Therapeutic Drug Monitoring of Daptomycin in OPAT: Nottingham University Hospitals Trust Experience

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Daptomycin therapeutic drug monitoring (TDM) may be useful in monitoring patients at risk of adverse effects, as any necessary dose adjustments can be made before significant creatine kinase (CK) rise or adverse effects are observed.

Introduction

Daptomycin is a useful treatment option in the management of Gram positive infections in the Outpatient Parenteral Antibiotic Therapy (OPAT) setting, owing to its once daily dosing regimen. TDM is not routinely recommended but may be **of value in difficult to treat infections and/or renal impairment** (1). The recommended pre-dose target range is 10-20 mg/L in severe infection, recommended by the Antimicrobial Reference Laboratory in Bristol (1)

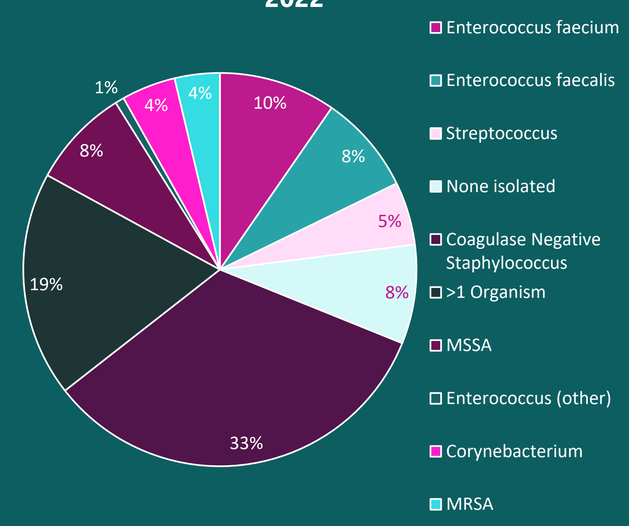
The correlation between daptomycin levels and risk of clinical adverse effects is not well understood**. Research suggests that the a pre-dose (trough) level of >24.3 mg/L is associated with increased risk of creatine kinase (CK) elevation** (2).

We report our experience of daptomycin TDM at Nottingham University Hospitals NHS Trust since August 2021. This was prompted by clinical need to avoid daptomycin toxicity leading to discontinuation in patients with limited treatment options.

Methods

- Data was collated from the OPAT electronic database with patient records accessed from January 2015- October 2022.
- **136 patient treatment episodes** with daptomycin during this time period
- Daptomycin pre-dose serum levels have been monitored since August 2021, measured 7 days into therapy and at weekly intervals thereafter for the duration of the antibiotic course.
- Levels were processed at Bristol Antimicrobial Reference Laboratory.
- **13 patients in total had TDM** between August 2021- October 2022. 1 patient has been excluded from the final analysis due to multiple courses and admissions.

Fig. 1 Organisms Implicated in Infections Treated with daptomycin in OPAT 2015-2022



Results

- The most common infection treated with daptomycin in OPAT was **prosthetic joint infection (33%).** Second most common was **diabetic foot infection (25%).**
- The most common organism implicated in infections treated with daptomycin was **Coagulase Negative Staphylococcus** (CoNS) at 33% (fig 1.)
- **Mean patient age**: **65.2 years old**
- **Average duration of therapy 30.5 days**

Pre Introduction of daptomycin TDM:

- **Adverse event rate was 22%** (27/122),
- **Asymptomatic CK rise** the most common reason for terminating the course.
- **14%** (18/122) of all patients **stopped** the daptomycin course earlier than planned

Post Introduction of daptomycin TDM:

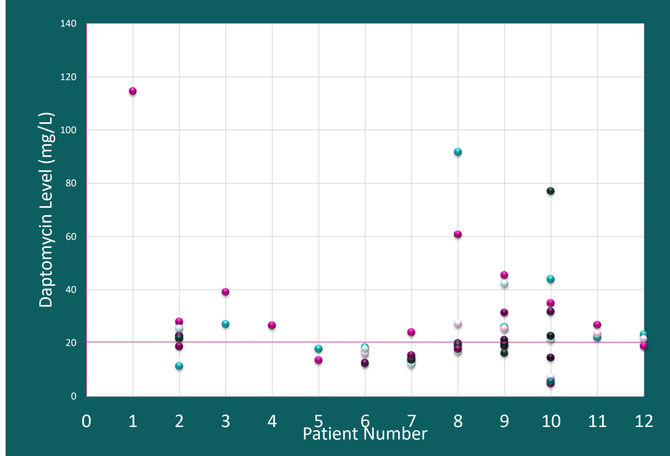
- **Adverse event rate 33%** (4/12) with **myalgia** being the most common.
- **33% (4/12)** stopped the daptomycin course earlier than planned and switched to a 2nd line agent.

