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Therapeutic Drug Monitoring for Antibiotics: Bridging the gap between bench and bench

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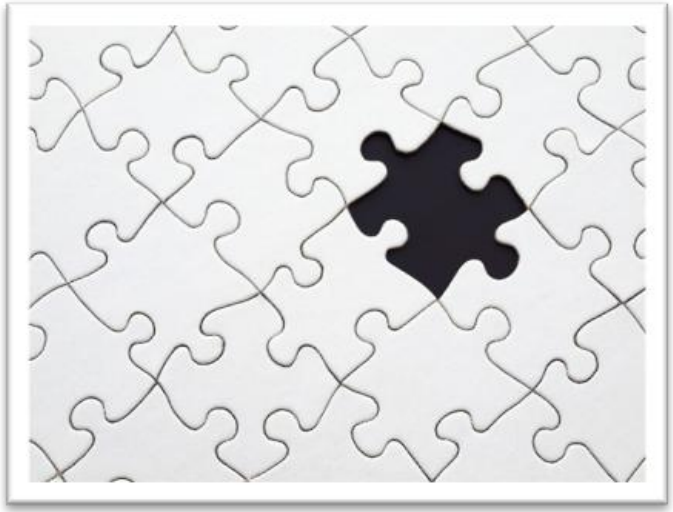
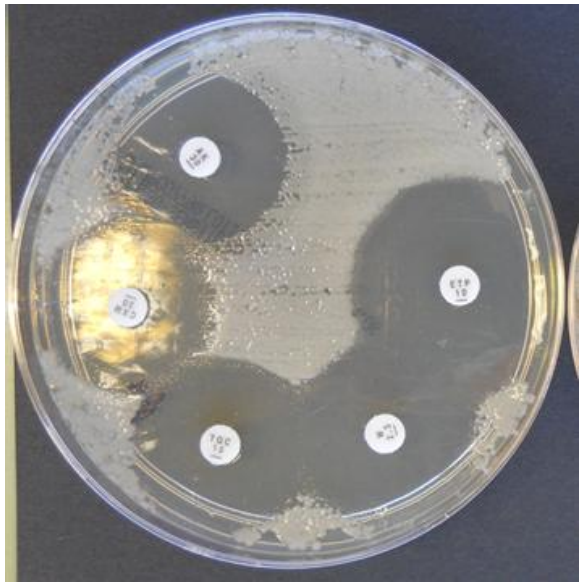
care / listen / excel

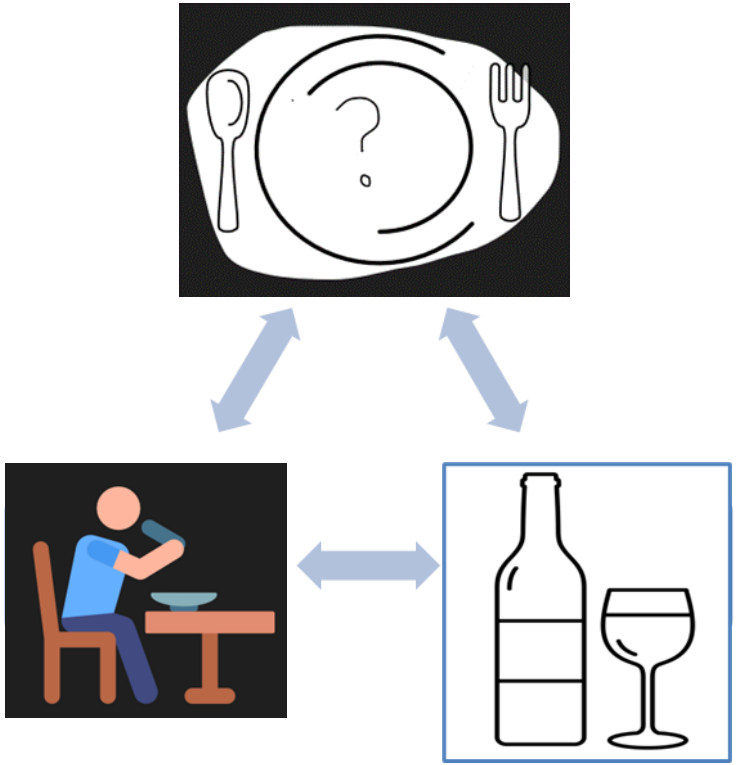
Role of the Microbiologist

- 2-Dimensional
- Bug- drug, yes or no, positive or negative
- Part of the larger picture
- Impact of patient factors
- Impact of focus of infection
- #BenchtoBedside



The Infection Sommelier





The Human Factor

“ Our study is man, as the subject of accidents or diseases. Were he always, inside and outside, cast in the same mould, instead of differing from his fellow man as much in constitution and in his reaction to stimulus as in feature, we should ere this have reached some settled principles in our art.”

