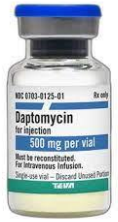
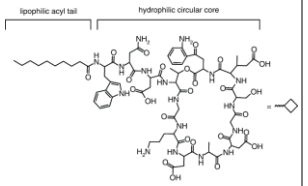




DAPTOMYCIN TDM: NOTTINGHAM UNIVERSITY HOSPITALS OPAT EXPERIENCE

BSAC Midlands Regional OPAT Workshop 23rd June 2023
Dr Francesca Heard
Infectious Diseases and Microbiology ST5

Daptomycin use in OPAT at Nottingham University Hospitals Trust

- A patient incident prompted daptomycin TDM to be introduced for **all patients commencing daptomycin therapy under OPAT at NUH from August 2021**
- **Patient receiving OPAT daptomycin had severe adverse effects and myopathy symptoms, with a normal CK, but extremely high/toxic daptomycin pre-dose level (>100) and daptomycin course was stopped.**

Daptomycin TDM- Bristol Antimicrobial Reference Laboratory Recommendations

- Assay interval 6-8 days
  - Check first trough/**pre dose level** at **day 7** (taken immediately before the dose)
  - Repeat pre dose level **routinely weekly** (also option to do 1 hour post dose level)
- Patients with CK elevation
- High dose therapy (>6 mg/kg) or
- Renal impairment
  - Pre dose target: **5-20mg/L or 10-20mg/L** in severe sepsis.
  - Pre dose levels **>20mg/L are 'associated with increased risk of toxicity'**
    - **Target levels based on 6-8mg/kg dosing**

Additional monitoring

- **CK Range = 0-145 IU**
  - Daptomycin package labelling recommends:
    - **discontinuation** of **daptomycin <u>with</u> significant myopathy symptoms in association with a <u>CK elevation ≥ 5x ULN,</u>**
    - or in patients **<u>without</u> reported symptoms and have <u>marked elevations in CK >10 x ULN (2).</u>**
  - Monitor **CK** every 2-3 days if symptoms of myopathy develop
- Monitor more frequently in patients at increased risk of myopathy:
  - Renal impairment
  - HD/PD
  - Concomitant medications i.e statins/fibrates (if medications not stopped)

- Baseline clotting (can cause elevated INR/PT)

Daptomycin levels- is TDM necessary?

- **Optimum daptomycin trough level (C_{min}) is not well-described**
- Although a **toxicity threshold** has been proposed for daptomycin induced CK-elevation, no clinical trials exist that define optimal effective daptomycin plasma concentrations in different types of infection

- One highly regarded study demonstrated that **daptomycin C_{min} >24.3 mg/L was associated with an increased probability of CK elevation with or without myopathy (by >30 fold)** (3) and this has been accepted as a cut off for 'safe' daptomycin dosing
  - Antimicrobial Reference Lab dosing based on this with a safety margin built in (upper limit of 20 mg/L)

Daptomycin Levels- is TDM necessary?

- Another single centre study evaluating the widely adopted cut off also found that **none of their patients with daptomycin C_{min} >24.3 mg/L had CK elevation suggesting tolerability towards higher trough levels than this**(4)

- **CrCl has been found to significantly influence daptomycin clearance:**
  - Compared to patients with normal renal function, those with **CrCl <40 ml/min** had significantly **higher mean C_{min} and prolonged plasma life** (5)
  - Current daptomycin literature is based on dosing of 6-8mg/kg
  - Serial daptomycin TDM is thought to be helpful as **daptomycin 'creep'** can occur where **C_{min} /** trough levels increase over time

Daptomycin levels- is TDM necessary?

