# Non-Antibiotics und vergessene Antibiotika: antimikrobielle Wirksamkeit von Azidothymidin und Terizidon gegenüber Enterobacteriaceae

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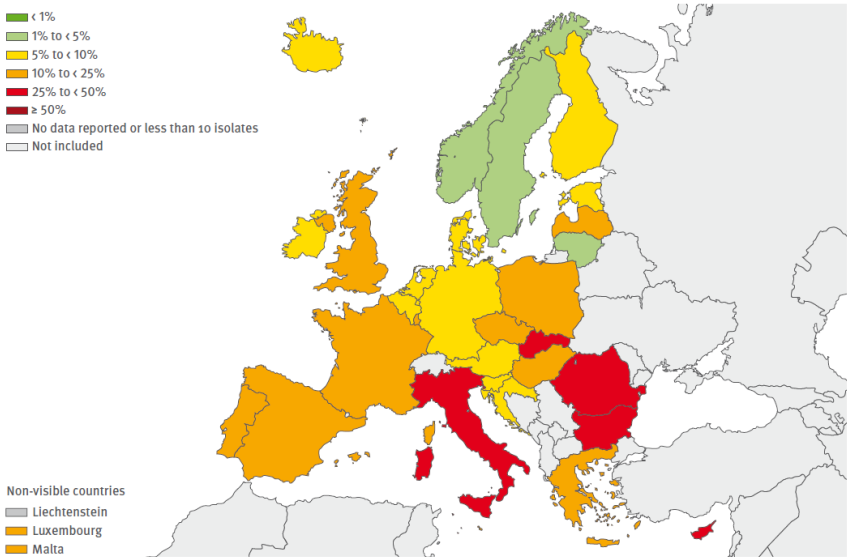
# Was sind Non-Antibiotics?

- **Klinisch zugelassene Pharmaka, die für verschiedenste nicht-antibakterielle Indikationen eingesetzt werden (z.B. Neuroleptika), jedoch auch eine antibakterielle /synergistische (Neben-) Wirkung aufweisen**
- **Erweiterte Definition: Pharmaka mit günstigem Einfluss auf den Verlauf einer bakteriellen Infektion auch unabhängig von direkter antibakterieller Wirksamkeit (z.B. Einfluss auf Immunantwort des Wirtes)**

# Warum Non-Antibiotics?

- **Deutliche (Multi-)Resistenzzunahme vor allem bei Gramnegativen schränkt Behandlungsoptionen ein -> ESBL**
- **Wenig neue Substanzen insbesondere aus neuen Wirkstoffklassen in der Pipeline**

Figure 3.1. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country, EU/EEA countries, 2012





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# Welche Non-Antibiotics mit antibakterieller in-vitro Wirksamkeit sind bekannt?

- **Neuroleptika (z.B. Thioridazin, Haloperidol, Pimozid)**

*The Open Microbiology Journal*, 2013, 7, (Suppl 1-M7) 83-86

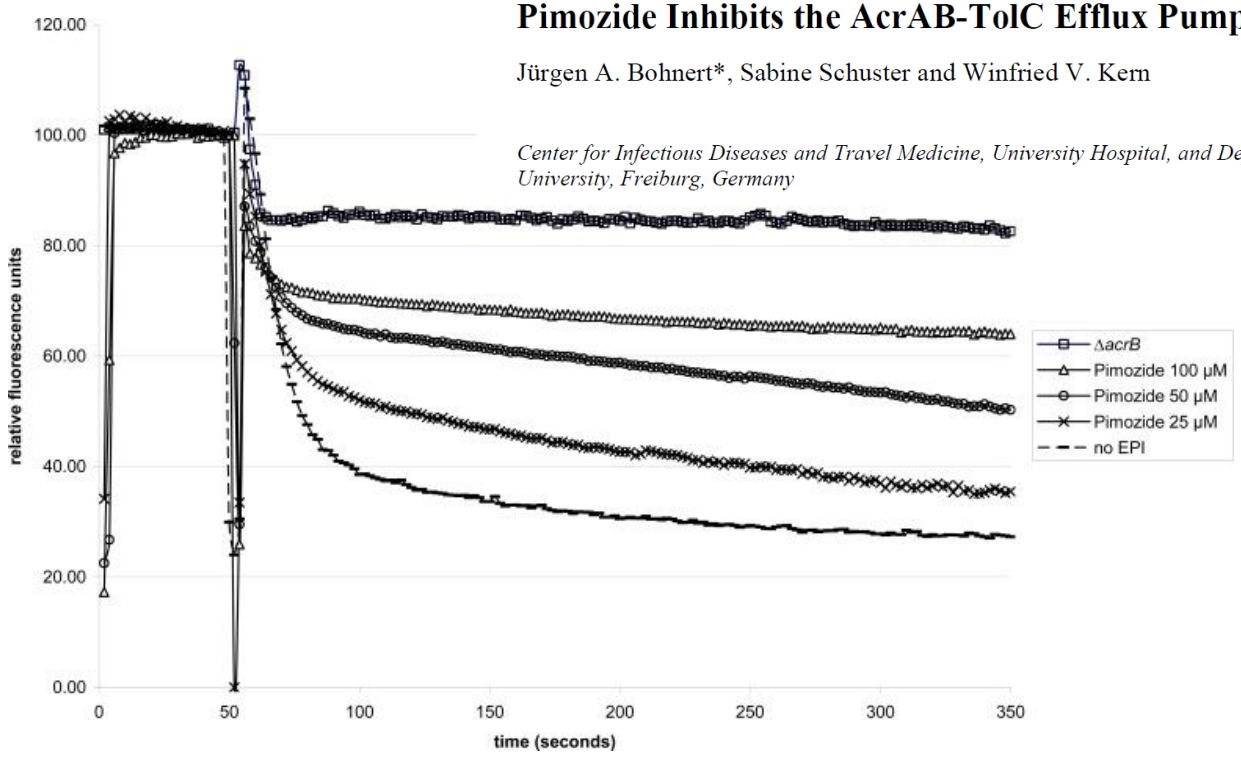




**Pimozide Inhibits the AcrAB-TolC Efflux Pump in *Escherichia coli***

Jürgen A. Bohnert*, Sabine Schuster and Winfried V. Kern

*Center for Infectious Diseases and Travel Medicine, University Hospital, and Department of Medicine, Albert-Ludwigs-University, Freiburg, Germany*



# Welche Non-Antibiotics mit antibakterieller in-vitro Wirksamkeit sind bekannt?

- Neuroleptika (z.B. Thioridazin, Haloperidol, Pimozid)
- Statine (Simvastatin)
- Virostatika (Azidothymidin)
- Antiphlogistika (Diclofenac)
- Ca-Antagonisten (Amlodipin)

**In-vivo Blut- oder Urinkonzentrationen >= MHK**

# Welche Non-Antibiotics mit antibakterieller in-vitro Wirksamkeit sind bekannt?

- Neuroleptika (z.B. Thioridazin, Haloperidol, Pimozid)
- Statine (Simvastatin)
- Virostatika (Azidothymidin)
- Antiphlogistika (Diclofenac)
- Ca-Antagonisten (Amlodipin)

**Hinweise auf in-vivo Wirksamkeit bei Infektionen**

# Neuroleptika als Non-Antibiotics: Thioridazin

- **Thioridazin als Kombinationspartner bei der XDR-Tuberkulose bei 14 Patienten**
- **Behandlungsabbruch bei 2 Patienten wg. NW**
- **11 geheilt**

