

# Daptomycin > 6 mg/kg/day in Patients with Complex Bone and Joint Infection: Prospective Cohort Study in a Regional Reference Center

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Hospices Civils de Lyon

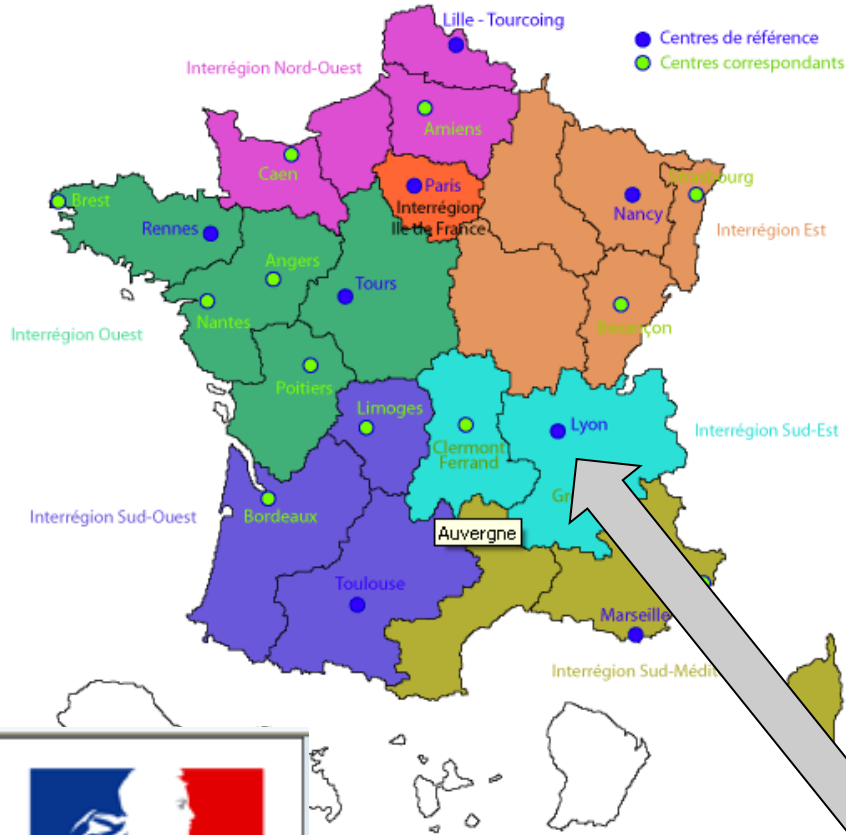


# Background

- 9 regional reference centers in France

- **Complex BJI in a patient**

- With relapsing BJI
- With intolerance to a first line antimicrobial therapy
- Requiring surgery with large bone resection and/or reconstruction
- Infected with a glycopeptide-resistant Gram-positive isolate



**Lyon metropolis**  
2,000,000 inhabitants

**Rhône-Alpes Auvergne region**  
7,500,000 inhabitants



Liberté • Égalité • Fraternité  
RÉPUBLIQUE FRANÇAISE

MINISTÈRE  
DES AFFAIRES SOCIALES  
ET DE LA SANTÉ



# Background

- Daptomycin is approved for the treatment of infective **endocarditis** (6 mg/kg/d), but not for BJI  
*Fowler V New Engl J Med 2006;355:653-665*
- Daptomycin is an **alternative option** for the treatment of prosthetic joint infection (6 mg/kg/d) ***IDSA guidelines***  
*Osmon et al. Clin Infect Dis 2013;56:e1-25*
- Doses **>6 mg/kg/d (i.e. 8 mg/kg/d)** seem to be **more appropriate** for optimal daptomycin concentration in bone  
*Montange D et al. Antimicrob Agent Chemother 2014;58:3991-3996*
- Data from the Eu-core® study (sponsored by novartis) **support the use of daptomycin in BJI**  
*Seaton RA et al. J Antimicrob Chemother 2013;68:1642-1649*

- **Prospective cohort** study including **consecutive** patients (creatinine clearance >30 mL/min) **with complex BJI**
- Requiring **daptomycin as salvage therapy** and receiving **> 6 mg/kg/d** in 2010-2013
- **All adverse events** were prospectively collected
- Daptomycin  $C_{\min}$  was determined in plasma **every month** **and at the onset of serious adverse event** from October 2012 (overdose was defined as a  $C_{\min}$  **>24 mg/L**)  
*Bhavnani SM et al. Clin Infect Dis 2010;50:1568-74*
- Cox univariate analysis and Kaplan Meier curves were used to **determine risk-factors for treatment failure**