William Osler

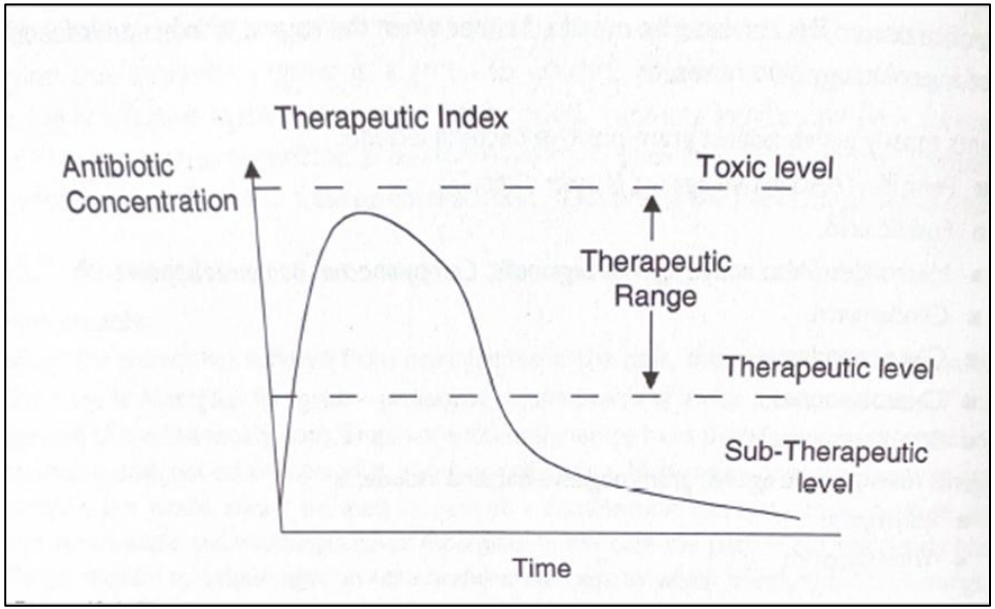
Why is TDM important?

- Bridges the gap between microbiology and biochemistry
- Precision medicine
- 3 aims of TDM:
  - Narrow therapeutic range
  - Toxicity- accumulation
  - Drug interactions

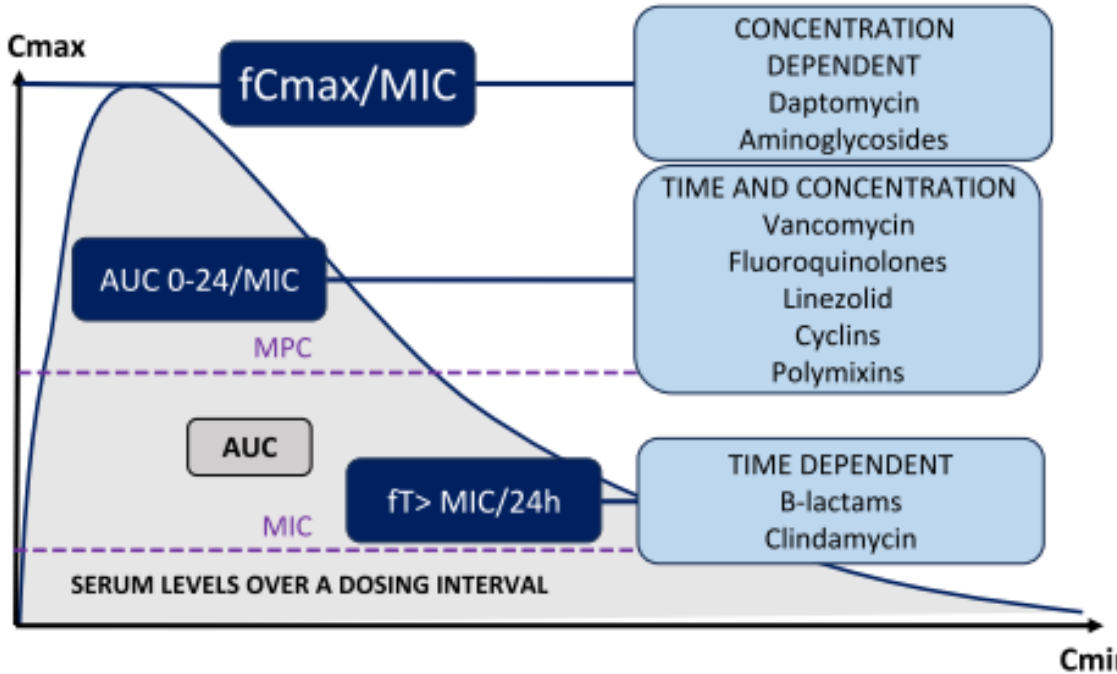
Right drug+ Right bug+ Right level

Why is TDM important?