- In critically ill patients with Gram-positive sepsis, hypoalbuminaemia affects highly protein bound drugs such as daptomycin→**higher volume of distribution and increased daptomycin clearance. (7)**
- Therefore TDM in this population might be warranted to optimize the dosing regimen and **prevent underdosing**

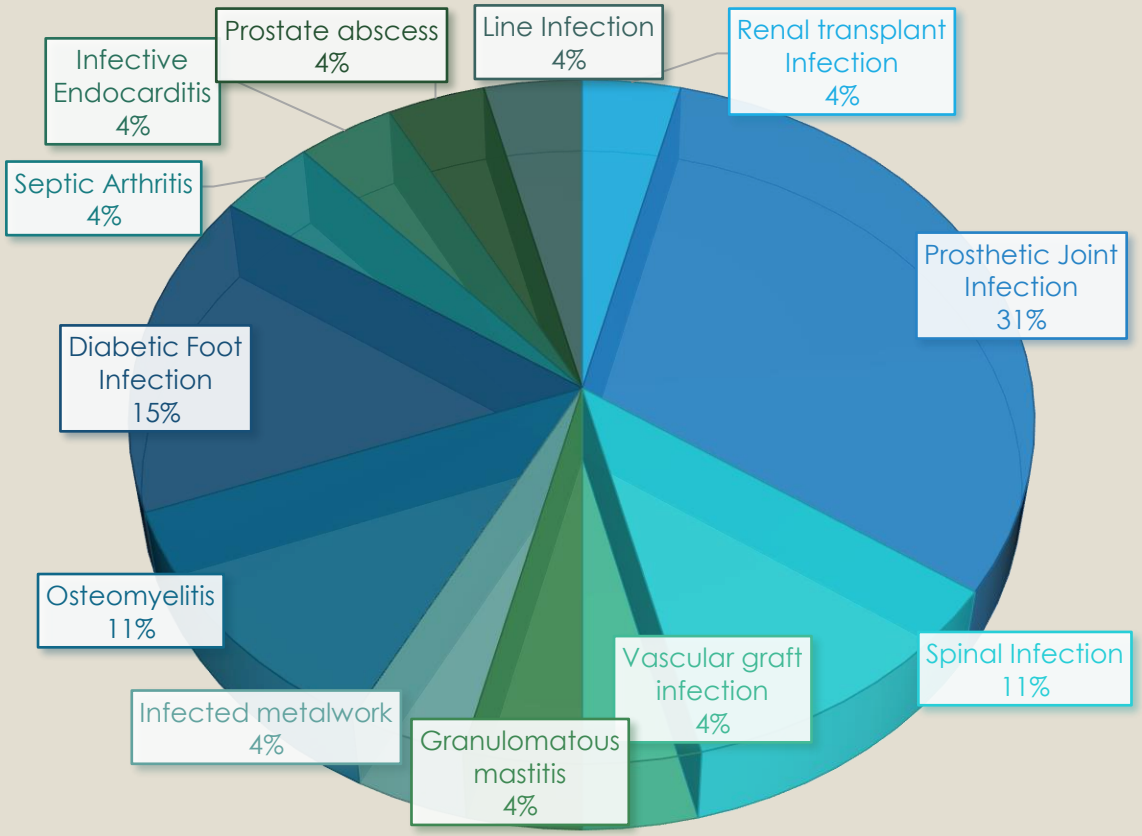
Daptomycin and CK

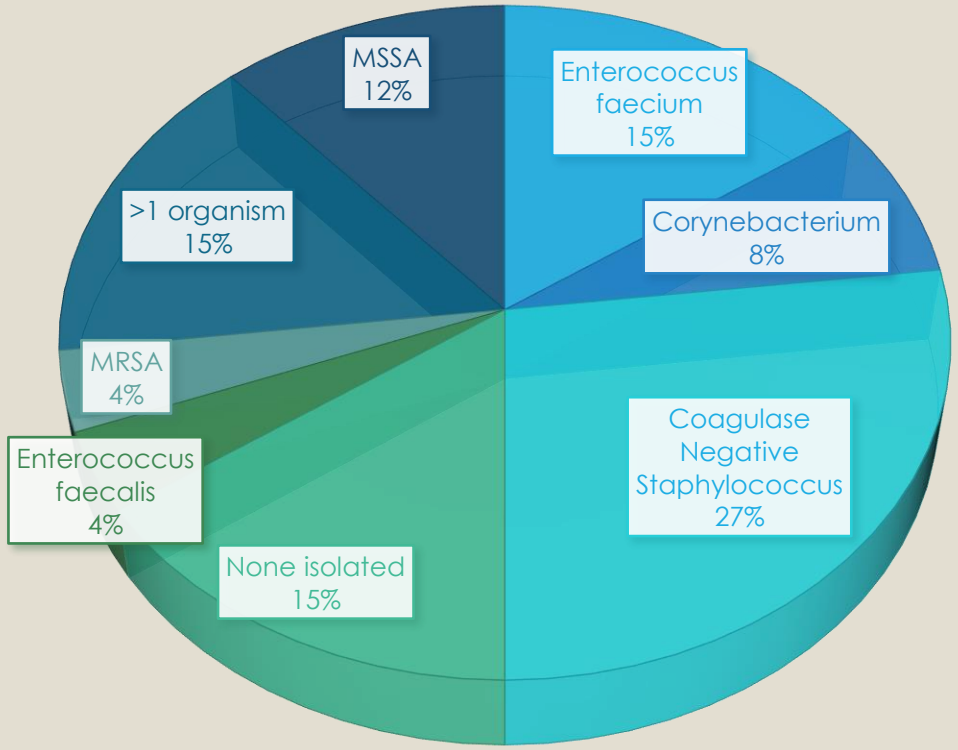
- Mechanism not well understood and may be dose dependent
  - Related to **skeletal myocyte membrane disruption**
- Case series found that **all patients on daptomycin had asymptomatic increases in CK**, but in the study it resolved with **holding 1 dose and resuming therapy 24 hours later**, (most often at the same dosage). This enabled patients to complete daptomycin therapy without further increases in CK elevations. (8)

Daptomycin TDM @ NUH

- **Methods**:
  - Audit of all patients that received daptomycin TDM in OPAT 2021-2023 (accurate at time of presentation)
  - Accessed OPAT database and patient electronic records for data
    - Type of infection, organism/s isolated, duration of therapy, outcome, CK levels, renal function, daptomycin levels (where applicable)
- **Total number of patients = 26**

