Optimisation of therapy : general principles

Translational basic research for old antibiotics: What is lacking?

Alasdair MacGowan
Public Health England, North Bristol NHS Trust, University of Bristol

Bristol Centre for Antimicrobial Research & Evaluation (BCARE)

www.bcare.nbt.nhs.uk

ESCMID Online Lecture Library
© by author

Forgotten antibiotics (Pulcini et al, 2012)

temocillin
pristinamycin
fosfomycin iv/po
quinupristin-dalfopristin
mecillinam/pivmecillinam
aztreonam
chloramphenicol
trimethoprim
fusidic acid
colistin

In addition -

Revived antibiotics/old antibiotics in ICU
(Cassir et al, 2014; Falagas & Kopterides 2007)

teicoplanin
nitrofurantoin
co-trimoxazole
clindamycin
isepamicin
minocycline iv

ESCMID Online Lecture Library
©by author

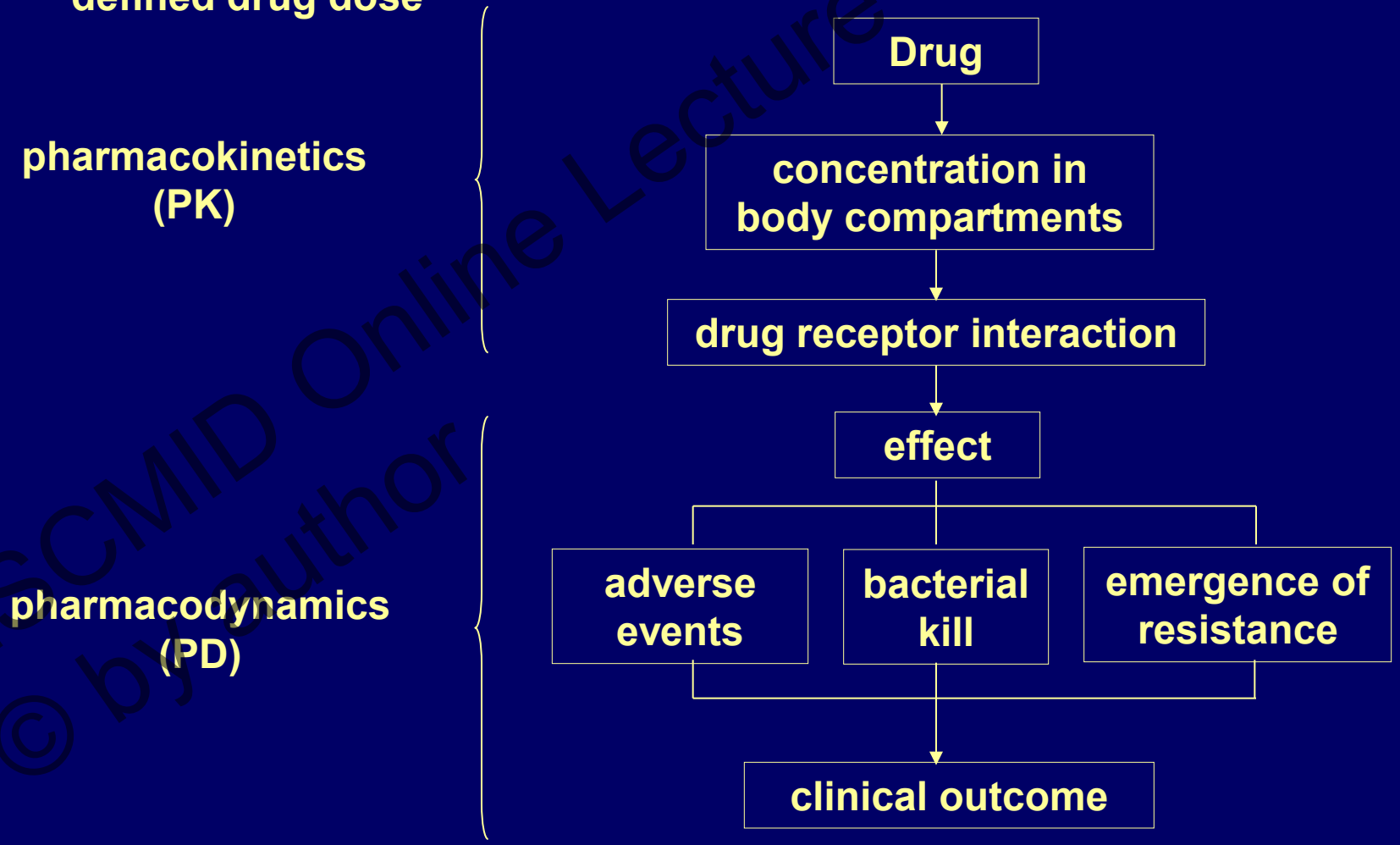
Topics

- what basic science PK-PD do we need for old antibiotics?
- how does this contribute to wiser and sustainable use of old antibiotics?
- assessment of gaps in the knowledge base

ESCMID Online Lecture Library
© by author

Objectives of PK-PD optimisation

- maximise bacterial inhibition/kill for a defined drug dose
- minimise risk of emergence of antibacterial resistance for a defined drug dose



ESCMID Online Lecture Library
© by author

Basic PK-PD questions in developing anti infective dosing regimen

Which dose?

Which frequency of dosing?

Which duration?