- Majority of systemic antimicrobials do not need monitoring
- Essential:
  - Aminoglycosides
  - Glycopeptides
  - Daptomycin
  - Chloramphenicol
  - Antifungals (azoles)



Tutorial Topics in Infection for the Combined Infection Training Programme (2019) Edited by Tong et al.



Probable optimal antibiotic exposure for best patient outcome

Drug Class	Patient Group
Aminoglycosides	Cmax:MIC>8, AUC0-24/MIC≥72
Carbapenem	Cmax/MIC>5, 50-100% fT>MIC
Cephalosporins	100% T>MIC
Colistin	no data
Daptomycin	AUC0-24/MIC≥666
Quinolones	AUC0-24/MIC≥125
Vancomycin	AUC 0-24/MIC>451
Linezolid	AUC0-24/MIC≥ 85
Tigecycine	fAUC0-24/MIC ≥ 0,9

Comments:

AUC0-24/MIC=ratio of area under the concentration curve (0 to 24 hours) to MIC

Cmax/MIC = ratio of the maximum concentration of antibiotic to MIC

Cmin = minimum concentration of antibiotic

f = free fraction of the drug notbound to plasma proteins

MIC = minimum inhibitory concentration

T> MIC = Percentage of dosing interval that antibiotic concentration is above MIC

Fig. 7 Elements to consider to optimise antibiotic therapy (adapted from [81, 87]). Cmax: peak concentration; Cmin: though concentration; AUC area under the curve; MIC: minimum inhibitory concentration: is defined as the lowest concentration of a drug, which prevents visible in vitro growth of bacteria or fungi. MPC: mutation prevention concentration describes a drug concentration threshold or lowest drug concentration blocking growth of mutant bacterial sub-populations that spontaneously arise in bacterial densities of 10^7–10^9 cfu—densities seen with infection. NB: The clinical impact of other elements related to the interaction between antimicrobials and bacteria (bactericidal activity, inoculum effect, and post-antibiotic effect) are debated