Types of Infections Treated with Daptomycin in OPAT 2021-2023



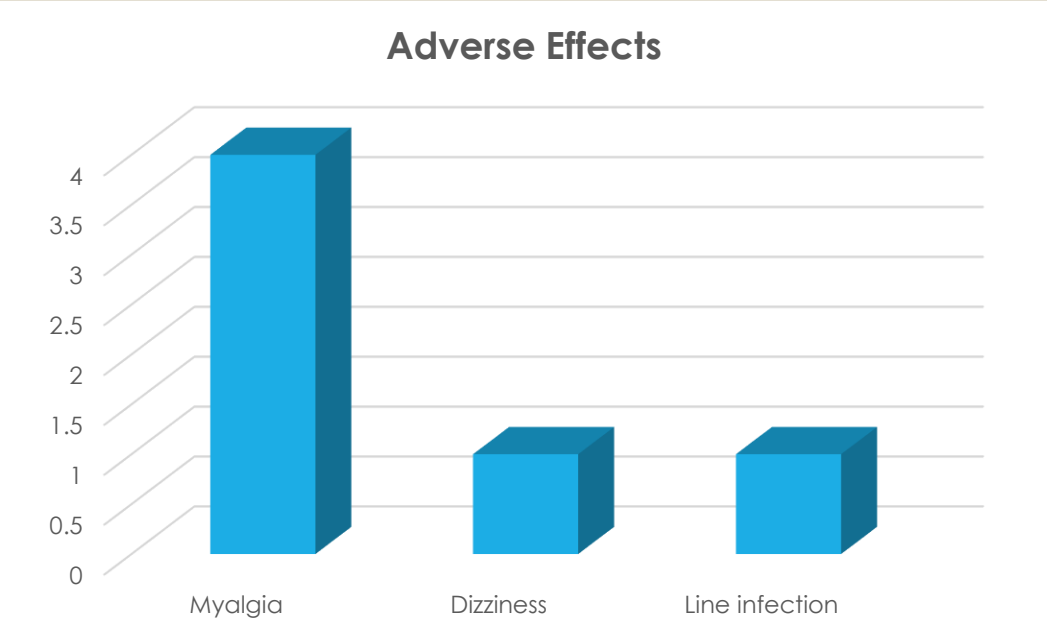


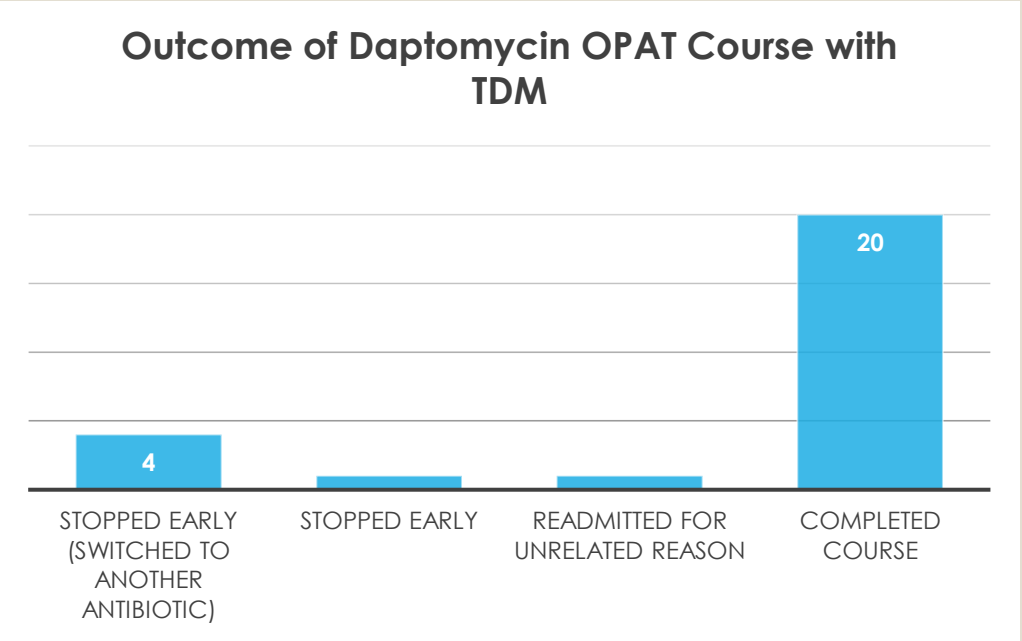
Results

- **<u>Pre Introduction of daptomycin TDM</u>**
  - Adverse event rate **22%** (taken from analysis of historical OPAT data)
  - **14%** of all patients **stopped** the daptomycin course earlier than planned (either switching to another antibiotic or stopping antibiotics altogether)
    - Some cases were managed with holding daptomycin temporarily and then restarting course

