24 years of ISAP: Achievements in the PK/PD field

A lecture *In Memoriam* Bill Craig

Paul M. Tulkens, MD, PhD
Former President of ISAP (1998-2000)

Invited Professor
Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Health Science Sector
Université catholique de Louvain
Brussels, Belgium

ISAP Annual Meeting & post-ICAAC symposium
September 21, 2015, San Diego, CA, USA

Disclosures
(those who paid for our research and talks)

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, AstraZeneca
- Decision-making and consultation bodies
  - General Assembly (current) and steering committee (part) of the European Committee for Antibiotic Susceptibility Testing [EUCAST]
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)
  - Belgian Antibiotic Policy Coordination Committee (BAPCOC)

What shall I talk you about ?

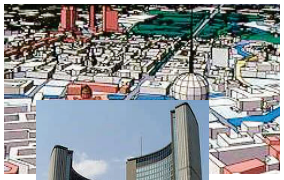
From Stockholm 1989 …

lobbying

1998

W.A. Craig

education



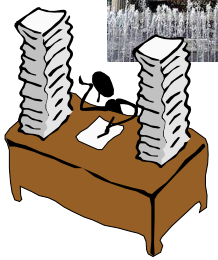
ECCMID 1991

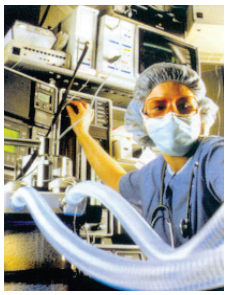
lobbying

publications

ICAAC 2000

1999





EMA

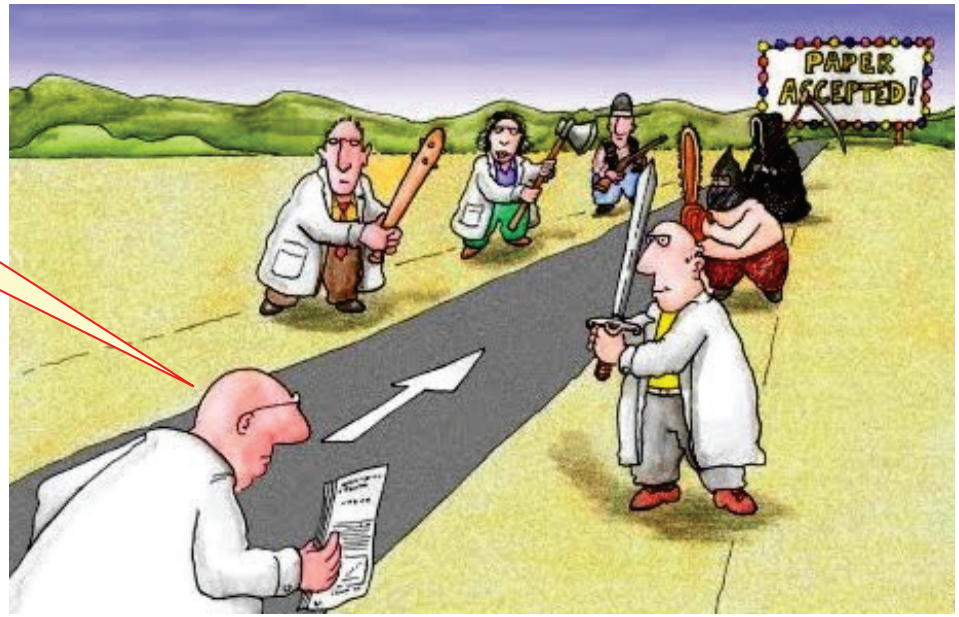
to clinical practice

Disclaimer …

- This is a personal view …, and therefore not that of ISAP…
- I have certainly missed many points and forgotten many of the key actors…
- Most of what I'll show is based on public documents … which means that the reality could be different …
- Thanks to Johan Mouton for the many pictures of ISAP members…

Publications

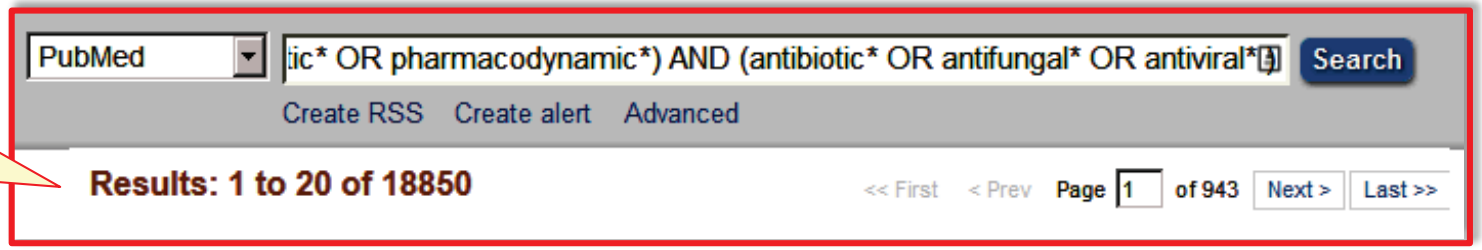
Often the hard road



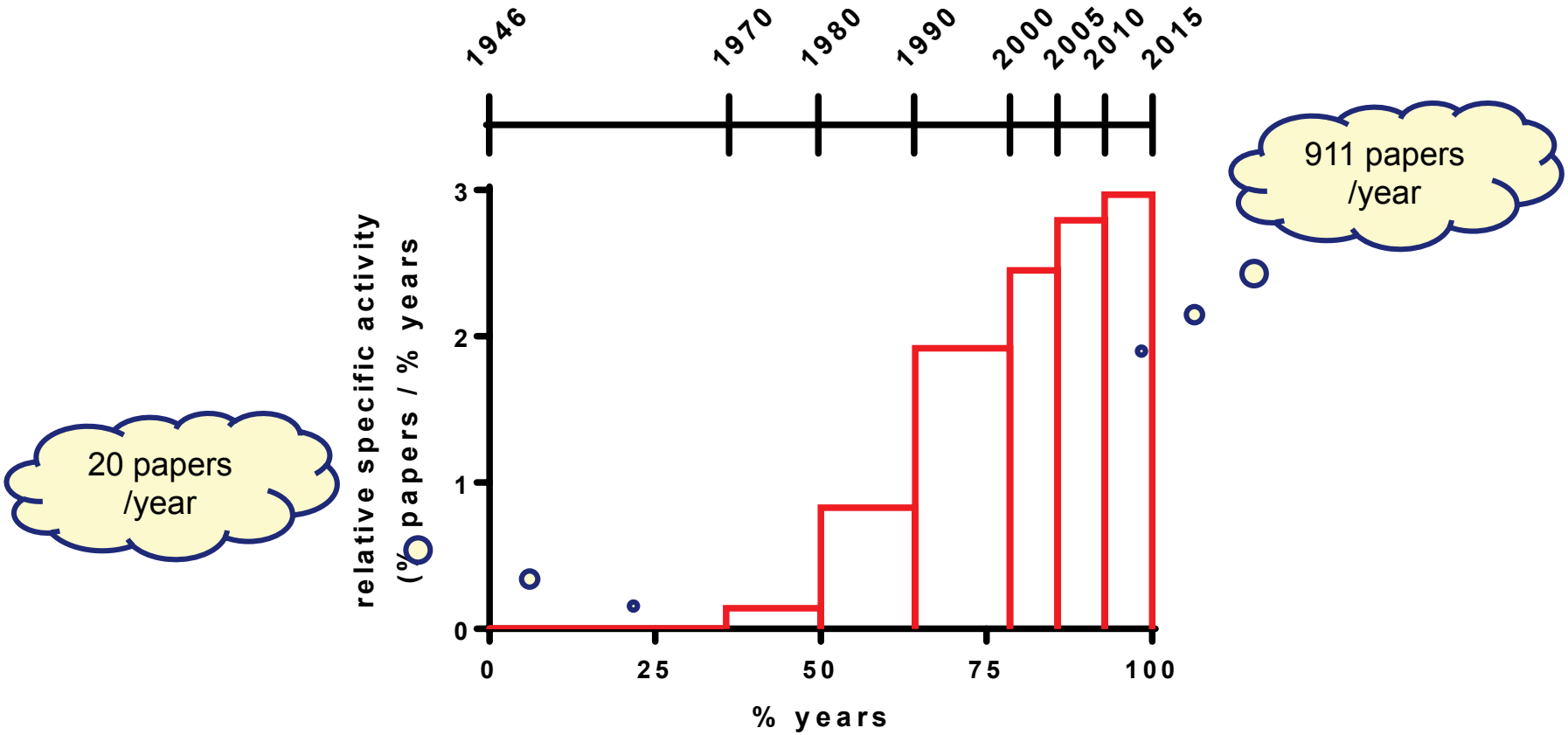
But try this !

(pharmacokinetic* OR pharmacodynamic*) AND (antibiotic* OR antifungal* OR antiviral*)

And you get this

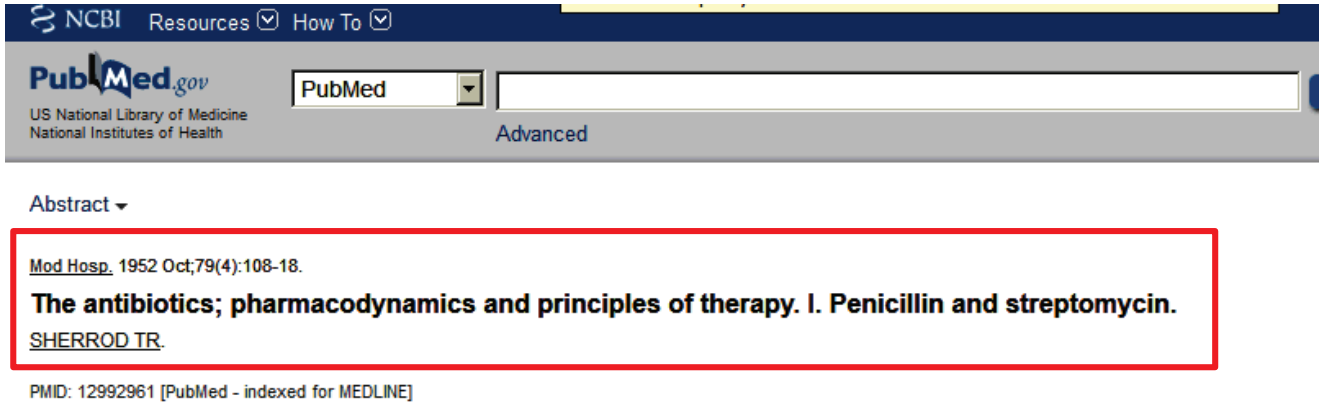


Publications from 1946 to 2015 *



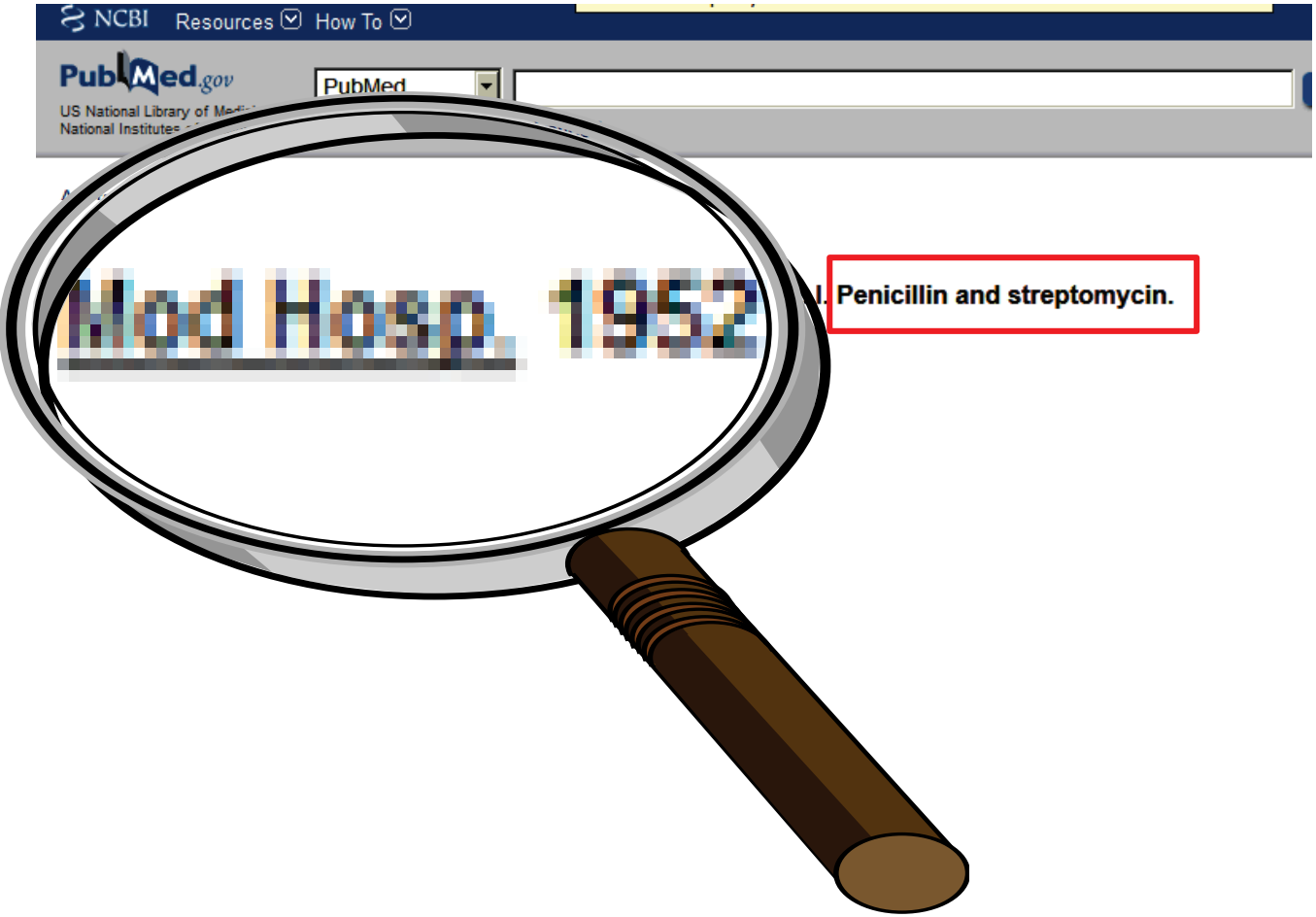
* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Publications from the earliest …



