

South African Society of Clinical Microbiology (SASCM)

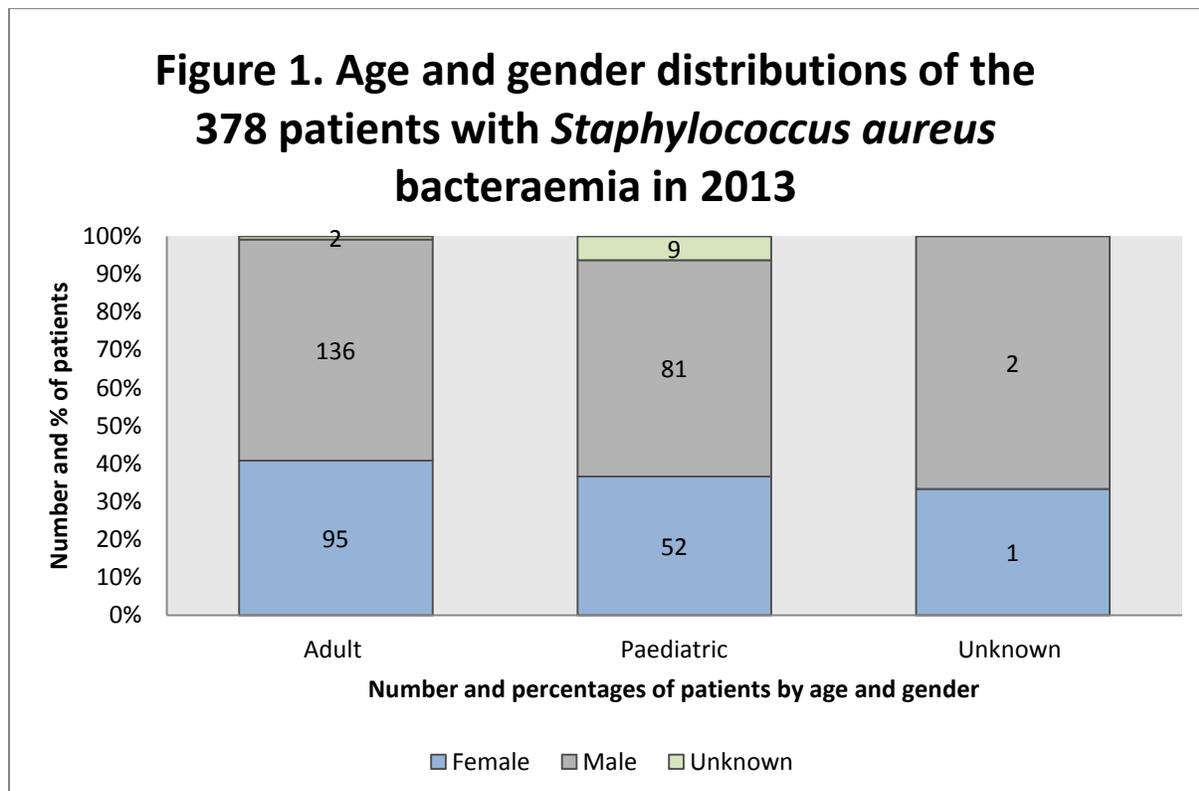
Guideline for daptomycin use in South Africa 2014

