AMINOGLYCOSIDES TDM

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OUTLINE

- Introduction about Aminoglycosides.
- Spectrum/uses.
- TDM
- Aminoglycosides TDM
- Pharmacodynamics
- Pharmacokinetics.
- Dosing in AG.
- Sampeling time and Monitoring.
- Toxicity
- Cases

INTRODUCTION

- Aminoglycosides are widely used antibacterial agents, particularly for serious infections.
- They are bactericidal agents that inhibit protein synthesis.
- They have a narrow therapeutic index.

SPECTRUM/USES

- Single treatment for gm-ve bacilli.
- Empiric therapy.
- Combination with another drug for specific gm+ve infections, like Endocarditis.
- Combination with β-lactams.
- Surgical prophylaxis.

THERAPEUTIC DRUG MONITORING

To use drug concentrations to manage a patient's medication regimen and optimize the outcomes.

WHEN DO WE NEED TDM?

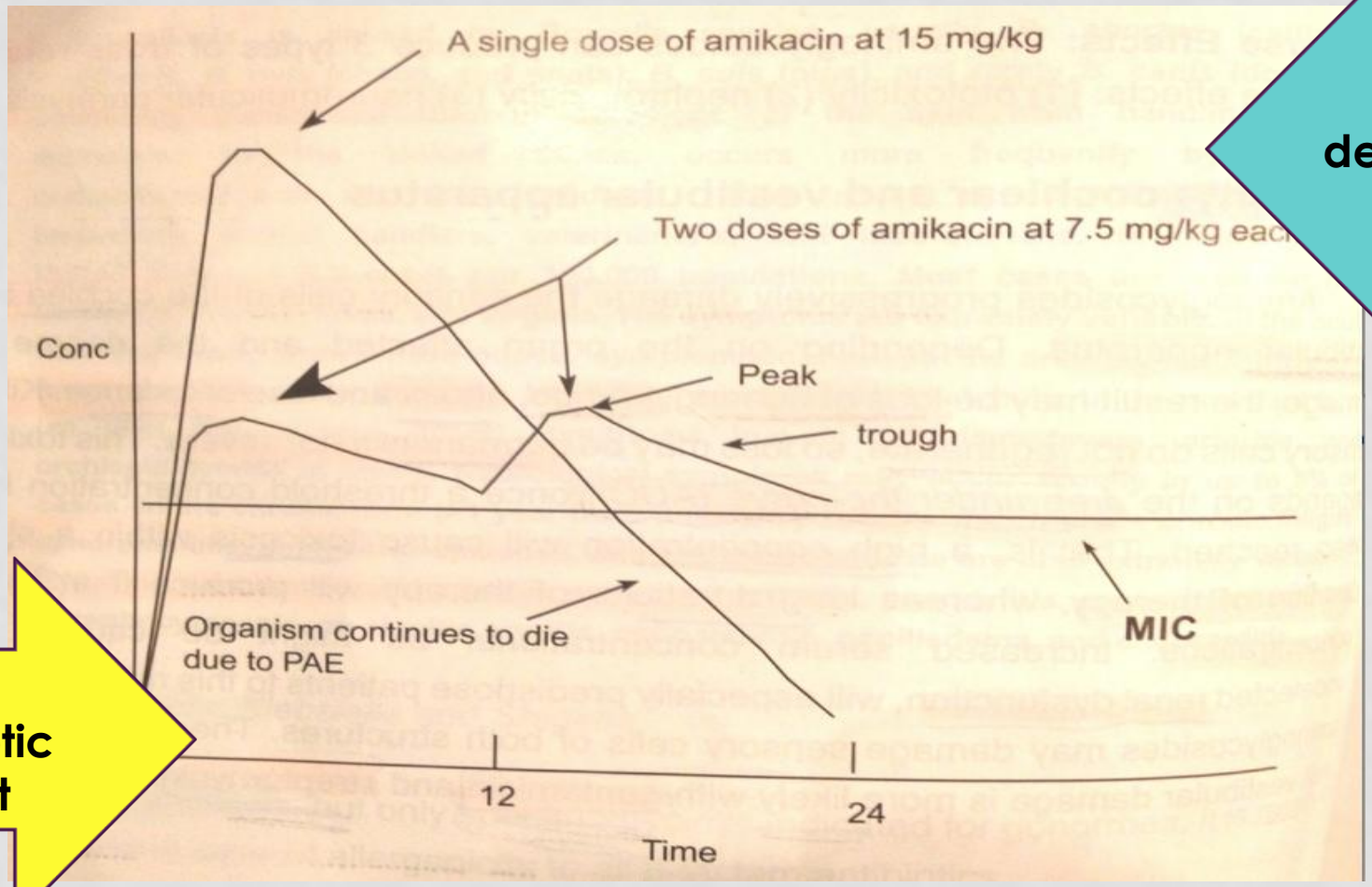
- Toxicity
- Lack of response
- Compliance assessment
- Changes in dose regimen
- Clinical state changes
- Drug interactions
- Efficacy