*J Antimicrob Chemother* 2012; **67**: 473–477
doi:10.1093/jac/dkr500 Advance Access publication 1 December 2011

Journal of Antimicrobial Chemotherapy

## Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine

Eduardo Abbate[1], Marisa Vescovo[1], Marcela Natiello[1], Mónica Cufré[1], Ana García[1], Pablo Gonzalez Montaner[1], Marta Ambroggi[1], Viviana Ritacco[2,3]* and Dick van Soolingen[4,5,6]

# Neuroleptika als Non-Antibiotics: Haloperidol

- **Haloperidol reduziert 28-Tages-ITS-Sterblichkeit (HR 0,8)**
- **177 prophylaktisch behandelte Patienten mit Risiko für Delirium vs. retrospektive Kontrollgruppe (299 Patienten)**

van den Boogaard *et al. Critical Care* 2013, **17**:R9
http://ccforum.com/content/17/1/R9

CRITICAL CARE

RESEARCH Open Access

Haloperidol prophylaxis in critically ill patients with a high risk for delirium

Mark van den Boogaard[1*], Lisette Schoonhoven[2,3], Theo van Achterberg[2], Johannes G van der Hoeven[1,4] and Peter Pickkers[1,4]

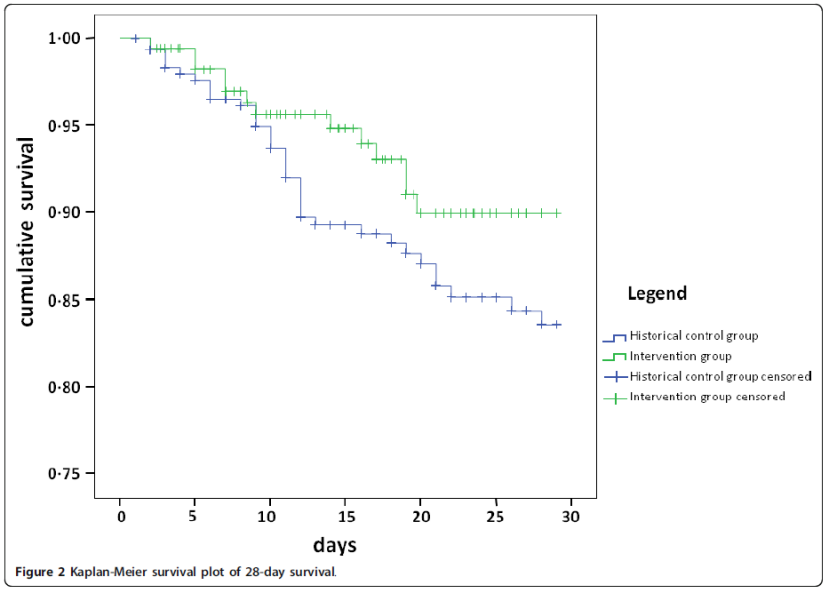



Figure 2 Kaplan-Meier survival plot of 28-day survival.

# Statine als Non-Antibiotics

- **Statine reduzieren *S. aureus* –Sepsissterblichkeit in prospektiver Kohortenstudie (14 Tages-Sterblichkeit 6 % vs. 25 %)**
- **33 von 160 Patienten erhielten Statine (52 % Atorvastatin, 42 % Simvastatin, 6 % Pravastatin)**

December 2013 | Volume 8 | Issue 12 |

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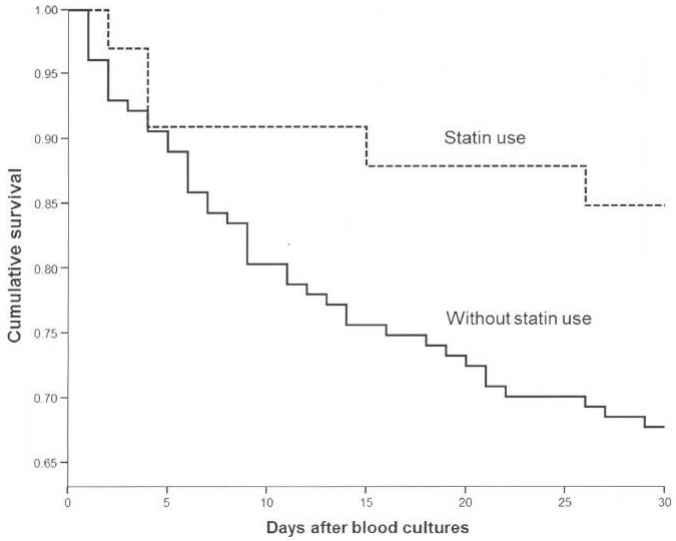
PLOS ONE

**Effect of Statin Therapy in the Outcome of Bloodstream Infections Due to *Staphylococcus aureus*: A Prospective Cohort Study**

Luis E. López-Cortés[1], Juan Gálvez-Acebal[1,2,4], María D. del Toro[1,2,4], Carmen Velasco[2,3], Marina de Cueto[1,2], Francisco J. Caballero[2], Miguel A. Muniain[1,2,4], Álvaro Pascual[1,2,3], Jesús Rodríguez-Baño[1,2,4]*

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# Confounder? Plausibler Mechanismus?

## Why Most Published Research Findings Are False

John P. A. Ioannidis

**Summary**

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

factors that influence this problem and some corollaries thereof.

### Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

**It can be proven that most claimed research findings are false.**

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful.

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R+1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, $\alpha$. Assuming that $c$ relationships are being probed in the field, the expected values of the $2 \times 2$ table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2



