Interactive Session:

How to optimise the use of IV antibiotics

CASE HISTORY

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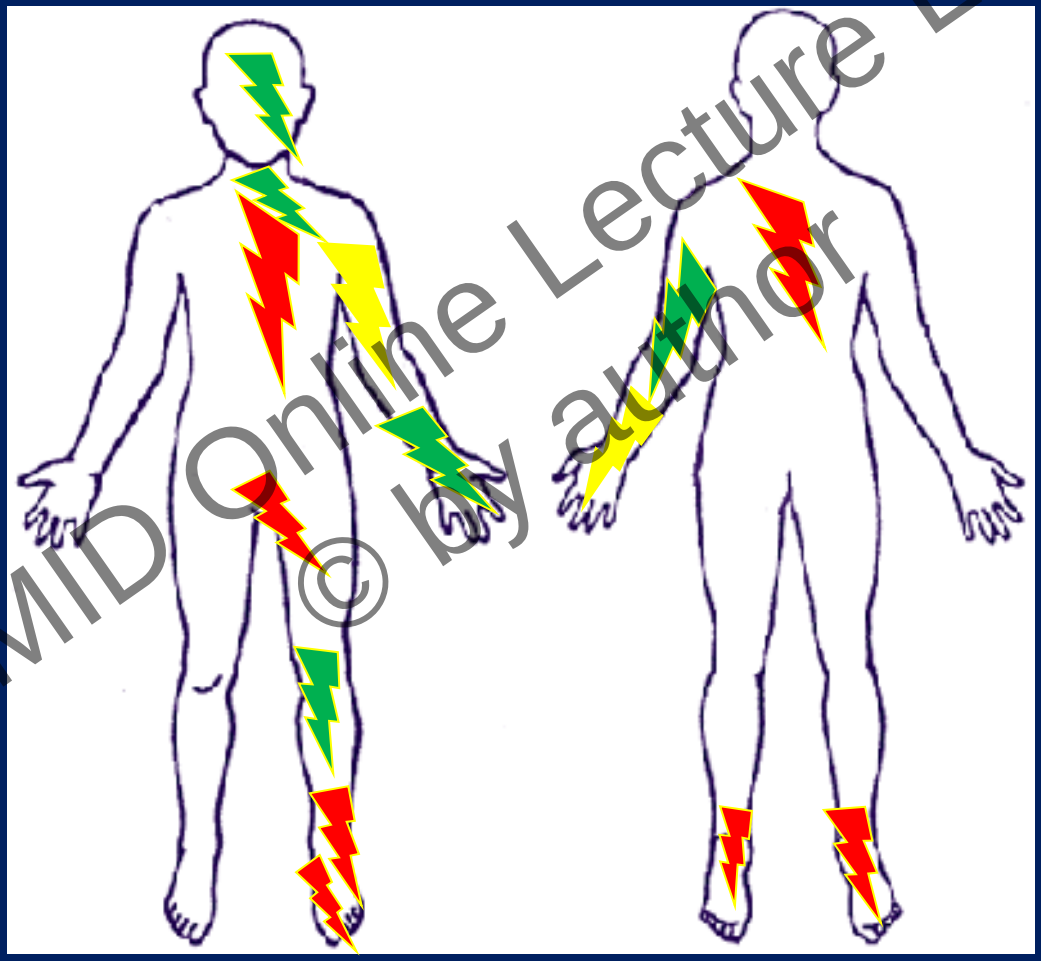
Case

- April 13th 2014
  Plastic surgeon: notified the Infection Doctor of a patient coming home from India with severe burns.
- He has been in two Indian hospitals recently
- He has had various antibiotics – not sure which ones – don't think he has completed a full course of any treatment.
- In complete information available.
- 'Could he have the multi resistant New Delhi bug??'
- Patient en route to your hospital now.