# Patient characteristics



**43 patients (61 ± 17 years) received daptomycin**

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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 <sub>min</sub> at SAE onset (mg/L)
1	9	Rifampin	Neutropenia	73	-
2	7	Rifampin	<u>Pneumonia</u> Hypereosinophilia	92	-
3	8	Rifampin	<u>Eosinophilic pneumonia</u> , Hypereosinophilia, Rhabdomyolysis	6	134
4	9	None	<u>Eosinophilic pneumonia</u> , Hypereosinophilia	23	38
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**18 other patients for whom C<sub>min</sub> was performed (totaling 52 C<sub>min</sub>)**



15 patients with C<sub>min</sub> always <24mg/L

3 patients with asymptomatic mild transient C<sub>min</sub> ≈24-30 mg/L

# Efficacy

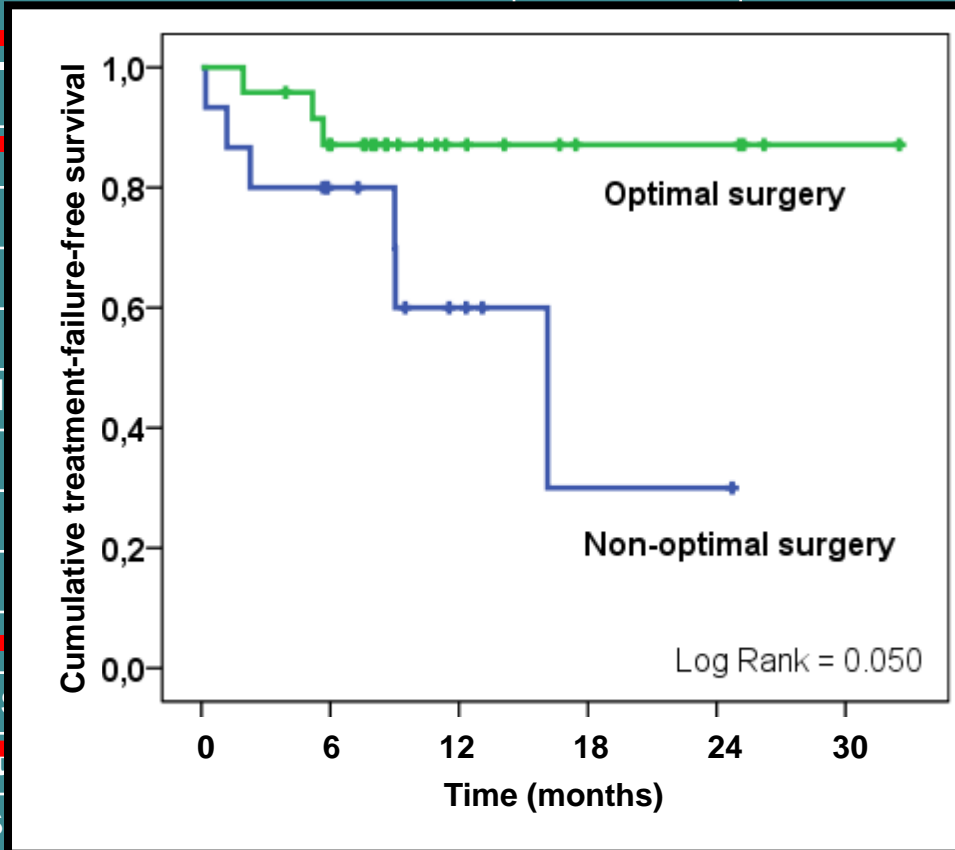
- **4 patients were excluded** from the efficacy analysis:
  - No deep samples available
  - One deep sample positive for coagulase-negative staphylococci
- **Surgery:**
  - Could not be performed in 2 patients (5%) with severe comorbidities
  - Was considered as optimal in 24 other patients (62%)
- **Treatment failure:**
  - 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)	-	<b>1.89 (1.03-3.47)</b>	<b>0.041</b>
Male sex	25 (39)	1.48 (0.23-1.48)	0.243
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
Surgical	11 (28)	0.59 (0.12-2.89)	0.517
<b>No or non-optimal surgery</b>	<b>15 (38)</b>	<b>3.63 (0.91-14.73)</b>	<b>0.068</b>
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 $\leq$ 8 mg/kg/d	26 (67)	0.676 (0.18-2.55)	0.563
Daptomycin discontinuation for SAE	<b>5 (12)</b>	<b>4.680 (1.14-19.17)</b>	<b>0.032</b>

