Clinical Experience with Daptomycin Therapeutic Drug Monitoring in a Tertiary Care Institution, Republic of Ireland

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BACKGROUND

Daptomycin (DAP) is increasingly used at higher doses for complex Gram-positive infections, particularly enterococcal disease. Marked inter-patient variability in serum concentrations has prompted interest in therapeutic drug monitoring (TDM), although its clinical value in routine practice remains uncertain. This study aimed to describe variability in pre-dose DAP concentrations (C_{min}) in a real-world hospital cohort and to examine associations with dosing, creatine phosphokinase (CPK) changes, and clinical outcomes.

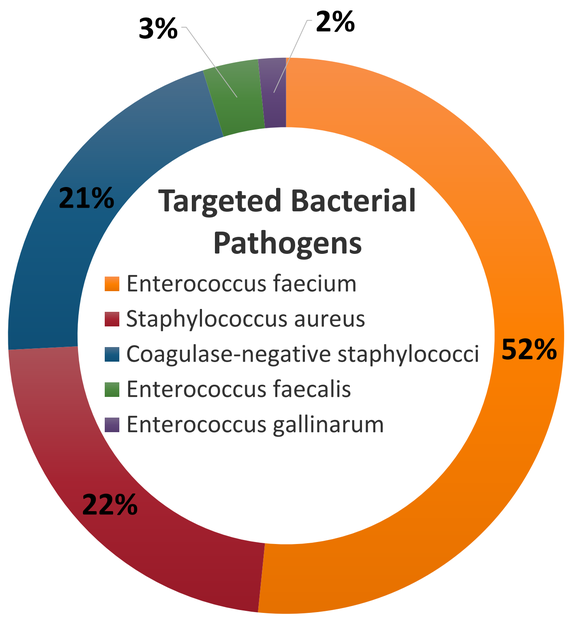
METHODOLOGY

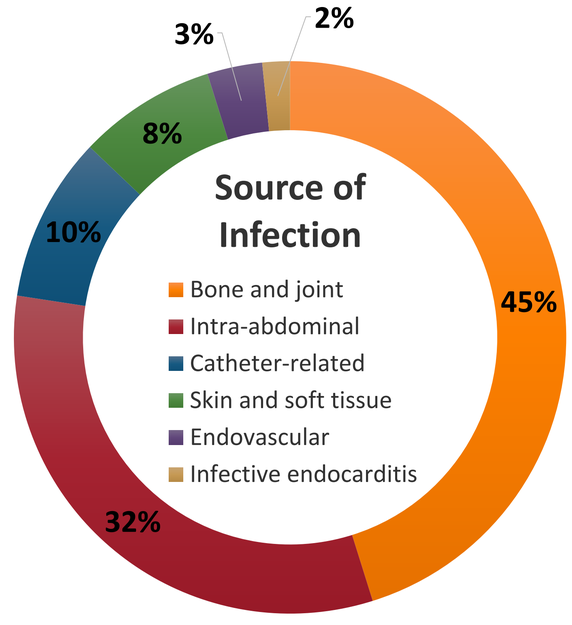
A retrospective observational study was conducted at a tertiary university hospital in Ireland. Adult patients receiving DAP in 2022 with at least one recorded C_{min} were included, excluding intensive care and renal replacement therapy patients. Demographic, clinical, microbiological, and biochemical data were extracted from healthcare records. A pre-defined C_{min} ≥25 mg/L was used as a pragmatic toxicity threshold. Associations between exposure, dosing, and outcomes were analysed using non-parametric methods and multivariable linear regression.

RESULTS

Table 1: Study population characteristics and DAP dosing (n=62)

Characteristic	Value
Demographic data	
Age, years, median (IQR)	61.5 (49.3–77.0)
Gender, n (%)	
○ Male	41 (66.1)
○ Female	21 (34.9)
Body weight, kg, median (IQR)	71.1 (60.9–83.9)
Biochemical data	
Creatinine clearance (CrCl), mL/min, median (IQR)	83 (54–137)
Serum albumin, g/L, median (IQR)	24 (20–29)
Change in CPK in IU/L, median (IQR)	0 (0-7.5)
DAP data	
Daptomycin dose, mg/kg, median (IQR)	8 (8–8)
≥10 mg/kg dosing, n (%)	12 (19.4)
Pre-dose concentration (C_{min}), mg/L, median (IQR)	18.9 (14.9–23.5)