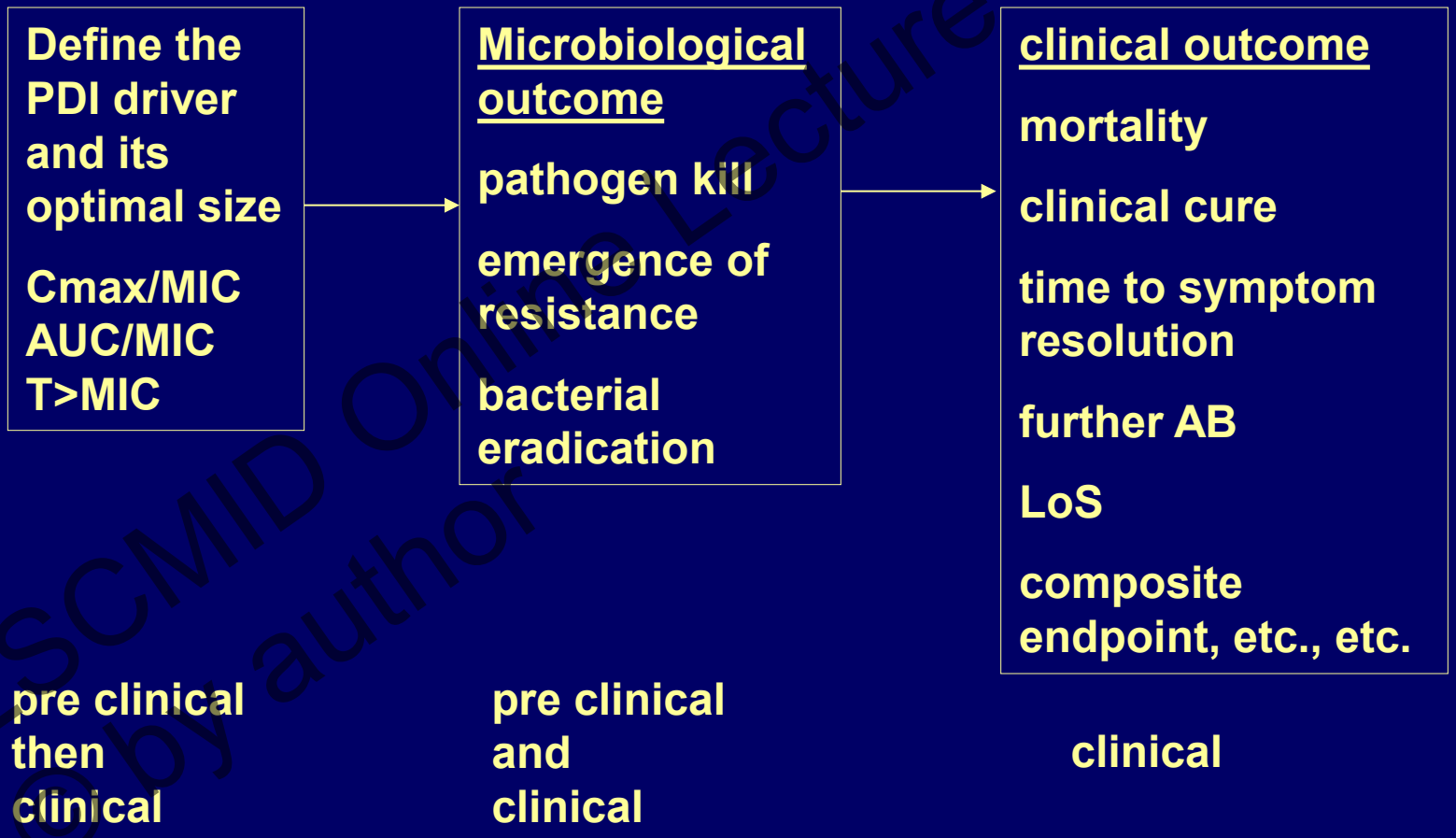
Which are the target pathogens?

What is the clinical breakpoint?

Is combination therapy needed?

ESCMID Online Lecture Library
© by author

The PK-PD Paradigm



ESCMID Online Lecture Library
© by author

Basic PK-PD tools for translational research (1)

In vitro experiments

- MICs: wild type and with relevant resistance mechanisms
- Patterns of bacterial killing in fixed concentration kill curves
- persistent antibiotic effects
- pharmacokinetic modelling:
  - simulation of human dosing
  - defining PDI targets
  - determining risk of emergence of resistance
  - combination therapy
  - Other: i.e. inoculum, mixed infection

  Often use wild type strains and those with relevant mechanisms of resistance

ESCMID Online Lecture Library
©by author

Basic PK-PD tools for translational research (2)

Animal experiments

neutropaenic murine thigh model

neutropaenic murine pulmonary model
± humanised dosing

peritonitis murine model

septicaemia models

endocarditis models

bone infection models

meningitis models

foreign body infection models

(mice, rats, guinea pigs, rabbits)

ESCMID Online Lecture Library
© by author

PK-PD pathway

Basic microbiology
MICs
patterns of kill
persistent effects

Basic PK
- ADME
- protein binding
- serum time

concentration course

pre clinical PK-PD models
- determine PDI driver
- determine the exposure response relationship

→ PDI driver target
(dose fractionation/escalation : dosing matrix)

use the PDI target with the PK to determine likely breakpoints and target pathogen