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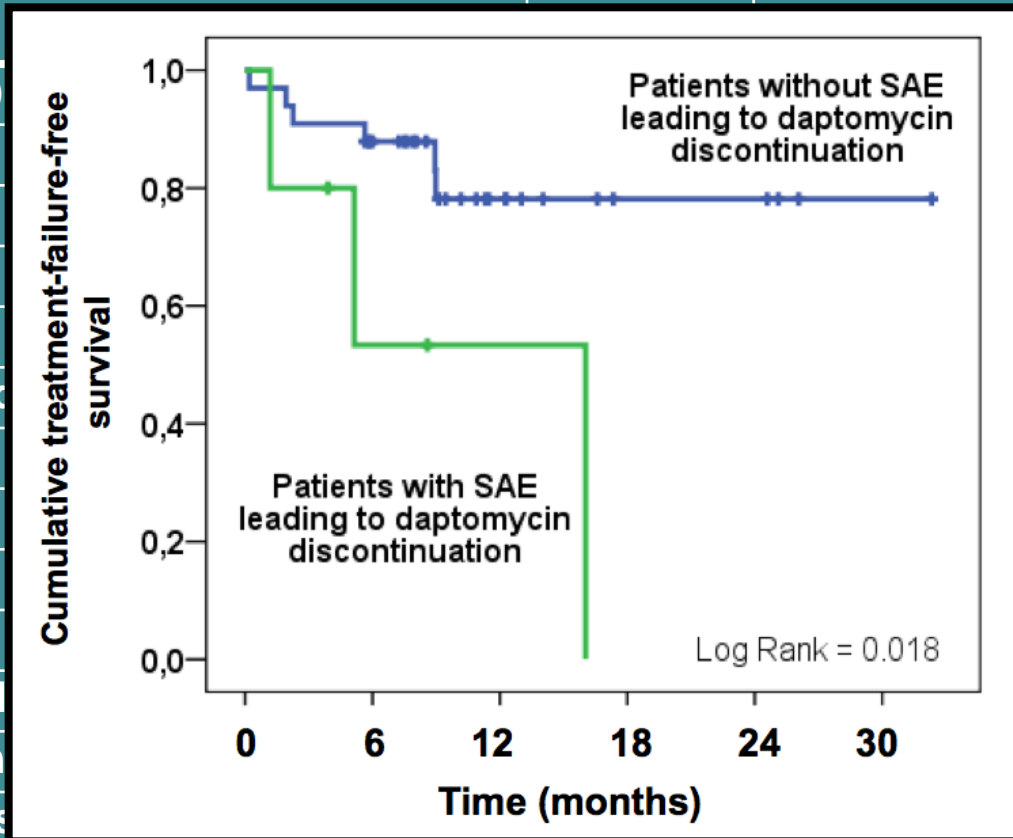


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Age (per 10 years)	-	<b>1.89 (1.03-3.47)</b>	<b>0.041</b>
Male sex	23 (59)	1.48 (0.25-1.48)	0.245
Obesity	12 (31)	1.06 (0.93-1.06)	0.932
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# Conclusion

- **Optimal surgery** in tertiary reference centers is essential for the prognosis of complex BJI
- The use of prolonged high doses of daptomycin was associated with a **high success rate**
- Daptomycin was safe, but we recorded a **higher incidence of eosinophilic pneumonia than expected (5% vs. 0.5% in Eurocore<sup>sm</sup>)**, which was associated with **overdose**
- **Therapy-drug monitoring of daptomycin** could be useful for patients with complex BJI to:
  - Limit occurrence of potential dose-dependent SAE
  - Avoid daptomycin withdrawal



# Lyon BJI study group

**Physicians** – Tristan Ferry, Thomas Perpoint, André Boibieux, François Biron, Florence Ader, Judith Karsenty, Florent Valour, Fatiha Daoud, Johanna Lippman, Evelyne Braun, Marie-Paule Vallat, Patrick Mialhes, Christian Chidiac

**Surgeons** – Sébastien Lustig, Philippe Neyret, Olivier Reynaud, Vincent Villa, Jean-Baptiste Bérard, Frédéric Dalat, Olivier Cantin, Romain Desmarchelier, Michel-Henry Fessy, Cédric Barrey, Francesco Signorelli, Emmanuel Jouanneau, Timothée Jacquesson, Pierre Breton, Ali Mojallal, Fabien Boucher, Charles Hirtum, Hristo Shipkov

**Microbiologists** – Frederic Laurent, François Vandenesch, Jean-Philippe Rasigade, Céline Dupieux;

**Nuclear Medicine** – Isabelle Morelec, Marc Janier, Francesco Giammarile

**PK/PD specialists** – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle

**Clinical Research Assistant** – Eugénie Mabrut



Hospices Civils de Lyon





Optimal surgery?



Necrotic infected bone



Large bone resection



Cement



Bone grafting



2 years  
Functional cure



Antimicrobial therapy



*E. faecalis*  
*Streptococci*  
*F. magna*



Microbiological cure



Free flap

2<sup>nd</sup> stage  
Consolidation



glycopeptide-resistant  
*S. epidermidis*

**SUPERINFECTION**

High Dose Daptomycin Therapy