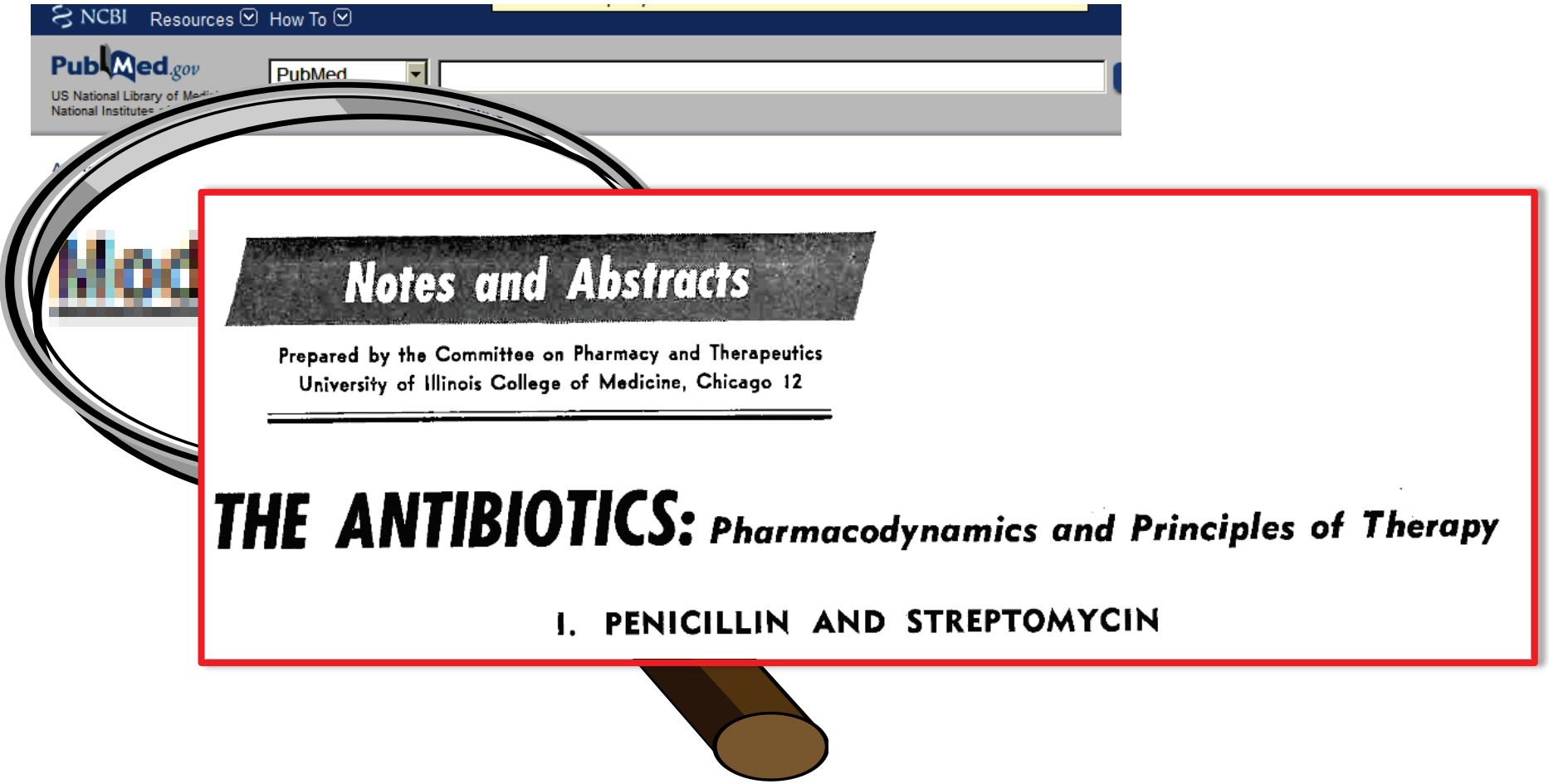
* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Publications from the earliest …



* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Publications from the earliest …



* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Publications … to the last ones

AAC Accepted Manuscript Posted Online 8 September 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.01347-15

Population pharmacokinetics of piperacillin in the early phase of septic shock –does standard dosing result in therapeutic plasma concentrations?

Kristina Öbrink-Hansen[a]#, Rasmus Vestergaard Juul[b], Merete Storgaard[a], Marianne Kragh Thomsen[c], Tore Forsingdal Hardlei[d], Birgitte Brock[d], Mads Kreilgaard[b], Jakob Gjedsted[e]

AAC Accepted Manuscript Posted Online 8 September 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.01368-15

Augmented renal clearance implies a need for increased amoxicillin/clavulanic acid dosing in critically ill children

Pieter A.J.G. De Cock,[a,b,c]# Joseph F. Standing,[d,e,f] Charlotte I.S. Barker,[d,g] Annick de Jaeger,[c] Evelyn Dhont,[c] Mieke Carlier,[h] Alain G. Verstraete,[h,i] Joris R. Delanghe,[h,i] Hugo Robays,[a] Peter De Paepe[b]

Journal of Antimicrobial Chemotherapy Advance Access published September 7, 2015

J Antimicrob Chemother
doi:10.1093/jac/dkv233

A mechanism-based pharmacokinetic/pharmacodynamic model allows prediction of antibiotic killing from MIC values for WT and mutants

David D. Khan[1]*, Pernilla Lagerbäck[2], Sha Cao[3], Ulrika Lustig[3], Elisabet I. Nielsen[1], Otto Cars[2], Diarmaid Hughes[3], Dan I. Andersson[3] and Lena E. Friberg[1]

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

1st series of achievements

- Publishing about pharmacokinetics/pharmacodynamics of antibiotics has become a very popular topic…
- This large amount of scientific data has allowed to characterize the PK/PD parameters of most antibiotics, which is now almost “common knowledge …, was disseminated through workshops, … and is now in most textbooks…
- But special populations, specific uses, specific targets still need further studies and publications …

Workshops of various kinds

from the personal collection of J.W. Mouton

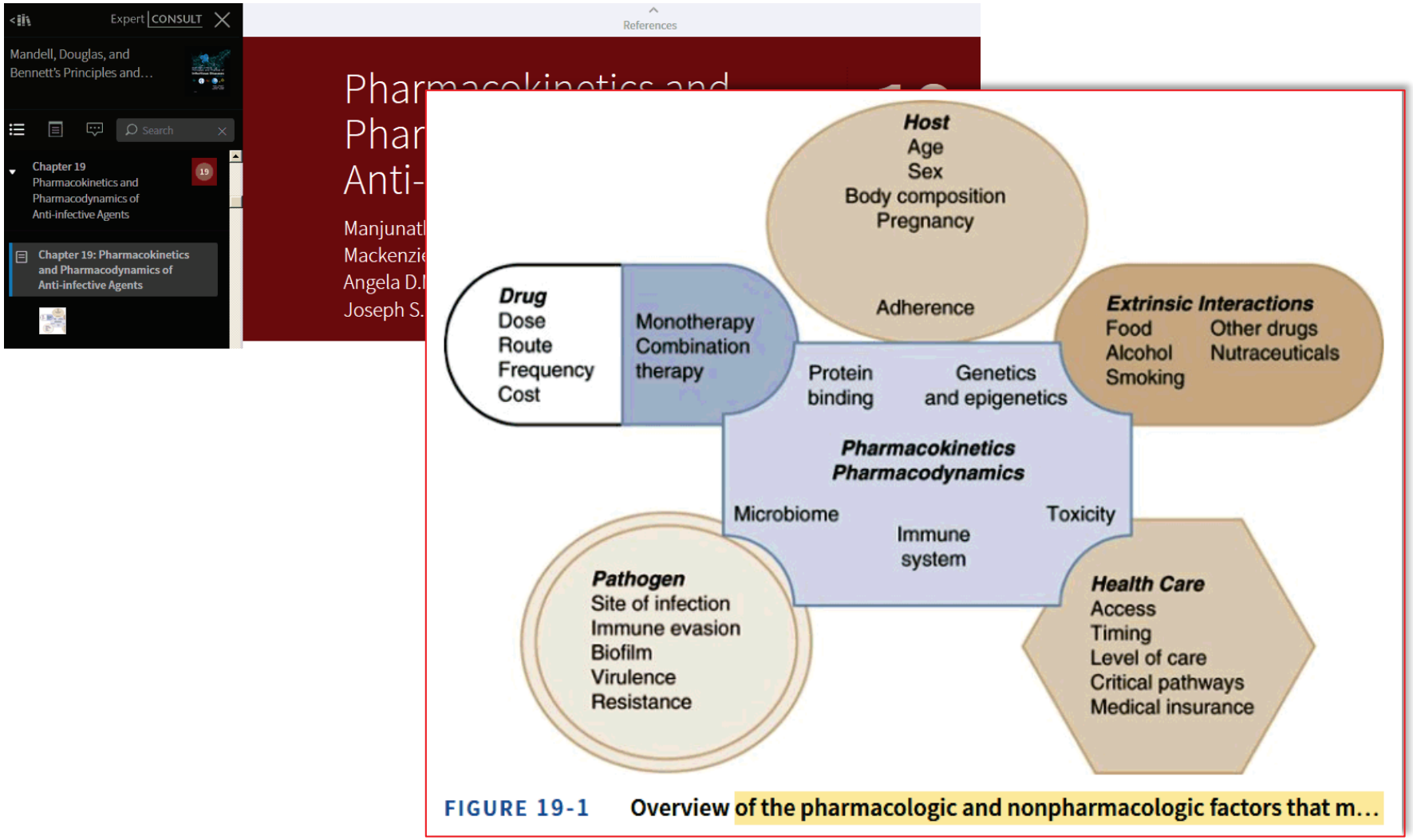
Workshops of various kinds

from the personal collection of J.W. Mouton

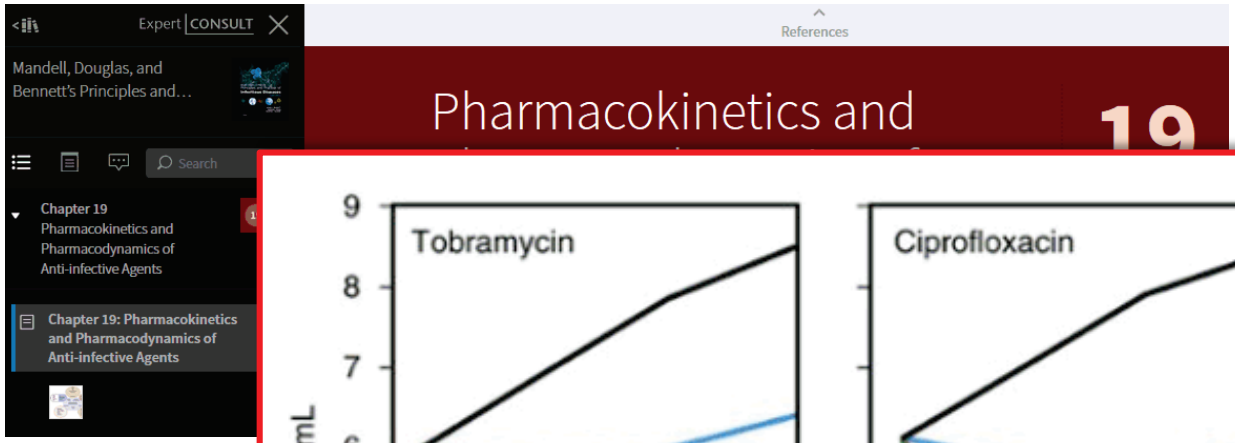
Textbooks


Expert CONSULT
Mandell, Douglas, and Bennett's Principles and…
Search
Chapter 19
Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
19
Chapter 19: Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
References
Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
19
Manjunath P. Pai
Mackenzie L. Cottrell
Angela D.M. Kashuba
Joseph S. Bertino Jr.

Textbooks

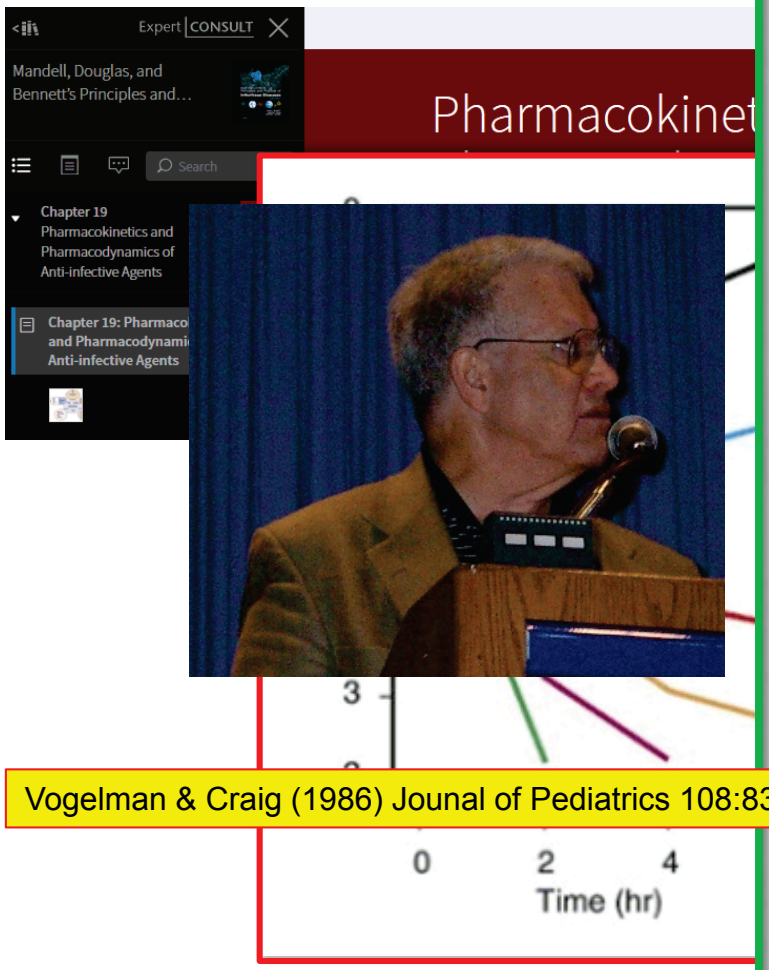

Expert CONSULT
Mandell, Douglas, and Bennett's Principles and…
Search
Chapter 19 Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
Chapter 19: Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
References
Host
Age
Sex
Body composition
Pregnancy
Adherence
Drug
Dose
Route
Frequency
Cost
Monotherapy
Combination therapy
Extrinsic Interactions
Food
Alcohol
Smoking
Other drugs
Nutraceuticals
Protein binding
Genetics and epigenetics
Pharmacokinetics
Pharmacodynamics
Microbiome
Toxicity
Immune system
Pathogen
Site of infection
Immune evasion
Biofilm
Virulence
Resistance
Health Care
Access
Timing
Level of care
Critical pathways
Medical insurance
FIGURE 19-1 Overview of the pharmacologic and nonpharmacologic factors that m…