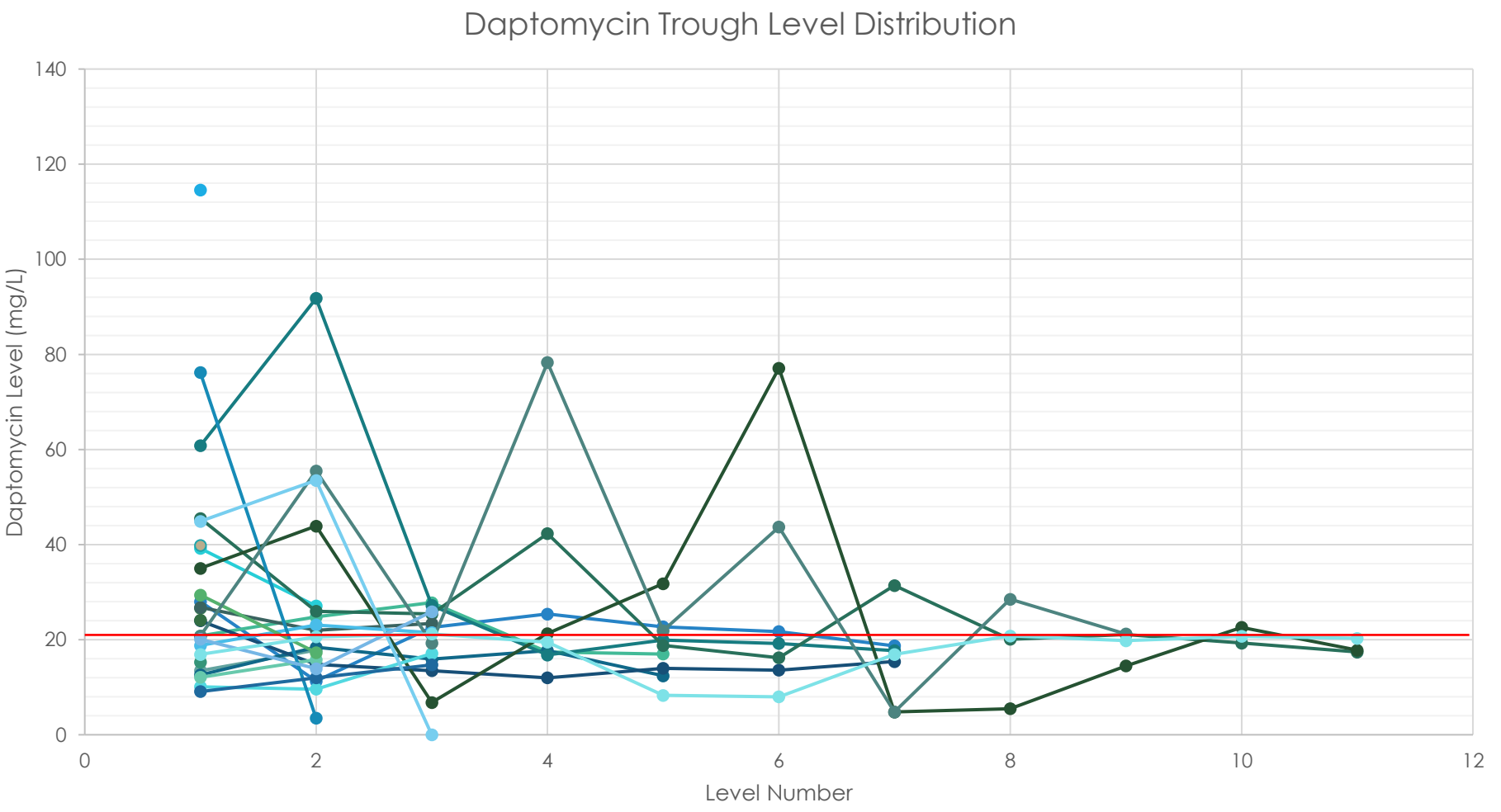
Results

- **Post introduction of daptomycin TDM-** adverse event rate **6/26 (23%)**
- **Myalgia** being the most common (4/6 patients)
- **All of the patients with an adverse effect stopped the daptomycin** earlier than planned and switched to the second agent.





Results



The range of levels was **<3-114.6mg/L**

High levels were common: **69%** (**18/26**) patients had **at least 1 pre-dose level >20 mg/L**

