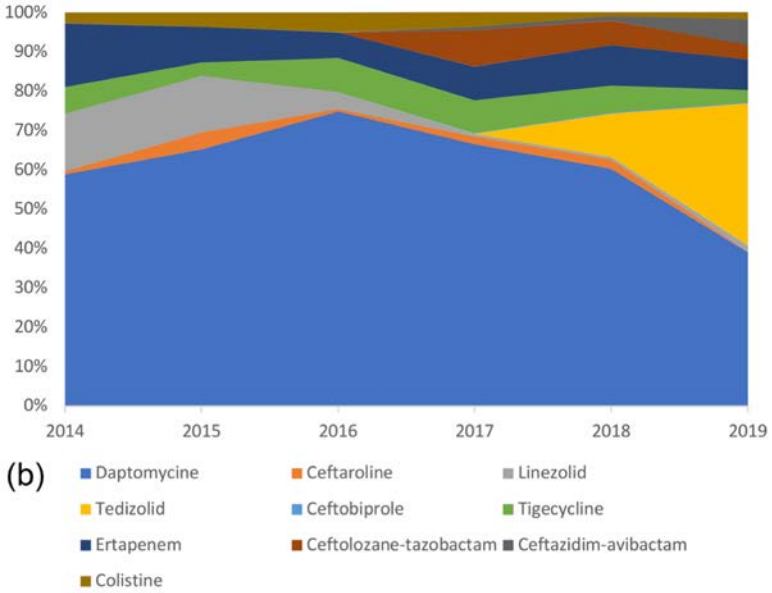
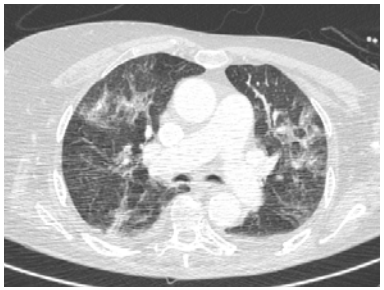
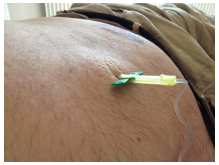


Figure 3. Cumulative **(a)** and proportional **(b)** costs (EUR) related to expensive treatments, by molecule.

Conclusion



- Pratique **fréquente**
- **Responsabilité** du prescripteur
- Nécessité de **validation en RCP**
- Les antibiothérapies hors AMM apparaissent dans les **recommandations**
- Importance de ce que la **recherche** apporte dans la pratique et l'évaluation de l'exposition
- **Coût** important
- Importance des **génériques**



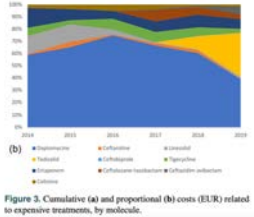


Figure 3. Cumulative (a) and proportional (b) costs (EUR) related to expensive treatments, by molecule.

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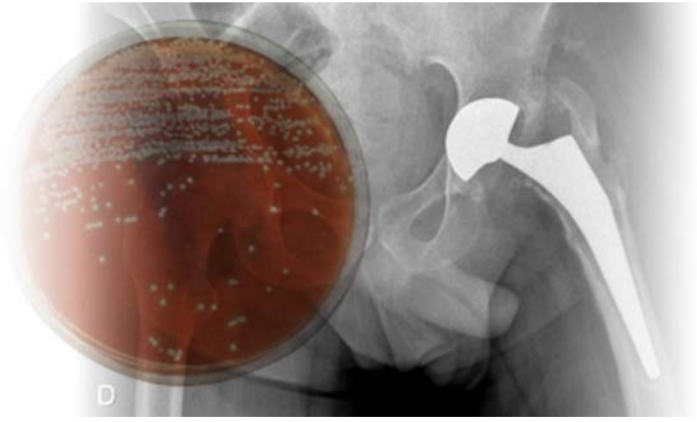

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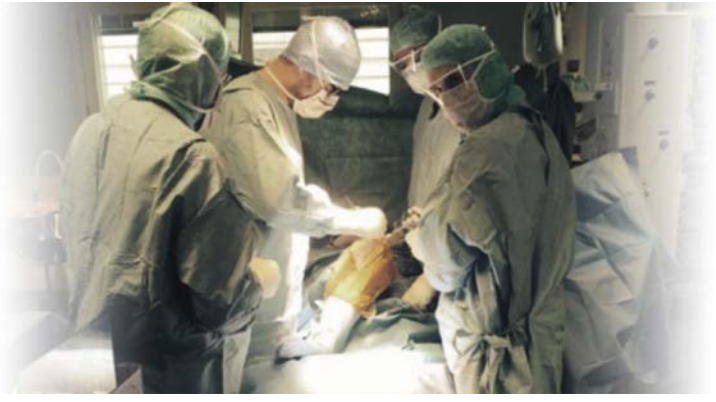

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