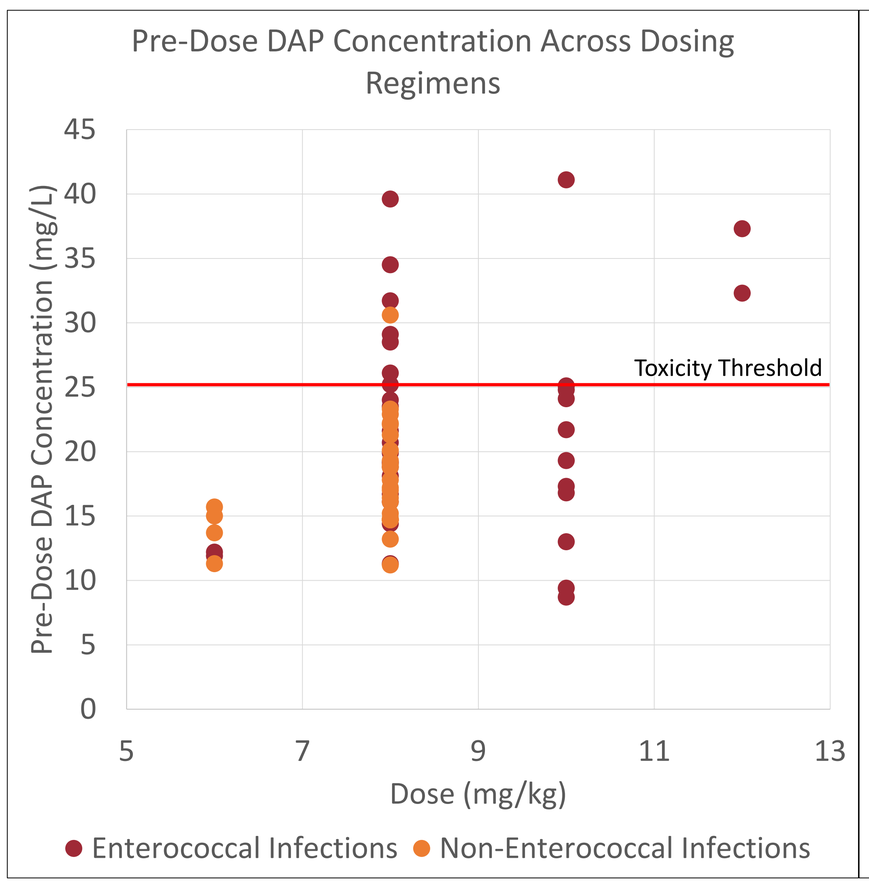




Enterococci accounted for **56.5%** of targeted pathogens, driven **predominantly by *Enterococcus faecium* (51.6%)**, with *Staphylococcus aureus* (22.6%) and coagulase-negative staphylococci (21.0%) comprising most remaining cases. DAP was most frequently prescribed **for bone and joint infection (45.2%)** and **intra-abdominal infection (32.3%)**, clinical contexts commonly associated with complex or deep-seated disease. Catheter-related (9.7%), skin and soft-tissue (8.1%), endovascular (3.2%), and infective endocarditis (1.6%) indications were less frequent.

Patients receiving DAP were typically **older** adults, predominantly **male**, with **preserved renal function** but **low serum albumin** levels. **Higher-dose regimens** were commonly employed, and in all cases DAP use was **pathogen directed**, informed by microbiological identification and antimicrobial susceptibility results. **Trough concentrations varied widely** between individuals.

Higher-dose daptomycin was safely used in enterococcal infection, with no exposure-related toxicity observed, supporting current practice.