confirm targets clinically

ESCMID Online Lecture Library
© by author

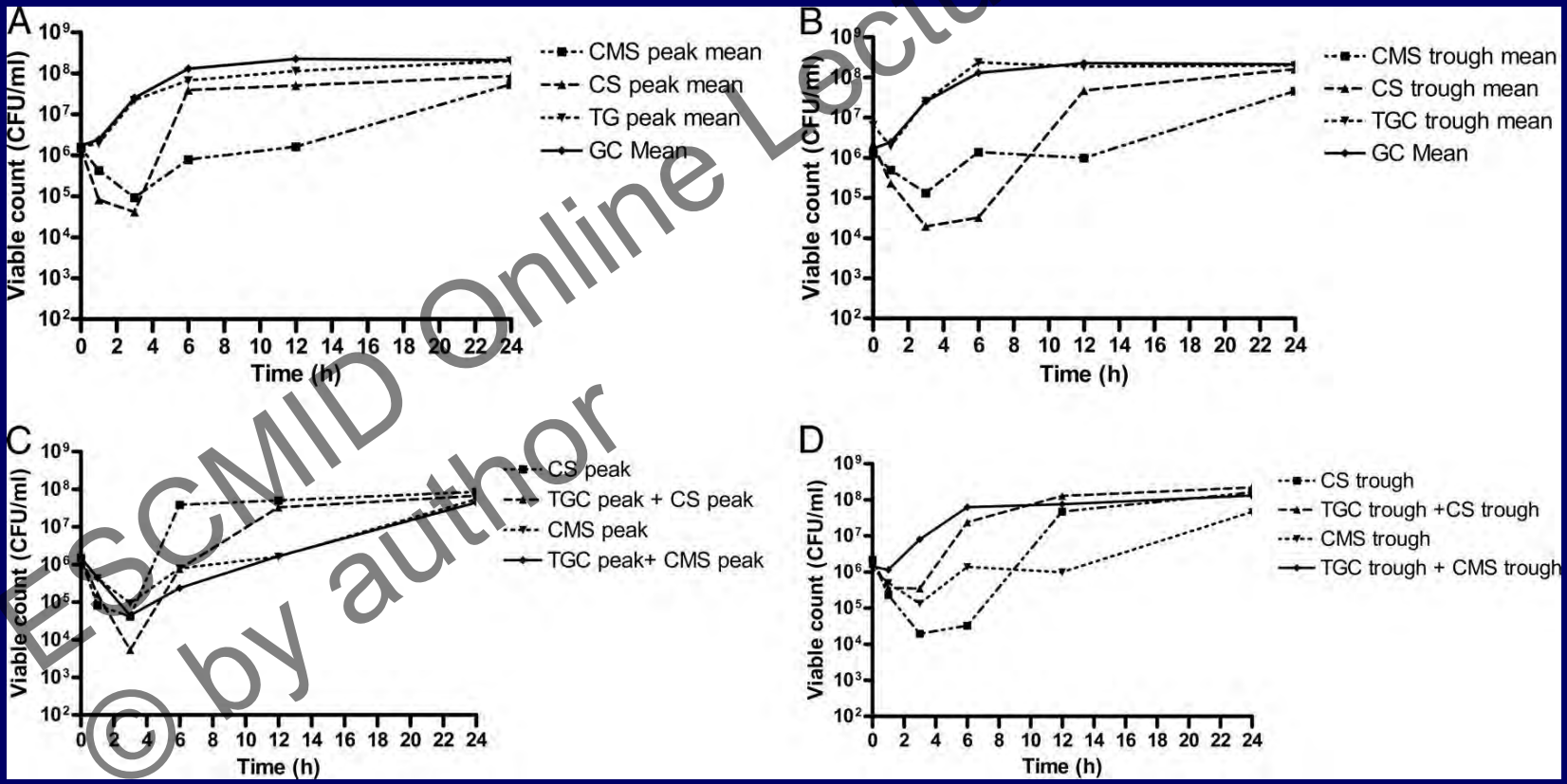
Some examples

- static concentration kill curves (colistin)
- simulated human doses (temocillin, teicoplanin, minocycline, comparisons and combinations)
- determining the pharmacodynamic driver (minocycline)
- exposure (using PDI driver) response relationships (minocycline)
- emergence of resistance (minocycline)

ESCMID Online Lecture Library
© by author

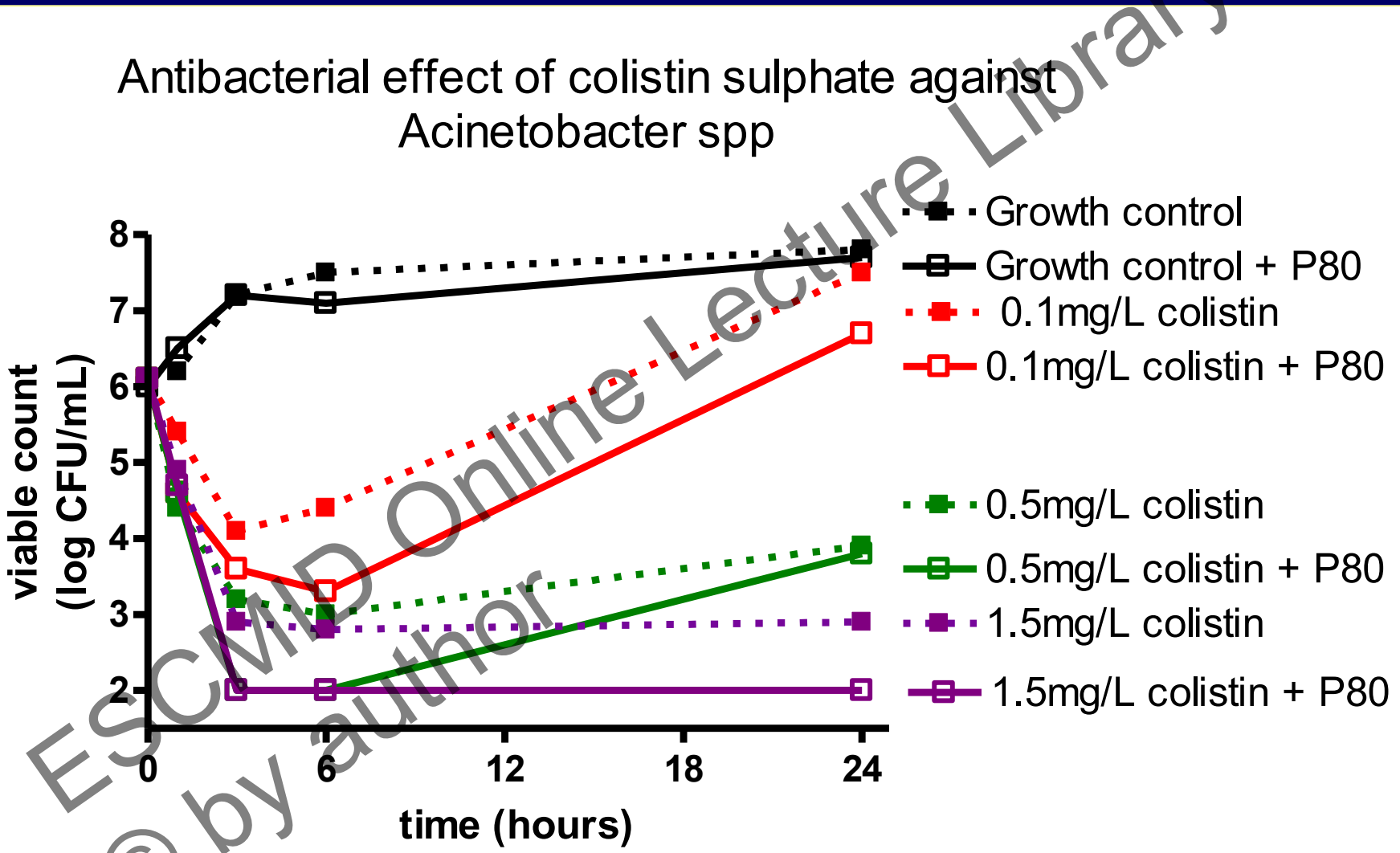
Static concentration time-kill curves

Antibacterial activities of tigecycline, colistin sulfate, and colistin methanesulfonate against NDM-1-producing Enterobacteriaceae at free peak concentrations of individual drugs (A), free trough concentrations of individual drugs (B), combinations of peak concentrations (C), and combinations of trough concentrations (D)