Textbooks


Expert CONSULT
Mandell, Douglas, and Bennett's Principles and…
Search
Chapter 19 Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
Chapter 19: Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
References
Pharmacokinetics and
19

Tobramycin
Ciprofloxacin
Ticarcillin
Log10cfu/mL
9
8
7
6
5
4
3
2
0
2
4
6
8
Time (hr)
64 MIC
16 MIC
4 MIC
1 MIC
1/4 MIC
Control

Textbooks



Vogelman & Craig (1986) Jounal of Pediatrics 108:835-840

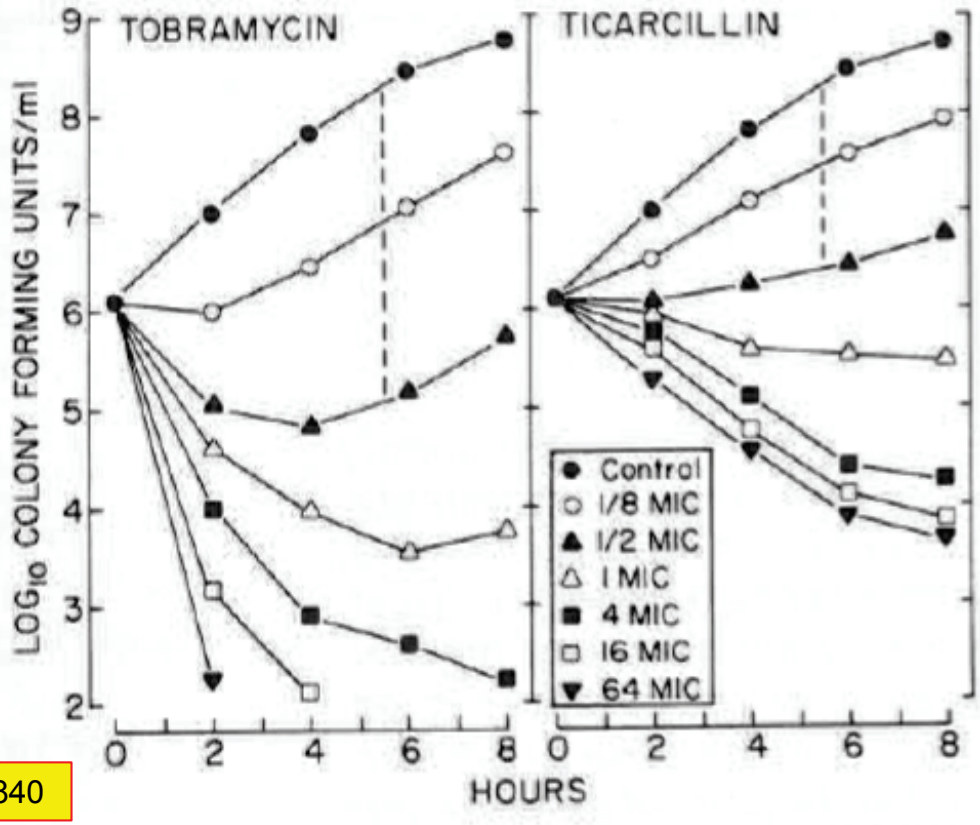
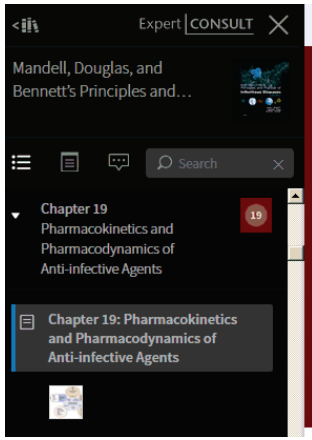


Fig. 1. Kill curves of *Pseudomonas aeruginosa* ATCC 27853 with tobramycin and ticarcillin at concentrations one eighth to 64 times MIC. *Vertical dashed line* estimates number of organisms at 5½ hours.

Textbooks



Concentration-Dependent Killing Agents

Time-Dependent Killing Agents

Postantibiotic Effect

Higher-Dose Extended-Interval Dosing

Continuous-Infusion and Extended-Infusion Regimens

Dose-Refinement Considerations

Textbooks

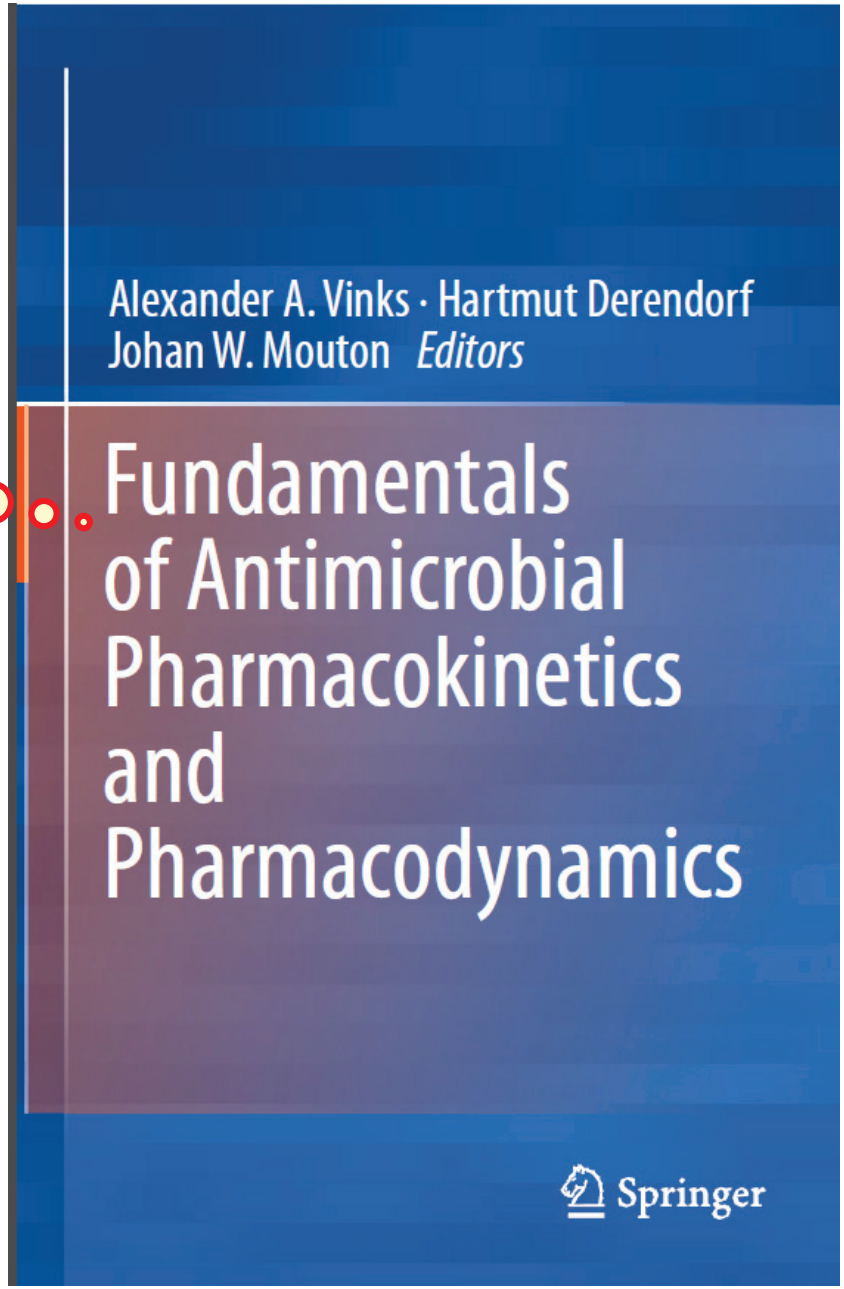
Antiretroviral Pharmacodynamics

TABLE 19-2 Inhibitory Concentrations and Therapeutic Drug Monitoring (TDM) Recommendations for 14 Commonly Used Antiretroviral and Antiviral Agents

ANTIRETROVIRAL OR ANTIVIRAL AGENT	EC_{50}	TDM RECOMMENDATION	
		Monitoring Parameter	Target Concentration
Atazanavir	2.62-5.28 nM	C_{trough}	150 ng/mL
Darunavir	1-5 nM	C_{trough}	Not established
Lopinavir	17-100 nM	C_{trough}	1000 ng/mL
Ritonavir	60 nM-1040 nM		
Nelfinavir	6.14-25.9 nM	C_{trough}	800 ng/mL
[illegible]rapine	8.94-34.14 nM	C_{trough}	3000 ng/mL
[illegible]irenz	0.31-1.73 nM	C_{random}	1000 ng/mL
[illegible]rivirine	0.13-0.73 nM	Not established	Not established
Raltegravir	5-12 nM	C_{trough}	Not established
Elvitegravir	32 nM	C_{trough}	Not established
Telaprevir	1100 nM	C_{trough}	Not established
Boceprevir	480 nM	C_{trough}	Not established
Foscarnet	151-155 μM*	C_{max}	500-800 μM
Valacyclovir	HSV-1 0.09-60 μM	C_{max}	Not established
	HSV-2 0.53-48 μM		

And books…

Very good book …



What do we know today about determinants of activity of most antibiotics…

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1992, p. 2577–2583 Vol. 36, No. 12
0066-4804/92/122577-07$02.00/0

MINIREVIEW

Continuous Infusion of β-Lactam Antibiotics

WILLIAM A. CRAIG[1,2,3]* AND STEVEN C. EBERT[3,4]

Department of Medicine[1] and School of Pharmacy,[3] University of Wisconsin, Madison, Wisconsin 53792; Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin 53705[2]; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715[4]

What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotic**s are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1992, p. 2577–2583 Vol. 36, No. 12
0066-4804/92/122577-07$02.00/0

MINIREVIEW

Continuous Infusion of β-Lactam Antibiotics

WILLIAM A. CRAIG[1,2,3]* AND STEVEN C. EBERT[3,4]

Department of Medicine[1] and School of Pharmacy,[3] University of Wisconsin, Madison, Wisconsin 53792; Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin 53705[2]; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715[4]

- **But monitoring may be essential as serum levels are largely unpredictable…**

What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1992, p. 2577–2583 Vol. 36, No. 12
0066-4804/92/122577-07$02.00/0

Co

Department of M
Department o
53705[2]

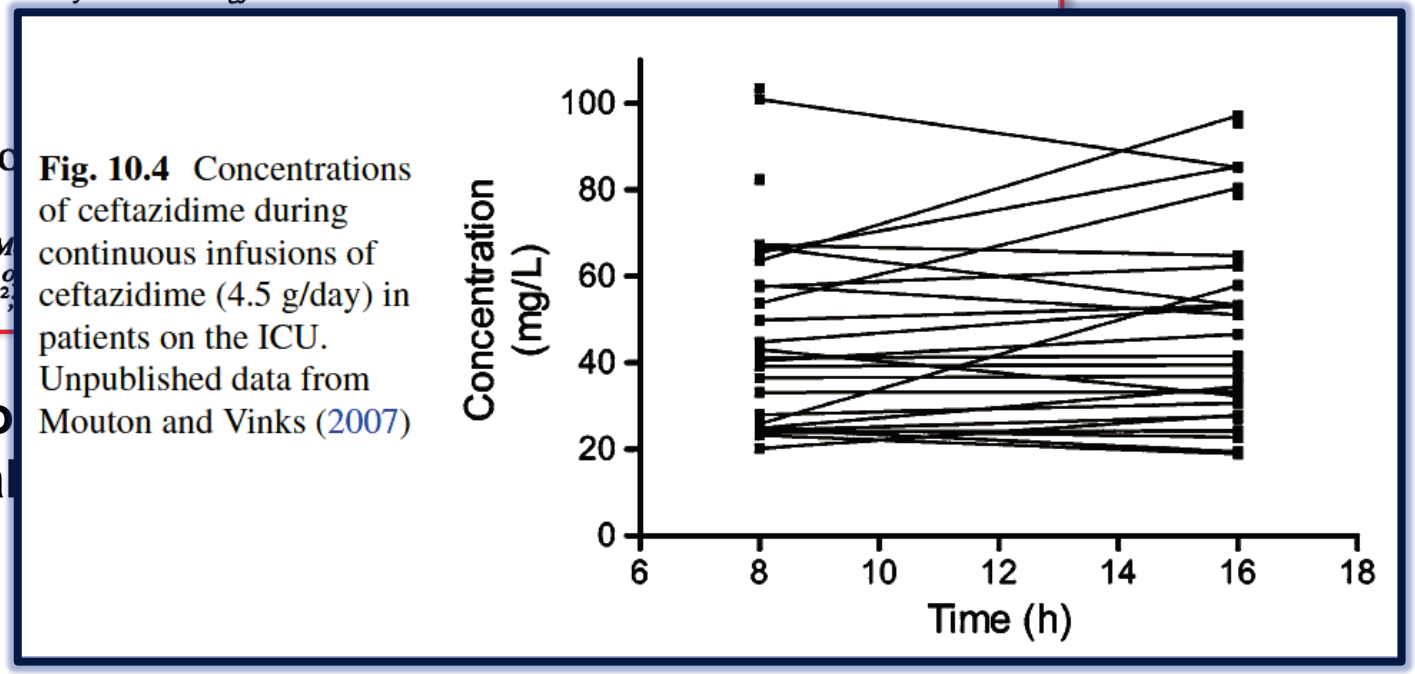


Fig. 10.4 Concentrations of ceftazidime during continuous infusions of ceftazidime (4.5 g/day) in patients on the ICU. Unpublished data from Mouton and Vinks (2007)

- **But monito**
  unpredicta

Muller & Mouton, Continuous Infusion of Beta-lactam Antibiotics In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinvk, H. Derendorf & JW Mouton eds, Springer, 2014, p 223-256

What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1992, p. 2577–2583 Vol. 36, No. 12
0066-4804/92/122577-07$02.00/0