Intensive Care Med https://doi.org/10.1007/s00134-025-08063-0

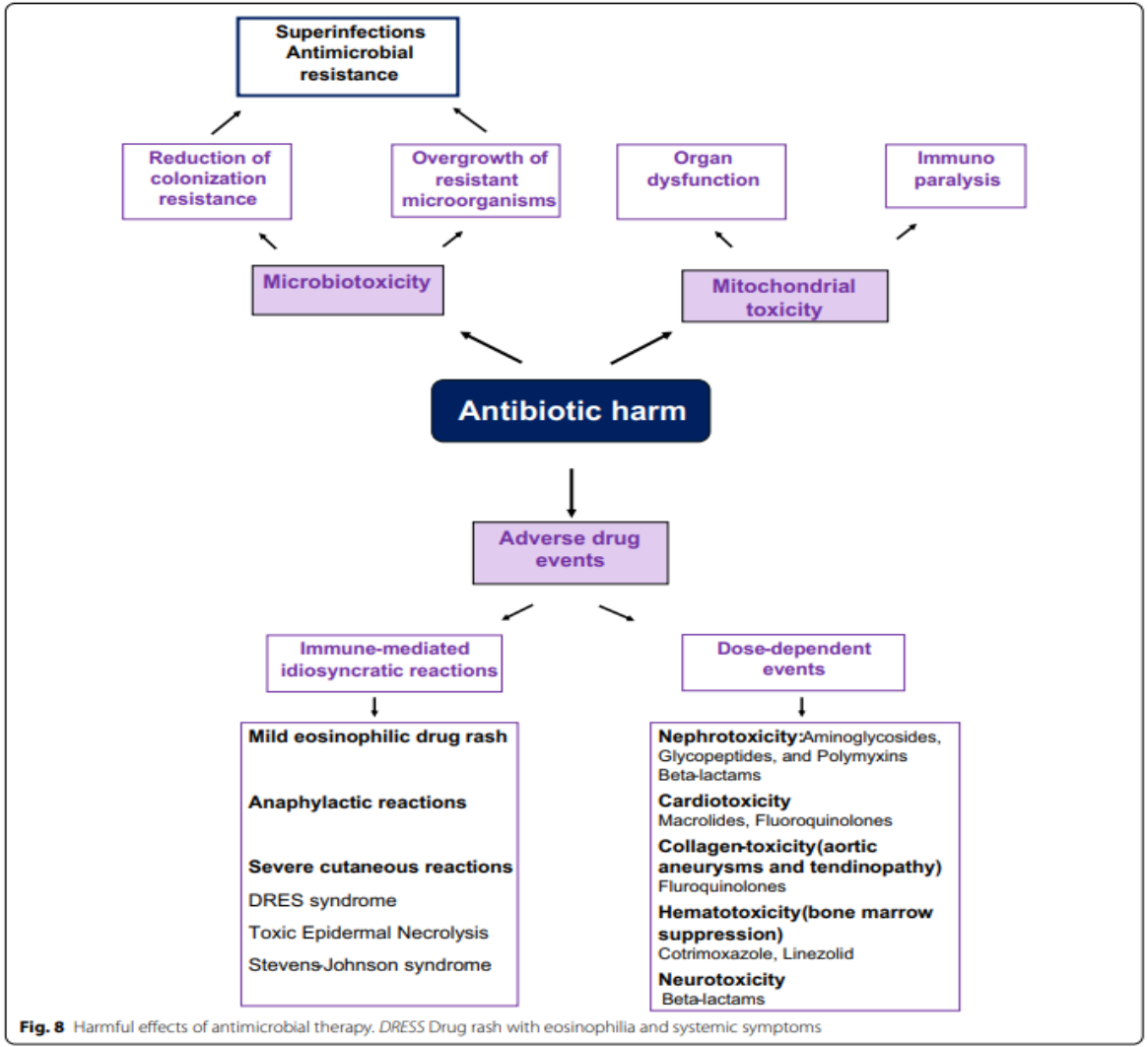
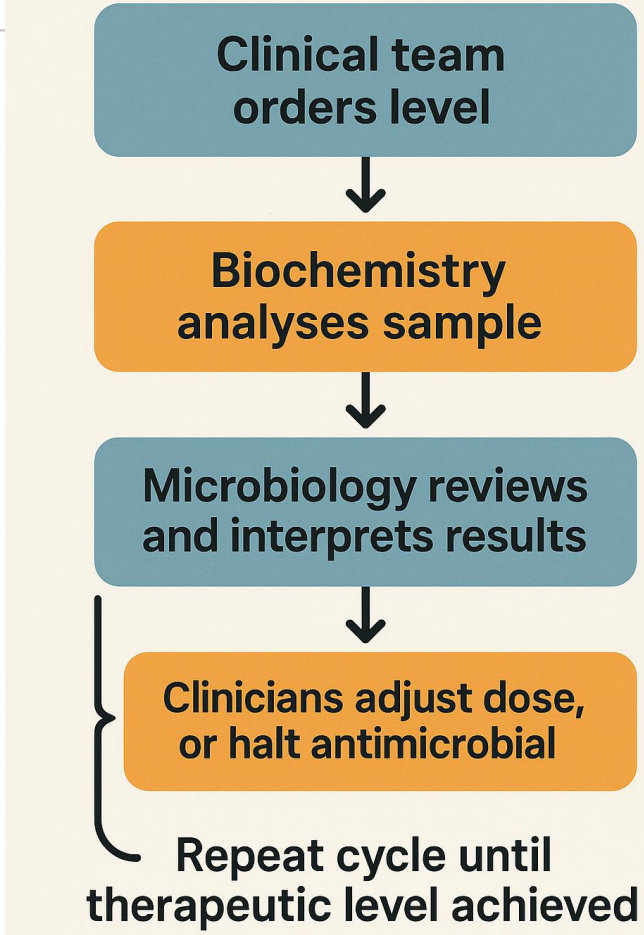


Fig. 8 Harmful effects of antimicrobial therapy. *DRESS* Drug rash with eosinophilia and systemic symptoms