Immediate Plan:-

- Isolate patient in single room on burns and plastics ward, strict infection control practice
- Screen patient for multi-resistant GNBs on arrival
- Assume he has a multi-resistant organism until known otherwise

13.4.14 initial screening swab sites

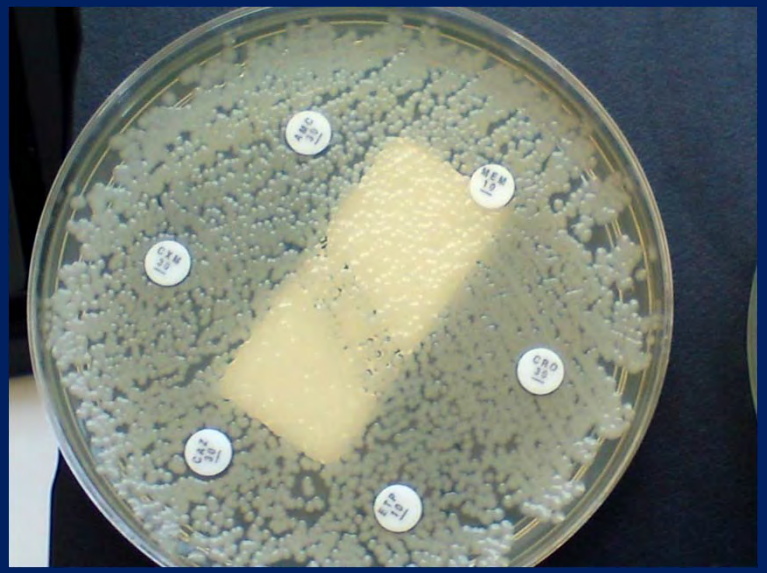


Burns swabs:

- Swabs received from 14 burn skin sites
- 7 swabs growing various and GNBs with unusual sensitivity patterns...

CA

CAX



E.coli from burn sites (red)

ampicillin^{R}, co-amoxiclav^{R,} piperacillin/tazobactam^{R}, ertapenem^{R}, meropenem^{R}, gentamicin^{R}, ciprofloxacin^{R}, co-trimoxazole^{R}, ceftriaxone^{R}, ceftazidime^{R}

Clinical Progress:

Stable on admission: burn to left arm so severe that amputation performed. After dressings changed, becomes hypotensive, febrile, tachycardic.

Blood cultures taken.

Blood cultures:

Gram GNB MALDI-TOF, E.coli direct from blood culture bottles

What to do next?

What to do next?

a) Commence colistin

b) Commence colistin+meropenem

c) Commence colistin+meropenem+tigecycline

d) Commence piperacillin-tazobactam

e) Commence tigecycline+fosfomycin

f) Commence amikacin+temocilin

g) Perform further susceptibilities

h) Perform MICs on resistant agents

What additional laboratory test would you do?

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Amikacin

Minocycline

Tigecycline

Fosfomycin

Temocilliin

Mecillinam

Colistin

Aztreonam

E.coli MIC values and interpretations

	MIC mg/L)
Ampicillin	>128
Co-amoxiclav	>128
Piperacillin/tazobactam	32
Ertapenem	2
Meropenem	8
Gentamicin	<128
Ciprofloxacin	>128
Co-trimoxazole	>128
Ceftriaxone	>128
Ceftazidime	>128
Amikacin	4
Minocycline	4
Tigecycline	2
Fosfomycin	2
Temocillin	>128
Colistin	8
Aztreonam	>128

E.coli MIC values and interpretations

	MIC mg/L)	Potential categorisation
Ampicillin	>128	R
Co-amoxiclav	>128	R
Piperacillin/tazobactam	32	I/R
Ertapenem	2	I/R
Meropenem	8	I/R
Gentamicin	<128	R
Ciprofloxacin	>128	R
Co-trimoxazole	>128	R
Ceftriaxone	>128	R
Ceftazidime	>128	R
Amikacin	4	S
Minocycline	4	-
Tigecycline	2	I/R
Fosfomycin	2	S
Temocillin	>128	R
Colistin	8	R
Aztreonam	>128	R

Dosing strategies for treating pathogens with elevated but borderline MICs

Aminoglycosides	1) 24hrly dosing 2) 8-12hrly dosing 3) prolonged/continuous infusion
B.lactams	1) 24hrly dosing 2) 6-8-12hrly dosing 3) prolonged/continuous infusion
Tigecycline	1) 24hrly dosing 2) 12hrly dosing 3) prolonged/continuous infusion

What new agents would you test?