TDM IN AMINOGLYCOSIDES

- Narrow therapeutic index.
- Guide and monitor any dosing regimens.
- Evaluate for efficacy.
- Evaluate for potential toxicity.

Nephrotoxicity.
Ototoxicity.

PHARMACODYNAMICS



Conc. dependent killing

Post Antibiotic Effect

PHARMACOKINETICS

Absorption:

- Poorly absorbed orally, given IV infusion or

Distrubution:

- Vd ranges from 0.2 -0.4 L/kg, and is increa
  conditions.
- High conc in urine, low in CSF, bile and bronchial secretions.

Cystic fibrosis Vd= 0.35 L/kg
Ascites Vd = 0.32 L/kg

Elimination:

- Almost 99% is excreted unchanged by glomerular fil ration.
- Half life (1.5 to 3.5 hrs).

Prolonged in neonates, infants and reduced renal function

DOSING

Exclusions!

Extended interval dosing (ODD):

- Concentration dependent antibiotics.
- Optimum bactericidal activity when conc 8 -10 times the MIC.
- 7 mg/kg q24hrs. (Genta, Tobra)

Multiple daily dosing (traditional):

CrCl	Dose (gentamicin, tobramycin)
>60 ml/min	1.5-1.7 mg/kg/dose IV q8h
40-60 ml/min	1.2 - 1.5 mg/kg/dose IV q12h
20-40 ml/min	1.2-1.5 mg/kg/dose IV q12-24h
<20 ml/min	2 mg/kg loading dose

Gram positive-synergy Dosing.

CONT

- IBW (males) = 50 + (2.3 x inches above 60 inches)
- IBW, (females) = 45 + (2.3 x inches above 60 inches)
- ABW= IBW + [0.4 x (TBW - IBW)]

Dosing :

- TBW in non-obese patients.
- AdjBW as the dosing weight in obese patients.
- Calculate CrCL with the Cockcroft-Gault equation.

Loading Dose:

Site of infection or indication	Desired peak concentration	Loading dose, mg/kg
Uncomplicated lower urinary tract infection, gram-positive endocarditis, synergy with beta-lactams for serious gram-positive infections	2 to 4 µg/mL	0.6 to 1.2
Gram-negative sepsis or other serious gram-negative infections	6 to 8 µg/mL	2.5
Gram-negative pneumonia or acute life-threatening gram-negative infection in a critically ill patient	7 to 9 µg/mL	3.0

CONT

Maintenance Dose:

A. Gentamicin & Tobramycin Initial Dosing

CrCL (mL/min)	High-Dose Extended-Interval* (Gentamicin/Tobramycin)	Conventional / Traditional (Gentamicin/Tobramycin)	Synergy** (Gentamicin/Tobramycin)
> 60	7 mg/kg Q24H	1.7 mg/kg Q8H	1 mg/kg Q8H
40-59	4 – 7 mg/kg Q36H	1.7 mg/kg Q12H	1 mg/kg Q12H
30-39	4 – 7 mg/kg Q48H	1.7 mg/kg Q24H	1 mg/kg Q24H
20-29	Not recommended	1.7 mg/kg Q24H	1 mg/kg Q24H
<20	Not recommended	2 mg/kg load, then dose by level	1 mg/kg load, then dose by level
Hemodialysis	Not recommended	2 mg/kg load, then 1.5 mg/kg post-HD	1 mg/kg q48-72H; consider redosing for pre-HD or post-HD Cp < 1mg/L
CRRT	Not recommended	1.5 – 2.5 mg/kg Q24-48H	1 mg/kg Q24H, then by level