The TDM Workflow

Interdisciplinary communication



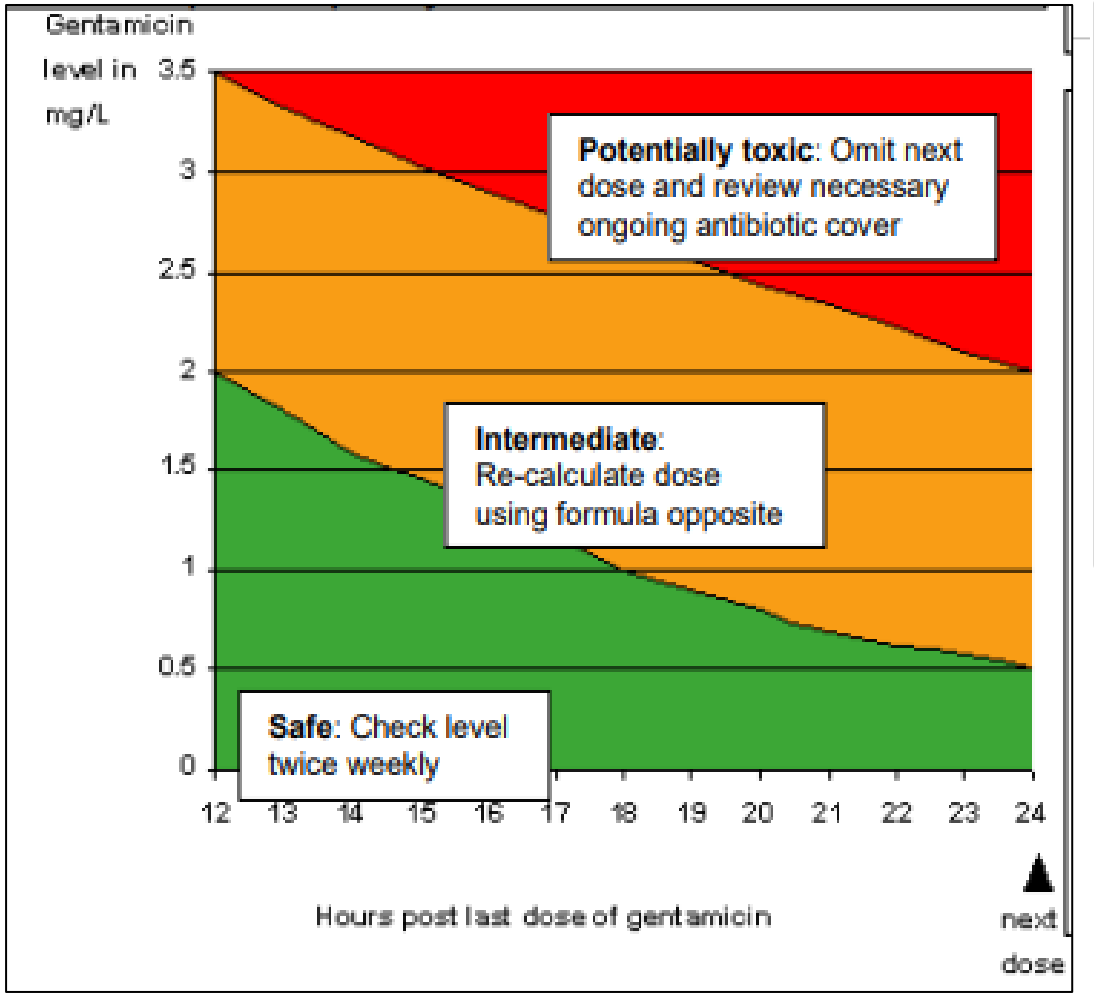
Common pitfalls in TDM

- Poor sample timing
- Misinterpreting trough (post dose) vs peak (pre-dose)
- Lack of MIC data
- Assuming ‘therapeutic’ equals ‘curative’
- Missing renal changes

Gentamicin TDM

- Aminoglycoside – concentration dependent killing
- Can be given once, twice daily or thrice daily
- Peak level (post dose)
- Trough level (pre dose)
- Dose calculated using (ideal) body weight and kidney function
- Toxicity
  - Nephrotoxicity – reversible
  - Ototoxicity – transient, irreversible high frequency hearing loss

	CrCl above 30ml/min	CrCl of 10-30ml/min	CrCl less than 10ml/min
Age 65 and over	3mg/kg* iv od	2mg/kg* iv od	**Do not use gentamicin**
Age under 65 years	5mg/kg* iv od	3mg/kg* iv od	**Do not use gentamicin**



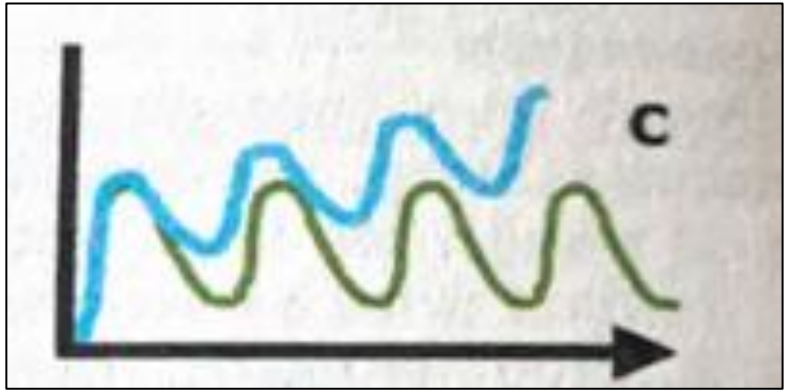
Intermediate area - Formula to re-calculate gentamicin dose:

New Dose = $\frac{\text{Previous dose x Target serum level}}{\text{Actual serum level}}$

(round new dose to the nearest 20mg)

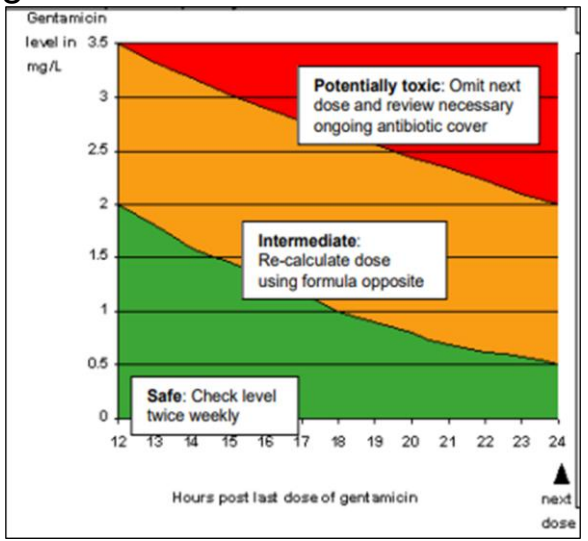
Serum gentamicin levels should be rechecked 12 to 18 hours after the new dose.