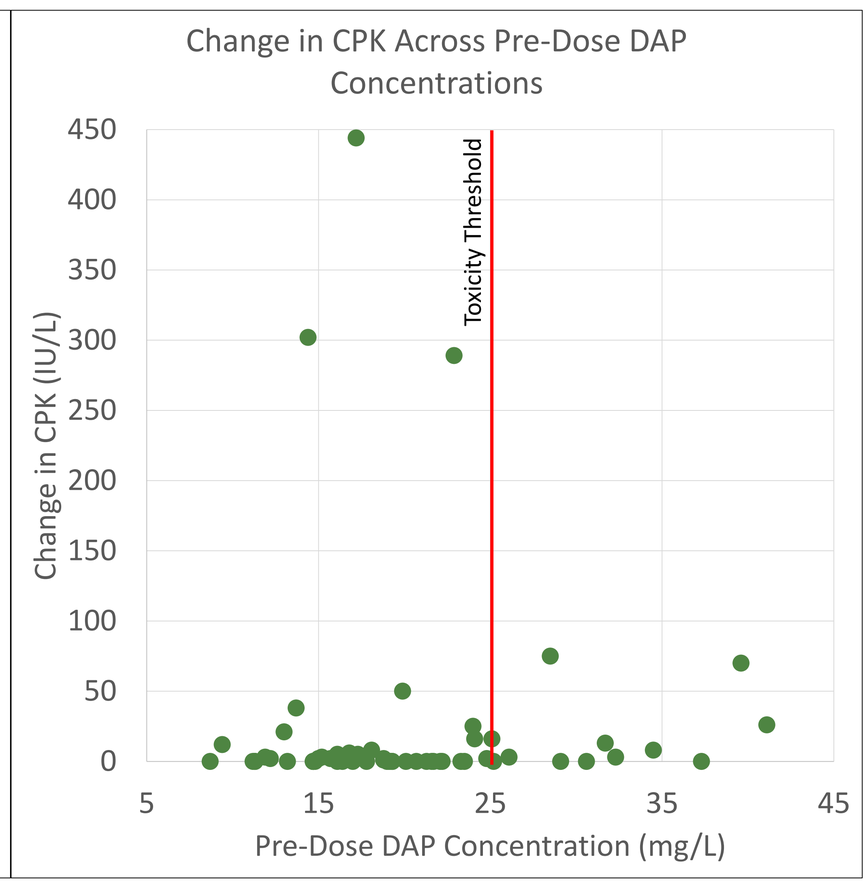


Table 2: Multivariable linear regression for predictors of pre-dose DAP concentration (log C_{min})

Variable	β coefficient	95% CI	p-value
Dose (mg/kg)	0.083	0.012–0.154	***0.023***
Creatinine clearance	−0.0008	−0.002 to 0.001	0.288
Serum albumin	−0.0039	−0.017 to 0.010	0.561
Body weight	0.0007	−0.005 to 0.006	0.804
Adjusted R^2 = 0.069			

On multivariable analysis, administered **DAP dose was the only variable independently associated with higher C_{min}**. Renal function, serum albumin, and body weight were not significantly associated with C_{min} after adjustment. Overall, the model explained a small proportion of the observed variability in DAP serum concentration (adjusted R^2 = 0.069), indicating that **most inter-patient variability remained unexplained**.

Marked inter-patient variability in C_{min} was observed **across all weight-based dosing regimens**, with substantial overlap between enterococcal and non-enterococcal infections. Although higher doses were associated with higher C_{min}, **no single dosing strategy reliably predicted attainment of a pre-defined toxicity threshold of 25 mg/L**. Changes in CPK occurred across a wide range of C_{min}, and **no clear exposure–toxicity relationship was evident**.

All dosing regimens achieved therapeutic concentrations, and routine daptomycin trough monitoring provided limited additional clinical value beyond standard clinical assessment and CPK monitoring.

CONCLUSION

- DAP C_{min} exhibited substantial inter-individual variability across all weight-based dosing regimens, highlighting the heterogeneity in routine hospital practice.
- No individual clinical or biochemical variable, nor any single weight-based dosing threshold, reliably predicted C_{min}.
- CPK changes occurred across DAP C_{min}, with no consistent concentration-dependent association observed, suggesting that serum exposure alone is insufficient to explain biochemical toxicity in clinical practice.
- Clinical outcomes were independent of DAP C_{min} and were primarily influenced by non-pharmacological factors, including infection complexity and adequacy of source control.
- Collectively, these findings highlight the limited interpretability of isolated DAP C_{min} in routine care and emphasise the continued importance of clinical assessment alongside standard biochemical monitoring.

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