*See Hartford nomogram for monitoring of once-daily dosing regimens
**Alternative for synergy: 3mg/kg Q24H for Streptococci and *Streptococcus bovis* endocarditis

B. Amikacin Initial Dosing

CrCL (mL/min)	High-Dose Extended-Interval* (Amikacin)	Conventional / Traditional (Amikacin)
> 60	15 – 20 mg/kg Q24H	5 – 7.5 mg/kg Q8H
40-59	15 mg/kg Q36H	5 – 7.5 mg/kg Q12H
30-39	15 mg/kg Q48H	5 – 7.5 mg/kg Q24H
20-29	Not recommended	5 – 7.5 mg/kg Q24H
<20	Not recommended	5 mg/kg load, then dose by level
Hemodialysis	Not recommended	5 – 7.5 mg/kg post-HD
CRRT	Not recommended	10 mg/kg load, then 7.5 mg/kg Q24-48H

See Hartford nomogram for monitoring of once-daily dosing regimens- divide level by half then plot on graph

SPECIAL POPULATIONS

population	dosing
Neonates, children	**0-7 days old:** 4-5 mg/kg/day. **Infants-children:** 5-7.5 mg/kg/day.
Dialysis	Supplemental doses of gentamicin or tobramycin of 1 to 2 mg/kg after each dialysis.
CRRT	LD= 2-3 mg/kg MD= 1-2 mg/kg q48-72 hrs. " serum conc"
Cystic fibrosis	7.5-10.5 mg/kg/day "divided q8hr"
Burn patients	Doses up to 7 to 8 mg/kg per day.
Renal impairment "elderly"	According to CrCL "mentioned before"

SAMPLING TIME

- After three to five half-lives of the drug.
- Trough concentrations are measured within 30 minutes of the next dose.
- Peak concentrations within 30-60 minutes after the end of IV infusion, approximately 60 minutes after IM.

LEVELS MONITORING

- Peak indicates efficacy.
- Trough indicates toxicity.