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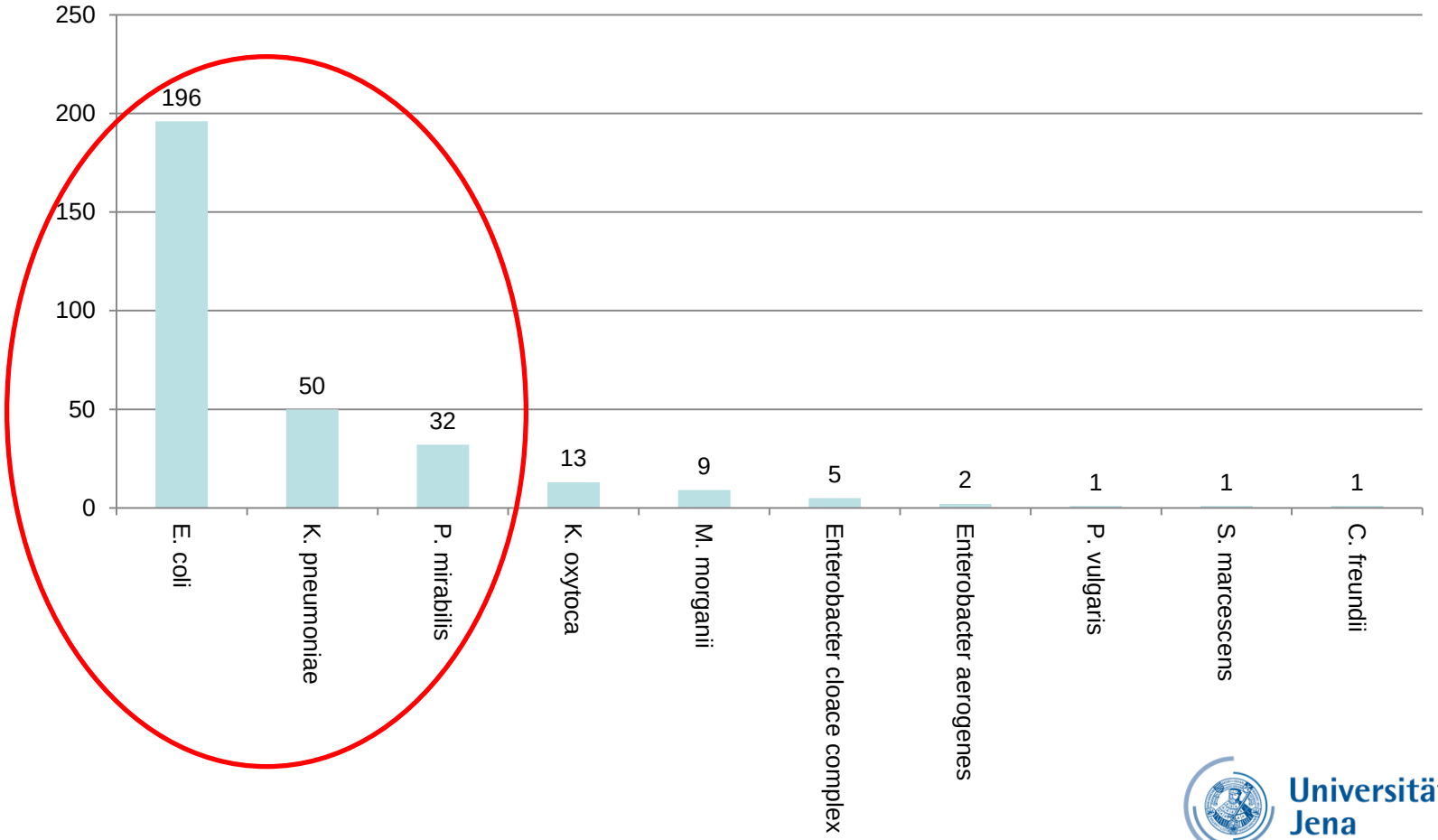
# Vom Wirt zum Erreger – die Jenaer Urinstudie

- **310 Enterobacteriacae Urinisolate, gesammelt vom 4. Februar – 22. März 2014**

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# MHKs der wichtigsten Erreger: *E. coli*

| Substanz | | MHK (mg/l) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | < 0,125 | 0,25 | 0,5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | > 256 | %-S | %-I | %-R |
| Ampicillin | absolut | - | - | - | - | 44 | 28 | 12 | 4 | 108 | - | - | - | 42,9 | - | 57,1 |
| | kum.-% | - | - | - | - | 22,4 | 36,7 | 42,9 | 44,9 | 100,0 | - | - | - | | | |
| Ampicillin/Sulbactam | absolut | - | - | - | - | 97 | 4 | 5 | 61 | 29 | - | - | - | 54,1 | - | 45,9 |
| | kum.-% | - | - | - | - | 49,5 | 51,5 | 54,1 | 85,2 | 100,0 | - | - | - | | | |
| Fosfomycin | absolut | - | - | - | - | - | - | - | 188 | 3 | 0 | 0 | 0 | 100,0 | - | 0,0 |
| | kum.-% | - | - | - | - | - | - | - | 98,4 | 100,0 | 100,0 | 100,0 | 100,0 | | | |
| Cef/Axet | absolut | - | - | - | 10 | 12 | 123 | 4 | 11 | 1 | 34 | - | - | 76,4 | - | 23,6 |
| | kum.-% | - | - | - | 5,1 | 11,3 | 74,4 | 76,4 | 82,1 | 82,6 | 100,0 | - | - | | | |
| Ceftazidim | absolut | - | - | - | 176 | 4 | 9 | 0 | 4 | 0 | 3 | - | - | 89,8 | 7,0 | 3,2 |
| | kum.-% | - | - | - | 89,8 | 91,8 | 96,4 | 96,4 | 98,5 | 98,5 | 100,0 | - | - | | | |
| Meropenem | absolut | - | 195 | 0 | 0 | 1 | 0 | 0 | 0 | - | - | - | - | 100,0 | 0,0 | 0,0 |
| | kum.-% | - | 99,5 | 99,5 | 99,5 | 100,0 | 100,0 | 100,0 | 100,0 | - | - | - | - | | | |
| Ciprofloxacin | absolut | - | 144 | 4 | 4 | 0 | 43 | - | - | - | - | - | - | 75,9 | 2,1 | 22,0 |
| | kum.-% | - | 73,8 | 75,9 | 77,9 | 77,9 | 100,0 | - | - | - | - | - | - | | | |
| Gentamicin | absolut | - | - | - | 185 | 1 | 0 | 0 | 10 | - | - | - | - | 94,9 | 0,0 | 5,1 |
| | kum.-% | - | - | - | 94,4 | 94,9 | 94,9 | 94,9 | 100,0 | - | - | - | - | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | < 1 | 20 | 32 | 40 | 80 | > 320 | | | | | | |
| Cotrim | absolut | - | - | - | 1 | 123 | 1 | 0 | 0 | 71 | - | - | - | 63,8 | 0,0 | 36,2 |
| | kum.-% | - | - | - | 0,5 | 63,3 | 63,8 | 63,8 | 63,8 | 100,0 | - | - | - | | | |

3G-Cephalosporinresistenz 11 %

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# MHKs der wichtigsten Erreger: *K. pneumoniae*

| Substanz | | MHK (mg/l) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | < 0,125 | 0,25 | 0,5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | > 256 | %-S | %-I | %-R |
| Ampicillin | absolut | - | - | - | - | 1 | 0 | 0 | 8 | 41 | - | - | - | 2,0 | - | 98,0 |
| | kum.-% | - | - | - | - | 2,0 | 2,0 | 2,0 | 18,0 | 100,0 | - | - | - | | | |
| Ampicillin/Sulbactam | absolut | - | - | - | - | 28 | 2 | 1 | 6 | 13 | - | - | - | 62,0 | - | 38,0 |
| | kum.-% | - | - | - | - | 56,0 | 60,0 | 62,0 | 74,0 | 100,0 | - | - | - | | | |
| Fosfomycin | absolut | - | - | - | - | - | - | - | 21 | 8 | 10 | 2 | 9 | 58,0 | - | 42,0 |
| | kum.-% | - | - | - | - | - | - | - | 42,0 | 58,0 | 78,0 | 82,0 | 100,0 | | | |
| Cef/Axet | absolut | - | - | - | 10 | 8 | 8 | 3 | 5 | 0 | 16 | - | - | 58,0 | - | 42,0 |
| | kum.-% | - | - | - | 20,0 | 36,0 | 52,0 | 58,0 | 68,0 | 68,0 | 100,0 | - | - | | | |
| Ceftazidim | absolut | - | - | - | 38 | 0 | 1 | 1 | 3 | 0 | 7 | - | - | 76,0 | 2,0 | 22,0 |
| | kum.-% | - | - | - | 76,0 | 76,0 | 78,0 | 80,0 | 86,0 | 86,0 | 100,0 | - | - | | | |
| Meropenem | absolut | - | 49 | 0 | 0 | 0 | 0 | 0 | 1 | - | - | - | - | 98,0 | 0,0 | 2,0 |
| | kum.-% | - | 98,0 | 98,0 | 98,0 | 98,0 | 98,0 | 98,0 | 100,0 | - | - | - | - | | | |
| Ciprofloxacin | absolut | - | 24 | 3 | 8 | 6 | 9 | - | - | - | - | - | - | 54,0 | 16,0 | 30,0 |
| | kum.-% | - | 48,0 | 54,0 | 70,0 | 82,0 | 100,0 | - | - | - | - | - | - | | | |
| Gentamicin | absolut | - | - | - | 44 | 0 | 0 | 0 | 6 | - | - | - | - | 88,0 | 0,0 | 12,0 |
| | kum.-% | - | - | - | 88,0 | 88,0 | 88,0 | 88,0 | 100,0 | - | - | - | - | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | 1 | 20 | 32 | 40 | 80 | 320 | | | | | | |
| Cotrim | absolut | - | - | - | 0 | 30 | 0 | 2 | 2 | 16 | - | - | - | 64,0 | 4,0 | 32,0 |
| | kum.-% | - | - | - | 0,0 | 60,0 | 60,0 | 64,0 | 68,0 | 100,0 | - | - | - | | | |