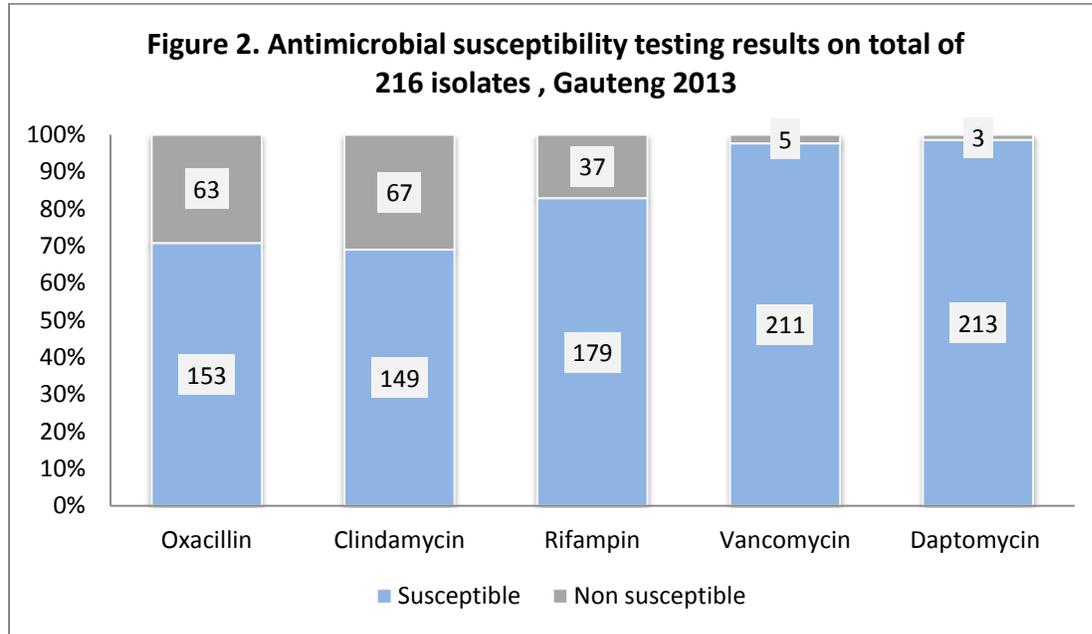
Introduction

Daptomycin is a recently approved agent in South Africa from a new class of antibiotics, the cyclic lipopeptide, with bactericidal activity. Daptomycin has unique mechanism of action by killing Gram-positive bacteria with binding to cytoplasmic cell membrane causing rapid depolarization.

Daptomycin has a very low frequency of spontaneous development of resistance in vitro, though resistance in vivo has been described in an MRSA endocarditis patient on daptomycin treatment (10).

Centre for Opportunistic, Tropical and Hospital Infections (COTHI) at NICD is performing enhanced surveillance for *Staphylococcus aureus* bacteraemia in Gauteng (three sentinel sites) (Figure 1). Antimicrobial susceptibility testing results for a selected number of antimicrobial agents including daptomycin is presented in the Figure 2.





Over a 5 year period, susceptibility testing for daptomycin has shown similar results. From daptomycin surveillance program, 12 443 organisms were collected between January 2007 and December 2008 from 27 US medical centres (11). The isolates were from hospitalized patients with bacteraemia, skin and soft tissue infection, and pneumonia (Table1). Daptomycin non-susceptibility rates are very low and periodic surveillance seems appropriate for clinically significant Gram-positive organisms.

Table 1

Frequency of occurrence of daptomycin MIC values for the organisms tested

Organism (no. total)	No. of isolates (%) inhibited at MIC (µg/mL) of							
	≤0.06	0.12	0.25	0.5	1	2	4	8
<i>S. aureus</i>								
Oxacillin-susceptible								
2007–2008 (3563)	5 (0.1)	207 (5.8)	2769 (77.7)	572 (16.1)	10 (0.3)	-	-	-
2002–2003 (1879)	2 (0.1)	123 (6.5)	1440 (76.6)	305 (16.3)	6 (0.3)	1 (<0.1)	-	-
Oxacillin-resistant								
2007–2008 (4514)	2 (<0.1)	106 (2.4)	3171 (70.3)	1189 (26.3)	38 (0.8)	7 (0.2)	1 (<0.1)	-
2002–2003 (1598)	1 (0.1)	32 (2.0)	1043 (65.3)	512 (32.0)	10 (0.6)	-	-	-
<i>E. faecalis</i>								
2007–2008 (1401)	5 (0.4)	9 (0.6)	48 (3.4)	484 (34.6)	726 (51.8)	125 (8.9)	4 (0.3)	-
2002–2003 (981)	2 (0.2)	10 (1.0)	87 (8.9)	478 (48.7)	367 (37.1)	38 (3.9)	2 (0.2)	-
<i>E. faecium</i>								
Vancomycin-susceptible								
2007–2008 (203)	0 (0.0)	2 (1.0)	4 (2.0)	7 (3.5)	57 (28.1)	117 (57.6)	14 (6.9)	2 (1.0)
2002–2003 (93)	0 (0.0)	2 (2.2)	1 (1.1)	1 (1.1)	12 (12.9)	52 (55.9)	24 (25.8)	1 (1.1)
Vancomycin-nonsusceptible								
2007–2008 (640)	2 (0.3)	2 (0.3)	10 (1.6)	14 (2.2)	204 (31.9)	376 (58.8)	30 (4.7)	2 (0.3)
2002–2003 (949)	1 (0.1)	3 (0.3)	5 (0.5)	29 (3.1)	153 (16.2)	535 (56.4)	219 (23.1)	4 (0.4)

- = No isolates with this MIC value.

Based on this and other data SASCM provides recommendations for appropriate use of daptomycin. These recommendations were formulated by members of the National Antimicrobial Committee (NAC), a sub-committee of SASCM, following consultation and review of the relevant literature.