MINIREVIEW

Continuous Infusion of β-Lactam Antibiotics

WILLIAM A. CRAIG[1,2,3]* AND STEVEN C. EBERT[3,4]

Department of Medicine[1] and School of Pharmacy,[3] University of Wisconsin, Madison, Wisconsin 53792; Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin 53705[2]; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715[4]

- But monitoring may be essential as serum levels are largely unpredictable…

- **And we may discuss what is the necessary C_s/MIC ratio (or C_{min} ?)**

What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

ANTIMICROBIAL AGENTS AND CHEMOT
0066-4804/92/122577-07$02.00/0

Continu

Department of Medicine[1] (
Department of Medici
53705[2]*; and Dep*

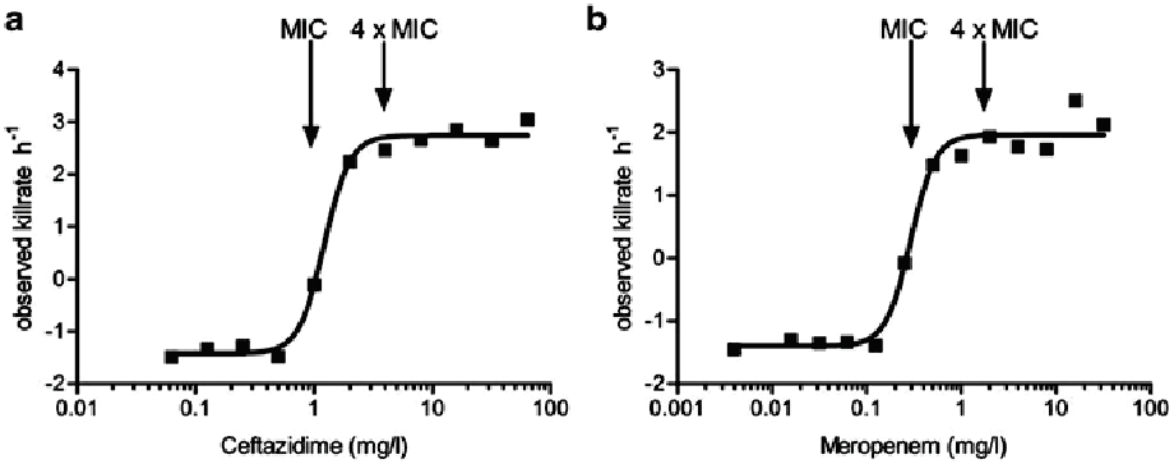


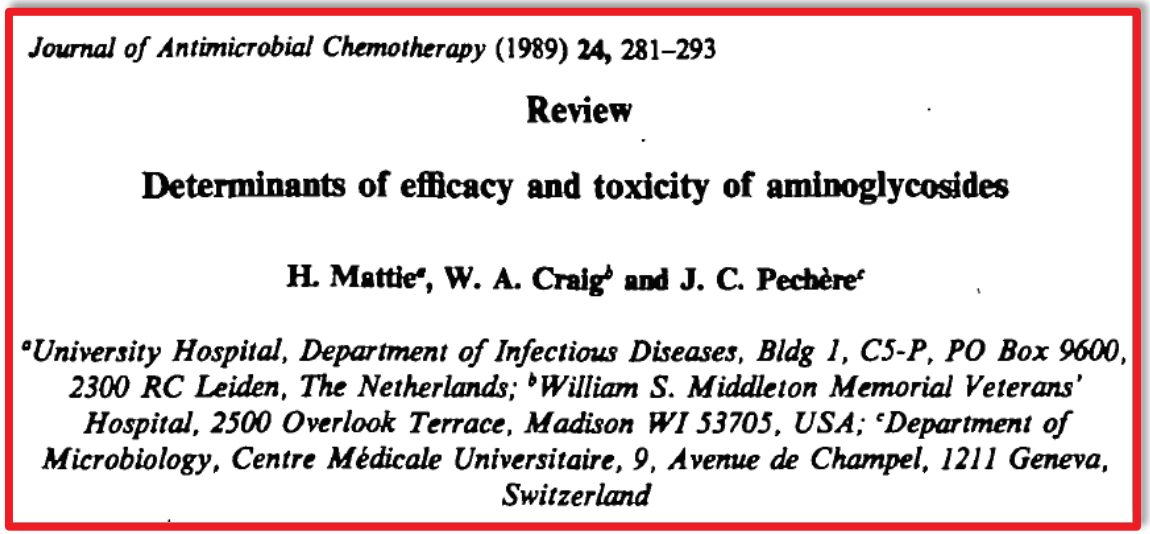
Fig. 10.2 Relationship between concentration of ceftazidime (**a**) and meropenem (**b**) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4× MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved

- But monitoring r
unpredictable…

- **And we may di**

What do we know today about determinants of activity of most antibiotics

- **aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity



Journal of Antimicrobial Chemotherapy (1989) **24**, 281–293

Review

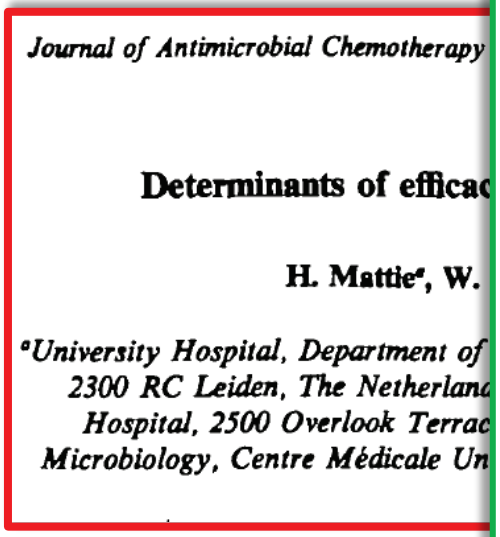
Determinants of efficacy and toxicity of aminoglycosides

H. Mattie[a], W. A. Craig[b] and J. C. Pechère[c]

[a]University Hospital, Department of Infectious Diseases, Bldg 1, C5-P, PO Box 9600, 2300 RC Leiden, The Netherlands; [b]William S. Middleton Memorial Veterans' Hospital, 2500 Overlook Terrace, Madison WI 53705, USA; [c]Department of Microbiology, Centre Médicale Universitaire, 9, Avenue de Champel, 1211 Geneva, Switzerland

What do we know today about determinants of activity of most antibiotics

- **aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity


Journal of Antimicrobial Chemotherapy

Determinants of efficac

H. Mattie[a], W.

[a]University Hospital, Department of
2300 RC Leiden, The Netherland
Hospital, 2500 Overlook Terrac
Microbiology, Centre Médicale Un

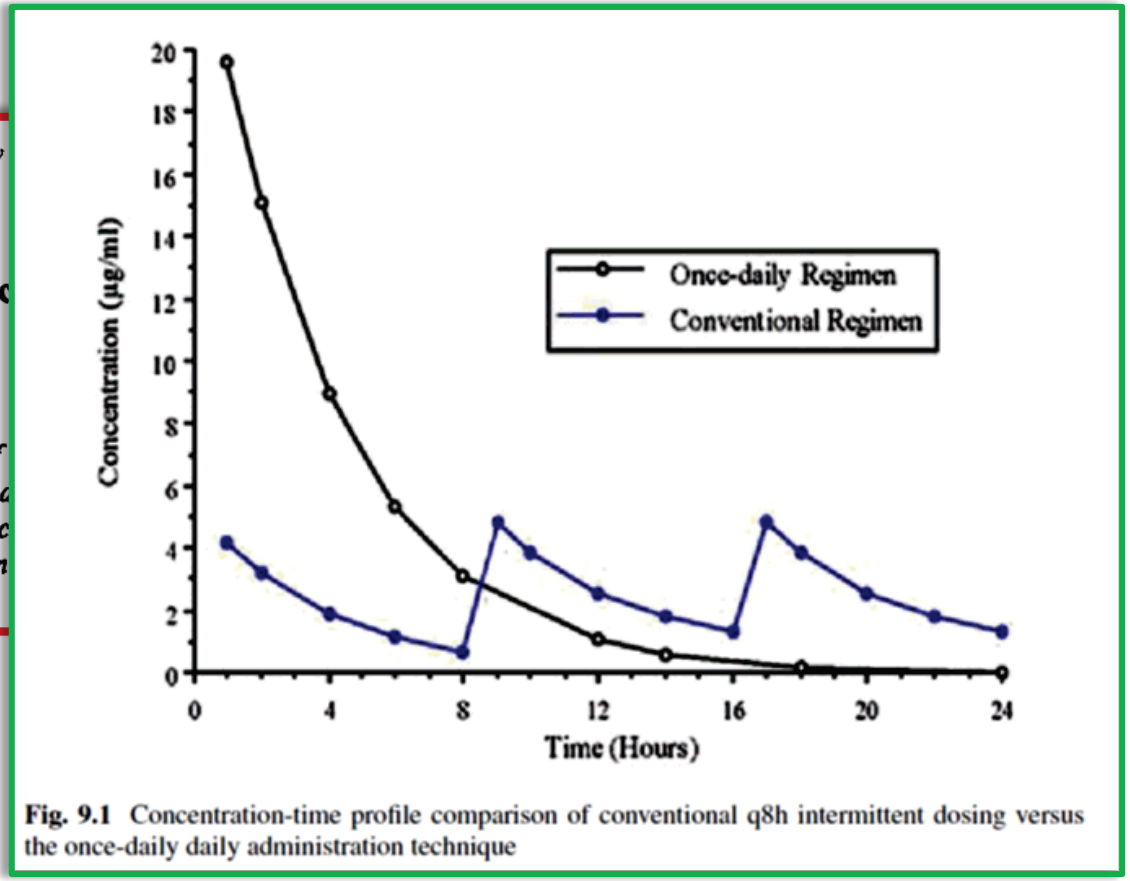
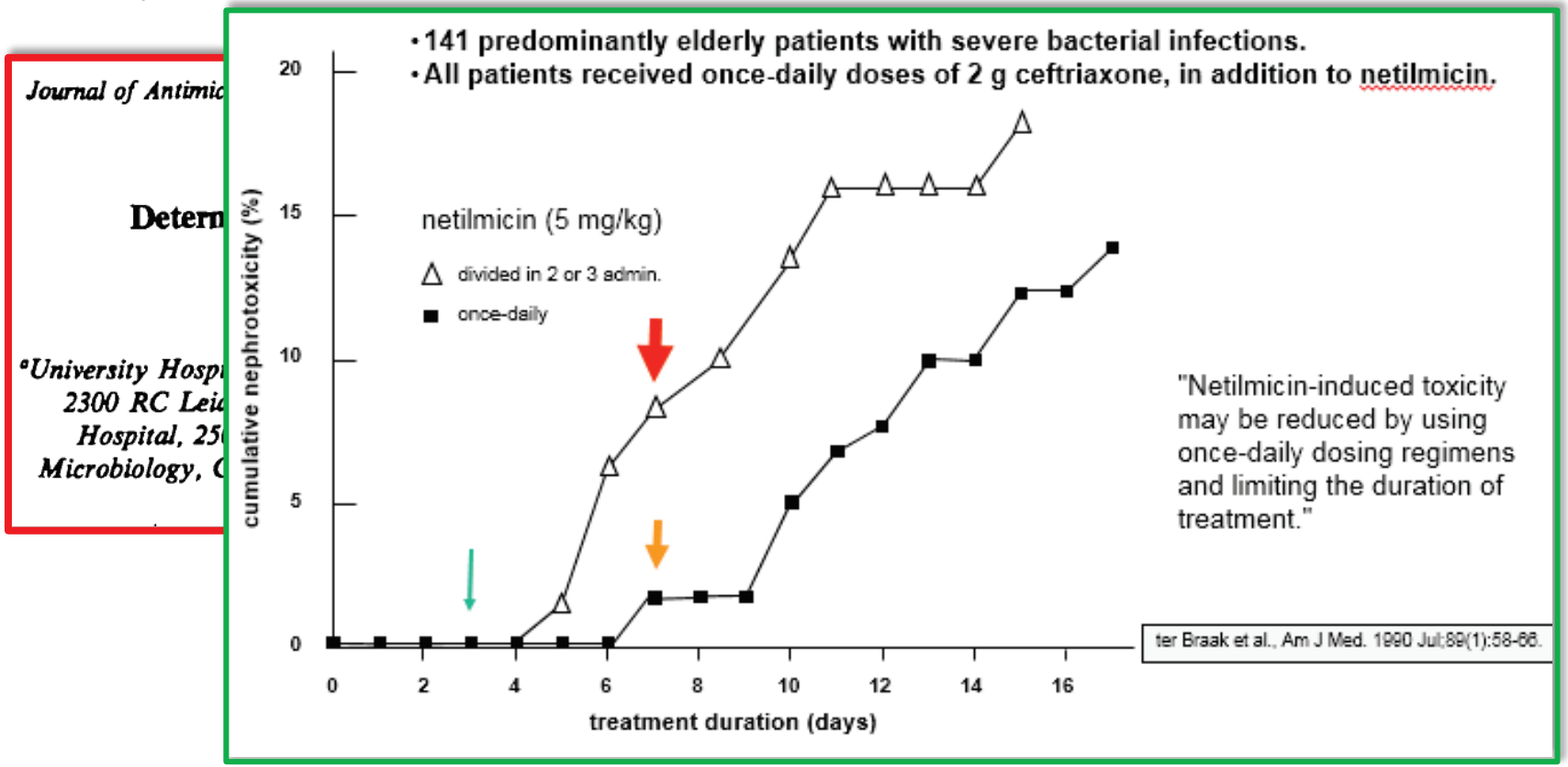


Fig. 9.1 Concentration-time profile comparison of conventional q8h intermittent dosing versus the once-daily daily administration technique

Bulik et al. Aminoglycosides, In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinvk, H. Derendorf & JW Mouton eds, Springer, 2014, p 201-222

What do we know today about determinants of activity of most antibiotics

- **aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity



What do we know today about determinants of activity of most antibiotics

- **fluoroquinolones** need to reach a sufficient AUC24h/MIC ratio (125 ?) to be effective against Gram-negative bacteria

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073–1081 Vol. 37, No. 5
0066-4804/93/051073-09$02.00/0

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS, MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

Received 19 February 1992/Accepted 5 February 1993

What do we know today about determinants of activity of most antibiotics

- **fluoroquinolones** need to reach a sufficient AUC24h/MIC ratio (125 ?) to be effective against Gram-negative bacteria

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 19
0066-4804/93/051073-09$02.00/0

Pharmacodynamics
Ser

ALAN FORREST, DAVID E.
MARY C. BIRMI

Center for Clinical Pharmacy Research,
Buffalo, New York 14260
Millard Fillmore

Received 19

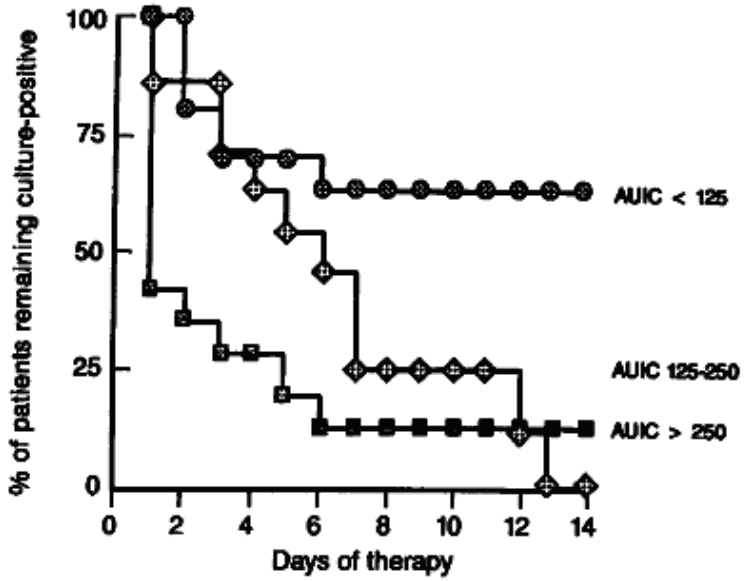


FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).

