International Conference
on Production Diseases in Farm Animals (ICPD)
„From Science to Practice“
Olten
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# Freie Themen:
# *Dauer der Antibiose*

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## Früher war die Welt in Ordnung ….

**„[…] müssen bei bakteriostatisch wirksamen Chemotherapeutika über das Abklingen der klinischen Symptome hinaus Wirkstoffkonzentrationen in den entsprechenden Geweben aufrechterhalten werden, die über den minimalen Hemmstoffkonzentrationen des betreffenden Erregers liegen […]**

**„Auch bei bakterizid wirksamen Antibiotika sollte die Anwendungsdauer bis über das Abklingen der klinischen Symptome hinaus durchgeführt werden.“**

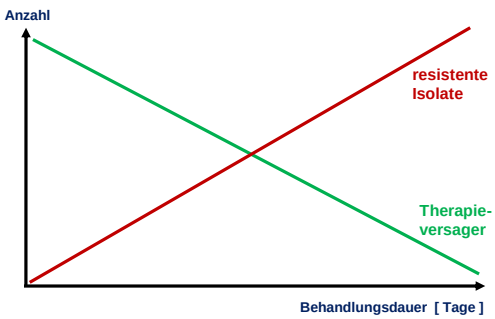
**„If you take an antibiotic, always complete the full prescription, even if you feel better, because stopping treatment early promotes the growth of drug-resistant bacteria“ (WHO 2015).**

**(Forth, Henschler u. Rummel 1983; Kroker 1991;)**

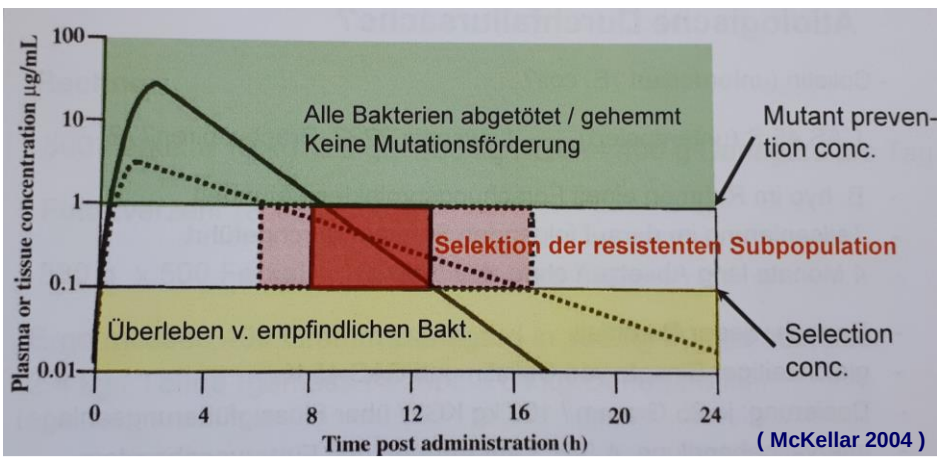
## Früher war die Welt in Ordnung ….

- ansonsten bei Bakteriostatika unmittelbare weitere Proliferation nach Absetzen der Therapie
- Gefahr durch Persister (ruhende, empfindliche Erreger, die die Initialdosis überlebt haben; 0.0001 bis 10 %)
- eine zu kurze Therapiedauer begünstigt die Entwicklung von Resistenzen
- im subinhibitorischen Bereich Veränderung der Oberflächenstruktur von Bakterienmembranen durch ß-Lactame, die die Phagozytose durch Granulozyten verstärken

- (partielle) Hemmung der Granulozytenfunktion durch Aminoglykoside, Tetrazykline und TMP
- ungünstige Beeinflussung des Mikrobioms mit erhöhter Gefahr einer Superinfektion
- je länger die Exposition der Erreger gegenüber AB, desto wahrscheinlicher sind Resistenzen




## Je schmaler das Selektionsfenster, desto weniger Resistenzen …




( McKellar 2004 )

**PK/PD-Optimierung: "Bug and drug"-Spezifität**

- konzentrationsabh. AB: $AUC_{0-24}$ / MIC > 125
  $C_{max}$ / MIC > 10
- zeitabhängige AB: > MIC um das 1-5-fache
  für 40-100 % des Dosierungsintervalls

## Ist ein Paradigmenwechsel notwendig ?

*J Theor Biol*. 2007 December 7; 249(3): 487–499.

