eP412

Daptomycin for the treatment of infections in overweight and obese patients: results from the European Cubicin® Outcome Registry and Experience

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INTRODUCTION

- Estimated worldwide overweight population: >1.6 billion including ≥25% obese[1]
- Obesity compromises the immune response and is a risk factor for infection-related mortality[2]
- Obesity may be associated with altered tissue distribution and clearance of antibiotics with the potential for increased toxicity or decreased efficacy,[1,2] however, data on dosing requirements in obese are sparse
- A pharmacokinetic study in obese healthy volunteers concluded that daptomycin (DAP) may be dosed based on total body weight with no dose adjustments required solely on obesity[3]
- DAP, a cyclic lipopeptide with bactericidal activity against Gram-positive (Gr+) pathogens, is approved in Europe for the treatment of complicated skin and soft tissue infections (cSSTIs), for right-sided *Staphylococcus aureus* endocarditis (RIE) and for *S. aureus* bacteraemia associated with RIE and cSSTI[4]

PURPOSE

- To evalute the characteristics and clinical outcomes in patients with different body mass index (BMI) using data from the European Cubicin® Outcomes Registry and Experience (EUCORE℠)

METHODS

- EU-CORE℠: a retrospective multinational, multicentre registry across European countries, Russia, Latin America and India; data collection on characteristics and clinical outcomes in patients treated with at least one dose of DAP between January 2006 and April 2012 and with at least 30 days of safety follow-up, using standardised case report forms
- BMI recorded for patients enrolled from July 2010 onwards. Current analysis includes all patients with BMI information available and a BMI of ≥18.5 kg/m². Evaluations according to the following categories:
  - Normal weight: BMI ≥18.5 and <25 kg/m²
  - Overweight: BMI ≥25 and <30 kg/m²
  - Obese: BMI ≥30 kg/m²
- Local investigators assessed clinical outcome at the end of DAP therapy according to the following protocol-defined criteria (**Table 1**)

Table 1. Clinical outcome definitions

Response*		
Success (Cured or Improved)	**Cured** • Clinical signs and symptoms resolved (and/or) • No additional antibiotic therapy necessary (or) • Negative culture at the end of therapy	**Improved** • Partial resolution of clinical signs and symptoms (and/or) • Additional therapy (e.g., oral antibiotics) at the end of therapy
Failure	• Worsening or new/recurrent signs/symptoms (or) • Need for a change in antibiotic therapy (or) • Positive culture reported at the end of therapy	
Non-evaluable	Unable to determine response due to insufficient information	

Statistical analysis

- Odds ratio and 95% confidence interval were calculated using univariate or multivariate logistic regressions analyses. If a factor appeared to be significant at 10% level of significance in univariate analysis, it was included in the multivariate model

RESULTS

- Of the 5551 patients enrolled in the registry, BMI data were available for 1576 (28%) patients and 1501 (27%) patients had a BMI ≥18.5 kg/m². For details on distribution across BMI categories see **Table 2**

Table 2. Distribution of patients across BMI categories

Patient groups	Number of patients (%)
Total patients in current analysis	**1501**
Normal weight (BMI ≥18.5 and <25 kg/m²)	598 (40)
Overweight (BMI ≥25 and <30 kg/m²)	558 (37)
Obese (BMI ≥30 kg/m²)	345 (23)

BMI, body mass index

- Demographic and baseline disease characteristics are shown in **Table 3**
- The majority of patients had significant underlying diseases, most frequently diabetes mellitus and cardiovascular disease; both increasing with increasing BMI

Table 3. Patient demographics and baseline disease characteristics

Parameters, n (%)	Normal weight n=598	Overweight n=558	Obese n=345
Male	368 (62)	357 (64)	172 (50)
Age, mean (SD)	55 (19)	62 (16)	60 (15)
<65 years	383 (64)	284 (51)	189 (55)
≥65 years	214 (36)	274 (49)	155 (45)
Race			
Caucasian	422 (75)	431 (84)	266 (86)
Others#	138 (25)	82 (16)	79 (14)
Body weight (kg), mean (SD)	64 (9)	78 (9)	98 (19)
Renal impairment (CrCl <30 mL/min), n (%)	84 (14)	58 (10)	21 (6)
Patients on renal replacement therapy*	37 (10)	26 (8)	17 (9)
Significant underlying disease (>15% in at least one of the BMI categories)			
Any	501 (84)	473 (85)	319 (93)
Cardiovascular disease	273 (46)	308 (55)	213 (62)
Diabetes mellitus	119 (20)	158 (28)	123 (36)
Oncologic disease	93 (16)	84 (15)	48 (14)
Pulmonary disease	55 (9)	67 (12)	55 (16)
Prior antibiotic use	391 (65)	340 (61)	220 (64)
Penicillin	156 (26)	133 (24)	96 (28)
Glycopeptide	151 (25)	141 (25)	75 (22)
Others	530 (81)	425 (76)	327 (95)

