Antibiotic dosing – any room for improvement?

Will English

“Dose optimisation may be the single most important and applicable antimicrobial stewardship strategy in the ICU”

Dellit TH et al, IDSA and SHEA guidelines, CID, 2009

Before assessing the merit of that statement plan is to re-cap some basic information …

What are bacteria?

What are antibiotics?

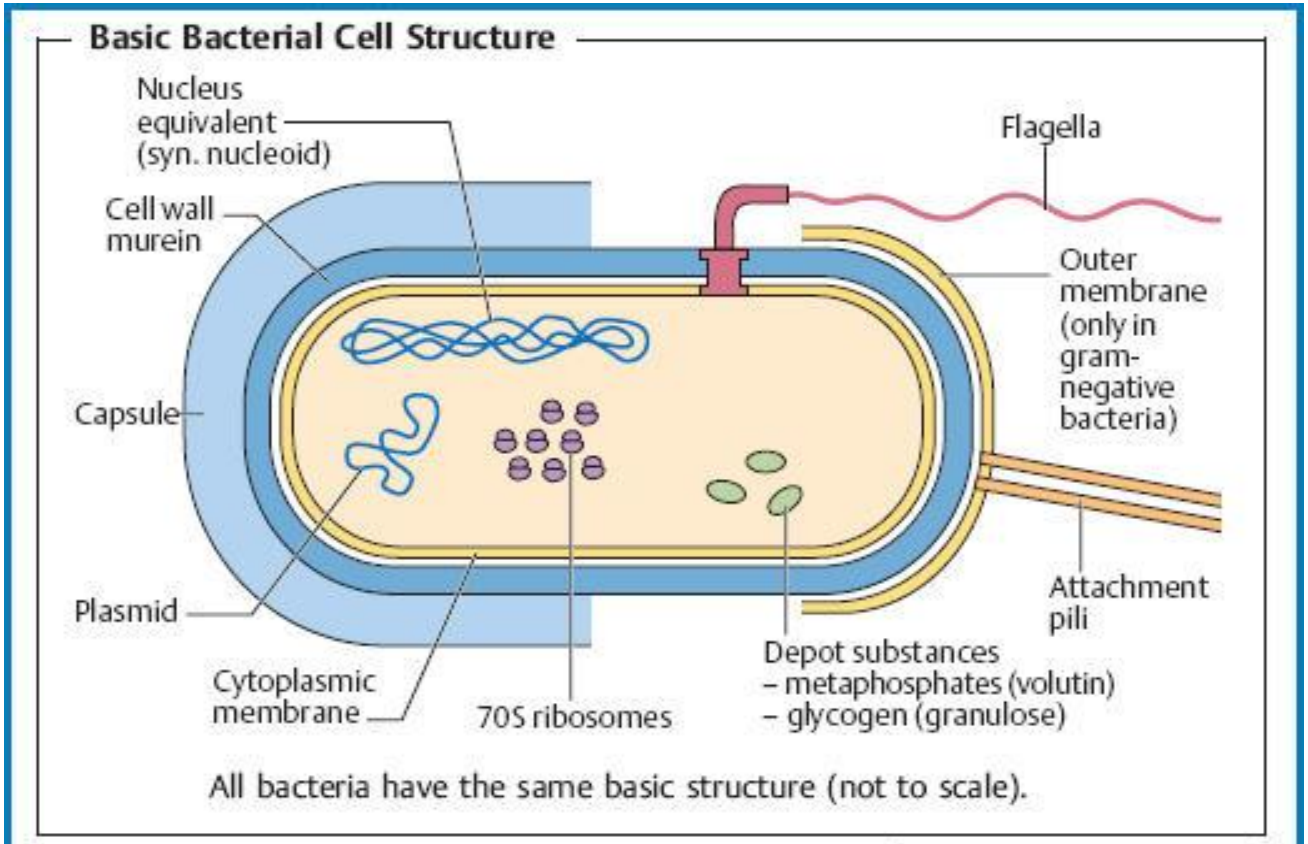
How does antibiotic resistance develop?

What are the methods for assessing dose optimisation?