If gentamicin levels are within the recommended range, with normal renal function, monitor levels / U&Es twice weekly.



Gentamicin TDM

- 96 yr old female admitted to FAU
- Presented with acute onset abdominal pain, collapse
- BG well controlled UC, recurrent UTI (PX antibiotics), lymphoma
- Antibiotics started to cover intra abdominal infection – Amoxicillin, gentamicin and metronidazole
- Given 150 mg at 15:06 on D1
- Trough level taken 05:44 am on D2
- Level was 4.0
- Gentamicin held, re-measure if going to continue with gent
- eGFR 30
- Change to another antibiotic – less renal impact



Genetic screening

- Gentamicin commonly used in neonatal sepsis
- M.1555A>G mutation associated with risk of hearing loss following gentamicin
- Can offer an alternative antibiotics if know status
- 1,249 babies a year born with the M.1555A>G mutation
- POCT test rolled out in Scotland

Teicoplanin TDM

- Glycopeptide – time over MIC and concentration dependent killing
- Can be given once
- Requires loading doses
- Peak level (post dose)
- Trough level (pre dose)
- Dose calculated using site of infection, body weight and kidney function
- Toxicity
    - Nephrotoxicity – reversible

Teicoplanin TDM

Body weight	Respiratory, Cellulitis, Neutropenic Sepsis and Unknown Source Infections	Bone and Joint Infections	Infective Endocarditis
<50 kg	400mg	600mg	600mg
50–74 kg	600mg	800mg	800mg
75–100kg	800mg	1000mg	1000mg
>100kg	1000mg	1200mg	1200mg

Loading dose

	Respiratory, Cellulitis, Neutropenic Sepsis and Unknown Source Infections	Bone and Joint Infections	Infective Endocarditis
Frequency	12 hourly	12 hourly	12 hourly
Duration	4 doses	4 doses	5 doses

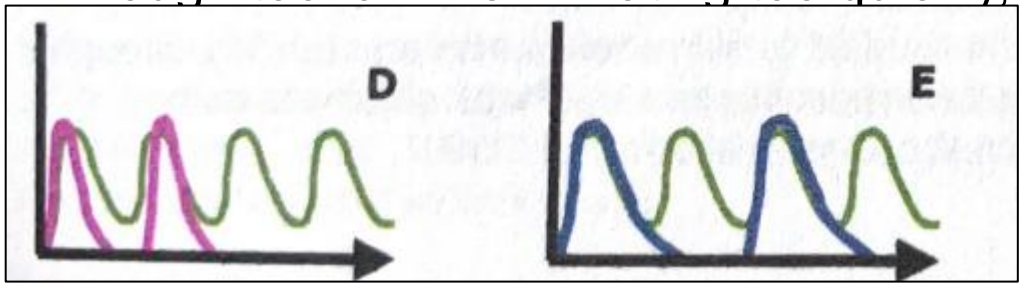
Teicoplanin TDM

- TDM not necessary if course is only 7-days then stop.
- Prolonged treatment need monitoring weekly or if renal function changes

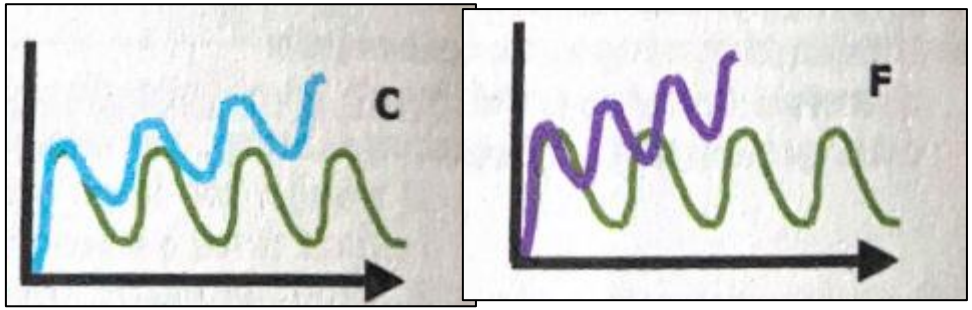
	Respiratory, Cellulitis, Neutropenic Sepsis and Unknown Source Infections	Bone and Joint Infections	Infective Endocarditis
When	**Prior to the 7th dose given including loading doses (ie. around Day 5 - 6)** For patient with renal impairment (CrCl < 30ml/min), See Teicoplanin: Dose Adjustment for Renal Impairment		
Target range	15–60mg/L	20–60mg/L	30–60mg/L

