Time is of the Essence: Rethinking Duration and Dosing of Antibiotics

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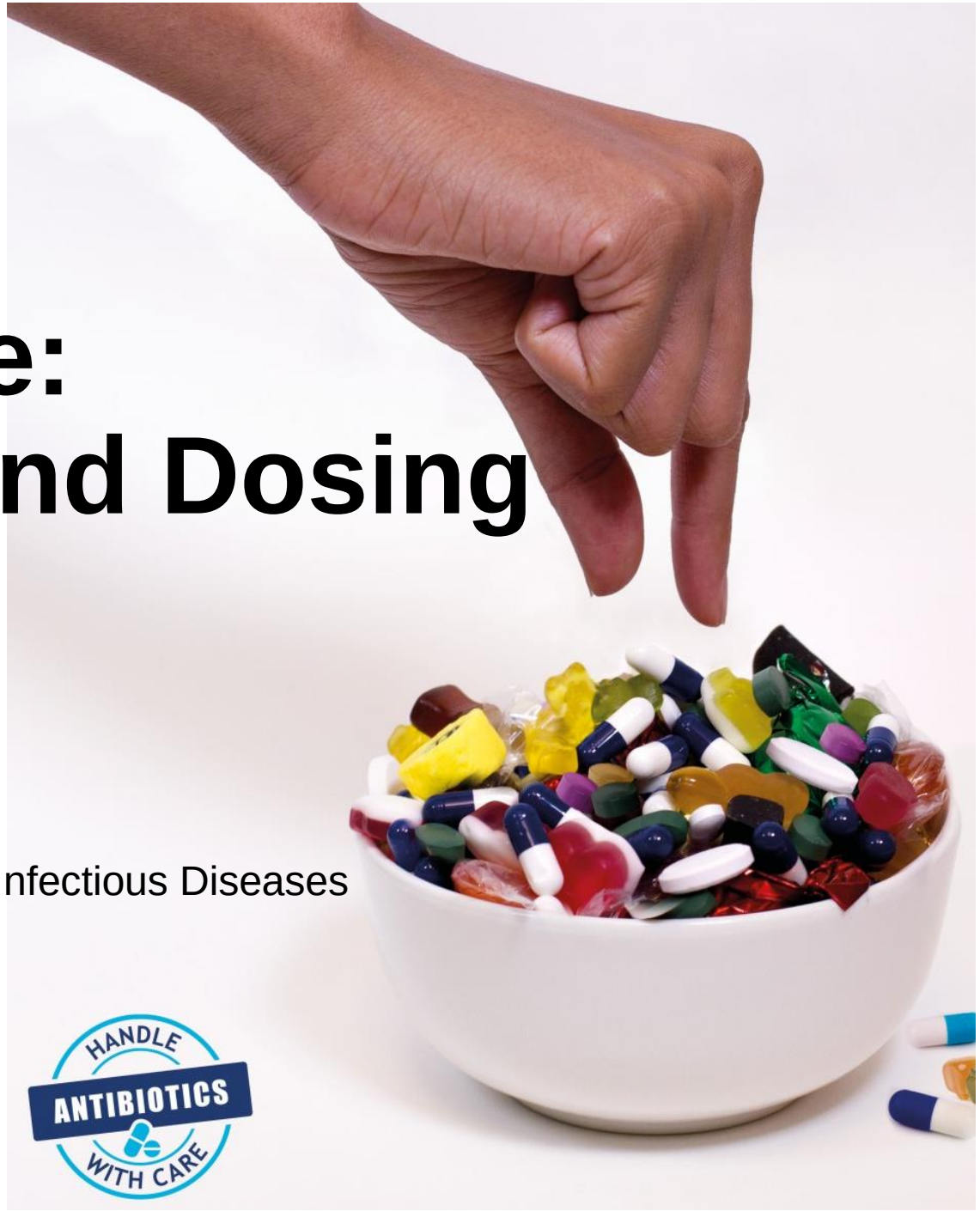
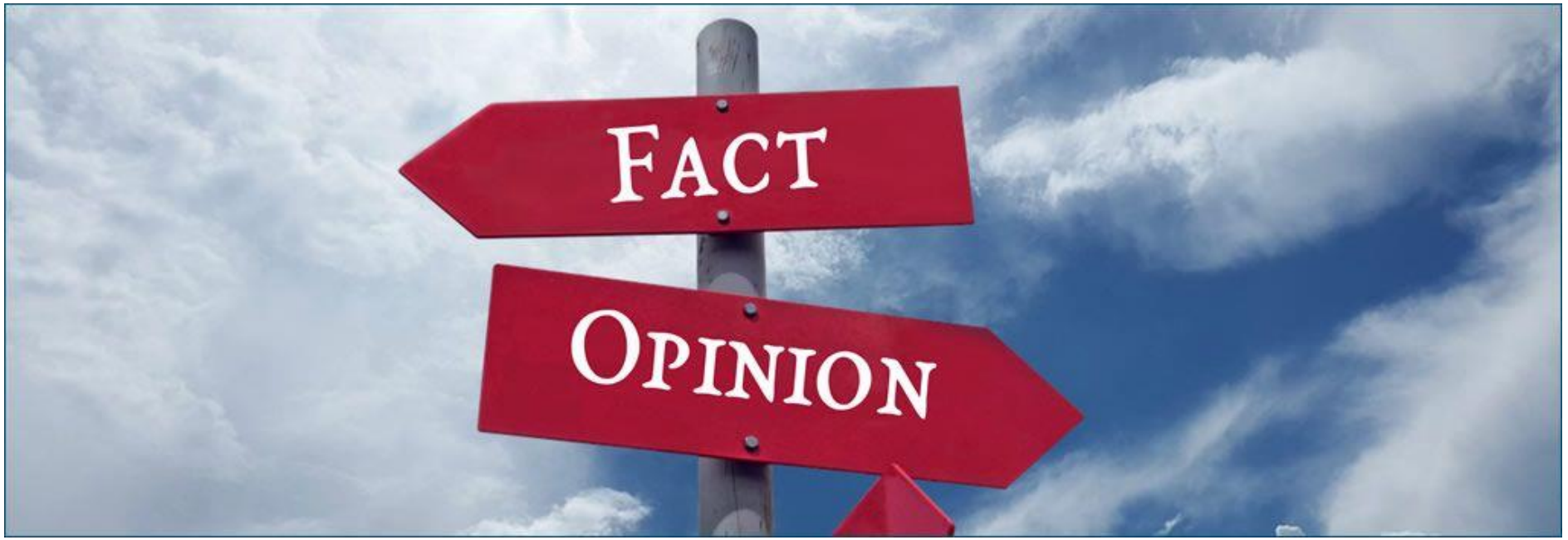