3G-Cephalosporinresistenz 36 %

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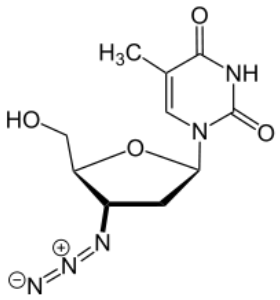
# MHKs der wichtigsten Erreger: *P. mirabilis*

| Substanz | | MHK (mg/l) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | < 0,125 | 0,25 | 0,5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | > 256 | %-S | %-I | %-R |
| Ampicillin | absolut | - | - | - | - | 20 | 0 | 0 | 0 | 12 | - | - | - | 62,5 | - | 37,5 |
| | kum.-% | - | - | - | - | 62,5 | 62,5 | 62,5 | 62,5 | 100,0 | - | - | - | | | |
| Ampicillin/Sulbactam | absolut | - | - | - | - | 23 | 0 | 0 | 7 | 2 | - | - | - | 71,9 | - | 28,1 |
| | kum.-% | - | - | - | - | 71,9 | 71,9 | 71,9 | 93,8 | 100,0 | - | - | - | | | |
| Fosfomycin | absolut | - | - | - | - | - | - | - | 23 | 2 | 5 | 1 | 1 | 78,1 | - | 21,9 |
| | kum.-% | - | - | - | - | - | - | - | 71,9 | 78,1 | 93,8 | 96,9 | 100,0 | | | |
| Cef/Axet | absolut | - | - | - | 19 | 7 | 6 | 0 | 0 | 0 | 0 | - | - | 100,0 | - | 0,0 |
| | kum.-% | - | - | - | 59,4 | 81,3 | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | - | - | | | |
| Ceftazidim | absolut | - | - | - | 31 | 0 | 0 | 1 | 0 | 0 | 0 | - | - | 96,9 | 0,0 | 3,1 |
| | kum.-% | - | - | - | 96,9 | 96,9 | 96,9 | 100,0 | 100,0 | 100,0 | 100,0 | - | - | | | |
| Meropenem | absolut | - | 32 | 0 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 100,0 | 0,0 | 0,0 |
| | kum.-% | - | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | - | - | - | - | | | |
| Ciprofloxacin | absolut | - | 22 | 0 | 2 | 6 | 2 | - | - | - | - | - | - | 68,7 | 6,3 | 25,0 |
| | kum.-% | - | 68,8 | 68,8 | 75,0 | 93,8 | 100,0 | - | - | - | - | - | - | | | |
| Gentamicin | absolut | - | - | - | 27 | 0 | 2 | 0 | 2 | - | - | - | - | 87,0 | 6,5 | 6,5 |
| | kum.-% | - | - | - | 87,1 | 87,1 | 93,5 | 93,5 | 100,0 | - | - | - | - | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | 1 | 20 | 32 | 40 | 80 | 320 | | | | | | |
| Cotrim | absolut | - | - | - | 0 | 14 | 0 | 3 | 0 | 15 | - | - | - | 53,2 | 0,0 | 46,8 |
| | kum.-% | - | - | - | 0,0 | 43,8 | 43,8 | 53,1 | 53,1 | 100,0 | - | - | - | | | |

# Azidothymidin (AZT) – ein klassisches Non-Antibiotic

- Inhibitor der Reversen Transkriptase von HIV (Einbau von AZT statt Thymidin)
- Thymidinkinasen (auch bei Enterobacteriacae vorhanden) erzeugen die aktive Form AZT-Triphosphat, die die Kettenverlängerung bakterieller DNA terminiert
- Ca. 75 % werden glucuronidiert und renal ausgeschieden
- Ca. 15 % werden in AMT umgewandelt



# Klinische Wirksamkeit von AZT

## Zidovudine Therapy Protects against *Salmonella* Bacteremia Recurrence in Human Immunodeficiency Virus–Infected Patients

Jose L. Casado, Silvia Valdezate, Celia Calderon, Enrique Navas, Begoña Frutos, Antonio Guerrero, and Jesús Martinez-Beltran

*Infectious Diseases Unit and Department of Microbiology, Hospital Ramón y Cajal, Madrid, Spain*

Fifty-five human immunodeficiency virus–infected patients with *Salmonella* bacteremia were studied to assess the rate of and causes for recurrence and to determine the influence on relapse of zidovudine, cotrimoxazole, and antimicrobial suppressive therapy according to the susceptibility of the isolates. Overall, 22% of patients relapsed in a median time of 87 days, independent of CD4 cell count, *Salmonella* serotype, or duration of antibiotic therapy. The use of zidovudine was associated with the lowest rate of recurrences compared with cotrimoxazole or amoxicillin as suppressive therapy. In the microbiologic assay, zidovudine showed bactericidal effect on *Salmonella* species at current dosages, and resistance to zidovudine was uncommon (2 cases, 4%). Due to its direct effect on *Salmonella* species, a zidovudine-containing regimen may protect against the recurrence of the disease.

**Table 1.** Rate of recurrence of *Salmonella* bacteremia according to type of maintenance therapy.

| Therapy | Patients with relapse/ total no. of patients |
|---|---|
| No treatment | 6/11 (55%) |
| Cotrimoxazole alone | 4/13 (30%) |
| Amoxicillin alone | 2/6 (33%) |
| Zidovudine | 0/13 |
| Zidovudine and ciprofloxacin | 0/2 |
| Zidovudine and cotrimoxazole | 0/12 |

JID 1999;179 (June)