Today, every new antibiotic is PK/PD assessed..

In Vivo Pharmacokinetics and Pharmacodynamics of the Lantibiotic NAI-107 in a Neutropenic Murine Thigh Infection Model

Alexander J. Lepak,[a] Karen Marchillo,[c] William A. Craig,[a] David R. Andes[a,b,c]

Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA[a]; Department of Medical Microbiology and Immunology, University of Wisconsin, Madison, Wisconsin, USA[b]; William S. Middleton Memorial VA Hospital, Madison, Wisconsin, USA[c]

Lepak et al. Antimicrob Agents Chemother 2015; 59:1258–1264. doi:10.1128/AAC.04444-14.

Today, every new antibiotic is PK/PD assessed..

AAC Journals.ASM.org

In Vivo Pharmacokinetics and Phar
NAI-107 in a Neutropenic Murine T

Alexander J. Lepak,[a] Karen Marchillo,[c] William A. Craig,[a] David R. A
Department of Medicine, University of Wisconsin School of Medicine and Public Healt
Immunology, University of Wisconsin, Madison, Wisconsin, USA[b]; William S. Middleton

Lepak et al. Antimicrob Agents Chemother 2015; 59:125

once again, an AUC/MIC-dependent antibiotic…

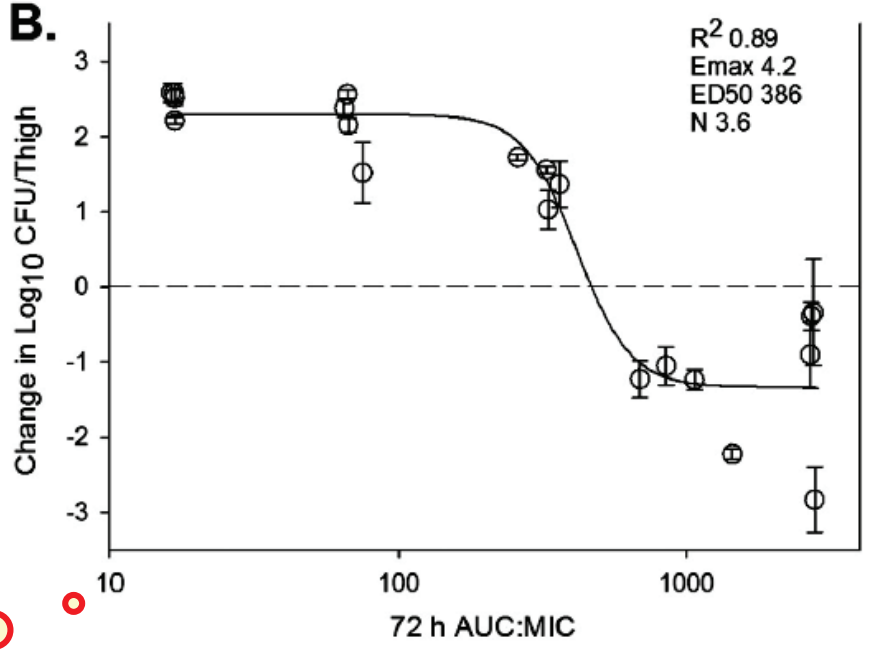
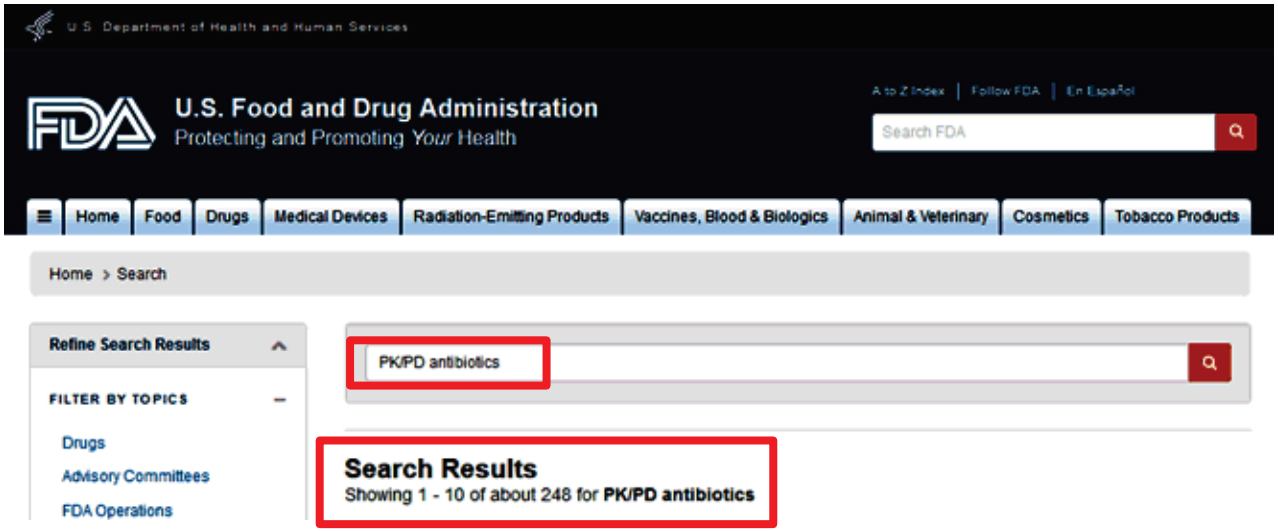


FIG 4 Impact of pharmacodynamic regression of the *in vivo* dose fractionation study with NAI-107 against *S. aureus* ATCC 25923. Each symbol represents the mean and standard deviation from four thighs. The dose data are expressed as either the C_{max}/MIC (A), the AUC/MIC (B), or the percentage of time drug concentrations exceeded the MIC over the dosing period (C) (% time above MIC). The R^2 represents the coefficient of determination. The ED_{50} represents the PD index associated with 50% of the maximal effect (E_{max}), and N is the slope of the relationship or the Hill coefficient. The line drawn through the data points is the best fit line based upon the sigmoid E_{max} formula. The horizontal dashed line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth.

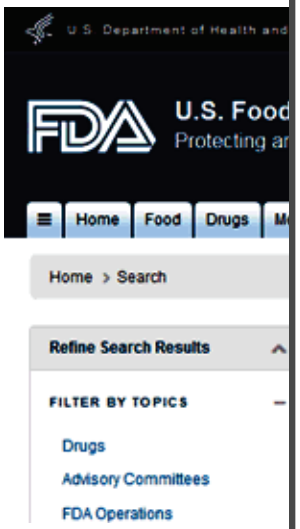
2d series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings

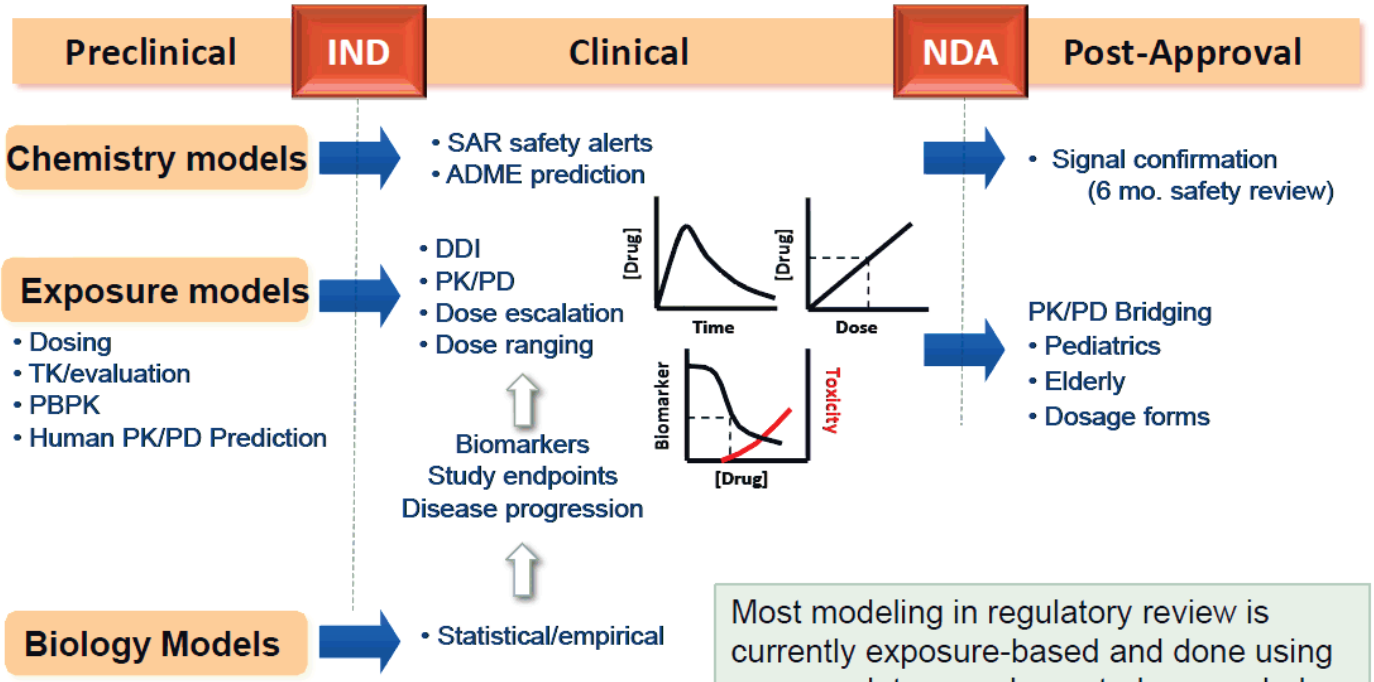


2d series of achievements

- Integrati
  and in b



Model-Based Drug Development Today



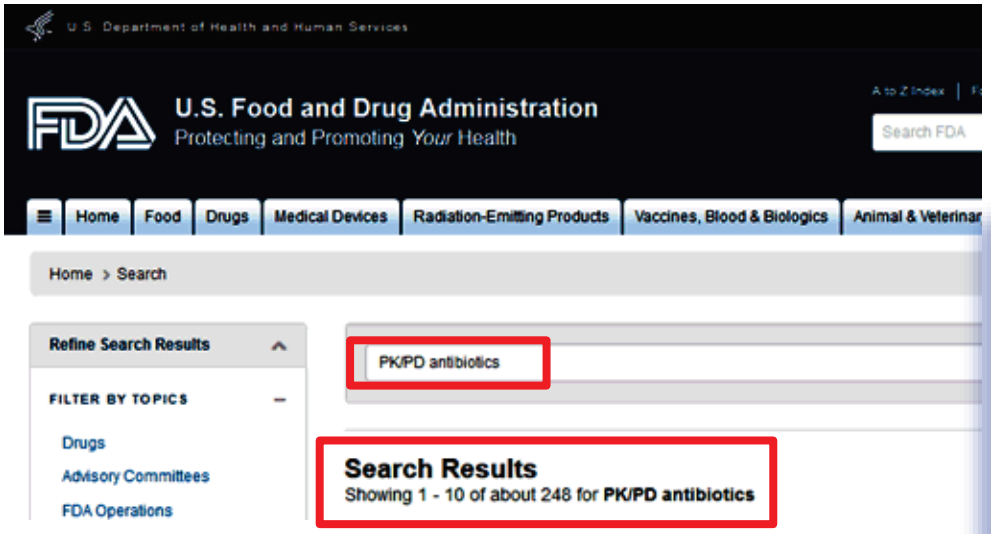
Most modeling in regulatory review is currently exposure-based and done using sponsor data, supplemented as needed with basic information on disease processes, drug properties, and patient populations