- I have no conflicts of interests to disclose

Educational Objectives

Review	the original literature on antibiotic treatment duration
Discuss	recent evidence comparing short versus longer courses of antibiotics
Examine	literature supporting earlier parenteral to enteral antibiotic conversion
Address	dose-optimization strategies for time-dependent antibiotics

History of Antibiotic Duration

THE TREATMENT OF LOBAR PNEUMONIA AND PNEUMOCOCCAL EMPYEMA WITH PENICILLIN*

WILLIAM S. TILLETT, MARGARET J. CAMBIER, AND JAMES E. MCCORMACK

The Department of Medicine of New York University College of Medicine and the Third Medical Division of Bellevue Hospital

The Bulletin, *NY Acad Med* 1944

Pneumococcal pneumonia
N=46

Etiology confirmed, 43 cases

Dose and duration were arbitrarily altered to observe the response to limited treatment

39 had rapid recovery (1-4 days)
3 died (without initial response)
4 indefinite response

In all of the patients without complications an initial definite response was noted within 16 to 20 hours of beginning treatment

WBC, unaffected by penicillin and returned to normal w/in 4-6 days post Rx interruption

Treatment interruption

	D 1 (7)	**D 2 (7)**
Relapse	2	4

It is also evident that relapse was liable to occur if treatment was not extended longer than two days

History of Antibiotic Duration

Community Acquired Pneumonia (CAP)

1943, Keefer et al. 500 patients

"…many patients recovered on therapy for 2-3 days"

1944, Dawson et al. 100 patients

"In general, the results were satisfactory after treatment for 1.5-2 days"

1945, Meads and Finland, 54 patients

"until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours…then given for another 2-3 days."