Teicoplanin TDM

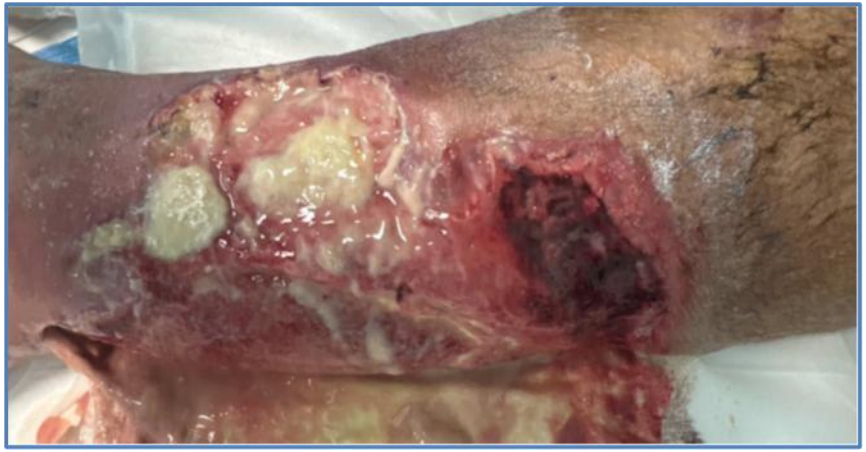
- Trough too low – eliminating too quickly, reduce time interval



- Trough too high – accumulating , increase time interval



Case Study



- 68 yr old male
- PC Fall
- Past medical history:
  - 2 x previous renal transplants
  - 1st transplant rejected
  - Longstanding pyoderma gangrenosum
  - T2DM, polycystic kidney disease, MGUS, spinal fractures, DVT, asthma
  - Immunosuppressed – tacrolimus, prednisolone, infliximab
  - Prophylactic penicillin V and ciprofloxacin

Case Study

- Apixaban 5MG BD
- Atorvastatin 10mg ON
- Tacrolimus Adoport 1.5mg BD
- Dapsone 100mg OD
- Doxazosin 1mg OM
- Empagliflolzin 10mg OM
- Gabapentin 600mg TDS
- Insulin Humulin 40 units OM
- Linagliptin 5mg OM
- Omeprazole 20mg OM
- Oxycodone MR 10mg BD
- Oxycodone Oral solution 2.5-5mg prn
- Paracetamol PRN
- Prednisone 40mg OM
- Ramipril 2.5mg OM

At admission:
CRP→130
WBC → 15.8
Neutrophils→ 13.45
NEWS → 2
eGFR→ 43

BBV screen→ negative
VZ IgG → DETECTED
BK VL→ Not detected
EBV VL→ Not detected
CMV VL→ Not detected/low level positive
T-SPOT→ Negative

Organism Pseudomonas aeruginosa
Antibiotic Panel
Antibiotic

Leg ulcer

Added AutoComments

Antibiotic Panel	Antibiotic	Report	Result	MIC
Pseudomonas	Ciprofloxacin	☑	Resistant	
Pseudomonas	Gentamicin	☐	Sensitive	
Pseudomonas	Piperacillin/tazobactam	☑	Resistant	
Pseudomonas	Tobramycin	☐	Sensitive	
Pseudomonas	Meropenem	☐	Sensitive	
Pseudomonas	Ceftazidime	☑	Resistant	

