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High-dose daptomycin in patients with infective endocarditis or sternal wound infections

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To the Editor,

Infective endocarditis (IE) and sternal wound infections (SWI) following heart surgery are severe diseases associated with high rates of mortality and significant morbidity¹. IE and SWI are most often caused by gram-positive organisms. Vancomycin is the standard therapy but it has been associated with a risk of renal failure and suboptimal outcomes, leading to the need of alternative antimicrobial agents^{2,3}. In this retrospective study (2009-2016), we reviewed the prescriptions of daptomycin in a French tertiary-care referral center for IE and SWI to assess the safety and outcomes among patients treated with high-dose daptomycin (HDD). We defined HDD as the use of daptomycin at a dose superior to 6 mg/kg/day in patients with normal renal function⁴. IE was defined according to European guidelines² and SWI was defined as need for reoperation for local or systemic infection involving the sternotomy scar⁵.

A total of 71 patients, 45 males (63%), of median age 66 years (IQR 56-76) were included. Half of them (48%) were admitted to an intensive care unit (ICU). Forty-seven patients (66%) had an IE (81% left-sided IE, 13% right-sided IE, 6% Cardiac Implantable Electronic Devices (CIED)). Twenty-four patients (34%) had a sternal wound infection (54% superficial SWI, 46% deep SWI). Seventy-two percent of isolated pathogens were Staphylococci (61% coagulase negative, 39% *Staphylococcus aureus*), with a median MIC of 1.5 mg/L (IQR 1.5-2) to vancomycin and 0.22 mg/L (IQR 0.125-0.38) to daptomycin (Table 2). Twenty-four patients with IE (51%) underwent surgical valve replacement and all patients with SWI underwent surgical debridement.

Sixty-four patients received daptomycin with microbiologically documented infections and seven as empirical therapy. The main indication for daptomycin use was acute kidney injury (41%), clinical failure of the previous antibiotic therapy (27%) and high vancomycin MIC (15%). Five patients (7%) received daptomycin because they did not tolerate vancomycin (two DRESS syndromes, one venous toxicity and one red-man syndrome) or aminoglycoside (one case of deafness). The median daptomycin daily dose was 8 mg/kg (IQR, 6.6-10 mg/kg), similar in IE and SWI patients. Thirty percent of the patients (14 patients with IE and 7 patients with SWI) received a daily dose \geq 10 mg/kg. The median duration of HDD was 21 days (IQR, 11.5-32.5 days). Plasma daptomycin concentration was measured in 40% of the patients, mostly because of renal failure; the median peak concentration was 79 μ g/mL (IQR, 74-94 μ g/mL) and the median trough concentration was 22 μ g/mL (IQR, 10-31 μ g/mL).

Overall, 80% of patients (n=57; 35 IE, 22 SWI) survived and were discharged alive and 20% (n=14, 12 IE, 2 SWI) died during their hospitalization. No death was linked to daptomycin use or linked to therapeutic failure or persistence of the initial causative pathogen. One patient presented a clinical and microbiological failure whilst on daptomycin. This 103-year old patient had a tricuspid IE caused by MRSA with a MIC of 1.5 mg/L to vancomycin and 0.5 mg/L to daptomycin. He was treated with daptomycin monotherapy 6 mg/kg/day and after 7 days the same MRSA was found on a blood culture. He was switched to vancomycin and fosfomycin with microbiological and clinical success.

Median eGFR did not seem to differ between baseline (44 mL/min, IQR 31-78) and end of daptomycin therapy (49 mL/min, IQR 34-73). Renal toxicity fulfilling RIFLE criteria occurred in 7 patients (10%) during the treatment. Renal impairment was compatible with a Risk grade in 5 patients, Injury grade in 1 patient and end-stage renal disease (ESRD) grade in 1 patient. All patients had a concomitant etiology of acute kidney injury and no renal toxicity was attributed to daptomycin. Creatine kinase (CK) was measured at baseline and followed in 77% of patients (n=55). Only 3 patients (5%) presented a CK increase compatible with muscle toxicity after 1 week of daptomycin at a respective dose of 10.4 mg/kg/day, 10 mg/kg/day and 8 mg/kg/day. The first patient had a CK increase (from 26 to 1036 IU/mL over 3 weeks) and an acute kidney injury whilst on daptomycin. He presented concomitantly a hemorrhagic colitis complicated by hypovolemic shock, multiple organ failure and death. The second patient developed a septic shock due to a urinary tract infection in the UCI. The third patient had a superficial SWI with no concomitant etiology of CK increase. CK increased from 13 IU/mL to 2836 IU/mL after 2 weeks of daptomycin, with no muscle symptoms nor modification of blood creatinine. As the planned duration of antibiotic therapy was 2 weeks, daptomycin was stopped after completion of therapy, followed by a progressive normalization of CK values.