# Pharmakokinetic von AZT nach oraler Gabe von 200 mg +/- Probenicid (500 mg 6-stündlich)

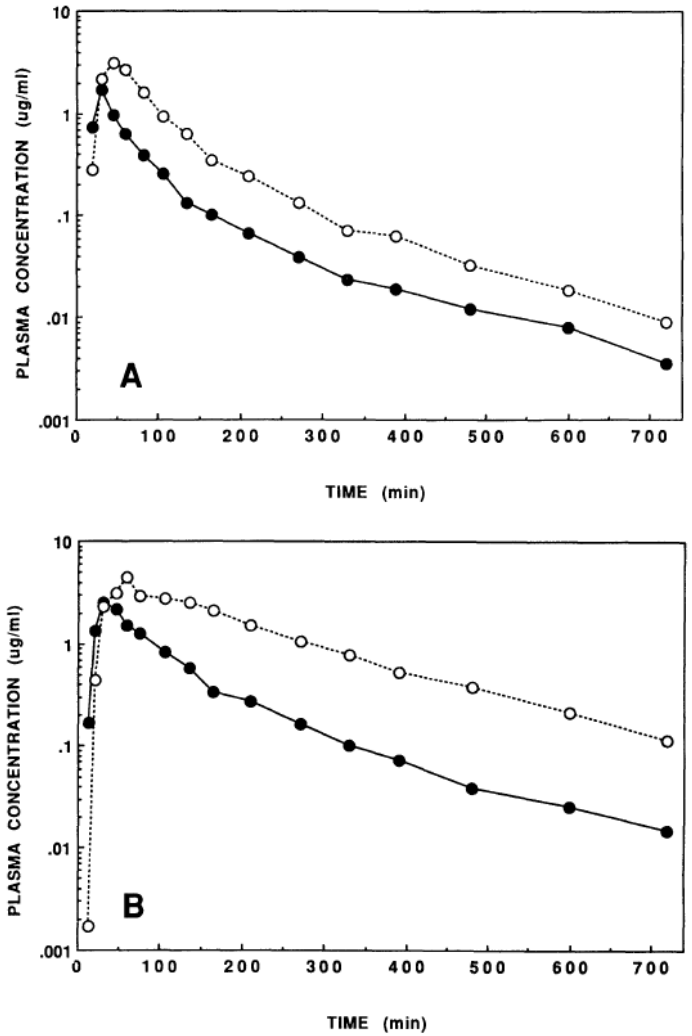



Fig. 1. Plasma concentration–time profiles of AZT (●) and GAZT (○) in subject 1 during (A) control and (B) probenecid treatment periods.

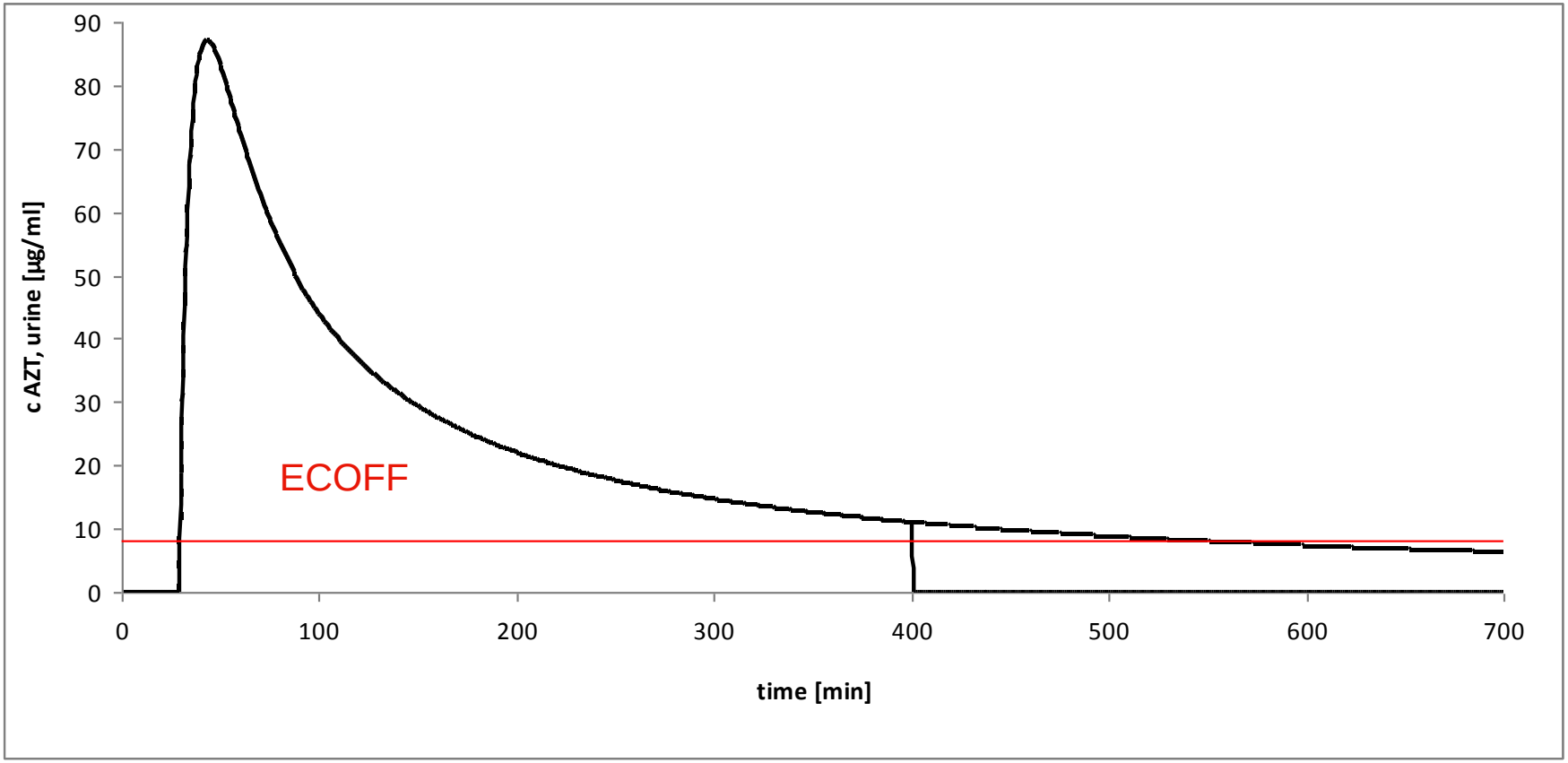
*Pharmaceutical Research, Vol. 7, No. 4, 1990*