ESCMID Online Lecture Library
© by author

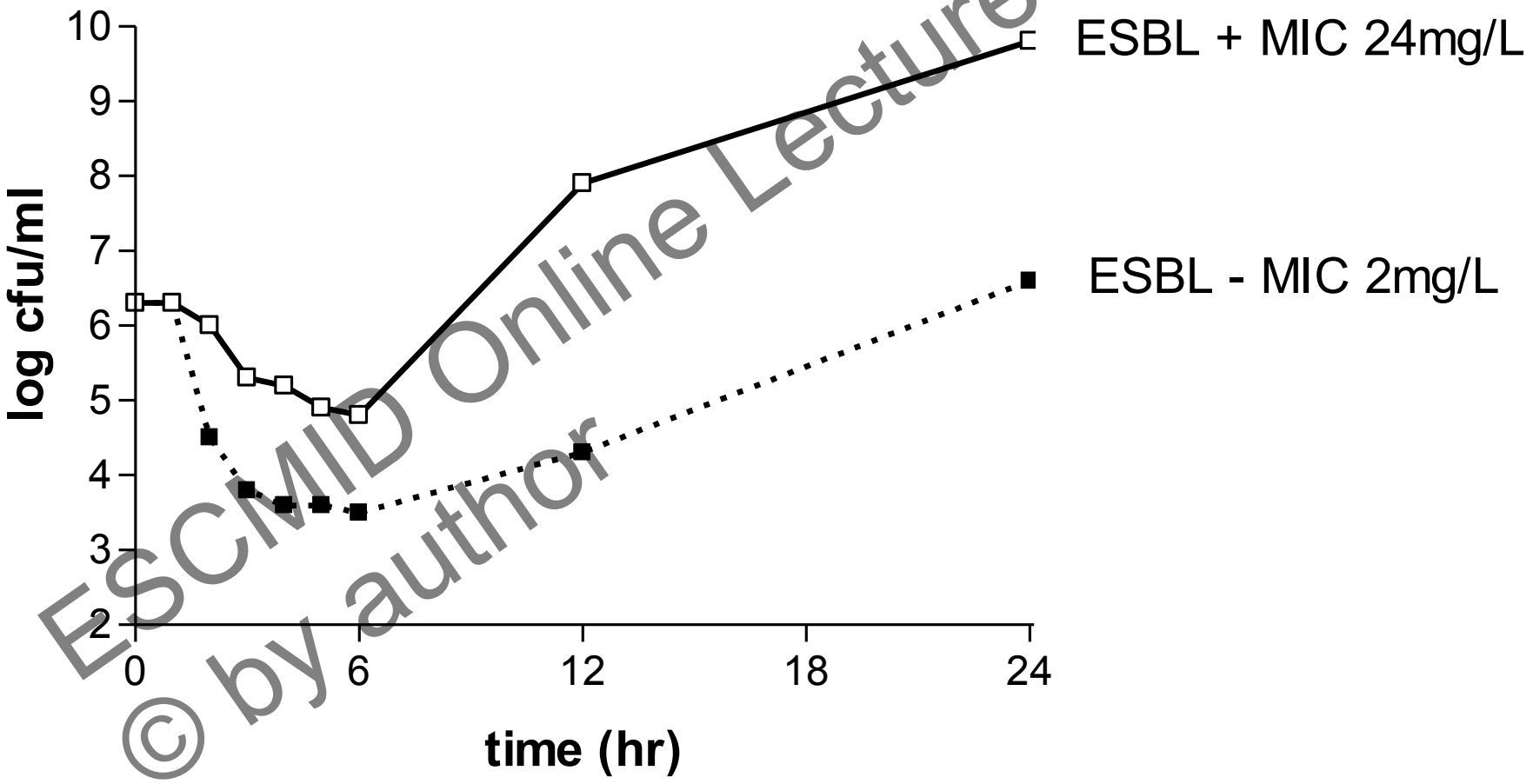
Albur M et al. Antimicrob. Agents Chemother. 2012;56:3441-3443



ESCMID Online Lecture Library
© by author

Simulated human doses

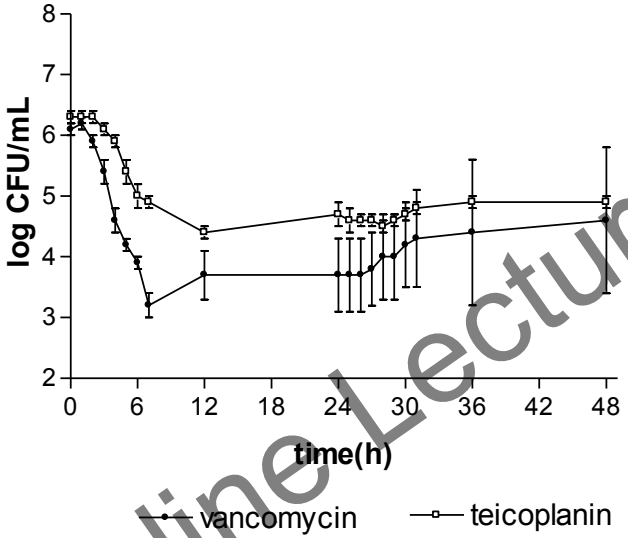
Activity of temocillin 2g 12hrly free drug concentration simulations against E coli



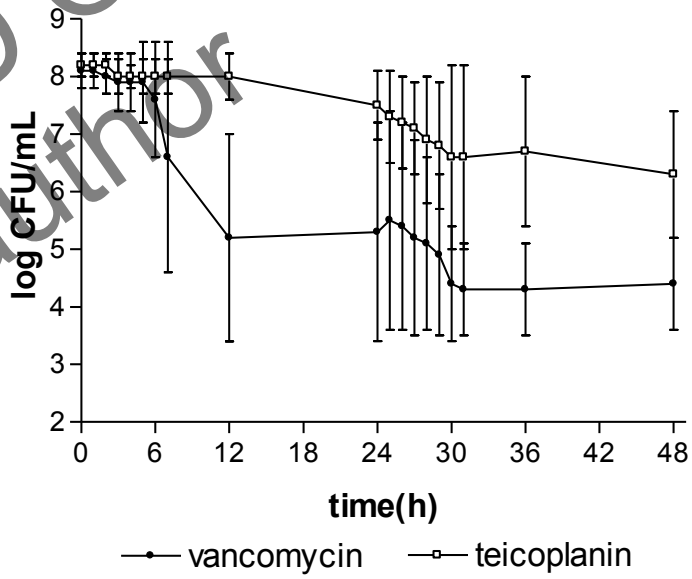
ESCMID Online Lecture Library
© by author