Daptomycin was prematurely discontinued, replaced by vancomycin due to a suspected AE in 3 patients. The first patient was the one who died of a hemorrhagic colitis. The second patient had an unexplained fever that stopped after the discontinuation of daptomycin. The third patient presented unexplained thrombocytopenia, daptomycin and proton-pump inhibitors were stopped, followed by a normalization of platelet values.

This observational study of 71 patients with severe infections and comorbidities adds to the evidence that HDD is effective and well-tolerated in both IE and SWI. Whether daptomycin should be

considered as a first-line therapy in patients with severe gram-positive heart or mediastinal infections remains to be determined with the help of randomized controlled trials.

Table 1: Antibiotic therapy and outcomes of 71 patients treated with high-dose daptomycin for infective endocarditis and sternal wound infections

	Patients
Infective endocarditis, n(%)	47 (66)
Left-sided	38
Right-sided	6
Native valve	24
Biological prosthetic valve	12
Mechanical prosthetic valve	6
CIED	8
Sternal wound infections, n(%)	24 (34)
Superficial sternal wound infection	13
Deep sternal wound infection	11
Reasons for daptomycin use, n(%)	
Acute kidney injury	29 (41)
Other prior antibiotic side-effects	5 (7)
Prior antibiotic failure	19 (27)
High vancomycin MIC	11 (15)
Empirical choice	7 (10)
Daptomycin dose (mg/kg), median (IQR)	8 (6.6-10)
Daptomycin plasma concentration (mg/L)	
Yes, n(%)	29 (41)
Peak, median (IQR)	79 (75-94)
Residual, median (IQR)	22 (10-31)
No, n(%)	42 (59)
Daptomycin duration (days), median (IQR)	21 (11-32)
Antibiotics associated with Daptomycin, n(%)	
Rifampicin	38 (54)
Aminoglycoside	19 (27)
β -lactam	17 (24)
Fosfomycin	7 (10)
Quinolone	6 (8)
Cyclines	6 (8)
Colimycin	4 (6)
Daptomycin monotherapy	7 (10)
Discontinuation of Daptomycin	
No, n(%)	37 (52)
Yes, n(%)	34 (48)
Antibiotic switch, n	21
Death, n	9
Side-effects, n	3 [†]
Failure, n	1
Outcome	
Clinical recovery, n (%)	57 (80)
IE (n out of 47)	35
SWI (n out of 24)	22
Death, n (%)	14 (20)
Left-sided IE (n out of 38)	8
Native valve, n	5
Bioprosthetic valve, n	2
Mechanical prosthetic valve, n	1
CIED (n out of 8)	3
Right-sided IE (n out of 6)	1
Superficial SWI (n out of 13)	1
Deep SWI (n out of 11)	1

CIED: Cardiovascular Implantable Electronic Devices

[†]: 1 patient had fever, 1 had rhabdomyolysis with acute kidney injury and 1 had thrombocytopenia

Table 2: Microbiology of infective endocarditis and sternal wound infections treated with high-dose daptomycin

Species	IE n = 47 (%)	SWI n = 31† (%)	Methicillin resistance, n (% among species)	Daptomycin MIC in µg/mL, median (IQR)	Vancomycin MIC in µg/mL, median (IQR)
<i>Staphylococci</i>	29 (61)	22 (71)	41 (82)	0.25 (0.13-0.35) (n=27)	1.50 (1.50-2.00) (n=27)
Coagulase-negative <i>staphylococci</i>	11	20	29 (94)	0.19 (0.13-0.25) (n=22)	1.50 (1.50-2.00) (n=20)
<i>Staphylococcus aureus</i>	18	2	12 (63)	0.25 (0.25-0.38) (n=5)	1.50 (1.37-1.62) (n=7)
<i>Streptococci</i>	7 (15)	0	-	0.30 (0.21-0.38) (n=2)	0.75 (0.75-0.75) (n=1)
<i>Enterococci</i>	7 (15)	2 (6)	-	0.56 (0.34-0.78) (n=4)	1.50 (1.00-1.50) (n=5)
<i>Enterococcus faecalis</i>	5	2	-	-	-
<i>Enterococcus faecium</i>	2	0	-	-	-
<i>Propionibacterium acnes</i>	1 (2)	0	-	-	-
Associated gram-negative bacilli	0	4 (13)	-	-	-
<i>Escherichia coli</i>	0	2	-	-	-
<i>Proteus mirabilis</i>	0	1	-	-	-
<i>Pseudomonas aeruginosa</i>	0	1	-	-	-
No pathogen isolated	3 (6)	3 (10)	-	-	-

†: 4 sternal wound infections were polymicrobial

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ETHICS STATEMENT

The Institutional Review Board of Bichat Hospital approved the study protocol and waived the need for informing patients.

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COMPETING INTERESTS

None

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