Bacteria

Genome held within DNA/protein complex - nucleoid

Other genes stored in separate circular DNA structures - plasmids



Antibiotics

Agents that kill bacteria or inhibit their growth

Recorded use of mixtures with antimicrobial properties in Ancient Greece and Egypt

Many different ways to classify

Most target bacterial functions or growth processes

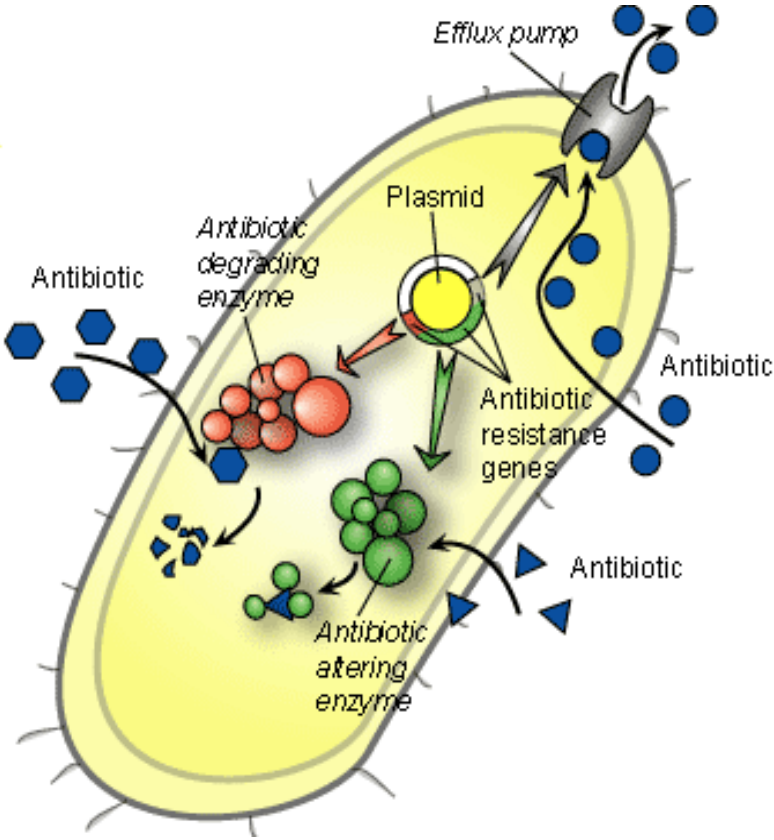
Antibiotic resistance

Intrinsic or acquired

Main mechanisms of resistance;

- enzymatic degradation of the antibiotic
- enzymatic modification of the antibiotic
- efflux or reverse transport pumps