Clinical Trials, Duration (Short = Long)

Diseases for which short course antibiotic therapy has been found to be equally effective to longer traditional courses of therapy

Diagnosis	# RCTs	Short (d)	Long (d)
Community acquired pneumonia, CAP	11	3 or 5	7, 8, or 10
Hospital acquired/ ventilator associated pneumonia	2	8	15
Complicated urinary tract infections/ pyelonephritis	7	5 or 7	10 or 14
Complicated/ post-operative intra-abdominal infections	2	4 or 8	10 or 15
Gram negative rod bacteremia	2	7	14
Empiric neutropenic fever	1	Afebrile and stable × 72 h	Afebrile and stable × 72 h and ANC > 500 cells/μL

Adapted from Brad Spellberg, MD- shorter-is-better

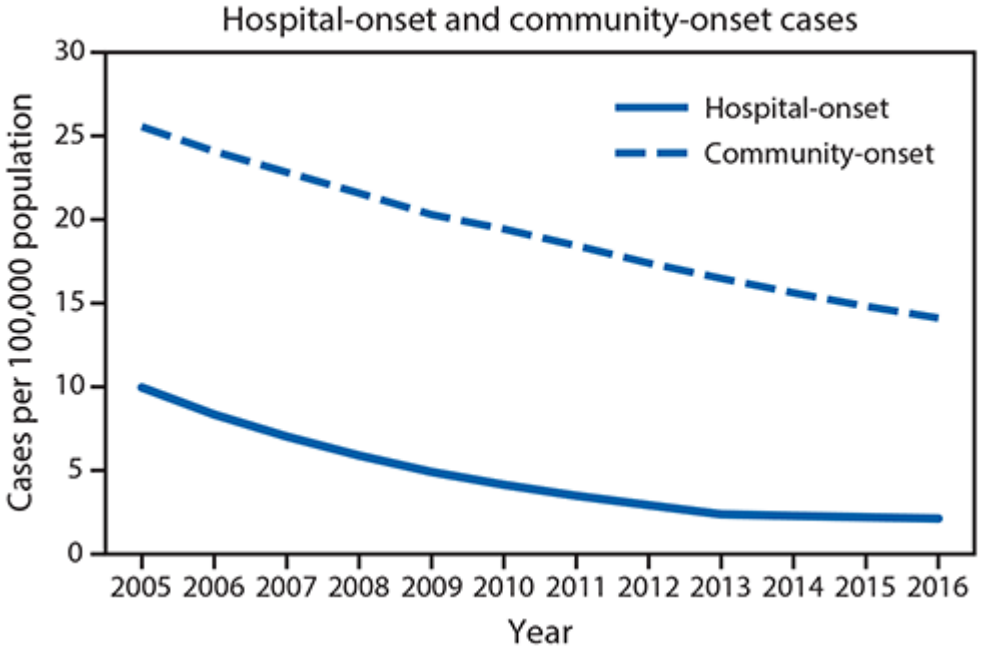
Clinical Trials, Duration (Short = Long)

Diseases for which short course antibiotic therapy has been found to be equally effective to longer traditional courses of therapy

Diagnosis	# RCTs	Short (d)	Long (d)
Latent TB infection	8	1-4 months	6-12 months
Acute bacterial sinusitis	6	5	10
Acute bacterial skin and skin structure Infections	4	5-6	10-12
Vertebral Osteomyelitis	1	42	84
Septic arthritis	2	10-14	28-30