Teicoplanin and vancomycin - antibacterial effects: impact of inoculum

S aureus strain 15841 - inoculum 10^6 CFU/ml

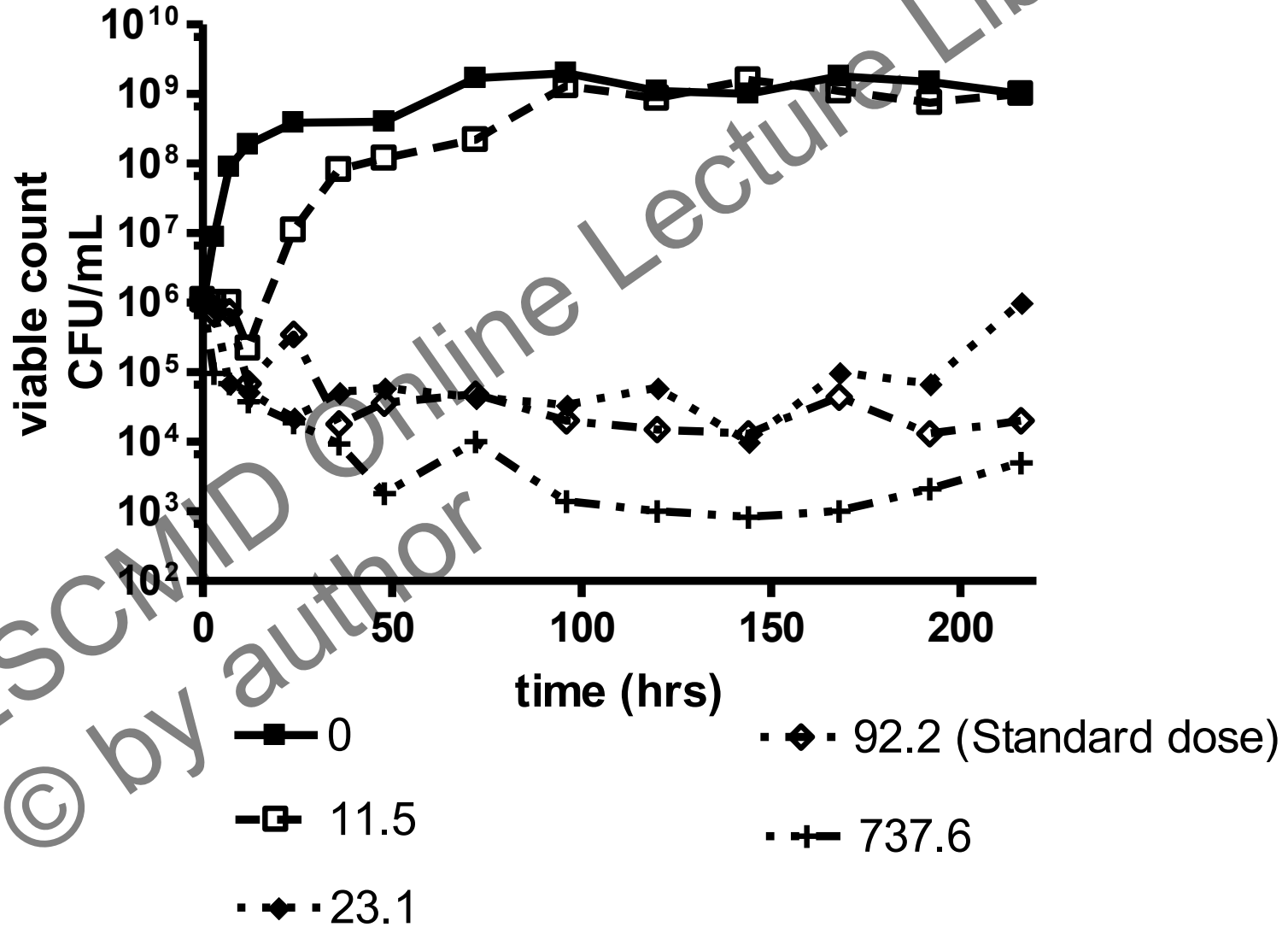


S aureus 15841 - inoculum 10^8 CFU/ml



ESCMID Online Lecture Library
© by author

Minocycline antibacterial effect against MRSA Strain 45494 - 10day exposure



ESCMID Online Lecture Library
© by author

In vitro activity of 2g 12hr temocillin against ESBL producing Enterobacteriaceae

strain	temocillin MIC (mg/L)	log drop at 12hr
31054	1.5	-0.2
35270	2.0	-2.1
36271	3.0	-2.8
ATCC 2922	8.0	+0.8
32427	16.0	+0.7
33212	24.0	+1.4
n=3	MIC <4mg/L	-1.3 ± 1.4
n=3	MIC >4mg/L	+3.3 ± 0.3

ESCMID Online Lecture Library
© by author

Bowker et al, 2006

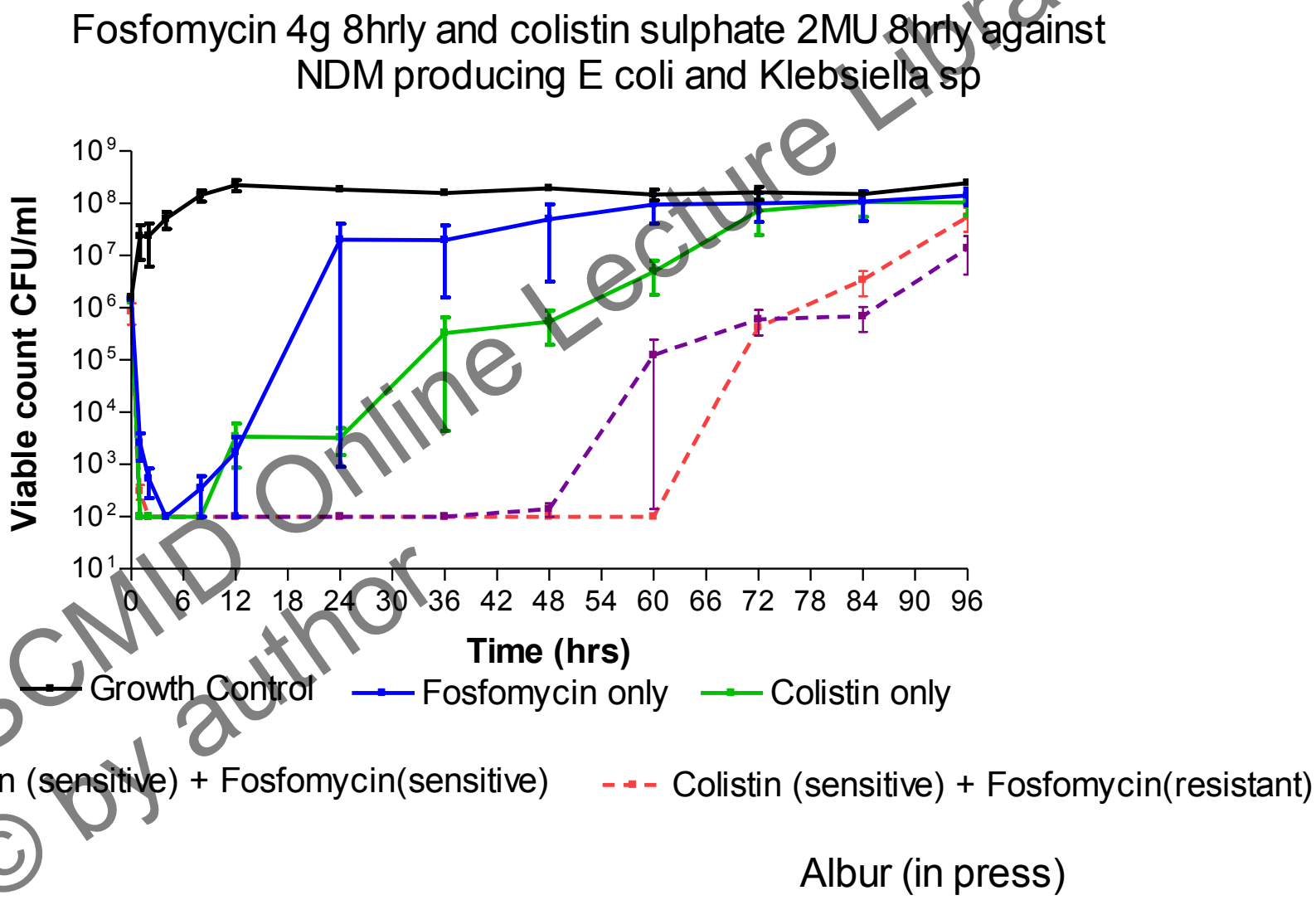
Comparative antibacterial effects of ertapenem, meropenem and temocillin in a hollow fibre *in vitro* model against 4 ESBL producing *Enterobacteriaceae*