Enzymatic inactivation most common method of acquired resistance



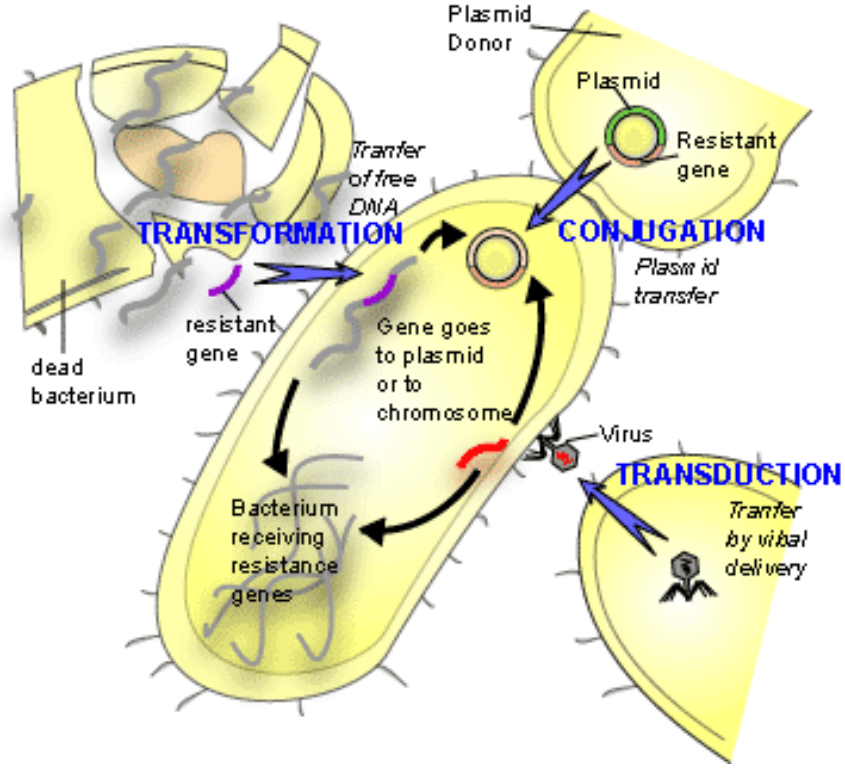
Acquired resistance

Mutation of own DNA or acquisition of resistance conferring DNA

Vertical or horizontal transmission

Horizontal gene transfer

- Conjugation
- Transformation
- Transsduction



What's the scale of the problem with multi-drug resistant organisms (MDROs) ?

Europe wide 25,000 people per year die as a result of MDRO hospital acquired infections, increasing costs by €1.5 billion pa [1]

Advances in medicine leading to an ever expanding pool of vulnerable patients

Near exponential rise in reporting of carbapenamase producing Enterobacteriacae [2]

ICUs have been described as factories for creating, disseminating and amplifying MDROs

1 EMEA ECDC technical report 2009
2 Hopkins S et al, HPA point prevalence study, 2012

How can MDROs be addressed?

Non pharmacological

- Infection prevention specific protocols
- Routine ***effective*** hand hygiene

Pharmacological

- Appropriate choice and dosing of antibiotics
- Shorter courses
- Narrower spectrum on basis of culture results
- Pharmacy restrictions

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Revisiting a few pharmacology principles