### Modeling antibiotic resistance in hospitals: The impact of minimizing treatment duration

**Erika M.C. D'Agata**[a,*], **Pierre Magal**[b], **Damien Olivier**[c], **Shigui Ruan**[d], and **Glenn F. Webb**[e]

Infections caused by antibiotic-resistant pathogens are a global public health problem. Numerous individual- and population-level factors contribute to the emergence and spread of these pathogens. An individual-based model (IBM), formulated as a system of stochastically determined events, was developed to describe the complexities of the transmission dynamics of antibiotic-resistant bacteria. To simplify the interpretation and application of the model's conclusions, a corresponding deterministic model was created, which describes the average behavior of the IBM over a large number of simulations. The integration of these two model systems provides a quantitative analysis of the emergence and spread of antibiotic-resistant bacteria, and demonstrates that early initiation of treatment and minimization of its duration mitigates antibiotic resistance epidemics in hospitals.

## Ist ein Paradigmenwechsel notwendig ?

*JAMA Intern Med*. 2016 September 01; 176(9): 1254–1255. doi:10.1001/jamainternmed.2016.3646.

### The New Antibiotic Mantra—"Shorter Is Better"

**Brad Spellberg, MD**

Across all end points, time points, and populations, short-course therapy was as effective as longer courses of therapy. Point estimates of success favored short-course therapy across most end points and time points. In the sickest cohort (Pneumonia Severity Index scores of IV-V), 30-day rates of clinical success in the intention-to-treat population were significantly higher for short-course vs standard therapy (93.1% vs 80.3%; $P = .04$). Furthermore, the readmission rate was significantly lower for patients receiving the short-course regimen (1.4% vs 6.6%; $P = .02$).

## Ist ein Paradigmenwechsel notwendig ?

# Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials

Alexandra M. Hanretty,[1] and Jason C. Gallagher[2*]
[1]St. Christopher's Hospital for Children, Philadelphia, Pennsylvania; [2]Department of Pharmacy Practice, Temple University, Philadelphia, Pennsylvania

Commonly prescribed durations of therapy for many, if not most, bacterial infections are not evidence-based. Misunderstandings by clinicians and patients alike influence perspectives on antibiotic use, including duration of therapy and its role in antibiotic resistance. To demonstrate that shorter durations of antibiotic therapy are as efficacious as longer durations for many infections, a systematic review was undertaken of English-language articles by using PubMed to identify articles for inclusion. Additionally, infection-specific guidelines were identified for review of recommendations. Search terms included *specific infection types, randomized controlled trial (RCT), duration of therapy, treatment duration, short course,* and *long course.* Only RCTs of single-agent antibiotic therapy for the treatment of bacterial infections in adults were included. Independent data extraction of articles was conducted by two authors by using predefined guidance for article inclusion. In total, 23 RCTs met our criteria for inclusion. All trials compared single-agent antibiotics for a short and long antibiotic course in six common infections: community-acquired pneumonia, ventilator-associated pneumonia, intraabdominal infections, skin and soft tissue infections, uncomplicated cystitis, and complicated cystitis or pyelonephritis. Clinicians can decrease net antibiotic use by recommending shorter courses where evidence supports them. Antimicrobial stewardship programs that systematically address treatment duration may significantly affect institutional antibiotic use without negatively affecting patient care.
KEY WORDS antimicrobial stewardship, duration of therapy, bacterial infections, antibiotics.
(Pharmacotherapy 2018;38(6):674–687) doi: 10.1002/phar.2118

## Ist ein Paradigmenwechsel notwendig ?

*J Hosp Med* 2018 May 01; 13(5): 336–342. doi:10.12788/jhm.2905.

# Shorter Versus Longer Courses of Antibiotics for Infection in Hospitalized Patients: A Systematic Review and Meta-Analysis

Stephanie Royer, MD[1,2,3,*], Kimberley M. DeMerle, MD[1], Robert P. Dickson, MD[1], and Hallie C. Prescott, MD, MSc[1,4]

**BACKGROUND**—Infection is a leading cause of hospitalization with high morbi
mortality, but there are limited data to guide the duration of antibiotic therapy.

**PURPOSE**—Systematic review to compare outcomes of shorter versus longer an
among hospitalized adults and adolescents.

**DATA SOURCES**—MEDLINE and Embase databases, 1990-2017.

**STUDY SELECTION**—Inclusion criteria were human randomized controlled tri
English comparing a prespecified short course of antibiotics to a longer course for
infection in hospitalized adults and adolescents aged 12 years and older.

**DATA EXTRACTION**—Two authors independently extracted study characteristic
statistical analysis, outcomes, and risk of bias.