agent	log drop in viable count at -	
	12h	24h
temocillin	+0.7 ± 0.8	+2.9 ± 0.7
ertapenem	-4.3 ± 0.4	-4.3 ± 0.4
meropenem	-4.7 ± 0.3	-4.6 ± 0.1

Bowker et al, 2006

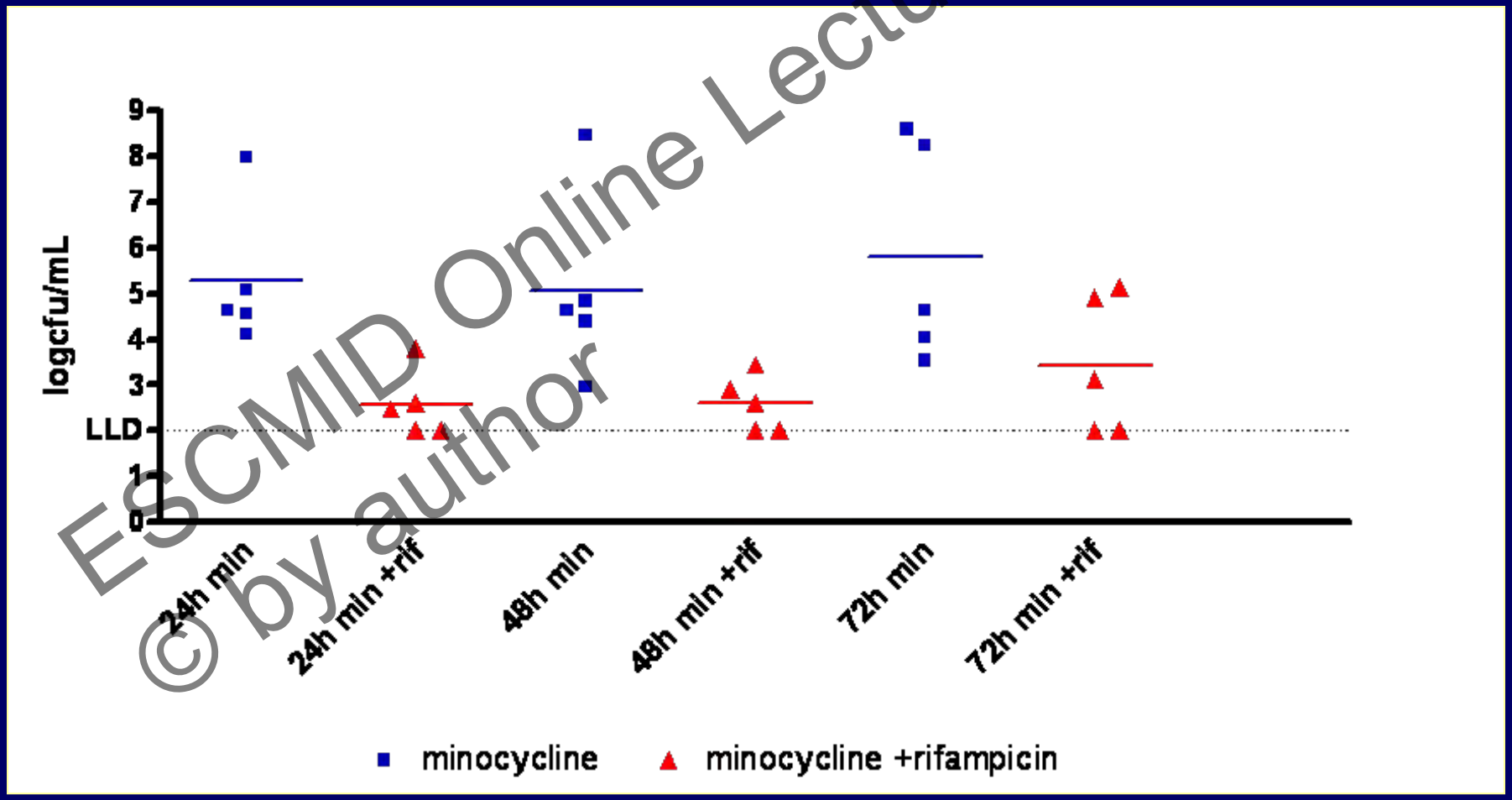
ESCMID Online Lecture Library
© by author

Combination therapy



ESCMID Online Lecture Library
© by author

Comparison of minocycline alone v minocycline plus rifampicin at the standard dose (AUC/MIC)