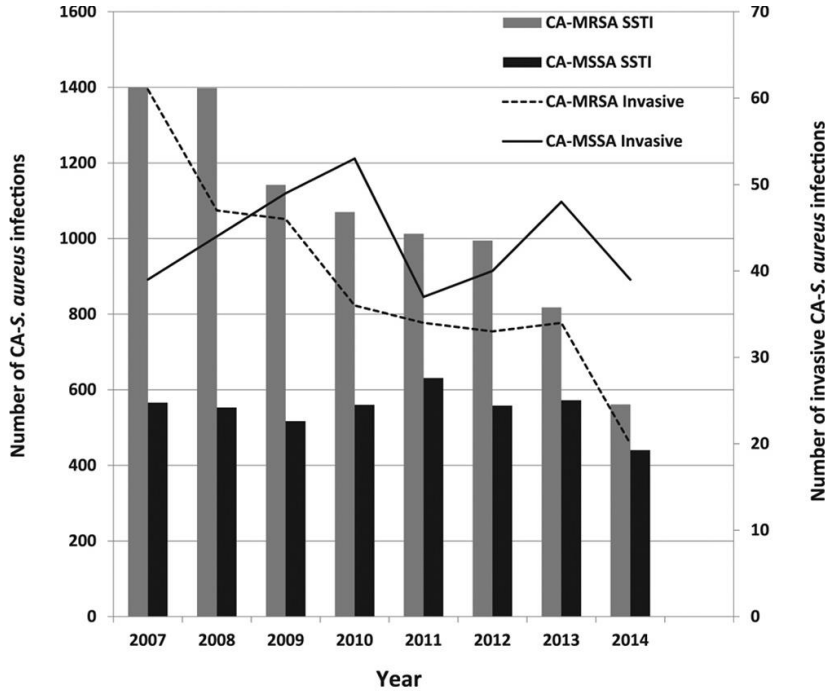
Adapted from Brad Spellberg, MD- shorter-is-better

Current state of Methicillin-resistant *Staphylococcus aureus* in the U.S.



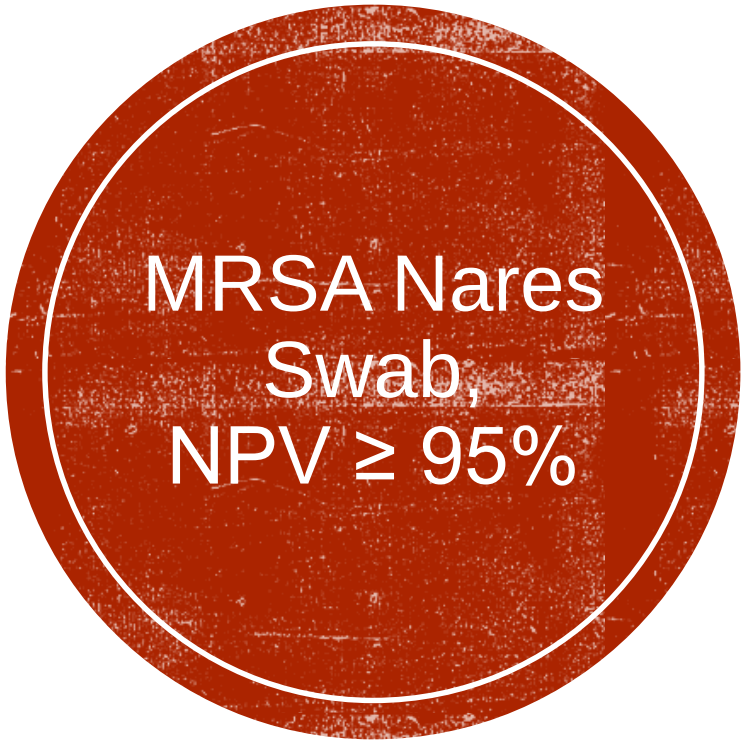
MRSA bloodstream infection rates from
6 U.S. Emerging Infections Program sites, 2005-2016

MMWR 2019;68:214–219



Community acquired *S. aureus* infections
at Texas Children's Hospital, 2007–2014

MMWR 2019;68:214–219



MRSA nares swab negative predictive value, NPV

- Retrospective cohort, VA medical centers *Clin Infect Dis* 2020
  - 96.5% (96.5% for BSI, 98.6% for respiratory infections, 93.1% for wound cultures)
- Adult AML pts, suspected infection *Infect Control Hosp Epidemiol* 2020
  - 99%

Vancomycin De-escalation

Minimizing Empiric Vancomycin

- Compare outcomes of CONS sepsis between vancomycin plus gentamicin versus oxacillin plus gentamicin empiric therapy

TABLE 1. Frequencies of Fulminant Late-Onset Sepsis for the Most Common Pathogens in the NICU, 1988–1997

Organism	Case Ratio	Frequency (%)
Pseudomonas sp.	20/36	56
Escherichia coli	5/27	19
Enterobacter sp.	4/28	14
Klebsiella sp.	4/31	13
Staphylococcus aureus	4/67	6
Enterococcus sp.	3/83	4
Candida sp.	4/143	3
Coagulase-negative staphylococci	4/277	1