**DATA SYNTHESIS**—Of 5187 unique citations identified, 19 RCTs comprising 2
met our inclusion criteria, including the following: 9 noninferiority trials, 1 superiority design trial,
and 9 pilot studies. Across 13 studies evaluating 1727 patients, no significant difference in clinical
efficacy was observed (d = 1.6% [95% confidence interval (CI), −1.0%-4.2%]). No significant
difference was detected in microbiologic cure (8 studies, d = 1.2% [95% CI, −4.1%-6.4%]), short-
term mortality (8 studies, d = 0.3% [95% CI, −1.2%-1.8%]), longer-term mortality (3 studies, d =
−0.4% [95% CI, −6.3%-5.5%]), or recurrence (10 studies, d = 2.1% [95% CI, −1.2%-5.3%]).
Heterogeneity across studies was not significant for any of the primary outcomes.

**CONCLUSIONS**—Based on the available literature, shorter courses of antibiotics can be safely utilized in hospitalized patients with common infections, including pneumonia, urinary tract

infection, and intra-abdominal infection, to achieve clinical and microbiologic resolution without adverse effects on mortality or recurrence.

**Keine Unterschiede bzgl.**

- **klinische Heilung**
- **mikrobiologische Heilung**
- **kurzfristige Mortalität**
- **langfristige Mortalität**
- **Rezidivrate**

*Clinical Infectious Diseases*

MAJOR ARTICLE

# Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

**Darunee Chotiprasitsakul,[1] Jennifer H. Han,[2] Sara E. Cosgrove,[3] Anthony D. Harris,[4] Ebbing Lautenbach,[2] Anna T. Conley,[5] Pam Tolomeo,[2] Jacqueleen Wise,[2] and Pranita D. Tamma[6]; for the Antibacterial Resistance Leadership Group**

***Background.*** The recommended duration of antibiotic treatment for Enterobacteriaceae bloodstream infections is 7–14 days. We compared the outcomes of patients receiving short-course (6–10 days) vs prolonged-course (11–16 days) antibiotic therapy for Enterobacteriaceae bacteremia.

***Methods.*** A retrospective cohort study was conducted at 3 medical centers and included patients with monomicrobial Enterobacteriaceae bacteremia treated with in vitro active therapy in the range of 6–16 days between 2008 and 2014. 1:1 nearest neighbor propensity score matching without replacement was performed prior to regression analysis to estimate the risk of all-cause mortality within 30 days after the end of antibiotic treatment comparing patients in the 2 treatment groups. Secondary outcomes included recurrent bloodstream infections, *Clostridium difficile* infections (CDI), and the emergence of multidrug-resistant gram-negative (MDRGN) bacteria, all within 30 days after the end of antibiotic therapy.

***Results.*** There were 385 well-balanced matched pairs. The median duration of therapy in the short-course group and prolonged-course group was 8 days (interquartile range [IQR], 7–9 days) and 15 days (IQR, 13–15 days), respectively. No difference in mortality between the treatment groups was observed (adjusted hazard ratio [aHR], 1.00; 95% confidence interval [CI], .62–1.63). The odds of recurrent bloodstream infections and CDI were also similar. There was a trend toward a protective effect of short-course antibiotic therapy on the emergence of MDRGN bacteria (odds ratio, 0.59; 95% CI, .32–1.09; $P = .09$).

***Conclusions.*** Short courses of antibiotic therapy yield similar clinical outcomes as prolonged courses of antibiotic therapy for Enterobacteriaceae bacteremia, and may protect against subsequent MDRGN bacteria.

## Ist ein Paradigmenwechsel notwendig ?

**Spellberg B (2016): The New Antibiotic Mantra—"Shorter Is Better". JAMA Intern Med. 176: 1254–1255.**

**Prof. Dr. Gerd Fätkenheuer**
**Präsident der Deutschen Gesellschaft für Infektiologie, Ärztlicher Leiter Klinische Infektiologie, Uniklinik Köln**

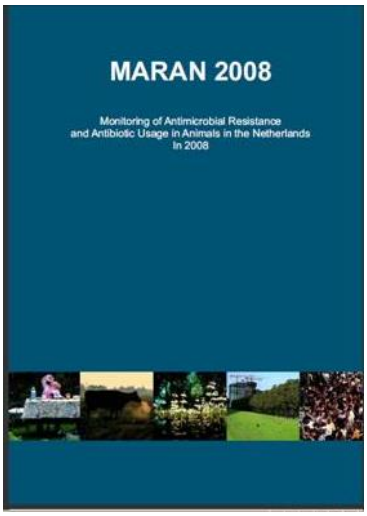
- **schwache bzw. fehlende Evidenz für Begünstigung der Resistenzentwicklung durch zu kurze Therapiedauer (Ausnahmen !)**
- **das Gegenteil trifft zu auf MRSA, ESBL, VRE**