*Report*

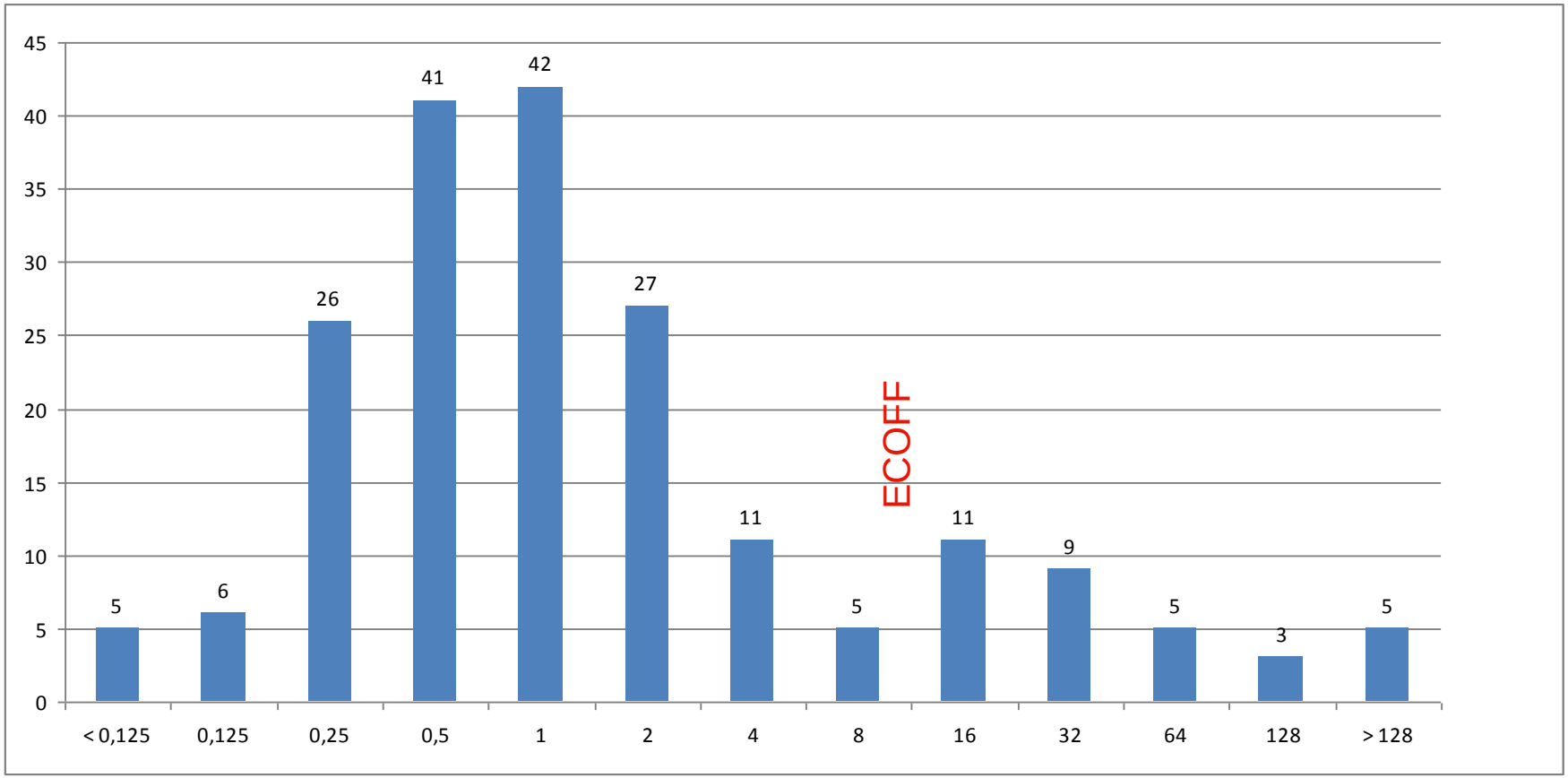
## Probenecid Inhibits the Metabolic and Renal Clearances of Zidovudine (AZT) in Human Volunteers

Mohsen A. Hedaya,[1] William F. Elmquist,[1] and Ronald J. Sawchuk[1,2]

# Modellierung der Urinausscheidung von AZT nach Hedaya et al. 1990



# AZT MHK-Verteilung bei den *E. coli* Stämmen




Turnidge J, Kahlmeter G, Kronvall G. Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values. *Clin Microbiol Infect* 2006; 12: 418–425.

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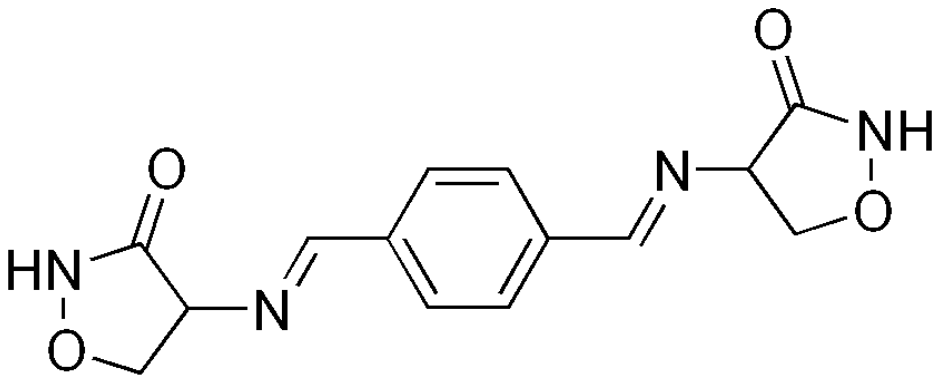
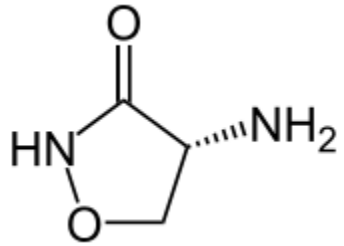
# Terizidon (TZ) – ein beinahe vergessenes Antibiotikum

- Second-line Tuberkulostatikum (in Deutschland zugelassen)
- Hemmt Peptidoglykansynthese durch Hemmung der L-Alanin Racemase und D-Alanin Ligase
- Wichtigster Metabolit Cycloserin (ebenfalls ein Oxazolidinon), wird jedoch überwiegend unverändert im Urin ausgeschieden
- Typische Dosierung bis 4 x 250 mg / die