Pharmacokinetics

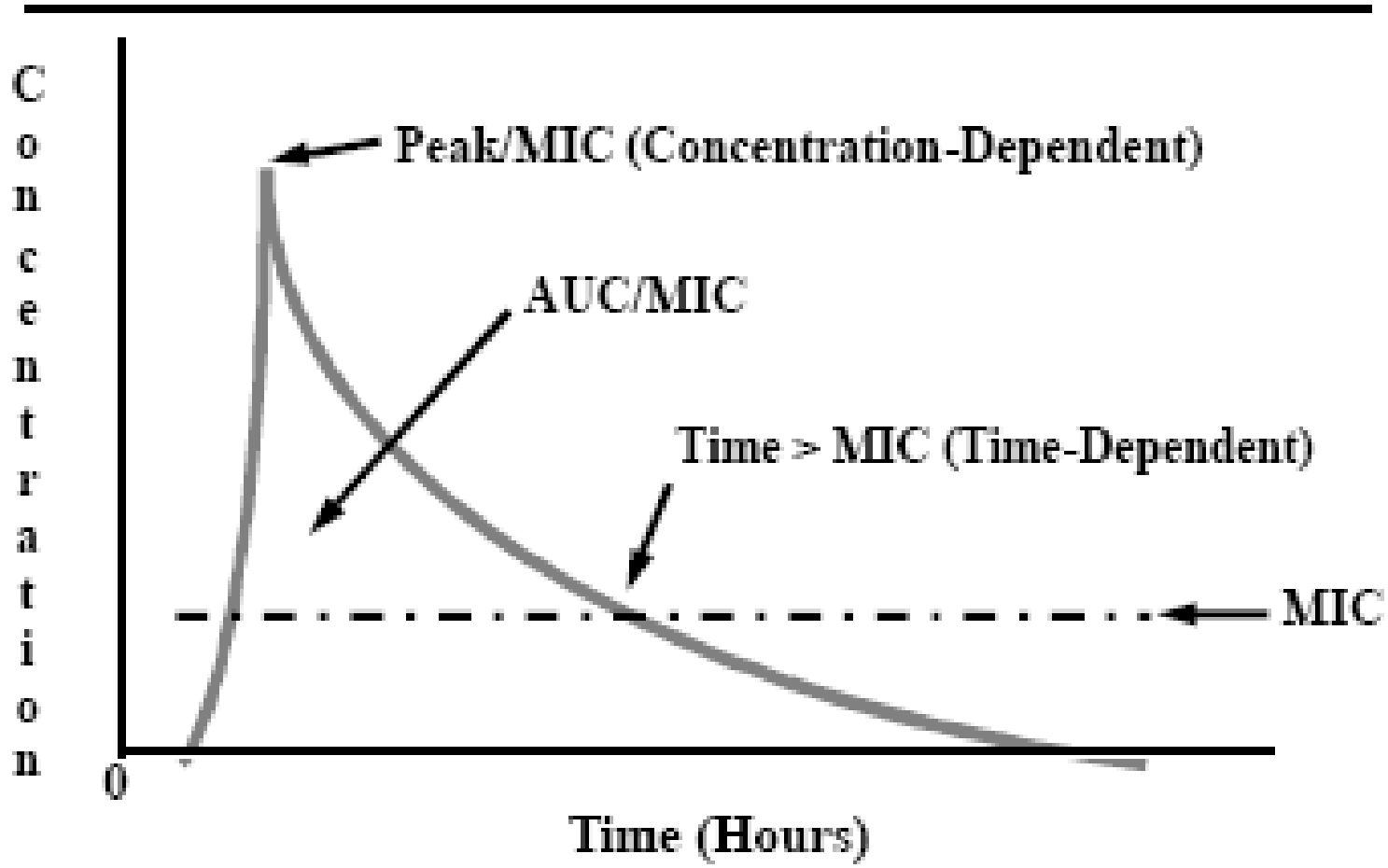
Pharmacodynamics

Time concentration curves

MIC

AUC

A typical time concentration curve



Description of antibiotic PK/PD relationships

PK parameters for time dependent antibiotics

T>MIC, AUC/MIC

Examples of time dependent antibiotics

PK parameters for concentration dependent antibiotics

CMax/MIC, AUC/MIC

Examples of concentration dependent antibiotics

Note effect of antibiotics with prolonged post antibiotic effect

β lactams

Referred to as concentration independent or time dependent killers

Whilst PK target aim is to prolong T>MIC, concentrations do not have to stay >MIC for entire dosing interval