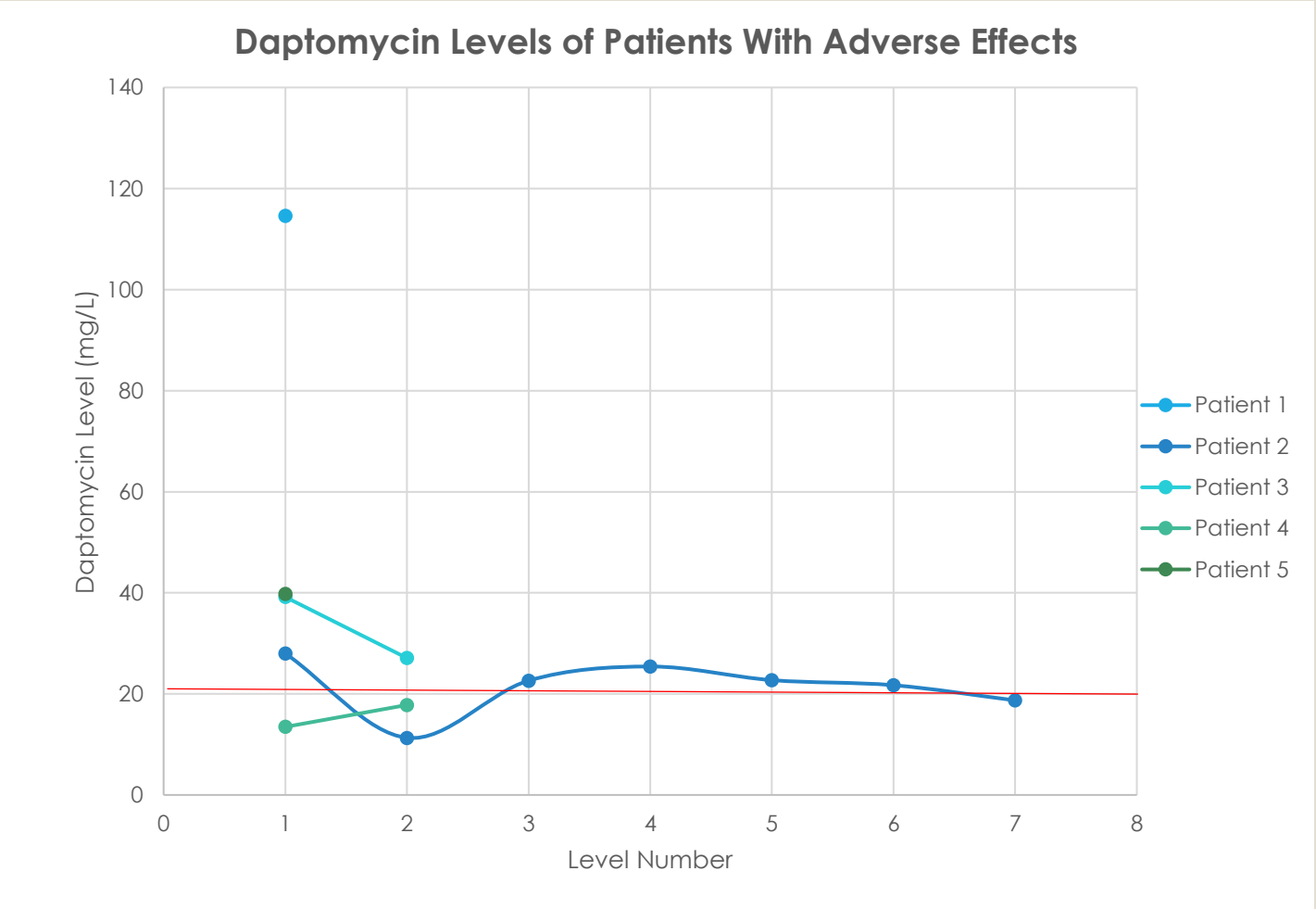
48% (51/106) of all daptomycin levels measured were above 20 mg/L.

The average pre-dose level in patients **with adverse effects** was **30.9 mg/L**