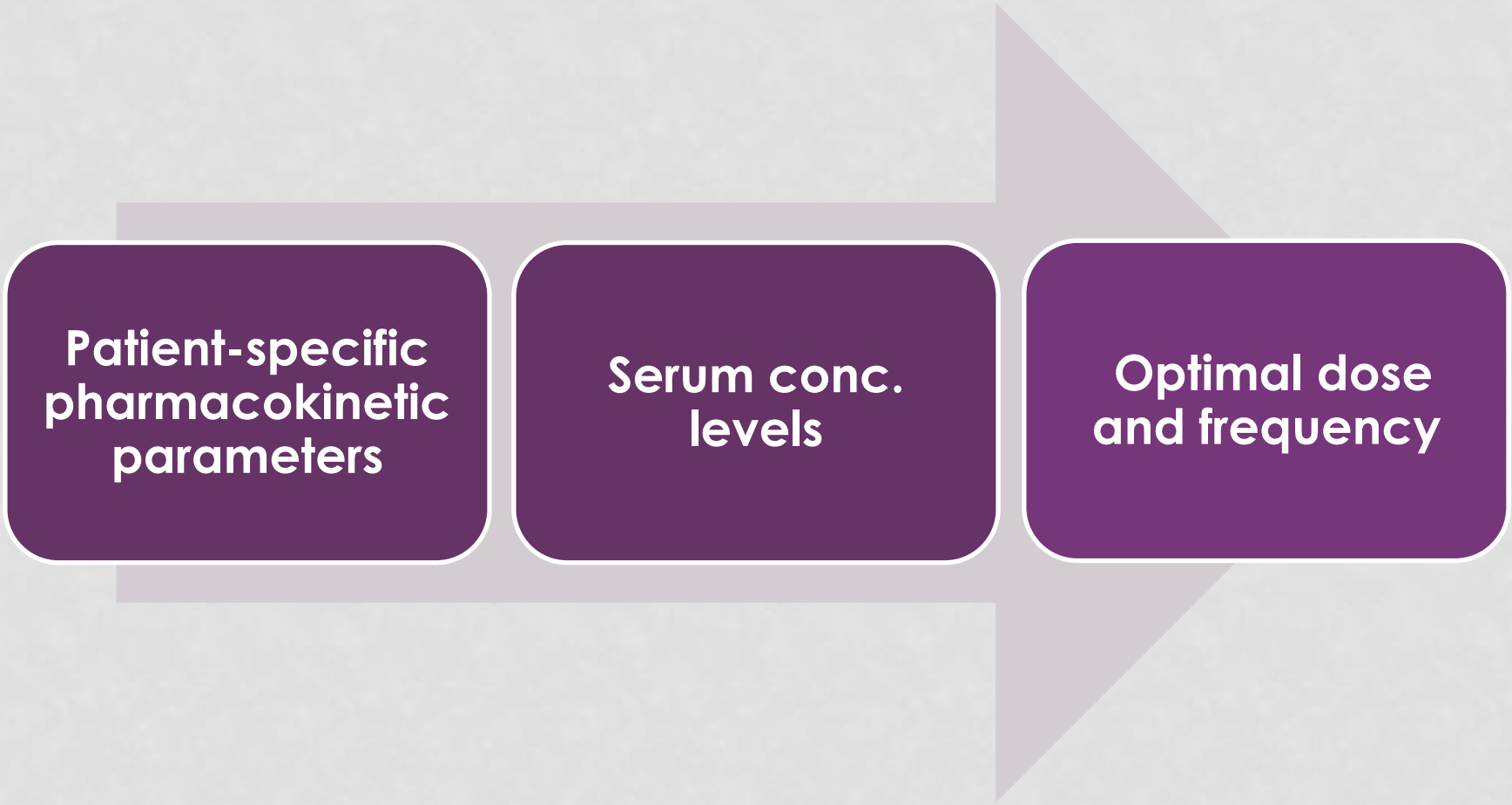
Peak

Serious infections: 6-8 mcg/mL
Life-threatening: 8-10 mcg/mL
UTI: 4-6 mcg/ml
Synergy: 3-5 mcg/mL

Trough

Serious infection:0.5-1 mcg/mL
Life-threatening: 1-2 mcg/mL
Hospital acquired pneumonia: <1 mcg/ml

INTERPRETATION+ DOSE ADJUSTMENT



TOXICITY AND MANA

- **OD.**
- **Least toxic agent.**
- **Correct electrolyte imbalance.**
- **Careful with nephrotoxic agents.**

Side effect	comments
Nephrotoxicity	• Estimated by 10-20%. • ODD vs conventional dosing. • Management.
Ototoxicity	• Can be irreversible. • cochlear and vestibular toxicit and disequilibrium.
Neuromuscular Blockade	• Most patients have disease states or a drug therapy that interfere with neuromuscular transmission. • Myasthenia gravis is an absolute contraindication

- **Same as above**
- **Autometric testing**
- **Genetic screening**
- **Family history**

CASE 1

A five years old female patient with a urinary tract infection being treated with Gentamicin 28 mg q 8hrs. She weighs 16 kg and 98 cm tall. Her serum Cr was 34. trough level came 0.4 mcg/L while peak level was 3 mcg/ml .. What's your recommendation ?

- Keep the same dose/frequency.
- Switch to a OD dosing (7 mg/kg q 24= 112 mg q24)
- Increase dose on an 8 hourly frequency.

CASE 2

- **A 55 years old male weighs 65 kg and 172 cm. Being treated with Tobramycin 110 mg q12 hrs (1.7 mg/kg) for Sepsis. Patient has serum Cr of 206, his peak level was 10 mcg/ml while trough level was 0.6 mcg/ml.. Your recommendations will be:**

- Hold dose, resample for another level.
- Decrease frequency to q 24 hrs with the same dose.
- Decrease dose and frequency.
- Do nothing.

THANK YOU

QUESTIONS?