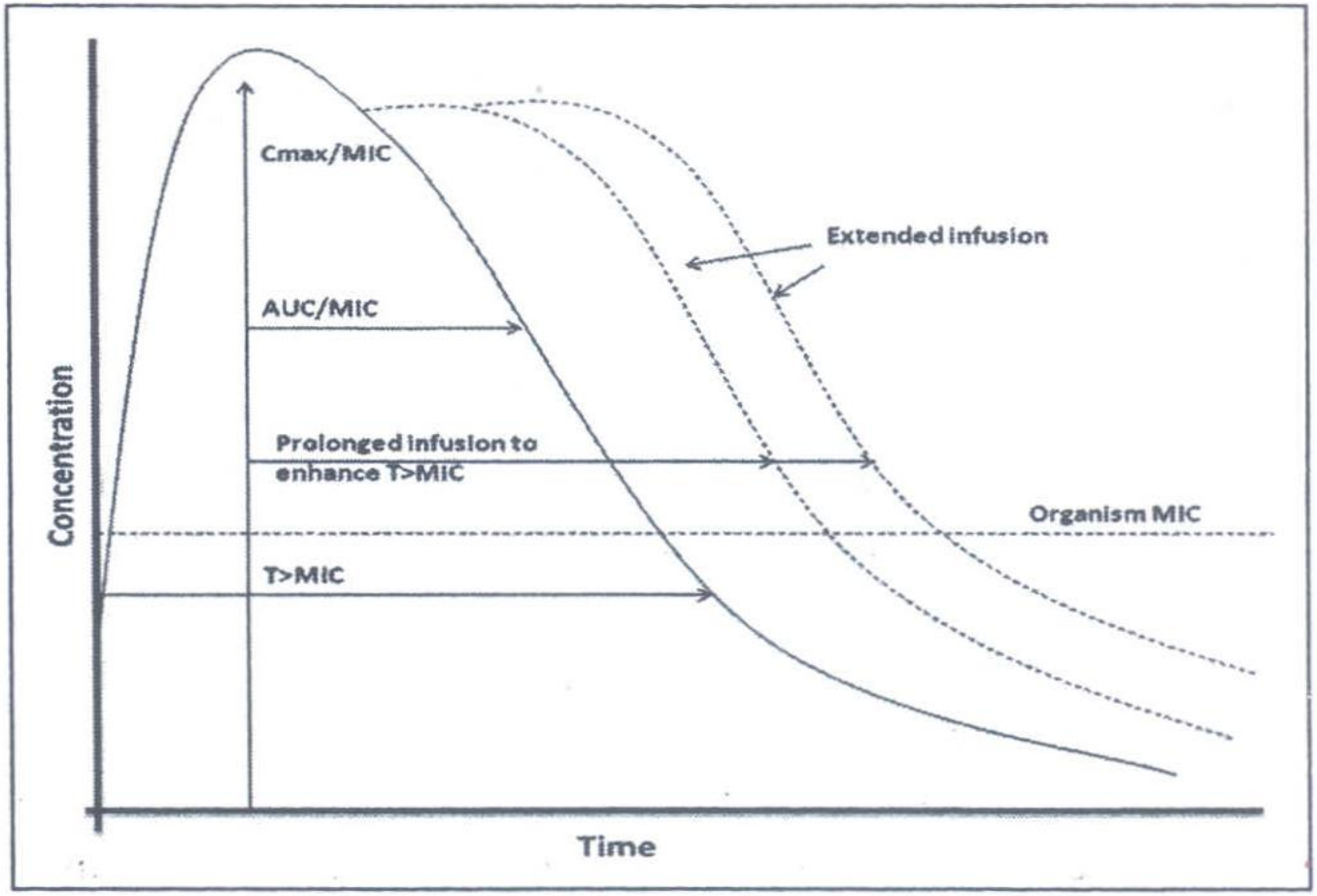
PK target for Tazocin against GNB is 50% fT>MIC