TABLE 2. Coagulase-Negative Staphylococcal Sepsis in the NICU from 1988–1997

Date of sepsis	1/88–9/94	10/94–12/97
Empiric antibiotics	Vancomycin and cefotaxime	Oxacillin and gentamicin
Cases of fulminant sepsis	2	2
Total sepsis cases	141	136
Frequency of fulminant sepsis (%)	1	1
Median duration of sepsis (range)	2 days (1–13)	2 days (1–11)

Pediatrics 2000;106:1387–1390

Pediatric Clinical Trials, CAP

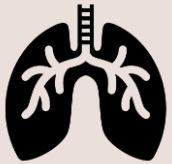
Community Acquired Pneumonia RCTs	Year of Publication, Journal	Country and Setting	Comparison	Results
Clinically diagnosed pneumonia (2-59 months)	2002, Lancet	7 clinics, Pakistan	Amoxicillin, 3 vs 5 days	Equal treatment failure rates
Clinically diagnosed pneumonia (2-59 months)	2004, British Medical Journal	7 clinics, India	Amoxicillin, 3 vs 5 days	Equal clinical cure and treatment failure
Radiologically confirmed pneumonia (6-59 months)	2014, Pediatric Infectious Diseases Journal	ED, Israel	HD-amoxicillin, 3 vs 5 days 5 vs 10 days	3 inferior, 5 and 10 no treatment failure
Chest-indrawing pneumonia in resource-limited setting (2-59 months)	2020, NEJM	2 clinics, Malawi	HD-amoxicillin 3 vs 5 days	Treatment failure non-inferior
Radiologically confirmed pneumonia (6 months-10 years)	2021, JAMA Pediatrics	2 EDs, Canada	HD-amoxicillin 5 vs 10 days	Equal clinical cure
SCOUT-CAP (6-71 months)	ongoing	Clinics and ED, U.S.	Beta-lactam abx, 5 vs 10 days	ongoing

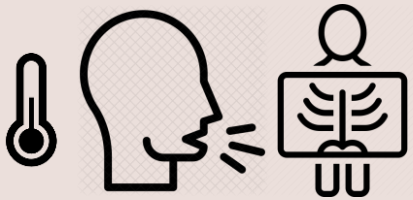
CAP in Children in Outpatient Setting

2-center, ED-based, noninferiority randomized clinical trial

STUDY POPULATION

6 mths-10 yrs





INTERVENTION, OUTCOME

5 vs 10 days HD amox
Clinical cure at 14 to 21 days

3-5 d, 7-10d

noninferiority margin, 7.5%

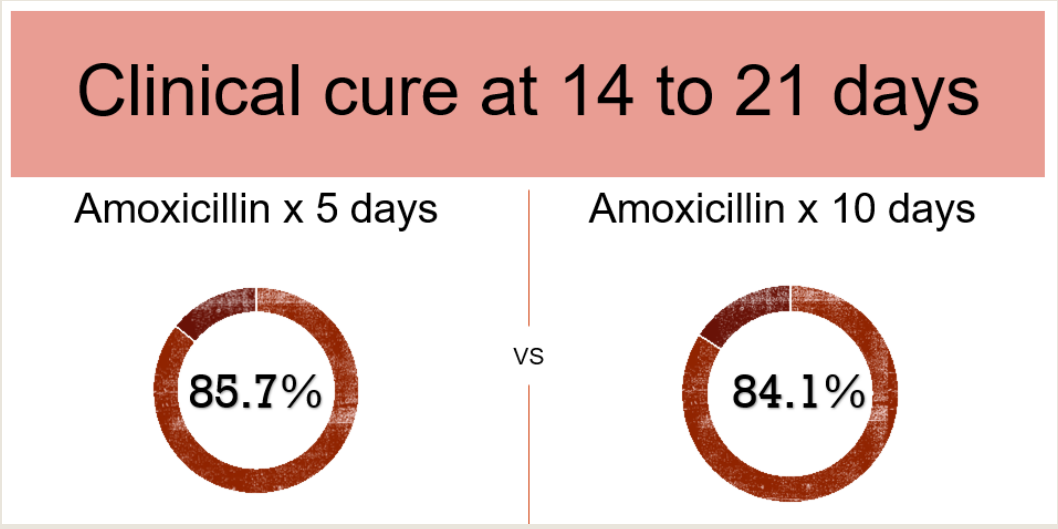
RESULTS

N = 281

Median age was 2.6 (IQR, 1.6-4.9)