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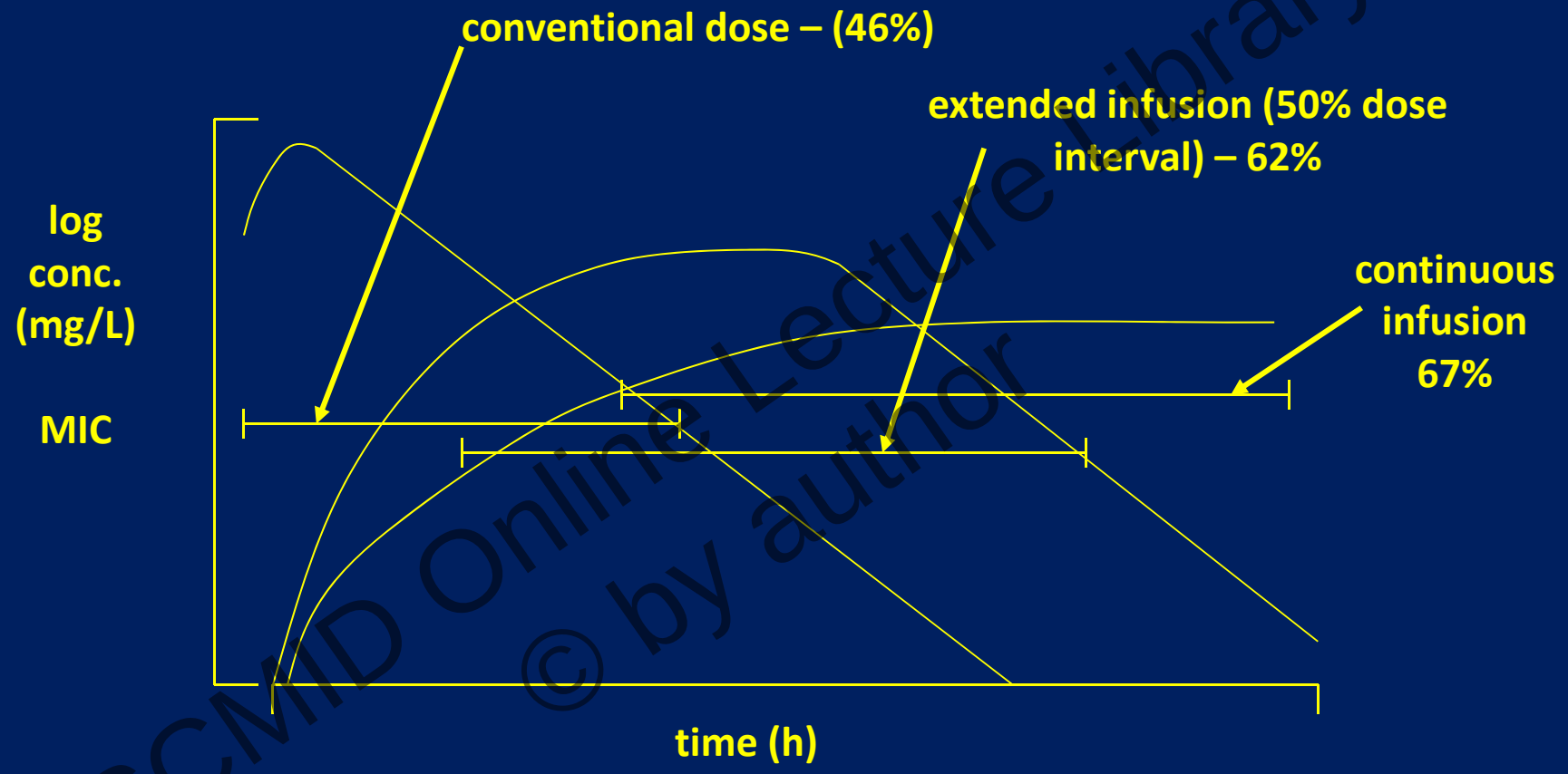
	MIC mg/L
Ceftazidime-avibactam	0.5
Ceftolozane-tazobactam	≥64
Aztreonam-avibactam	0.5

Case Study: Optimisation of B.lactam Therapy

Strategies for increasing optimums for antibacterial killing/B.lactam clearance T>MIC

- give more drug (bigger doses) at same frequency
- give same amount more frequently
- prolong half-life/reduce clearance
- extend period of infusion/continuous infusion