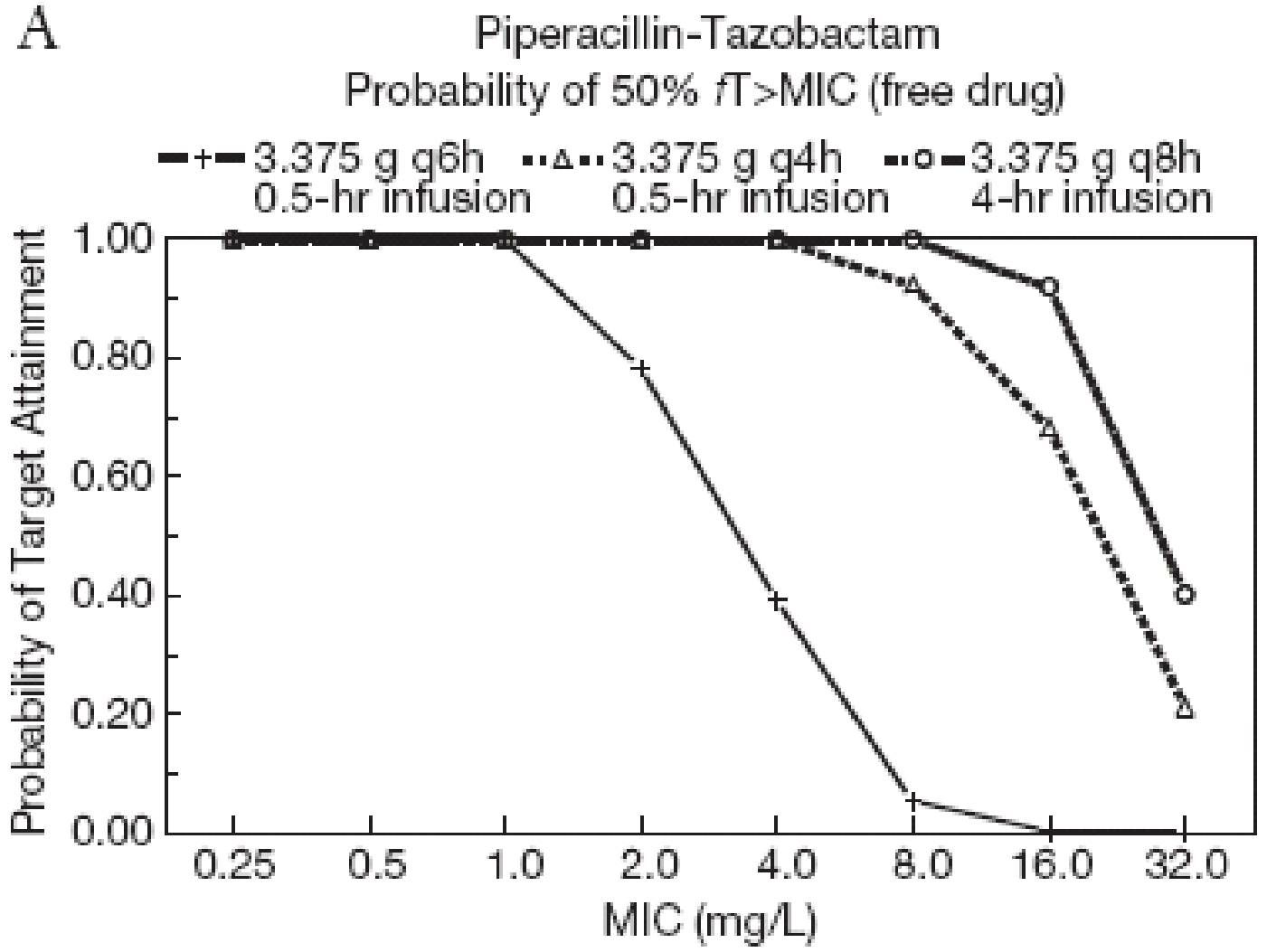
Clearly if MIC rises then T>MIC will fall

Approaches to combat rising MICs

- Dose escalation
- Extended or continuous infusions

Representation of the effect of an extended infusion time





Lodise TP et al, CID, 2007. Probability of target attainment for different dosing regimes for Tazocin against *P. auruginosa*