#Others include Asian/Oriental, Black/African American, unknown.
*Includes intermittent haemodialysis, continuous ambulatory peritoneal dialysis and continuous renal replacement therapy

- Treatment failure was the common reason for switching prior antibiotics to DAP in 89% of normal weight, 74% of overweight and 84% of obese patients
- Primary infections are mentioned in **Table 4** and primary pathogens in **Figure 1**

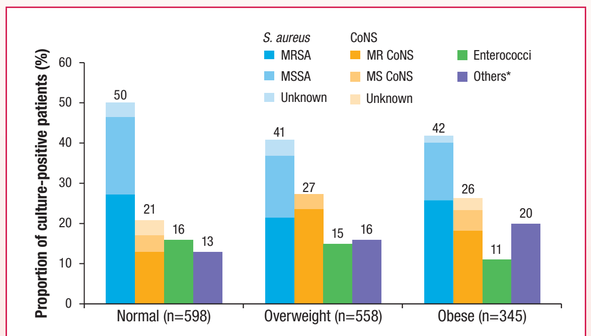
Table 4. Type of primary infections (>5% in at least one of the group)

Primary infection type	Normal weight n=598	Overweight n=558	Obese n=345
SSTI	218 (37)	247 (44)	172 (50)
cSSTI	169 (28)	177 (32)	112 (33)
uSSTI	49 (8)	70 (13)	60 (17)
Bacteraemia	105 (18)	79 (14)	48 (14)
Endocarditis	88 (15)	46 (8)	18 (5)
Foreign body/prosthetic	68 (11)	68 (12)	43 (13)
Osteomyelitis	49 (8)	63 (11)	35 (10)
Others	70 (12)	55 (9)	29 (8)

cSSTI, complicated skin and soft tissue infection; uSSTI, uncomplicated skin and soft tissue infection

- SSTI was more frequent in the overweight and obese patients; endocarditis was more frequent in the normal weight patients
- Culture results (**Figure 1**) were available for 493 (82%) normal weight, 450 (81%) overweight and 275 (80%) obese patients, of which 23% - 24% were negative in the 3 BMI groups. *S. aureus* was most frequently isolated in all the BMI groups

Figure 1. Primary infecting pathogens

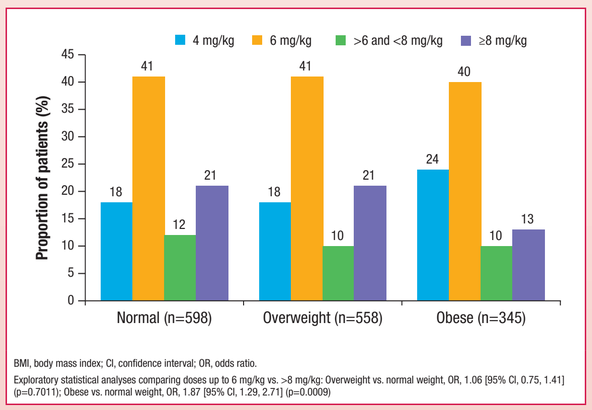


CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus;* MSCoNS, methicillin-susceptible CoNS; MRCoNS, methicillin-resistant CoNS. *Other includes: *Staphylococcus* spp.– coagulase not specified, *Streptococcus spp.*, viridans group Streptococci, Gr+ bacilli, Gr- bacilli, Gr– cocci, *Corynebacterium spp.* and other

DAP therapy details

- DAP initiated empirically in 55.4% normal weight, 60.2% overweight and 60.3% obese patients
- Proportion of obese patients receiving doses ≥8 mg/kg was lower in obese patients compared with normal or overweight patients (**Figure 2**)

Figure 2. Initial doses per BMI group

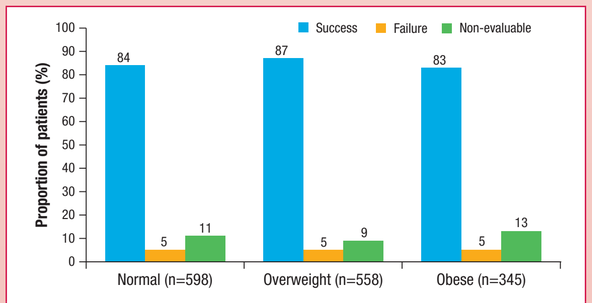


BMI, body mass index; CI, confidence interval; OR, odds ratio.
Exploratory statistical analyses comparing doses up to 6 mg/kg vs. >8 mg/kg: Overweight vs. normal weight, OR, 1.06 [95% CI, 0.75, 1.41] (p=0.7011); Obese vs. normal weight, OR, 1.87 [95% CI, 1.29, 2.71] (p=0.0009)