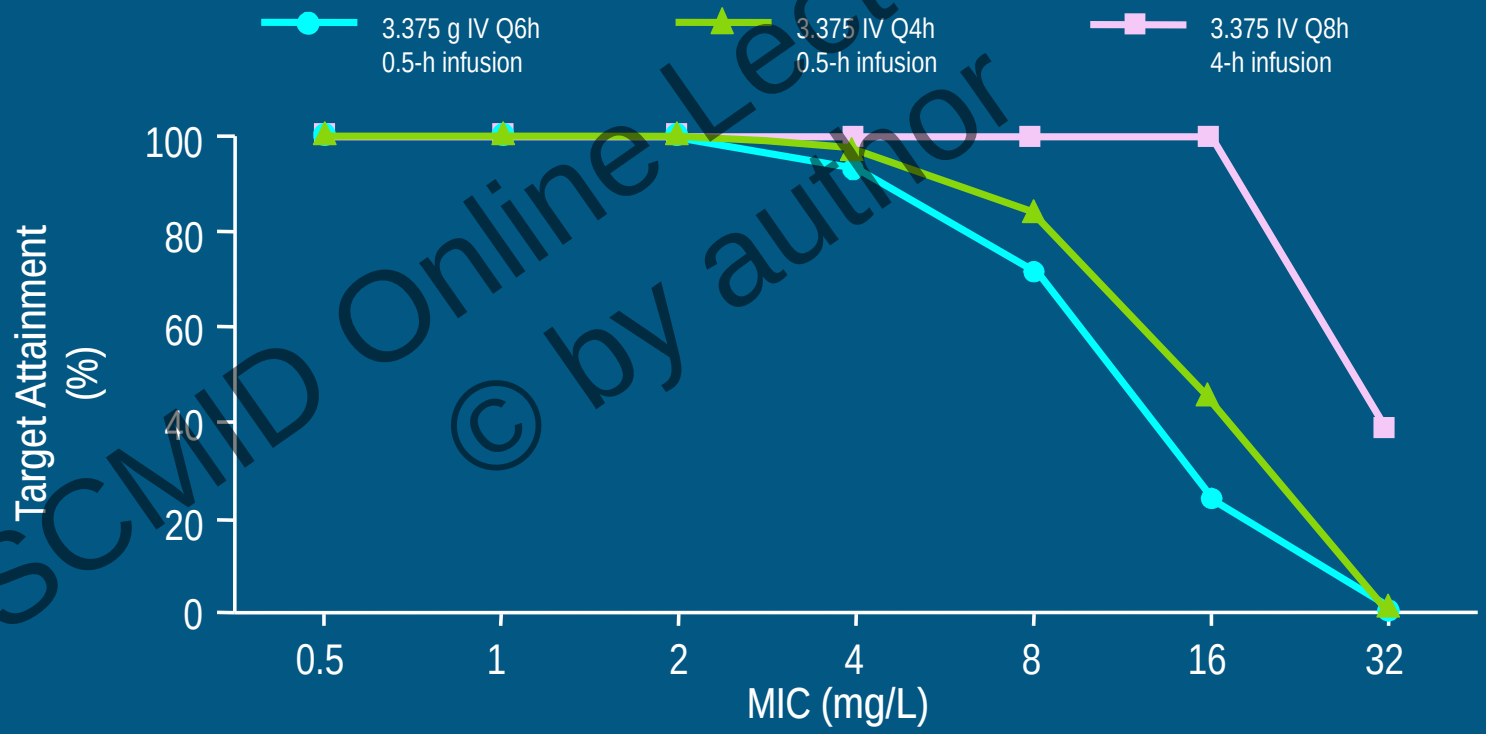


but: at high MICs T>MIC low despite dosing

: at low MICs T>MIC high, whatever dosing

Pharmacodynamic Profiling of Piperacillin-Tazobactam by Monte Carlo Simulation

PD Target = 50% T>MIC for pathogens at Albany Medical Center



Lodise TP et al. *CID*. 2007;44:357-363.

Comparison of EUCAST clinical breakpoints for standard dosing compound to save doses by PI or CI

	Clinical breakpoint (mg/L)		PI/CI breakpoint (mg/L)
	Enterobacteriaceae	*P.aeruginosa*	
ceftazidime	≤1	≤8	≤16
doripenem	≤1	≤1	≤4
meropenem	≤2	≤2	≤8
pip/tazobactam	≤8	≤16	≤16
meropenem 6g/day	-	-	≤16

For piperacillin/tazobactam

What are the MIC distributions?