**Wald-Dickler & Spellberg (2019): Short Course Antibiotic Therapy-Replacing Constantine Units with "Shorter Is Better". Clin Infect Dis. doi: 10.1093/cid/ciy1134.**

**Kürzere versus längere Dauer der Antibiotikatherapie – in klinischen Studien dokumentierte Äquivalenz (8)**

| Erkrankung | Behandlungsdauer (Tage) | |
|---|---|---|
| | Kurz | Lang |
| Ambulant erworbene Pneumonie (9, 10, 3) | 3–5 | 7–10 |
| Nosokomiale Pneumonie (11, 12) | ≤ 8 | 10–15 |
| Pyelonephritis (13) | 5–7 | 10–14 |
| Intraabdominale Infektion (4) | 4 | 10 |
| Chronische Bronchitis mit akuter Exazerbation und COPD (14) | ≤ 5 | ≥ 7 |
| Akute bakterielle Sinusitis (15) | 5 | 10 |
| Cellulitis (Haut-Weichteil-Infektion) (16) | 5–6 | 10 |
| Chronische Osteomyelitis (17) | 42 | 84 |

## … und in der Veterinärmedizin ?

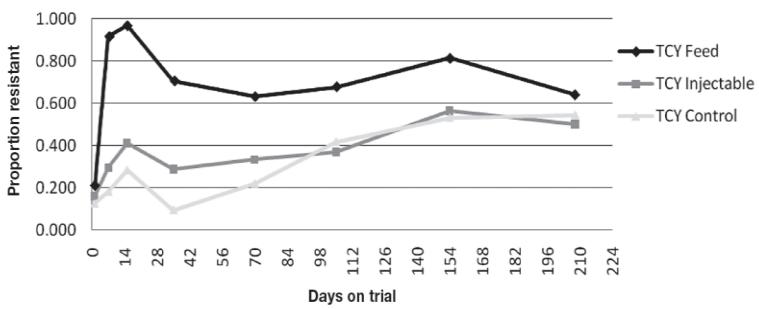



**„The use of group treatments with antibiotics leads to selection and spread of resistance genes in veal calves“**

**MARAN 2005, Monitoring of antimicrobial resistance and antibiotic usage in the Netherlands**

## … und in der Veterinärmedizin ?

| | Vergangen-heit | Gegenwart | Zukunft |
|---|---|---|---|
| **Applikation** | **oral** | **oral** | **parenteral** |
| **Spektrum** | **breit** | **eng** | **eng** |
| **Dauer** | **lang** | **kurz** | **kurz** |
| **Anzahl** | **alle** | **alle** | **wenige** |

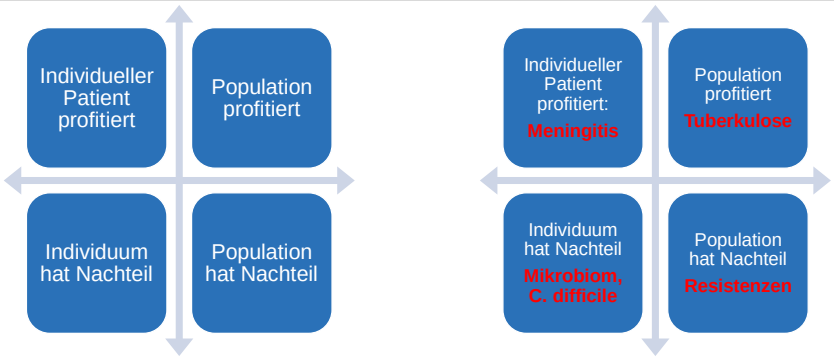



**Checkley et al. 2010; Mölder 2011**

## … wie sollte es in der Praxis laufen?

| | |
|---|---|
| **weniger Antibiotikazyklen<br>kürzere Therapien<br>schmaleres Spektrum** | **weniger Exposition** |
| **Hygienemassnahmen<br>Tiertransporte** | **weniger Transmission** |

**Expositionsdauer - Tiergesundheit: ein Zielkonflikt ?**




**( «Blaser-Schema», Rossi 2018 )**

## Offene Fragen

1. **Müssen wir etablierte Empfehlungen für die Dauer oraler antibiotischer metaphylaktischer Gruppenbehandlungen revidieren ?**
2. **Müssen wir etablierte Empfehlungen für die Dauer parenteraler antibiotischer Einzeltierbehandlungen revidieren ?**
3. **Müssen wir etablierte Empfehlungen zur Aussagekraft von Antibiogrammen überdenken und/oder neue Empfehlungen entwickeln ?**

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# Vielen Dank für Eure Aufmerksamkeit !

**Martin Kaske**

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