# Pharmakokinetik von Terizidon nach oraler Gabe

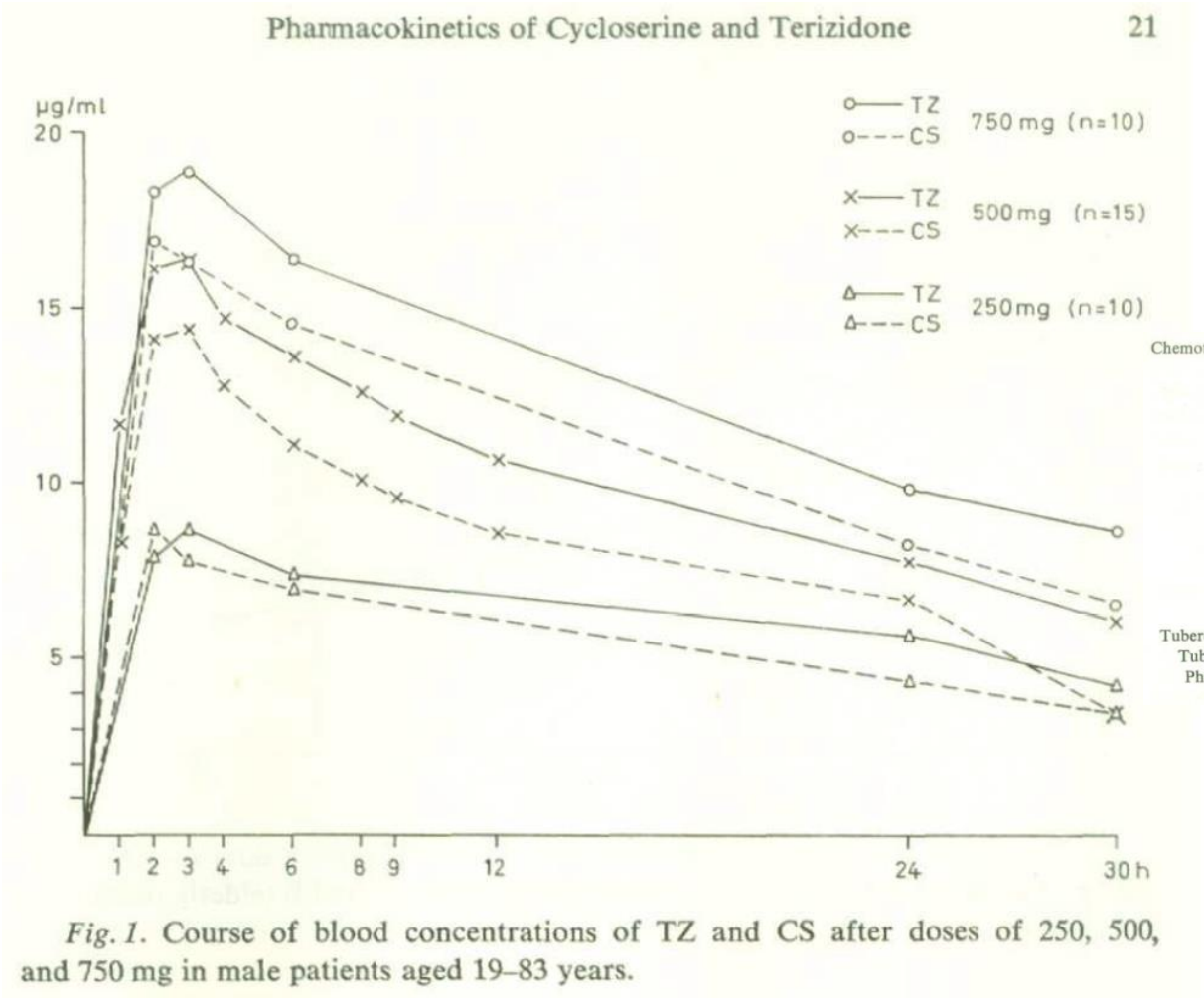



*Fig. 1.* Course of blood concentrations of TZ and CS after doses of 250, 500, and 750 mg in male patients aged 19–83 years.

Chemotherapy *20:* 18–28 (1974)

**Pharmacokinetics of Cycloserine and Terizidone**

A Comparative Study

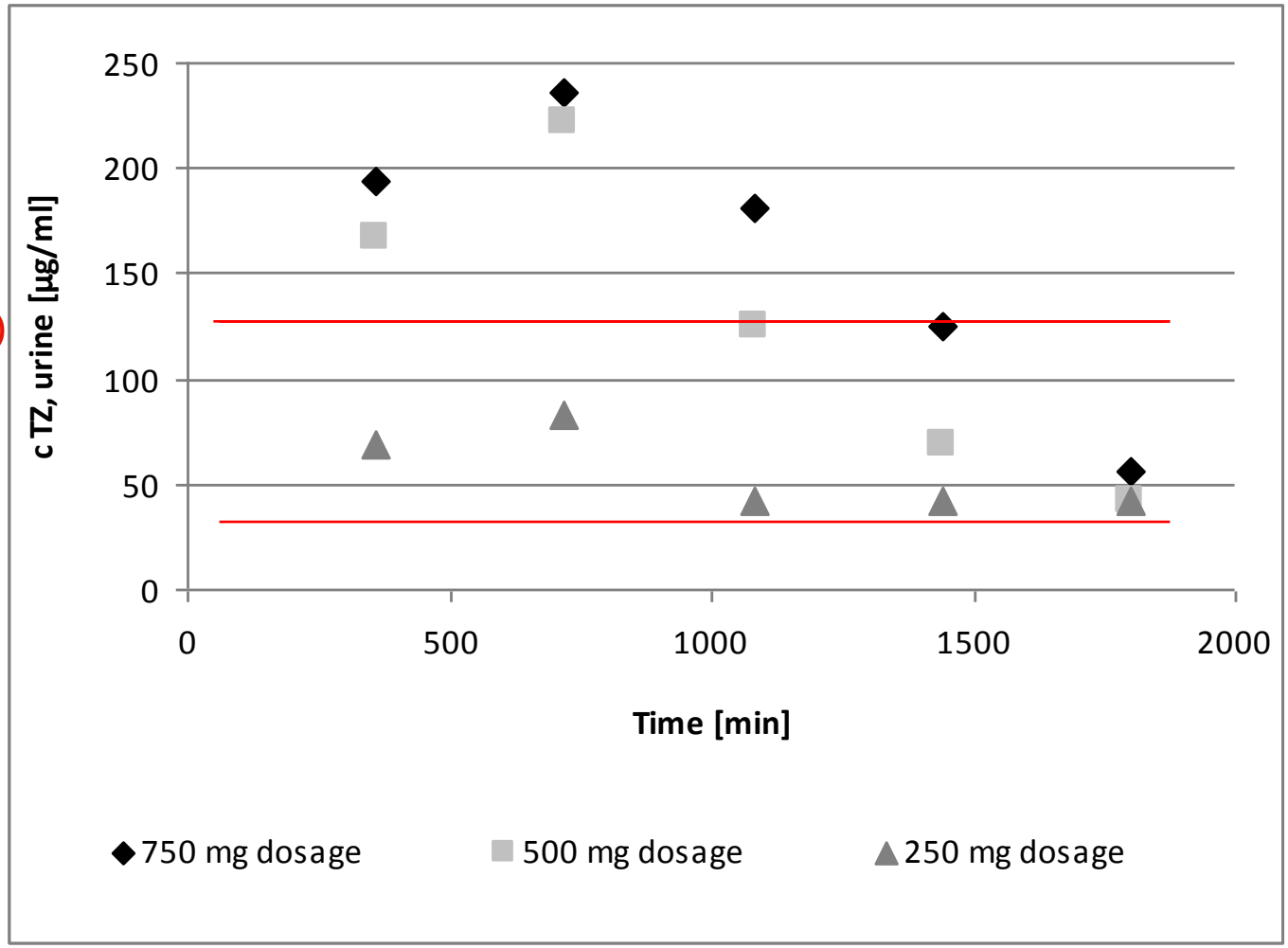
L. Zítková and J. Toušek

Tuberculosis and Respiratory Diseases Institute (Director: MUDr. P. Krákora) and Tuberculosis and Respiratory Diseases Department, Postgraduate Medical and Pharmaceutical Institute (Department Chief: Ass. Prof. R. Křivinka), Prague

# Modellierung der Urinausscheidung von TZ nach Zitkova et al. 1974

ECOFF (MHB)

ECOFF (M9)



# AZT und TZ MHKs

| ***E. coli*** | MIC [µg/ml] | **< 0,125** | **0,125** | **0,25** | **0,5** | **1** | **2** | **4** | **8** | **16** | **32** | **64** | **128** | **> 128** | **no growth** | %-S | **%-R** | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AZT | absolut | 4 | 6 | 26 | 41 | 42 | 27 | 11 | 5 | 11 | 9 | 5 | 3 | 5 | - | 83.1 | 16.9 | 195 |
| | cum.-% | 2,1 | 5,1 | 18,5 | 39,5 | 61,0 | 74,9 | 80,5 | 83,1 | 88,7 | 93,3 | 95,9 | 97,4 | 100,0 | - | | | |
| TZ (M9) | absolut | 28 | 3 | 3 | 11 | 23 | 16 | 40 | 38 | 11 | 9 | 3 | 4 | 6 | - | 93.3 | 6.7 | 195 |
| | cum.-% | 14,4 | 15,9 | 17,4 | 23,1 | 34,9 | 43,1 | 63,6 | 83,1 | 88,7 | 93,3 | 94,9 | 96,9 | 100,0 | - | | | |
| TZ (MHB) | absolut | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 10 | 19 | 23 | 14 | 14 | - | 82.9 | 17.1 | 82 |
| | cum.-% | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 1,2 | 2,4 | 14,6 | 37,8 | 65,9 | 82,9 | 100,0 | - | | | |