(www.bsacsurv.org; UK bacteraemia isolates 2001-05)

	% of distribution with each MIC							
	E coli (n=1216)		P. aeruginosa (n=927)		Serratia (n=315)		Acinetobacter (n=1721)	
≤ 0.5	6.5		1.5		5.7		53.5	
1	14.2		1.2		21.6		5.2	
2	40.8		11.0		29.5		6.4	
4	25.4		50.5		10.8		11.6	
8	9.3	13.9	17.7	27.7	7.3	12.4	4.1	8.2
16	4.6		10.0		5.1		4.1	
32	2.2		4.3		11.4		3.5	
≥ 64	2.7		3.8		8.5		11.7	

Impact of continuous infusion (CI) versus intermittent infusion (II) with non-concentration dependant antibacterials

Kasiakou et al, Drugs 65, 2499-511, 2005

Systematic review of RCT to evaluated PK and PD of CI vs II
(Jan 1950-Jan 2005)

Found 17 RCTs

Cmax higher in II than CI
Cmax 5.5 (1.9 – 11.2) x higher C_{ss} CI
C_{ss} (CI 5.8 (1.2 – 15.6) x higher C_{MIN} II

3/6 studies reported longer T>MIC

"data suggested that CI antibacterials with time dependant killing seems superior to II dosing from a PD view at least when treating bacteria with high MICs for the studied drugs"

Roberts et al, 2009; Crit Car Med 2009; 37 2071

RCTs in meta analysis
14 studies, 846 patients, 9 countries

- **Not associated with improvement in clinical cure (n=755 OR 1.04; 0.74-1.46)**
- **Not associated with improvement in mortality (n=541 OR 1.0; 0.48-2.06)**

However, in RCTs, bolis injections groups received a higher dose of antibiotic in most studies

How are you going to dose this patient?

How are you going to dose this patient?

a) Piperacillin-tazobactam 4.5g PI 6hrly or 18g over 24hr

b) P/T 4.5g load then 4.5g PI 6hrly or 18g over 24hr

a) Meropenem 1g PI 8hrly or 3g over 24hr

b) Meropenem 1g load then 1g PI 8hrly or 3g over 24hr

c) Meropenem 2g PI 8hrly or 6g over 24hr

d) Meropenem 2g load then 2g PI 8hrly or 6g over 24hr

e) One of the above plus a second agent

Why give a second agent?

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Yes: Give	No: With-hold
	- toxicity (amikacin)
- Prevent resistance	- emergence of resistance (fosfomycin)
- Increase ability to reduce - bacterial load	- uncertain effect on bacterial load
- Up regulation of B.lactamase	- No good trials evidence
- Uncontrolled observational data supports	

Would you now measure meropenem or pip/tazobactam serum concentrations?

If YES, what is your target?

Piperacillin-tazobactam concentrations in ICU patients with Gram-negative pulmonary infection receiving 4.5g TDS or QDS

Patient	Piperacillin concentration (mg/L)		Tazobactam concentration (mg/L)		Pathogen	MIC (mg/L)	Optimised for T>MIC 100%
	pre	post	pre	post			
1	2.2	46.2	0.7	1.3	E.coli	24	No
2	163.4	324.3	37.3	40.4	Enterobacter	≤8	Yes
3	97.8	205.8	3.3	3.4	Coliform	6	Yes
4	<1	24.6	3.0	11.8	E.coli	2	No
					Klebsiella	3	
5	14.0	56.6	6.5	7.9	P.aeruginosa	6	Yes
6	1.5	28.8	0.9	1.4	A.baumannii	1.5	Yes
7	29.1	153.8	2.4	4.0	P.aeruginosa	8	Yes
8	8.6	89.5	0.9	5.3	P.aeruginosa	3	Yes
9	<1	28.1	2.1	13.8	E.coli	1.0	No
					S.aureus	0.75	
Mean ± SD	35.4 ± 57.1	106.4 ± 103.0	6.3 ± 11.7	9.9 ± 12.2			Yes = 6 No = 3

Some basic principles in treating MDR Gram-negative rods

- Identify the species
- Know the MICs to a wide range of agents
- Focus on MICs in susceptible range of which are pharmacodynamically treatable with large doses and optimised regimens
- Adjust doses to be maximal and take advantage of the drugs PD properties
- Determine serum concentrations and adjust as needed
- Think about second agents and probably add
- Check for microbiological eradiation blood, CSF, urine, BAL as appropriate
- If re-isolate pathogens re-check susceptibility
- Remember about more common cases of therapeutic failure