- Concomitant antibiotics were used by 66%-70% of patients in the different BMI groups, most commonly carbapenems

Clinical outcome

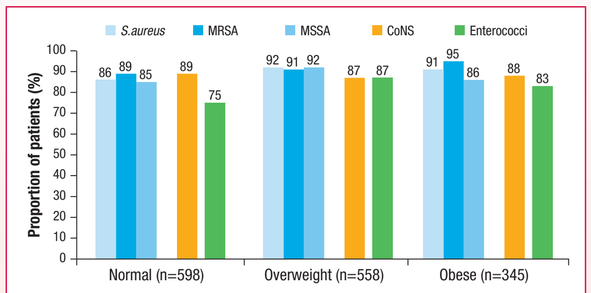
Figure 3. Clinical outcome at the end of the therapy as per the BMI group



Clinical success vs. failure: Exploratory statistical analyses comparing overweight vs. normal weight, OR: 1.22 [0.88, 1.70] (p=0.2367); Obese vs. normal weight, OR: 0.90 [0.63, 1.29] (p=0.2367)

- Overall, clinical success rates were high (>80%) with no obvious differences between the BMI groups (**Figure 3**)
- In morbidly obese patients (BMI ≥40, n=41), clinical success rate was 88%

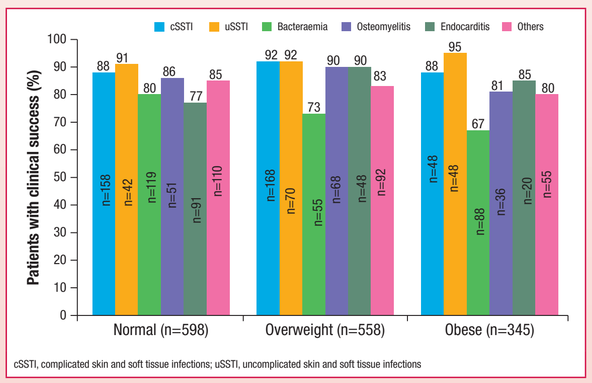
Figure 4. Clinical success rates by primary pathogens



CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*

- Clinical outcome across primary infections were generally similar between the BMI subgroups with the exception of bacteraemia for which clinical success appears to be somewhat lower in the obese patients (**Figure 5**)

Figure 5. Clinical success rates by type of primary infection



cSSTI, complicated skin and soft tissue infections; uSSTI, uncomplicated skin and soft tissue infections

Safety and tolerability

Table 5. AEs and SAEs possibly related to DAP treatment, according to the BMI subgroups

	Normal weight n=598	Overweight n=558	Obese n=345
Any AE*	22 (4)	21 (4)	12 (4)
Any SAE**	2 (0.3)	6 (1)	6 (2)
AEs of special interest by preferred term			
Blood CPK increased†	7 (1)	8 (1)	2 (1)
Musculoskeletal events	1 (0.2)	2 (0.4)	2 (1)
SAEs of special interest by preferred term			
Blood CPK increased†	1 (0.2)	0	0
Musculoskeletal events#	0	2 (0.4)	1 (0.3)

AE, adverse events; SAEs, serious adverse events; CPK, creatine phosphokinase
#Includes myopathy, rhabdomyolysis; DAP, daptomycin
Exploratory statistical analyses:
***AEs (DAP-related):** Overweight vs. normal weight, OR: 0.78 [0.56, 1.09], (p=0.1428); Obese vs. normal, OR: 0.86 [0.59, 1.25] (p=0.4226)
****SAEs (DAP-related):** Overweight vs. normal weight, OR: 0.75 [0.50, 1.13] (p=0.1664); Obese vs. normal, OR: 1.04 [0.68, 1.62] (p=0.8443)
†**CPK increase:** Overweight vs. normal weight, OR: 0.71 [0.29, 1.75] (p=0.4574); Obese vs. normal, OR: 0.57 [0.18, 1.79] (p=0.3379)

- Other possibly related SAEs were isolated cases of general disorders and administration site conditions, infections and infestations, blood and lymphatic system disorders, cardiac disorders, hepatobiliary disorders, renal and urinary disorders and nervous system disorders distributed across all BMI groups
- No cases of raised CPK or muscular events were reported in morbidly obese patients (BMI >40 kg/m²; n=41)

CONCLUSIONS

- The distribution of doses used for the three BMI groups was similar
- DAP was effective across all groups
- On the basis of the EU-CORE℠ data, there is no indication that specific dose adjustments are required solely based on BMI
- The safety profile of DAP was comparable across all BMI groups

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EUROPEAN CORE CUBICIN® Outcomes Registry and Experience

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