ESCMID Online Lecture Library
© by author

Determining the pharmacodynamic driver

- hollow fibre system, 1 strain *S.aureus* minocycline MIC 0.05mg/L

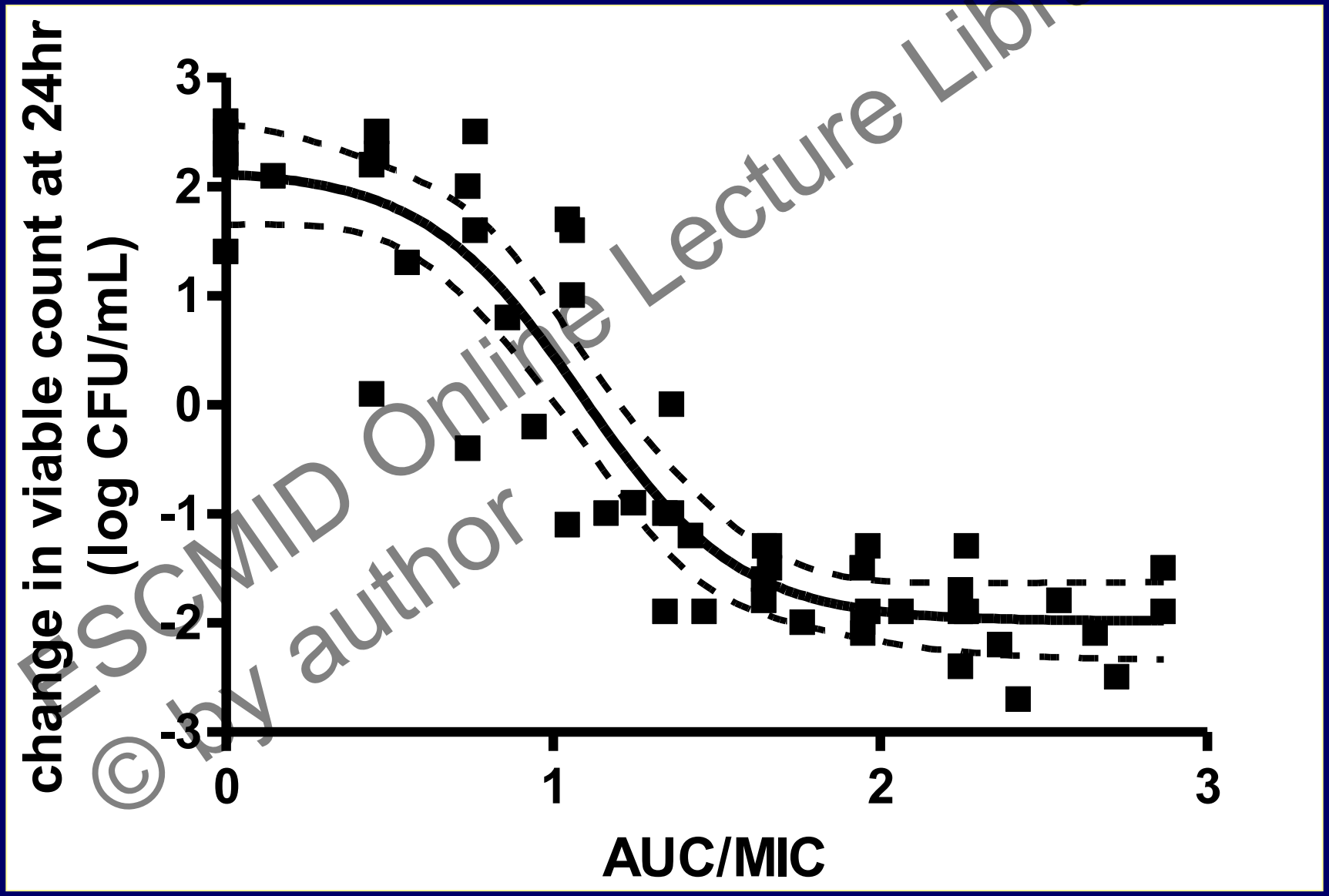
measure of antibacterial effect	dosing regimen			
	67mg TDS	100mg BD	200mg OD	P value
AUBKC(24)	71 ± 1	80 ± 2	74 ± 3	0.24
log drop at 24h (d24)	-1.7 ± 0.1	-1.5 ± 0.3	-1.6 ± 0.1	0.29
T99.9(h)	>24	>24	>24	>0.05

PD index	R^2 of sigmoid	
	AUBKC	d24
AUC/MIC	0.92	0.87
Cmax/MIC	0.75	0.51
T>MIC	0.63	0.41

Bowker et al, 2005

ESCMID Online Lecture Library
©by author

Exposure response relationship for minocycline against MRSA



ESCMID Online Lecture Library
© by author

fAUC/MIC ratios required for bacteriostatic and cidal effects for minocycline against MRSA (AIDA Programme data, FP7 EU)

strain	MIC (mg/L)	fAUC/MIC for 24hr static effect	24hr -1 log drop	24hr -2 log drop	fAUC/MIC for 12hr static effect	12hr -1 log drop	12hr -2 log drop
43241	0.25	11.2	20.5	41.5	13.9	20.1	31.7
33827	0.5	3.2	7.3	>200	10.3	13.9	19.5
ATCC 29213	0.19	9.0	17.4	51.2	29.8	56.6	105
45494	0.12	19.0	29.3	>200	38.5	47.7	>200
33922	1.0	19.2	38.2	>200	17.0	27.8	55.6
		12.3±6.8	22.5±11.8	-	21.5±11.2	33.2±18.4	-

Noel et al, 2013

ESCMID Online Lecture Library © by author

fAUC/MIC ratios required for bacteriostatic and cidal effects for minocycline versus Acinetobacter

strain	MIC (mg/L)	fAUC/MIC for 24hr static effect	fAUC/MIC for 24hr -1 log drop	fAUC/MIC for 48hr static effect	fAUC/MIC for 48hr -1 log drop
33980	0.5	14.2	26.1	15.4	24.9
35406	3.0	19.2	24.8	25.2	46.0
34958	4.0	15.8	19.1	18.0	20.3
		16.4±2.6	23.8±3.7	19.5±5.1	30.4±13.7

Noel et al, 2014

ESCMID Online Lecture Library
© by author

Minocycline Pharmacokinetics

dose	Cmax (mg/L)	t½ (h)	AUC (mg/L.h)	ref
200mg SD	3.1	17	43.9	Wood et al, 1975
200mg tablet	3.5	13	47.6	Cartwright et al, 1975
capsule	3.6	13	46.1	

protein binding is 76% (approx) so free AUC_{24} 11-12mg/L.h

ESCMID Online Lecture Library
© by author

Minocycline *S.aureus* and Acinetobacter spp MIC distributions (EUCAST)

MIC (mg/L)	*S.aureus* n	*S.aureus* proportion (%)		Acinetobacter n	Acinetobacter proportion (%)	
≤0.03	40	1.7		-		
0.06	549	22.9		-		
0.12	1,396	58.4		-		
0.25	322	13.5		-		
0.5	32	1.4	←	30	30	←
1.0	10	<0.5		7	7	
2.0	12	0.5		18	18	
4.0	16	0.6		15	15	
>4.0	9	<0.5		30	30	
PDI target fAUC/MIC		10-15			15-20	

ESCMID Online Lecture Library
© by author

Risk of emergence of resistance – measure by population profiles – at 72h stratified by fAUC/MIC for minocycline versus Acinetobacter spp