Results

Post Introduction of daptomycin TDM:

- **75%** (3/4) patients with adverse effects had a high daptomycin pre-dose level (>20 mg/L)
- 2 out of 12 patients had an asymptomatic **CK rise coupled with a high daptomycin level**, (patient 4 and patient 10) but were able to complete the course with dose adjustment, without any adverse effects reported.
- The range of daptomycin pre-dose levels was **5.5-114.6mg/L (fig. 2)**
- The average pre-dose level in patients **with adverse effects** was **46.1 mg/L**
- The average pre-dose level in patients **without** adverse effects was **21.6 mg/L.** In a 2 stranded T-test the difference between the daptomycin levels in patients with and without side effects was not significant. (t-value = 1.04, p= 0.30)
- A total of 59 daptomycin pre-dose levels were measured during the study period. **50.8% (30/59) of all levels were above 20 mg/L.**

Fig. 2 Distribution of daptomycin Pre-Dose Levels (mg/L)



Results

Table 1. Demographic data on all patients with daptomycin TDM in OPAT

Patient	Type of Infection	Initial daptomycin dose (mg/kg)	Adverse Effect	Dose Adjustment?	Creatinine Clearance (ml/min)	Highest Daptomycin Pre-Dose Level (mg/L)	Highest CK level U/L (0-170 IU/L))	Final Outcome
1	Prosthetic joint infection	7	Myalgia	No	105	28.0	372	Switched to alternative antibiotic
2	Prosthetic joint infection	7	N/A	No	113	26.6	48	Completed course of daptomycin
3	Prosthetic joint infection	8	N/A	Dose reduced	115	17.8	94	Completed course of daptomycin
4	Prosthetic joint infection	6	N/A	Dose reduced	99	45.4	661	Completed course of daptomycin
5	Prosthetic joint infection	6.7	N/A	No	182	23.1	92	Completed course of daptomycin
4	Renal transplant infection	6	Myalgia	No	41	114.6	172	Switched to alternative antibiotic
7	Granulomatous mastitis	6	Myalgia	No	131	17.8	Result not available	Switched to alternative antibiotic
8	Infected metalwork	6	N/A	No	178	17.7	119	Completed course of daptomycin
9	Spinal Infection	10	Dizziness	Dose reduced	103	39.2	82	Switched to alternative antibiotic
10	Osteomyelitis	6.6	N/A	Dose reduced	70	24.0	247	Completed course of daptomycin
11	Osteomyelitis	10	N/A	Dose reduced	50	45.5	99	Completed course of daptomycin
12	Diabetic foot infection	8	N/A	1 dose omitted then dose reduced	53	91.8	86	Completed course of daptomycin

Conclusion

Interestingly, we observed that the average pre-dose level in all patients was higher than the recommended threshold of 20 mg/L in patients with and without adverse effects.

Notably, **high daptomycin levels were also observed across a spectrum of renal functions** (measured by creatinine clearance), which implies that the relationship between renal function and daptomycin level is complex.

However in patients with side effects, a high daptomycin pre-dose level was observed in the majority. **High levels may herald impending adverse effects or CK rise**. **Therefore TDM may facilitate any necessary adjustments before such consequences are seen**; enabling patients to complete the antibiotic course as planned.

Whilst the numbers in our study are too small to draw any large scale conclusions, it highlights that **further studies are required** to establish the daptomycin level (or dosing regimens) at which toxicity may be seen.

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References

1. Bristol Antimicrobial Reference Laboratory Daptomycin | North Bristol NHS Trust STHW869 Antibiotic Guideline Ranges 2021 - 2022 (uhs.nhs.uk)
2. Bhavnani SM et al**.** Daptomycin Exposure and the Probability of Elevations in the Creatine Phosphokinase Level: Data from a Randomized Trial of Patients with Bacteraemia and Endocarditis. CID 2010;50 1568-1574.

Acknowledgments

Thank you to all of the OPAT Nurses, Pharmacists and Clinicians at Nottingham University Hospitals NHS Trust for facilitating daptomycin TDM in the delivery of the NUH OPAT service.

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