Dose optimisation of β lactams for improved efficacy – observational studies 1

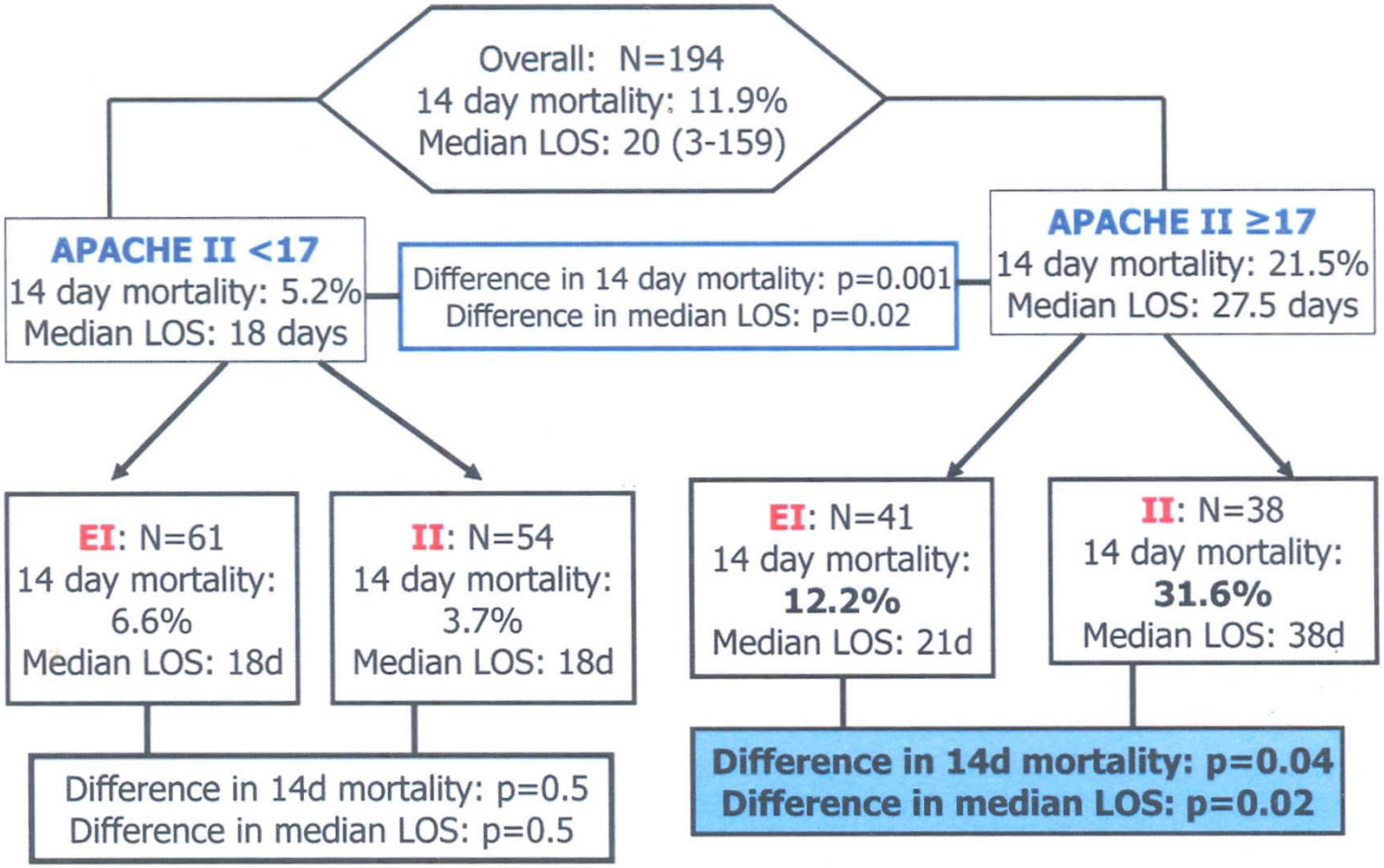
Lodise et al

Examined effect of hospital wide switch from intermittent bolus infusion of tazocin (II) to extended infusion (EI) over 4 hours in patients with a positive *P Aeurginosa* culture

Primary end points 14 day mortality, hospital length of stay after collection of positive culture

Main finding no significant difference in mortality overall

Lodise TP et al, CID, 2007



CART regression analysis to identify patients at lowest vs. greatest risk for 14-day mortality based on breakpoint APACHE II score of </≥ 17. EI= extended infusion; II= intermittent infusion; LOS= length of stay

Lodise TP et al, CID, 2007

Dose optimisation of β lactams for improved efficacy– observational studies 2

Lorente et al

Cohort study comparing continuous and intermittent infusion of tazocin for Rx of VAP in patients **without renal failure**

Significant increase seen in clinical cure rates

Lorente L et al, Int J Antimicrob Agents, 2009

Clinical cure rates (%) by infusion technique and MIC of pathogen		
MIC of pathogen	Continuous infusion	Intermittent infusion
≤ 8 mcg/ml	88.9%	40%
>8 ≤ 16 mcg/ml	87.5%	16.7%

Dose optimisation of β lactams for improved efficacy – meta-analysis

Roberts et al

Systematic review, 755 patients

14 RCTs comparing continuous (CI) or extended infusions (EI) of β lactams v bolus administration of the same antibiotic in treatment of hospital infections

Not restricted to tazocin

Primary end points, mortality and cure rates

Results

No significant improvement seen in overall survival or clinical cure rates

Roberts JA et al CM, 2009

Points to consider?

Effect of increased heterogeneity of patients in meta-analysis?

Patients in meta-analysis representative of target population?

Lack of dosing equivalence.

Few studies included PK analysis to ascertain target achievement.