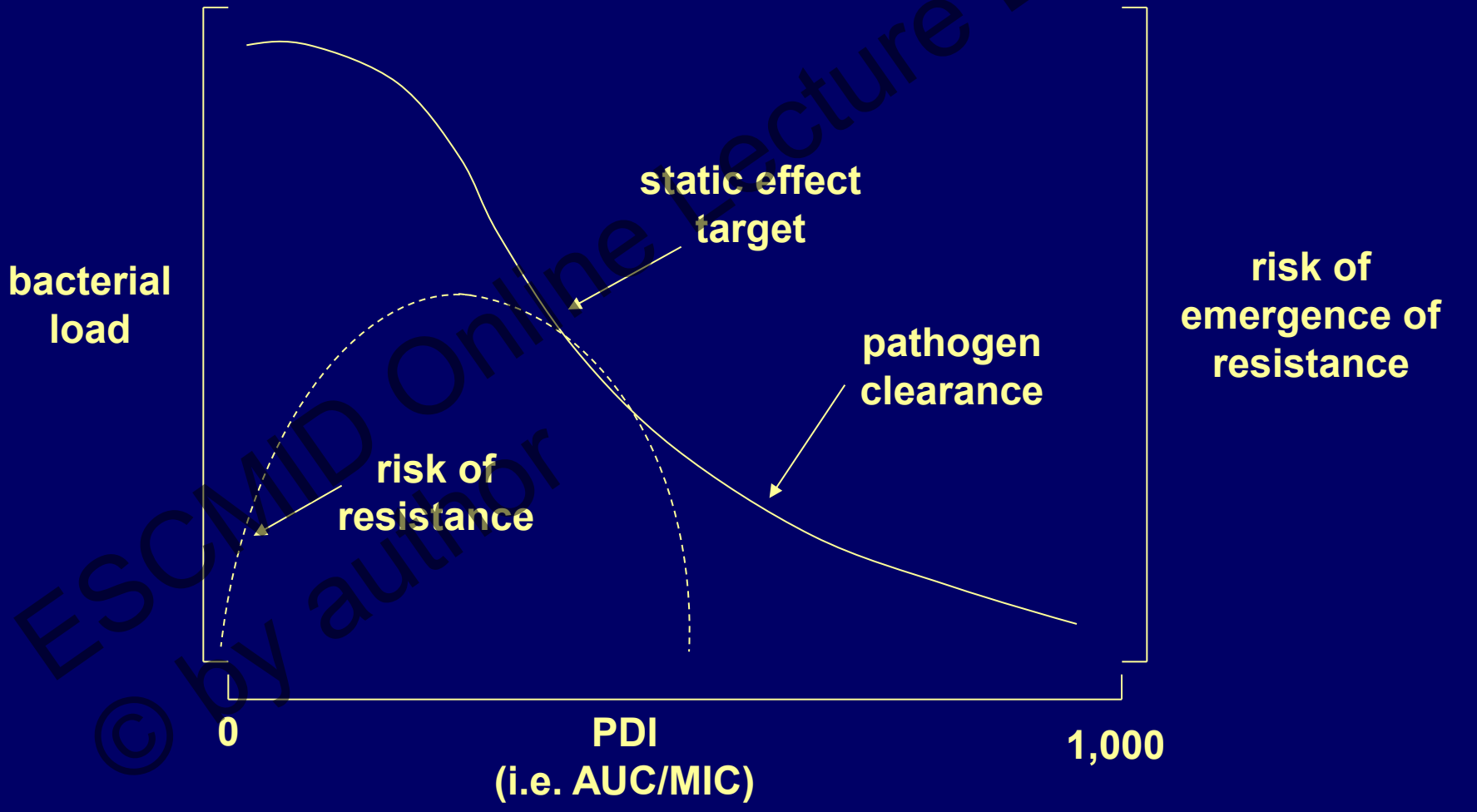
fAUC/MIC	MICx2 media		MICx4 media		MICx8 media	
	number of experiments	bacterial count	number of experiments	bacterial count	number of experiments	bacterial count
1-5	2/3	5.5	1/3	3.6	1/3	3.2
>5-10	2/3	7.8	2/3	7.2	2/3	5.5
>10-15	2/3	8.0	2/3	7.6	0/3	<2
>15-20	0/3	<2	0/3	<2	0/3	<2
>20	0/3	<2	0/3	<2	0/3	<2

- inverse "U" relationship of exposure to resistance

Noel et al, 2014

ESCMID Online Lecture Library
© by author

Exposure response relationships for bacterial clearance and risk of emergence of resistance



ESCMID Online Lecture Library
© by author

Translational messages – from examples

- temocillin 2g 12hrly insufficient to treat many ESBL producers (?increase dose or add second agent)
- minocycline 100mg 12hrly po probably okay for MRSA cSSTI
- minocycline 100mg 12hrly probably too low a dose for Acinetobacter spp (?increase dose or add second agent)

ESCMID Online Lecture Library
© by author

Measuring the translational gap – pharmacodynamically based clinical breakpoints – EUCAST

No Rationale Document

pristinamycin, quinupristin-dalfopristin, aztreonam, chloramphenicol, co-trimoxazole, isepamicin, minocycline iv

Rationale documents

	pre clinical PDI target	mathematic modelling of PD breakpoint	PK-PD breakpoint
colistin (2010)	Yes	No	No
doxycycline (2009)	No	No	No
fosfomycin iv (2013)	Yes	No	No
fosfomycin-trometamol (2013)	Yes	No	No
fusidic acid (2010)	No	No	No
mecillinam (2010)	Yes	No	No
minocycline (2009)	No	No	No
nitrofurantoin (2010)	No	No	No
trimethoprim (2010)	No	No	No
teicoplanin (2010)	No	No	No

ESCMID Online Lecture Library
© by author

What gaps do we expect to be filled by 2015-2017?

	PDI target	pop PK and modelling PD breakpoint	Clinical breakpoint
colistin (AIDA and many others)	Yes	Yes	Yes TATFAR
fosfomycin	Yes	No	No
fusidic acid (CEM-102, Cempra)	?	?	?
mecillinam	No	No	No
minocycline (AIDA)	Yes	Yes	Yes
nitrofurantoin (AIDA)	Yes	Yes	Yes
trimethoprim	No	No	No
teicoplanin	No	No	No
pristinamycin	No	No	No
Q-D	No	No	No
chloramphenicol	No	No	No
co-trimoxazole	No	No	No
isepamicin	No	No	No

ESCMID Online Lecture Library
© by author

Conclusions

- PK-PD development pathway for new agents is well established
- the essential pieces of information for old agents can also be easily defined
- further public sector funding (in USA and EU) will enable basic science gaps to be filled
- more thorough understanding of basic science PK-PD should enhance clinical use of old agents and development of new agents

ESCMID Online Lecture Library
© by author