| ***K. pneumoniae*** | MIC [µg/ml] | **< 0,125** | **0,125** | **0,25** | **0,5** | **1** | **2** | **4** | **8** | **16** | **32** | **64** | **128** | **> 128** | **no growth** | %-S | **%-R** | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AZT | absolut | 3 | 5 | 6 | 5 | 5 | 7 | 2 | 5 | 5 | 1 | 1 | 3 | 1 | - | 77.6 | 22.4 | 49 |
| | cum.-% | 6,1 | 16,3 | 28,6 | 38,8 | 49,0 | 63,3 | 67,3 | 77,6 | 87,8 | 89,8 | 91,8 | 98,0 | 100,0 | - | | | |
| TZ (M9) | absolut | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 7 | 35 | - | 12.2 | 87.8 | 49 |
| | cum.-% | 2,0 | 2,0 | 2,0 | 4,1 | 4,1 | 6,1 | 8,2 | 10,2 | 10,2 | 12,2 | 14,3 | 28,6 | 100,0 | - | | | |
| TZ (MHB) | absolut | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13 | 15 | - | 46.4 | 53.6 | 28 |
| | cum.-% | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 46,4 | 100,0 | - | | | |

| ***P. mirabilis*** | MIC [µg/ml] | **< 0,125** | **0,125** | **0,25** | **0,5** | **1** | **2** | **4** | **8** | **16** | **32** | **64** | **128** | **> 128** | **no growth** | %-S | **%-R** | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AZT | absolut | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 3 | 6 | 10 | 4 | 7 | - | 6.3 | 93.7 | 32 |
| | cum.-% | 0,0 | 0,0 | 0,0 | 3,1 | 3,1 | 6,3 | 6,3 | 6,3 | 15,6 | 34,4 | 65,6 | 78,1 | 100,0 | - | | | |
| TZ (M9) | absolut | 1 | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 0 | 1 | 1 | 0 | 0 | 22 | 90.0 | 10.0 | 10 |
| | cum.-% | 10,0 | 10,0 | 10,0 | 10,0 | 10,0 | 30,0 | 50,0 | 80,0 | 80,0 | 90,0 | 100,0 | 100,0 | 100,0 | - | | | |
| TZ (MHB) | absolut | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 5 | 14 | 8 | - | 72.4 | 27.6 | 29 |
| | cum.-% | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 3,4 | 3,4 | 6,9 | 24,1 | 72,4 | 100,0 | - | | | |

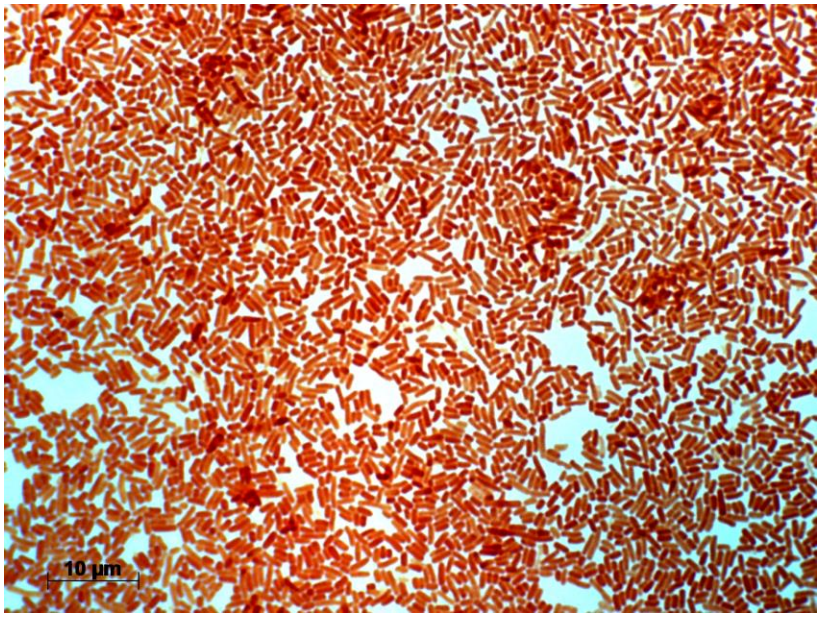
- **Gute Wirksamkeit von AZT bei *E. coli* und *K. pneumoniae***
- **Gute Wirksamkeit von TZ bei *E. coli* und *P. mirabilis***

# Wirksamkeit von AZT gegen 4MRGN *Klebsiella pneumoniae*

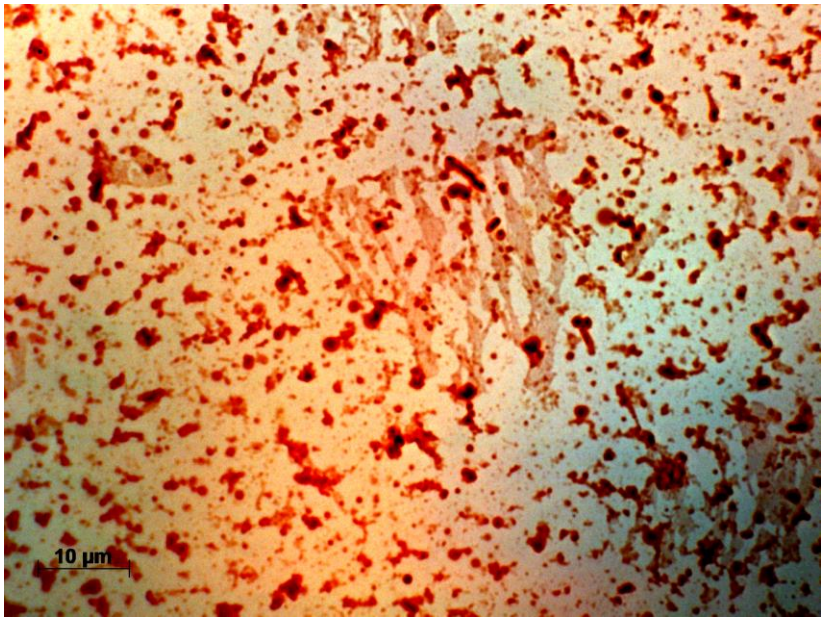
| Antibiotikum | MHK 1 | |
|---|---|---|
| ESBL | | Neg |
| Ampicillin | >=32 | R |
| Ampi/Sulb | >=32 | R |
| Fosfomycin | | R |
| Cef/Axet | >=64 | R |
| Ceftazidim | >=64 | R |
| Imipenem | 8 | I |
| Meropenem | 4 | I |
| Ciprofloxacin | >=4 | R |
| Levofloxacin | >=8 | R |
| Trim/Sulf | >=320 | R |
| Gentamicin | >=16 | R |
| Tigecyclin | | R |
| Polymyxin | | S |
| Amikacin | | R |

- **Pat. mit elektiver Nierentransplantation**
- **Post-OP *K. pneumoniae* Pneumonie / Sepsis**
- **Unter Meropenemtherapie Entwicklung des 4MRGN Phänotpys, nach zusätzlicher Gabe von Tigecyclin/Colistin rasche Entwicklung von Tigecyclin Res.**
- **AZT MHK 0,25 mg/l !**

# Ablösung von präformiertem *E. coli* ATCC 25922 Biofilm mit Kombination aus AZT + TZ




Ohne




Kombination AZT + TZ
(4 x MHK)

# Vielen Dank für die Aufmerksamkeit!

- **Wir danken der Firma RIEMSER Pharma GmbH für die Bereitstellung von Terizidon Reinsubstanz**