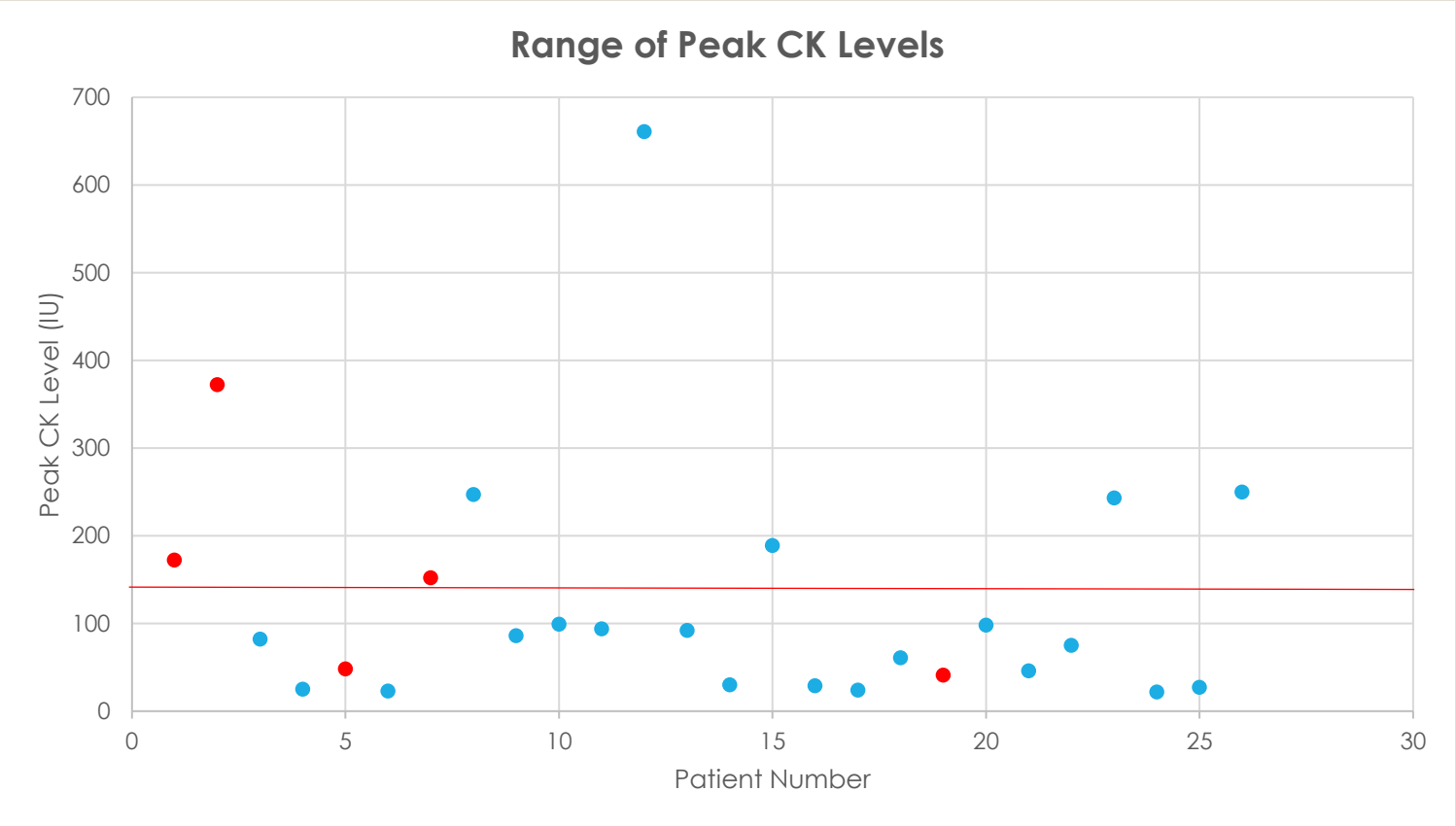
The average pre-dose level in patients **without** adverse effects was **23.7 mg/L**

Results

- Daptomycin levels of patients with adverse effects (line infection patient removed from the analysis) were generally above 20 g/L
  1 patient had normal daptomycin levels



Results



Majority of CK levels were within normal reference range

High CK levels were seen in patients who did not experience any adverse effects on daptomycin

Conclusions

- Very small numbers in audit limits conclusions that can be made
- **Average pre-dose daptomycin level in patients with and without documented side effects was higher than the recommended cut off of 20 mg/L**
- On average there was a higher pre-dose level seen in those with adverse effects than without. The average pre-dose level in those without side effects was below the accepted 'toxicity threshold' of 24.3 mg/L seen in studies
  - **High pre-dose levels were observed across a range of renal functions** (normal and abnormal)- multifactorial element / more complex than initially thought

Conclusions

- **High pre-dose daptomycin 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.

- Raised **CK was seen in patients without SE- ?normal in patients on daptomycin**
  - **Can be managed with dose reductions/holding**

References

1. Nottingham University Hospitals Trust Intranet Daptomycin page
2. Cucicin (daptomycin) injection label (fda.gov)
3. Bhavnani SM et al. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis 2010 Jun 15;50 (12): 1568-74
4. Ando M et al. Observational retrospective single-centre study in Japan to assess the clinical significance of serum daptomycin levels in creatinine phosphokinase elevation. J Clin Pharm Ther 2020 Apr; 45(2):290-297
5. Falcone M et al. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother 2013 Aug; 19(4): 732-9
6. Abdul-Aziz et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med (2020) 46:1127–1153
7. Lai CC et al. Safety and efficacy of high-dose daptomycin as salvage therapy for severe gram-positive bacterial sepsis in hospitalized adult patients. *BMC Infect Dis* 2013; 13:66
8. Burdette et al. Dosing strategy to allow continued therapy with daptomycin after asymptomatic increases in creatine kinase levels. Am J Health System Pharm. 2014 Jul 1;71(13):1101-7

Acknowledgements: Annette Clarkson and Dr Sue Snape for help with data collection and clinical interpretation