Both observational studies included patients with GN sepsis.

Dose optimisation of β lactams – conclusions

Routine use of extended or continuous infusions of β lactams cannot be recommended until benefits adequately demonstrated

Some however have taken the opposite view

No convincing data to support dose optimisation of β lactams leading to decreased development of resistance

Dose optimisation of fluoroquinolones for improved efficacy

Previous target was maximising CMax/MIC

Recent attention focussed on AUC/MIC ratios

1 Forest A et al Antimicrob Agents Chemother 1993

2 Zelenitsky SA et al, J Antimicrob Chemother, 2003

3 Wispelwey B, CID, 2005

Study	**Antibiotic studied**	**AUC/MIC Value**	**Cure rate %**
Forest A et al	Ciprofloxacin	<125	42%
		>125	80%
Zelenitsky SA et al	Ciprofloxacin	>123	100%
Wisplelwey B	Levofloxacin	>100	99%
		100-25	88%
		<25	43%

Dose optimisation of fluoroquinolones for reduced antibiotic resistance

Thomas et al

- Retrospective review with some methodological issues
- Reported AUC/MIC as significant predictor of resistance
- Emergence of resistant strains
- 82.4% if AUC/MIC < 100 v 9% if ratio > 100

Jumbe et al

- Similar results
- Levofloxacin for *P Aeurugisoa*
- AUC/MIC > 157 prevented development of resistance
- AUC/MIC < 52 increased occurrence of mutations

Thomas JK et al, Antimicob Agents Chemother, 1998
Jumbe N et al, J Clin Invest, 2003

Dose optimisation of aminoglycosides for improved efficacy

More than 16 years since benefits of switching from then conventional MDD to ODD demonstrated

Historical target peak concentrations were 20mcg/ml
With average Pseudomonas MIC of 2mcg/ml obtain CMax/MIC 10 [1]

Little specific data for aminoglycosides
Fluoroquinolones – if not attain CMax/MIC >10, AUC/MIC best parameter linked to survival [2,3]

Future optimal dosing of fluoroquinolones and aminoglycosides may be based on AUC/MIC – uncertain what value

1 Lacy MK et al, CID, 1998
2 Frimodt-Moller N, Int J Antimicrob Agents, 2002
3 Drusano GL et al, Antimicrob Agents Chemother, 1993

Dose optimisation of glycopeptides for improved efficacy

T>MIC is the most widely accepted PK monitoring parameter

No definitive clinical studies have correlated serum vancomycin concentrations to clinical outcomes

Some evidence to support switch to continuous infusions

Comparable efficacy and safety for hospital acquired MRSA infections [1]
Faster attainment of target concentration with CI
36hrs +/- 31 v 51hrs +/- 39 ($p<0.05$) and less variability of AUC

Trend towards less nephrotoxicity with CI [2]

1 Wysocki M et al, Antimicrob Agents Chemother, 2001
2 Hutschala D et al, Anaesthesiology, 2009

Dose optimisation of glycopeptides for reduced antibiotic resistance

No clear evidence suggesting link between trough levels and emergence of resistance

Observed that patients with hVISA found to be more likely to have had high bacterial load with low initial serum vancomycin concentrations [1]

IDSA consensus statement to consider 25-30mg/kg loading dose in order to achieve rapid attainment of target trough level [2]

1 Charles PGP, CID, 2004

2 Rybak M et al, Am J Health-Syst Pharm, 2009

Conclusions

MDROs are a health concern of truly epic proportions

Whilst effective hand hygiene and infection control procedures are of paramount importance, there has been some very interesting work investigating what constitutes optimal antibiotic dosing

However, I do not believe that
“Dose optimisation will be the single most important and applicable antimicrobial stewardship strategy in the ICU”

Conclusions

PK/PD principles should be given greater consideration in daily practice

I believe that antibiotic dose optimisation is an area that requires vigorous research, with the aim of providing more effective ways to both treat infections and slow the development of antimicrobial resistance

Close collaboration is required between critical care and both medical microbiology and pharmacy in order to deliver appropriate antimicrobial therapy