Antibiotics
Organism Pseudomonas aeruginosa
Antibiotic Panel
Antibiotic

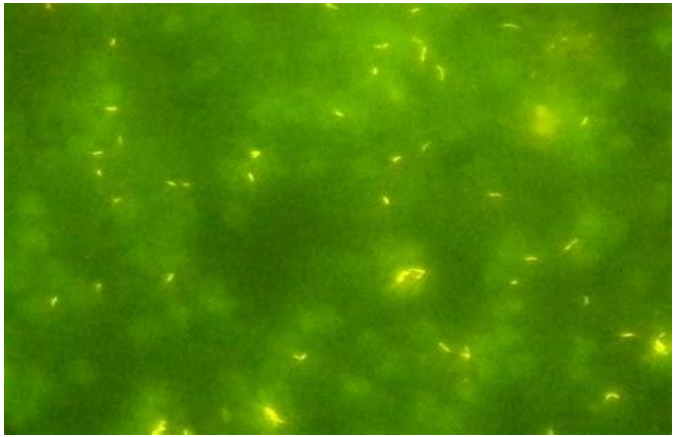
Leg ulcer

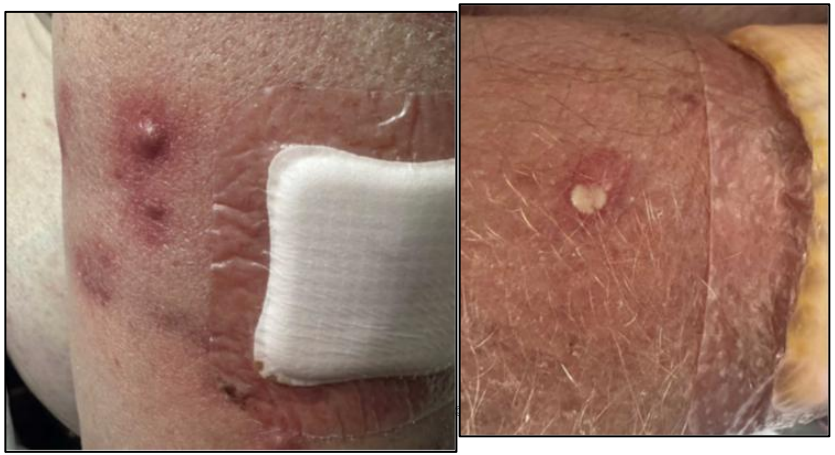
Added AutoComments

Antibiotic Panel	Antibiotic	Report	Result
Pseudomonas	Ciprofloxacin	☑	Sensitive - increased
Pseudomonas	Gentamicin	☑	Resistant
Pseudomonas	Piperacillin/tazobactam	☑	Resistant
Pseudomonas	Tobramycin	☑	Sensitive
Pseudomonas	Meropenem	☑	Sensitive
Pseudomonas	Ceftazidime	☑	Resistant

Case Study

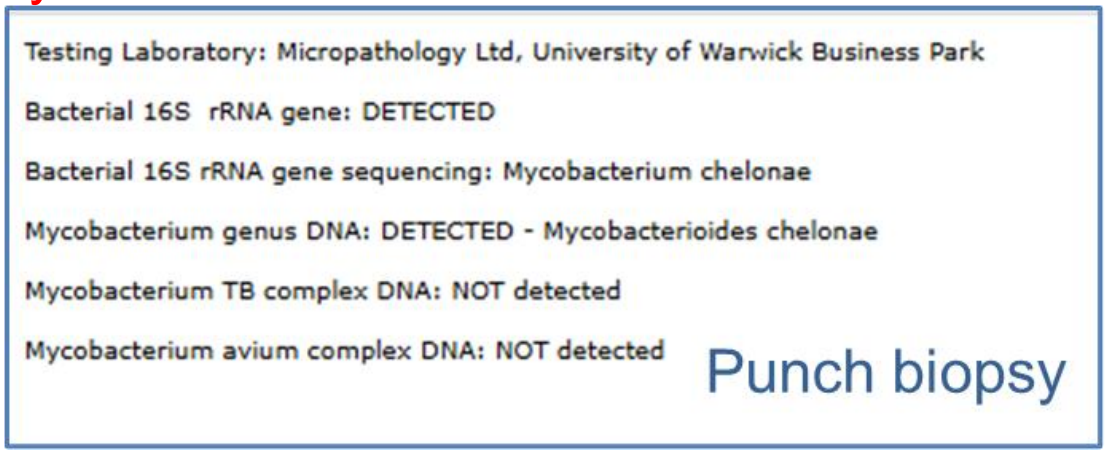
- Weaning prednisolone due to steroid induced myopathy
- Had infliximab dose
- Both biopsies smear positive for **AAFB** → PCR and culture
- Negative T-spot 7/12 ago





Case Study

- Treated with empirically clarithromycin 500mg bd, ethambutol 1500mg od and rifabutin 600mg od for AAFB, meropenem 1g tds for leg ulcers
  - clarithromycin and tacrolimus
  - rifampicin and tacrolimus
  - rifampicin and clarithromycin



Case Study

- Meropenem stopped after 11/7
- Low grade fevers every couple of days
- Fluctuating NEWS
- Re-cultured wounds – look clean
- Hallucinations
- Hold NTM treatment clarithromycin ethambutol and rifabutin - phone a friend
- Changed Clarithromycin 500mg bd, linezolid 600 mg bd and meropenem 2g tds
- Continued to monitor tacrolimus levels and adjust doses accordingly
- Minimum treatment of 4-6/12 for NTM

Future of TDM

- Genetic predisposition
- Expansion to other antimicrobials
  - Beta-lactam monitoring
- Integrated PK/PD software
  - Clinical decision aids, AI
- Personalised antimicrobial dosing
- Greater collaboration between specialities
- Greater input from clinical scientists to clinical services

Take home messages

- TDM sits at intersection between microbiology and biochemistry
- ‘Susceptible’ is not enough- need to reach therapeutic levels
- Antimicrobials aren’t safe drugs
- Biochemistry provide the accurate results
- Microbiology review in the patient context
- Together improve patient outcomes

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Thank you for listening
Any questions?