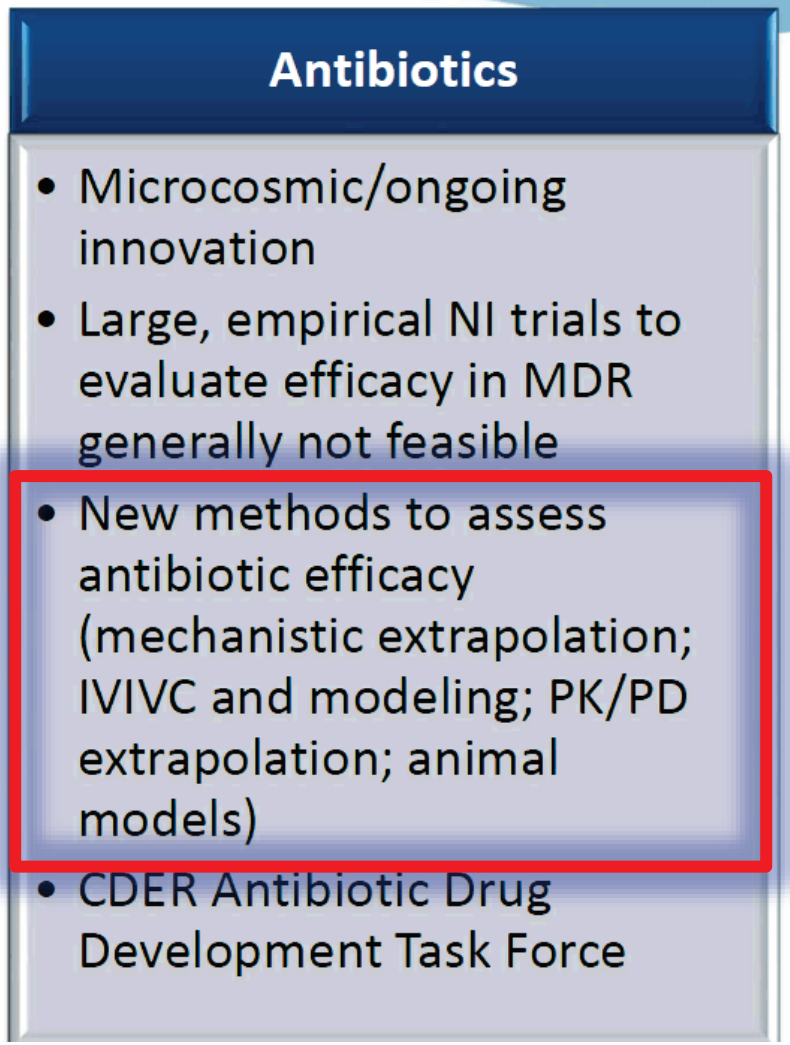
Courtesy of T. Colatsky

http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm344417.pdf

2d series of ach

- Integrating PK/PD in the process and in breakpoint settings





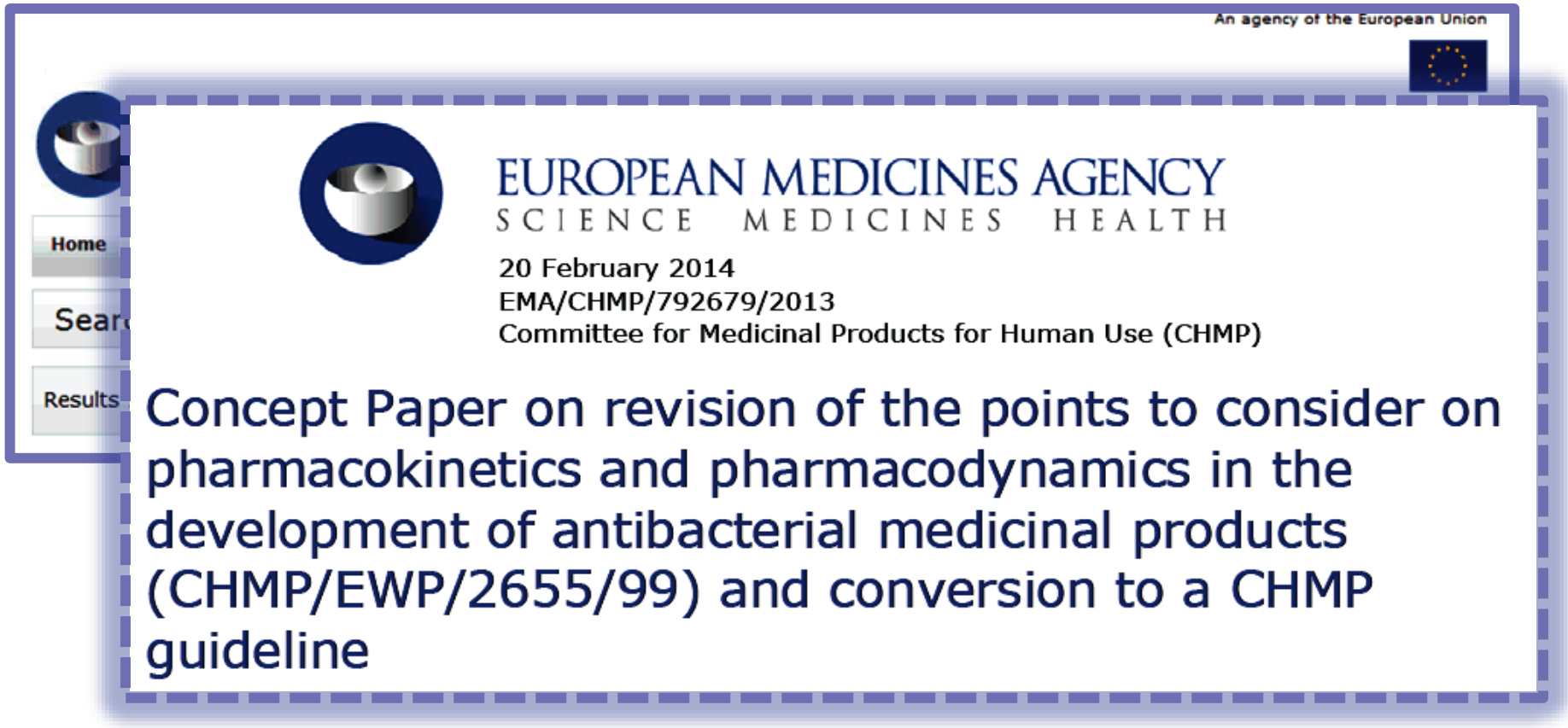
http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm344417.pdf

2d series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings

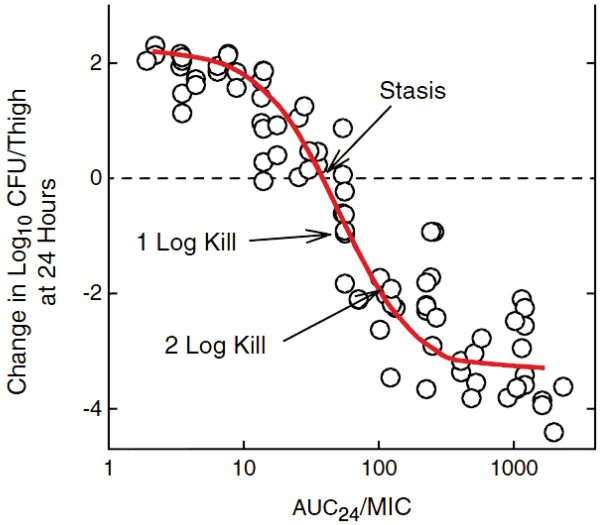
2d series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings



Breakpoint setting…

Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



Breakpoint setting…

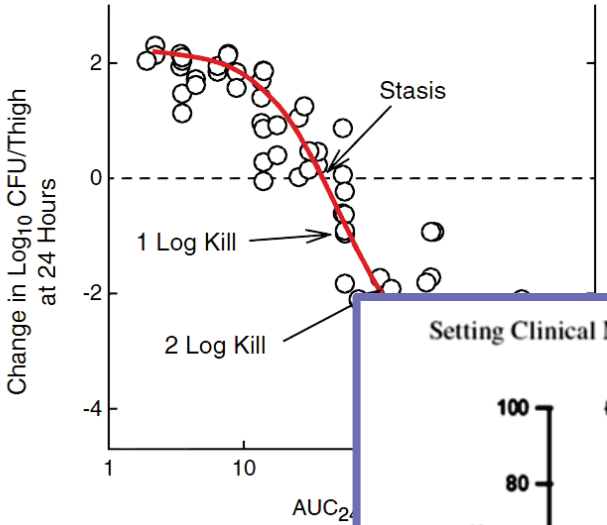


Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)

Setting Clinical MIC Breakpoints from a PK/PD Point of View…

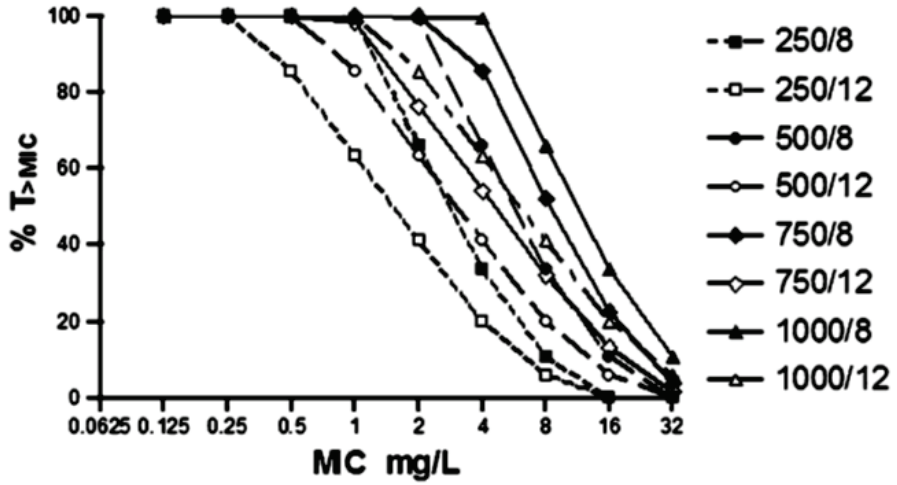
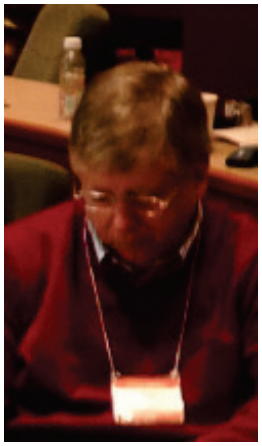


Fig. 3.2 Relationship between *%fT*>MIC and MIC for various dosing regimens of ceftobiprole. Illustrated is the close relationship between target MIC (usually the clinical breakpoint) and the dosing regimen. Adapted from Mouton et al. (2004)

Modeling and predicting…



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2001, p. 13–22 Vol. 45, No. 1
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.1.13–22.2001

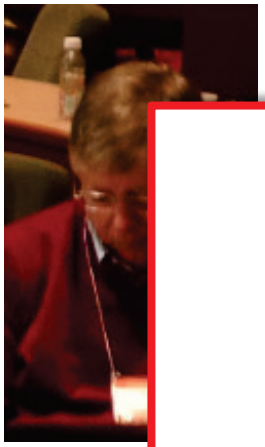
Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

G. L. DRUSANO,[1]* S. L. PRESTON,[1] C. HARDALO,[2] R. HARE,[2] C. BANFIELD,[2] D. ANDES,[3] O. VESGA,[3] AND W. A. CRAIG[3]

Division of Clinical Pharmacology, Albany Medical College, Albany, New York[1]; Schering Plough Research Institute, Kenilworth, New Jersey[2]; and Division of Clinical Pharmacology, University of Wisconsin, Madison, Wisconsin[3]

Received 22 November 1999/Returned for modification 26 April 2000/Accepted 1 September 2000

Modeling and predicting…



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2001, p. 13–22 Vol. 45, No. 1
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.1.13–22.2001

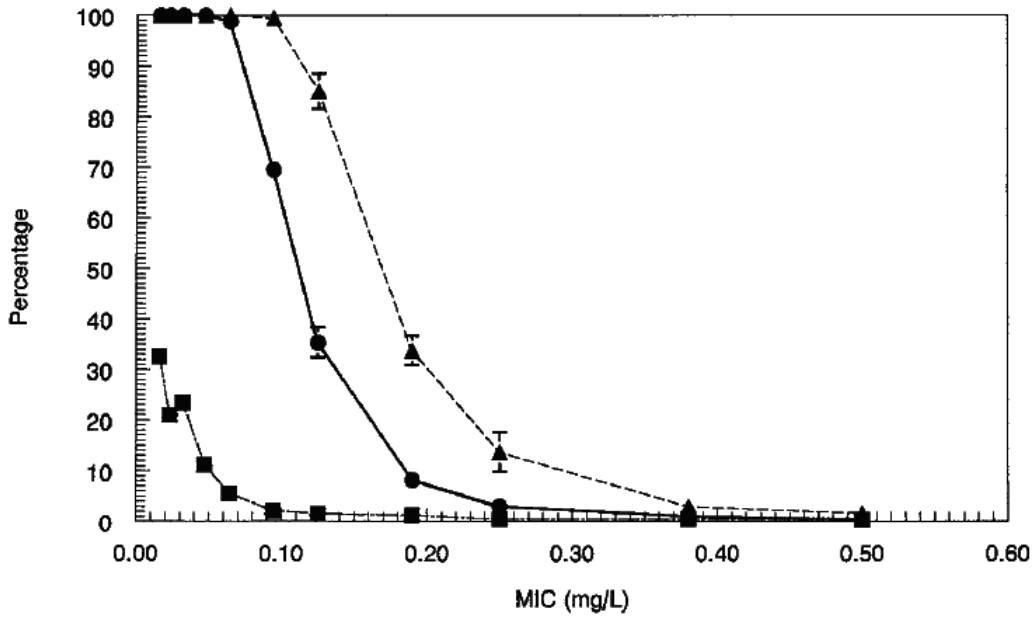


FIG. 4. Fractional attainment of the 90% E_{max} target for *S. pneumoniae* for the 6-mg/kg dose (●) and the 9-mg/kg dose (▲). The interval MIC distribution information is included (■).