Recommendations

A. Empiric therapy

Daptomycin can be used as empirical antimicrobial therapy where broad-spectrum Gram positive cover is necessary. The following principles and guidelines apply to its use as an empiric agent:

1. It is an alternative/substitute to glycopeptides (vancomycin or teicoplanin) and linezolid, where these agents may be considered as part of an empiric regimen.
2. The lower respiratory tract (LRT) must be excluded as a potential source of sepsis. If there is any concern or possibility that the LRT is the source then daptomycin should not be prescribed.
3. Antimicrobial stewardship principles should be adhered to in the use of this agent. There should be a valid reason and necessity for use of a broad-spectrum Gram-positive agent. Daptomycin should not be used in place of narrower-spectrum agents where these are appropriate e.g. if *Staphylococcus aureus* cover is necessary but the risk of MRSA is low, daptomycin should not be prescribed in place of cloxacillin. Similarly de-escalation to a narrower-spectrum agent is mandatory following susceptibility results.

B. Directed therapy

1. Although daptomycin has very specific clinical and microbiological indications, there is a wide experience and supporting literature for the use outside of these indications. From a clinical perspective, other than lower respiratory tract infections, it can be considered equivalent to counterparts' viz. glycopeptides and linezolid. Daptomycin broad-spectrum activity is suitable as directed therapy against a number of Gram-positive pathogens including MRSA but also streptococci and enterococci based on rational recommendations from the antimicrobial stewardship team. However, it is not considered a substitute for β -lactams agents as they remain the preferred treatment option when susceptibility to these agents is retained. In certain clinical instances e.g. hypersensitivity reaction to β -lactam agents' daptomycin may be a suitable alternative, although it is recommended that these be discussed with a clinical microbiologist.

2. For enterococci, especially vancomycin-resistant enterococci (VRE) daptomycin has a distinct role as directed therapy. It is an acceptable alternative to linezolid for directed therapy of VRE-associated infections. Dosing-modification (see below) is necessary when used as directed therapy for enterococcal infections.
3. Daptomycin can also be used as part of a combination-directed therapy regime for specific difficult-to-treat infections e.g. infective endocarditis. These indications and uses should be discussed with a clinical microbiologist.

C. Dosing of daptomycin

- The registered doses for daptomycin are 4 mg/kg daily for complicated SSTI and 6 mg/kg daily for bacteraemia and endocarditis.
 - In patients with renal failure (GFR of < 30 mls/min) the dosing interval is adjusted from 24 to 48 hours.
 - Daptomycin is a concentration-dependent agent
 - The Pk / PD parameter for significant bactericidal activity is an AUC_{free}/MIC ratio of 189
 - A Monte Carlo prediction model determined the probability of this being achieved in patients with normal renal function as:
 - 80.4% for a dose of 4 mg/kg daily
 - 91.1% for a dose of 6 mg/kg daily and
 - 95.6% for a dose of 8 mg/kg daily
 - In the Clinical Practice Guideline by IDSA higher doses of daptomycin of 8 – 10 mg/kg daily are recommended by some experts for treatment of bacteraemia as well as endocarditis, with a B-III recommendation.
1. Rationale for higher doses of daptomycin
 - High inoculum infections treated with subtherapeutic doses of daptomycin are associated with clinical failure and the development of reduced susceptibility to daptomycin. This allows for the accumulation of hetero-daptomycin resistant *S. aureus* (hDRSA) phenotypes.
 - In clinical trials increased daptomycin MICs developed in 6% of patients with bacteraemia with or without endocarditis, all of whom had received vancomycin previously.
 - Critically ill patients with augmented creatinine clearance have also been shown to have augmented daptomycin clearance, resulting in low drug exposures and increased mortality in spite of using doses of 6-8 mg/kg/daily.

- Other predictors of non-susceptibility included significant comorbidity, delay in source control and bacteraemic persistence despite prior vancomycin therapy.
 - Dosing strategies that have been evaluated to optimize the clinical outcome of patients whilst minimizing the selection for daptomycin resistant mutants include doses as high as 10-12 mg/kg/day, with prompt drainage or debridement of high-inoculum infections.
 - These doses have significantly increased the clinical and microbiological success rates for *S. aureus* blood stream infection without increasing toxicity.
2. Recommendations for higher doses of daptomycin
- Higher doses of daptomycin should only be used in consultation with an infectious diseases expert and/or clinical microbiologist.
 - Higher doses of daptomycin should be considered in the clinical scenarios described above.
 - Critically ill patients with augmented creatinine clearance and suspected MRSA bacteraemia.
 - Patients with high inoculum infections such as infective endocarditis, and significant comorbidities.
 - Patients with *S. aureus* bloodstream infections who are at high risk of clinical failure, i.e. persistent bacteraemia and previous failure of glycopeptide therapy.
 - Daptomycin can be used as directed therapy against enterococcal infections, especially in the treatment of vancomycin resistant Enterococci (VRE). The MICs to both *E faecalis* and *E faecium* are often very close to the breakpoint, namely 4µg/ml, and higher doses of daptomycin therefore need to be used in order to treat infections with these highly resistant organisms.

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