Breakpoint setting: the EUCAST way

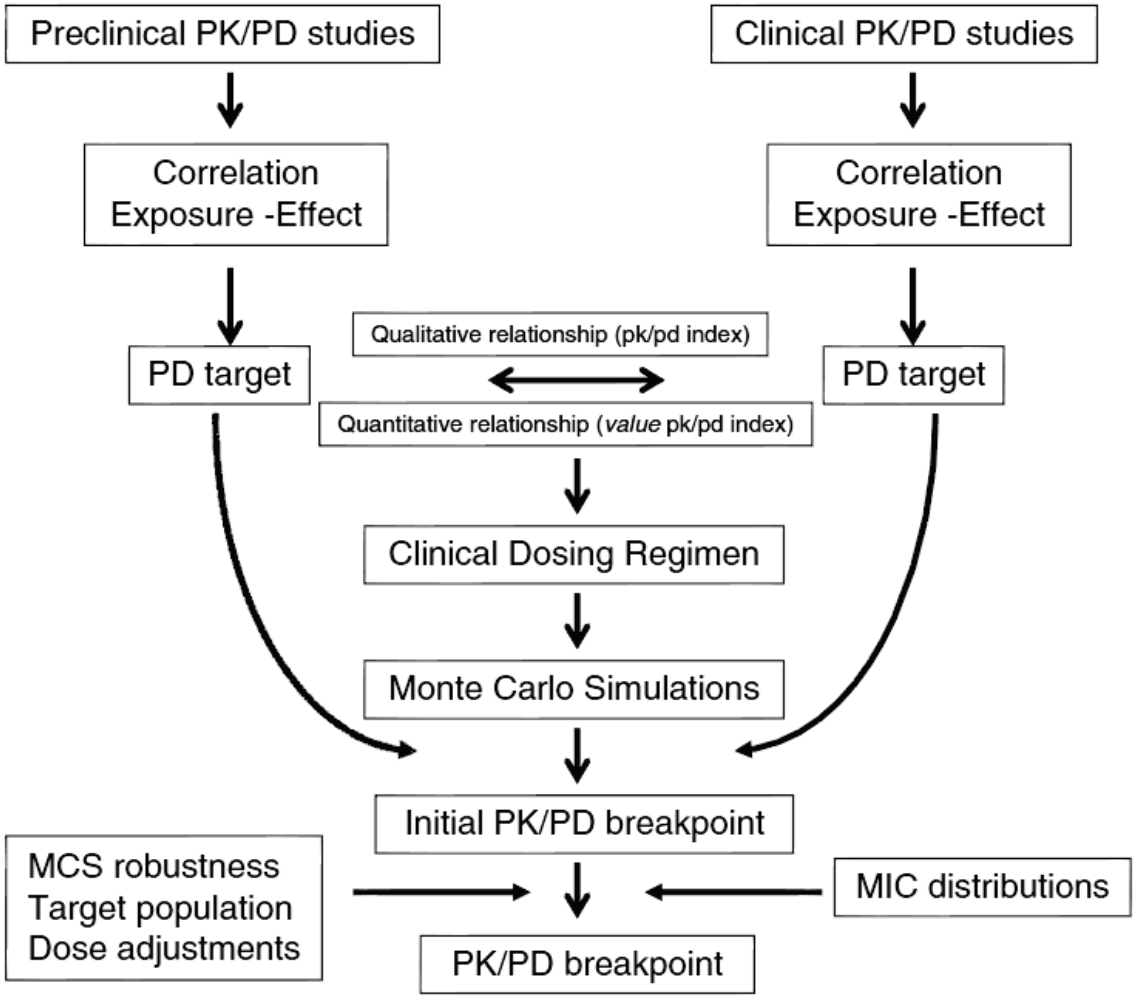


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

Where are we ?


0°
30°
270°
180°
Omega Centauri
NORMA ARM
CRUX ARM
CARINA ARM
SCUTUM ARM
SAGITTARIUS ARM
PERSEUS ARM
WE ARE HERE
Eta Carinae
Eagle Nebula
Lagoon
Ring Nebula
Trifid
Orion Nebula
ORION ARM
Crab Nebula
OUTER ARM

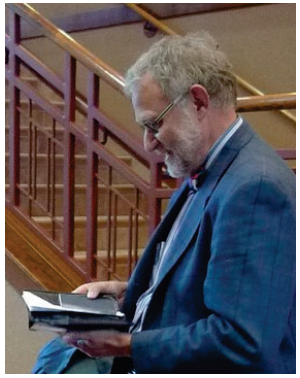
What do we need to do now ? *

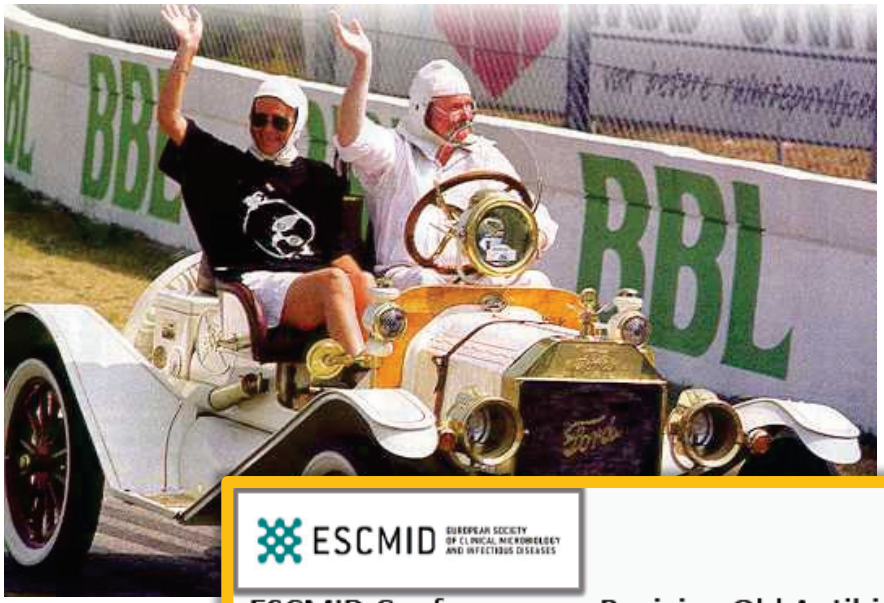
- cover "old antibiotics"
  - low interest from Regulatory bodies and NO interest from drug companies…
- individualized therapy
  - follow the path ...
- toxicodynamics
  - we may do better but mechanisms are complex ....
- prevention of resistance
  - this may be the real challenge

* personal views

Old antibiotics ?

Old antibiotics ?



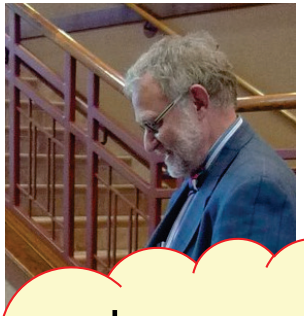


ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESCMID Conference on Reviving Old Antibiotics

Optimisation of therapy in Gram-negative infections

Old antibiotics ?



do you need help ?

Individualized therapy

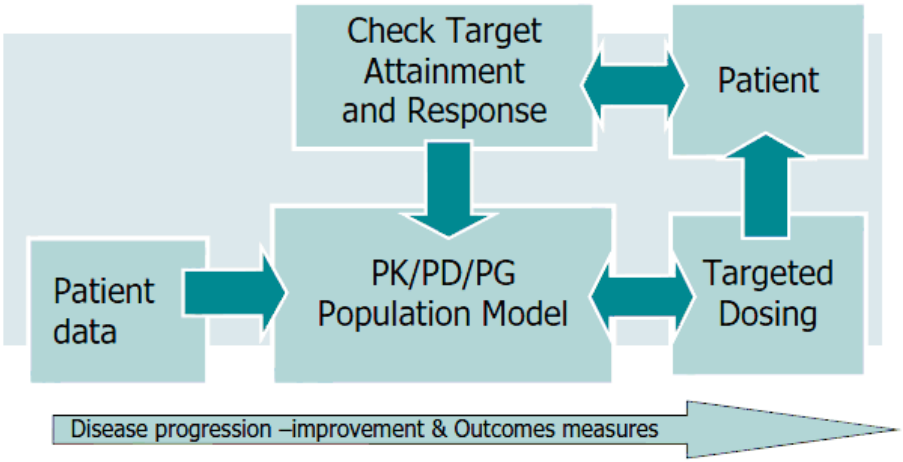


Fig. 6.5 Schematic representation of the target-controlled model-based individualized dosing strategy. A clinical pharmacokinetics program with a patient-specific population model describing absorption, distribution, and elimination of the antibiotic in relation to patient-specific parameters is used. Patient data and desired target concentrations are entered into the system. Next, a model-based loading dose and maintenance regimen required to optimally achieve the target concentrations is determined. This regimen is administered to the patient and subsequent concentration measurement(s) are used as feedback to check target attainment and update the model and/or design a new dosing regimen, if required. *PK* pharmacokinetics, *PD* pharmacodynamics, *PG* pharmacogenetics

Individualized therapy

Clinical Vignette 12.1: TDM of Vancomycin Administered by Continuous Infusion

A 21-year-old student has developed subacute meningitis and peritonitis in the presence of a ventriculoperitoneal shunt that was placed for hydrocephaly that developed following removal of a brain tumor. He has a fever of 38.9 °C, headache, and severe abdominal pain.

His length is 187 cm and his weight is 67 kg. The cerebrospinal fluid (CSF) WBC count is $>2.0 \times 10^9$/ml and the Gram stain shows Gram positive cocci in clusters.

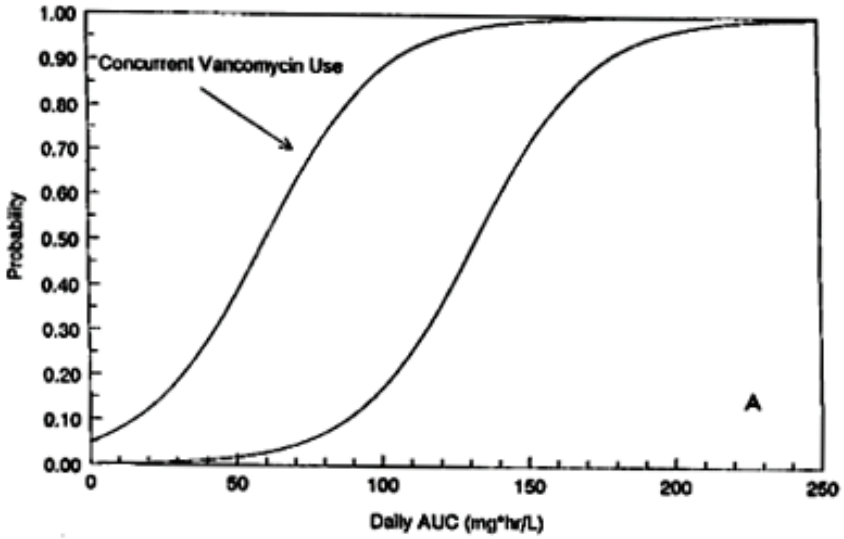
Empirical therapy with vancomycin is started at a loading dose of 15 mg/kg and a daily dose of 30 mg/kg/day by i.v. continuous infusion (CI). In practice, two syringes of 1 g are administered over 12 h with an infusion pump. Both *S. aureus* MSSA (MIC 1 µg/mL) and coagulase-negative staphylococci (MIC 2 µg/mL) are cultured from the CSF. The shunt is removed and a ventricular external drain is placed. Vancomycin 10 mg is given once intraventricularly.

A vancomycin serum level on Day 3 is 15 µg/mL. The daily CI vancomycin dose is increased to 2,250 mg (two syringes of 1,225 mg) and in the subsequent days target serum levels of 20 µg/mL are reached.

Because of the CI, each serum level sample is a correct one, regardless of the time of sampling, and adjustments of dosing are easily achieved in this neurosurgical department.

Toxicodynamics

The aminoglycosides revisited ….



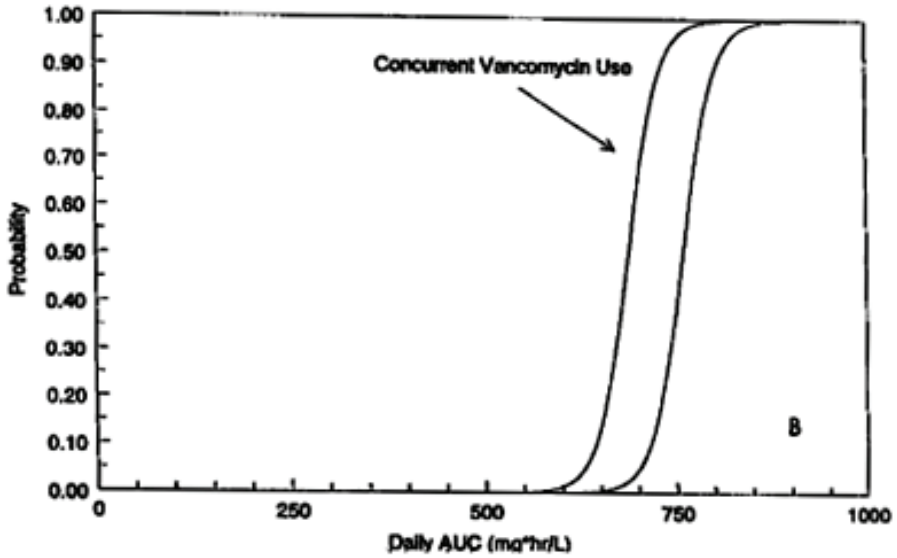


FIG. 1. (A) Curve of probability of development of aminoglycoside nephrotoxicity for patients receiving the drug on a twice-daily basis as estimated by multivariate logistic regression analysis. The probability rises as a function of increasing daily exposure to aminoglycoside, as indexed to the AUC. Concurrent vancomycin use provides a marked increase in the probability of nephrotoxicity for equivalent exposure to aminoglycosides, as indexed to the daily AUC. (B) Once-daily administration shifts the curves of probability of nephrotoxicity as influenced by daily aminoglycoside AUC to the right.

Toxicodynamics

The oxazolidinones visited ….

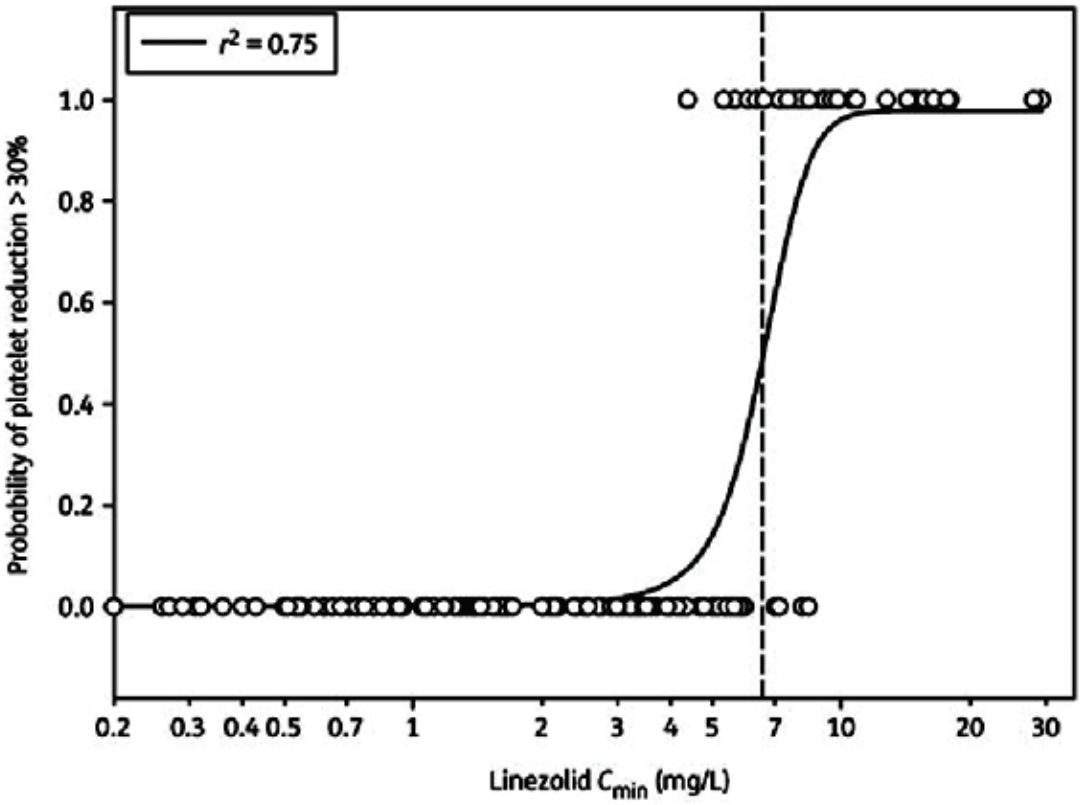


Fig. 16.13 Linezolid C_{min} and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the C_{min} observed over time in each patient with (*top*) or without (*bottom*) thrombocytopenia. The *continuous line* represents the result of the logistic regression model. The *vertical broken line* identifies the C_{min} value predicting 50 % probability of thrombocytopenia

Theuretzbacher U, PK/PD of Oxazolidinones In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinvk, H. Derendorf & JW Mouton eds, Springer, 2014, p 401-443

Toxicodynamics

The oxazolidinones visited ….in much more details….

Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak,[a]* Craig R. Rayner,[a,b] M. Lindsay Grayson,[c,d] David L. Paterson,[e]* Denis Spelman,[f] Sharmila Khumra,[c,h] Blair Capitano,[e]* Alan Forrest,[g] Jian Li,[a] Roger L. Nation,[a] Jurgen B. Bulitta[a,g,h]

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia[a]; d3 Medicine LLC, Parsippany, New Jersey, USA[b]; Department of Medicine, Austin Hospital, Melbourne, Australia[c]; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia[d]; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[e]; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia[f]; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA[g]; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia[h]

Antimicrob Agents Chemother 2014;58:334–2343

Toxicodynamics

The oxazolidinones visited ….in much more details….

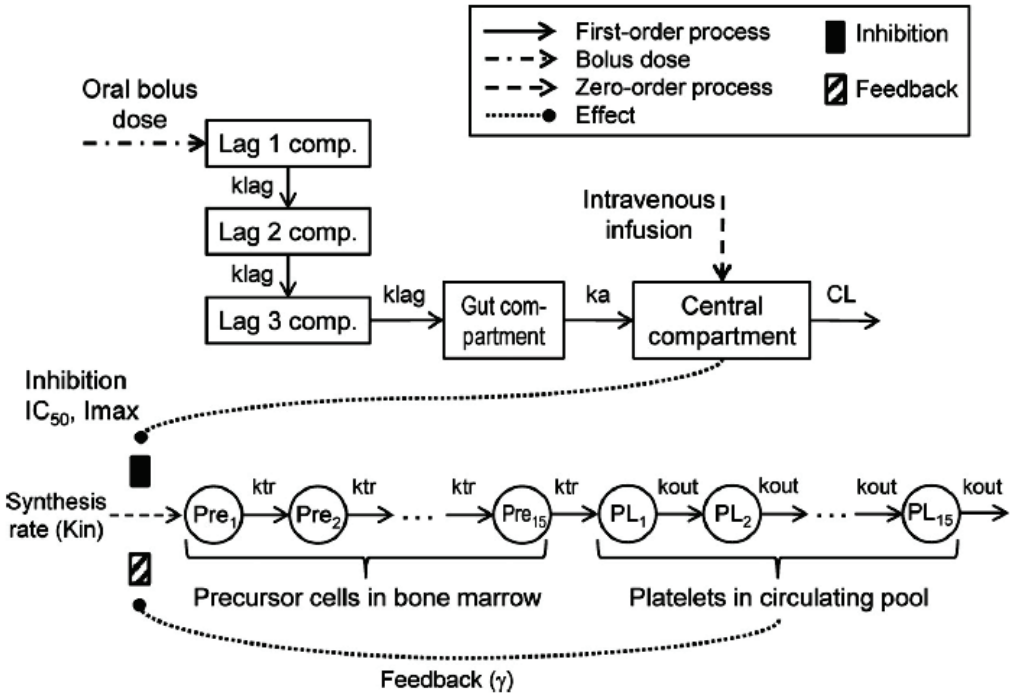


FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.

Toxicodynamics

The oxazolidinones visited ….in much more details….

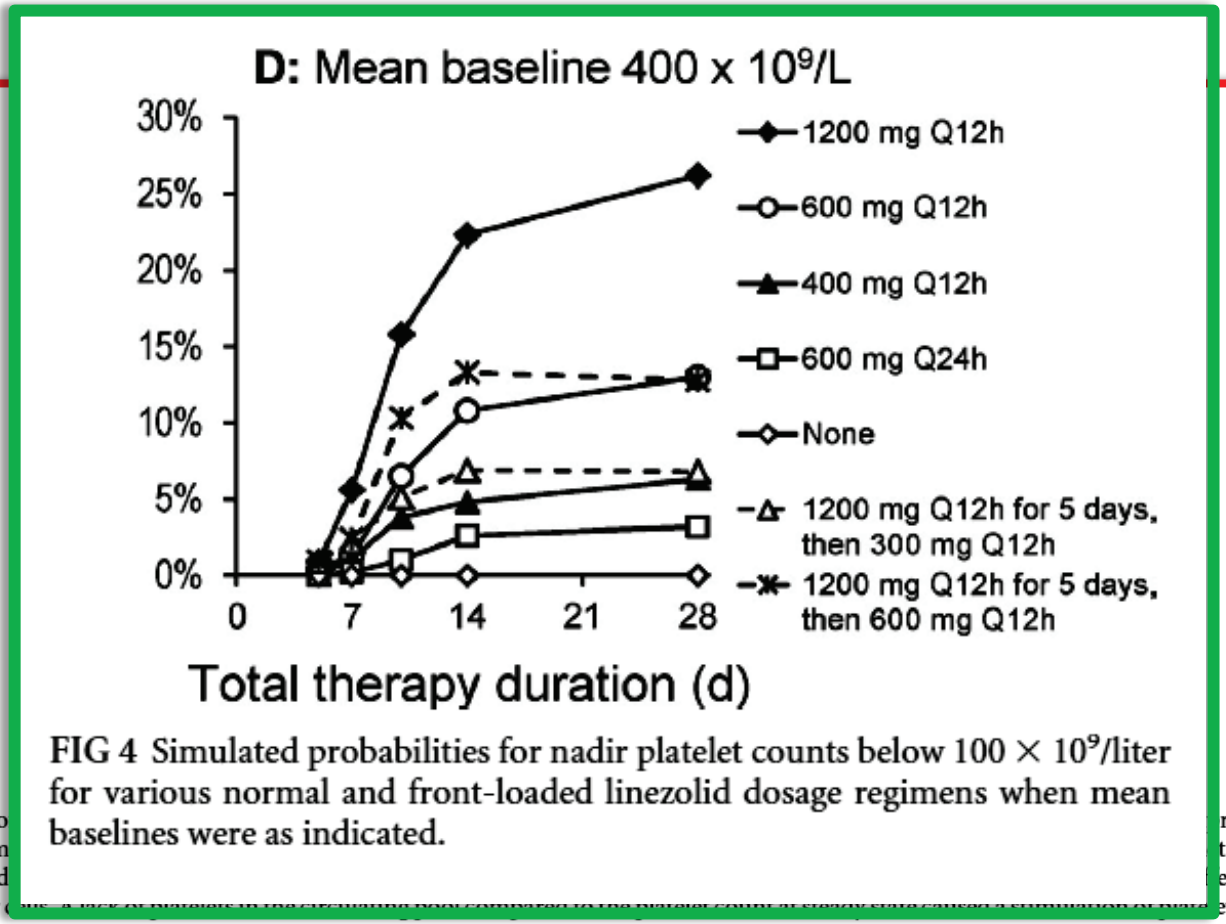


FIG 4 Simulated probabilities for nadir platelet counts below 100 × 10⁹/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

FIG 1 Structure o … rised of three absorption lag compartm … t precursor cells in the bone marrow, and … ect on the synthesis of platelet precursor … et precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.

Resistance

The saga of the fluoroquinolones and shutting down resistance…

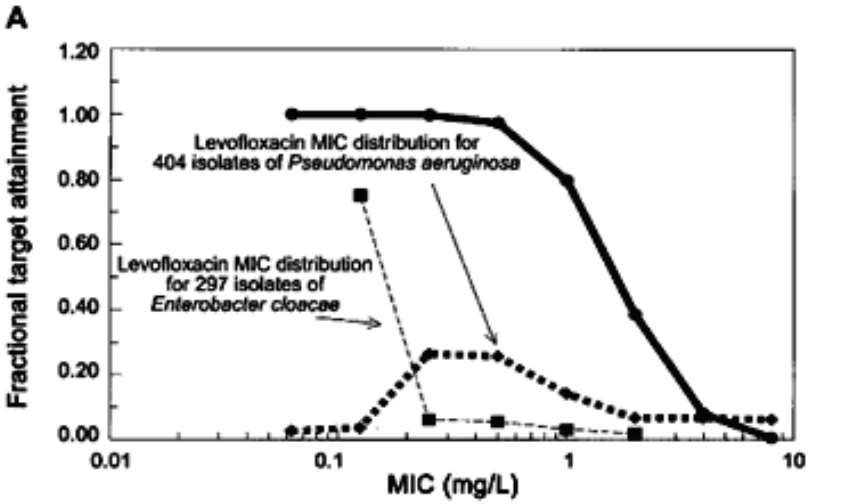


Figure 3. Ability of a dose of drug to attain an area under the curve (AUC):MIC ratio of 87 (the target ratio for eradication of the pathogen) is affected by the distribution of the drug's clearance in the population and by the MIC of the pathogen. The fractional target attainment for 10,000 simulated subjects is displayed as a function of MIC values for levofloxacin (750 mg intravenous once daily; *A*) and for ciprofloxacin (400 mg iv every 8 h; *B*). In addition, the fraction of isolates at a specific MIC value for levofloxacin is displayed for *Pseudomonas aeruginosa* and *Enterobacter cloacae*. For ciprofloxacin, these data are provided for *P. aeruginosa*. This allows placing the target-attainment fractions in perspective. The drug dose will be expected to perform better if the fraction of isolates is high, whereby the MIC values give a high level of target attainment. The pharmacokinetic data used for the analysis in panel *B* are from Forrest et al. [19].

Well, you did it, did you not ?

my simple interpretation is that the breakpoint should be <<< the CLSI breakpoint…

Drusano et al. The Journal of Infectious Diseases 2004; 189:1590–7

To finish

- We were helped by technical developments

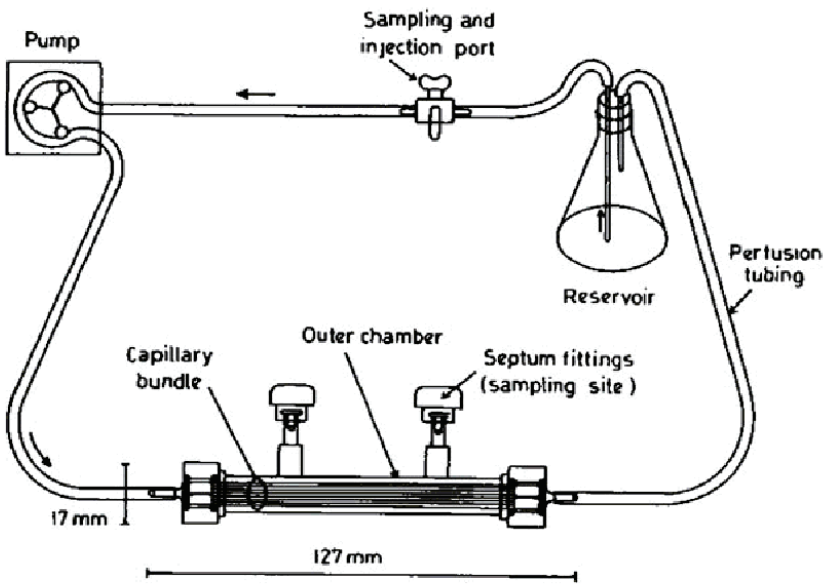


Fig. 5.21 Hollow fiber model by Zinner et al. (1981)

hollow fibers

pumps and tubing systems

humanized animal models

ex-vivo models

To finish

modelling

population PK with difficult antibiotics

sparse sampling

monitoring and adjusting

prevention of resistance

- and many other achievements

But who did it ?

The right team, folks

but hey were many others….

Two examples of people who should not have died…

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillin

Ann. Rev. Biochem. 1979. 48:73-101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

Jean-Marie Ghuysen, Jean-Marie Frère, Mélina Leyh-Bouille, Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection … caused by a resistant bacteria

AAC Journals.ASM.org

EDITORIAL

In Memoriam: William A. Craig

Ursula Theuretzbacher,[a] Paul G. Ambrose,[b] Alasdair P. MacGowan,[c] David R. Andes,[d] Fritz Sörgel,[e] Hartmut Derendorf,[f] Johan W. Mouton,[g] George L. Drusano,[h] Paul M. Tulkens,[i] Michael N. Dudley,[j] Otto Cars,[k] Roger L. Nation[l]

Center for Anti-Infective Agents, Vienna, Austria[a]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]; Bristol Centre for Antimicrobial Research and Evaluation, Department of Infection Sciences, North Bristol NHS Trust, Bristol, United Kingdom[c]; University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA[d]; IBMP—Institute for Biomedical and Pharmaceutical Research, Nürnberg-Heroldsberg, Germany[e]; University of Florida, College of Pharmacy, Gainesville, Florida, USA[f]; Department of Medical Microbiology and Infectious Diseases Erasmus MC, Rotterdam, The Netherlands[g]; Institute for Therapeutic Innovation, University of Florida College of Medicine, Orlando, Florida, USA[h]; Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium[i]; The Medicines Company, San Diego, California, United States[j]; Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden[k]; Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia[l]

Dr. Craig was renowned as a clinician-scholar in the fields of antimicrobial therapy and infectious disease. **His early work on quantifying the relationship between antimicrobial dosing and treatment effect led to the development of the field of antimicrobial pharmacodynamics.**

He died from infectious complications of anticancer therapy

I forgot many important points…