65% had virus detection at baseline

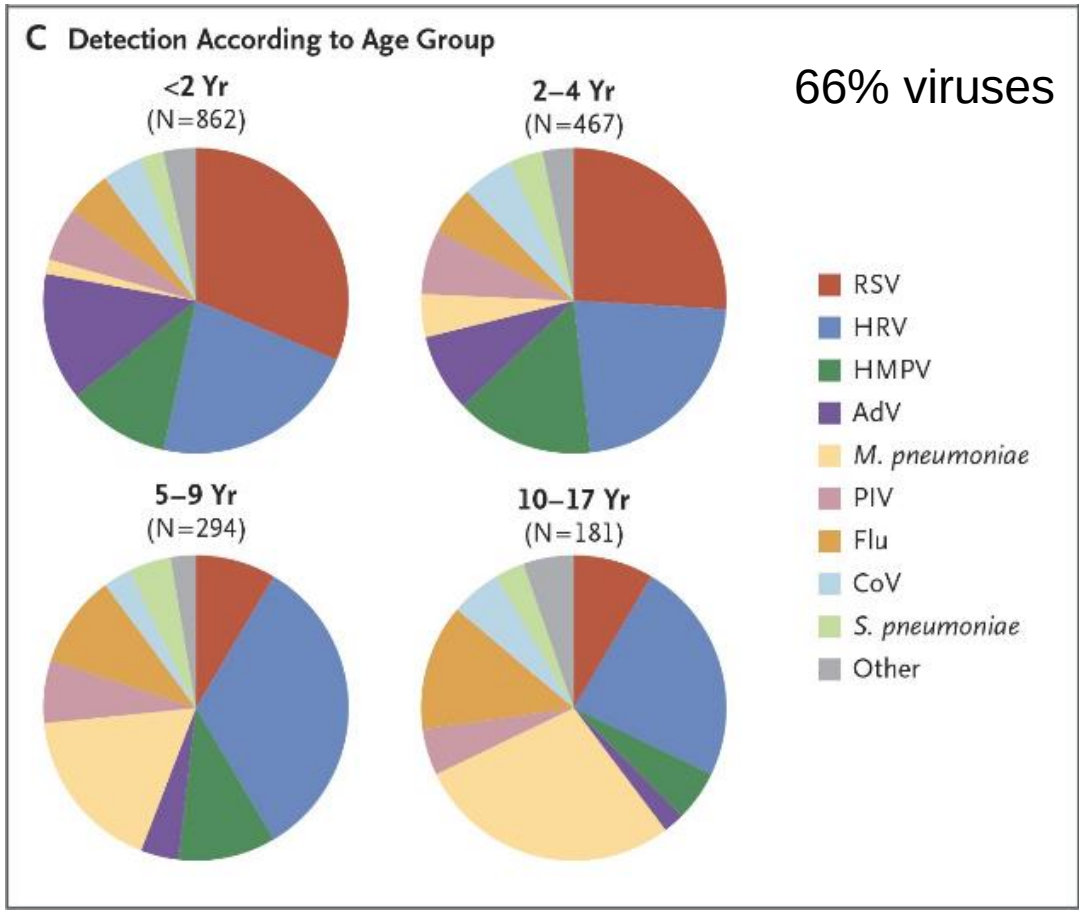
Clinical cure at 14 to 21 days



Baseline NPS test result positive for a respiratory virus[b]		
RSV	21 (21.9)	25 (25.8)
Rhinovirus/enterovirus	18 (18.8)	16 (16.5)
Metapneumovirus	12 (12.5)	7 (7.2)
Influenza	7 (7.3)	6 (6.2)
Parainfluenza	7 (7.3)	4 (4.1)
Adenovirus	4 (4.2)	6 (6.2)
Negative for all	35 (36.5)	37 (38.1)
Missing data, No.	44	44

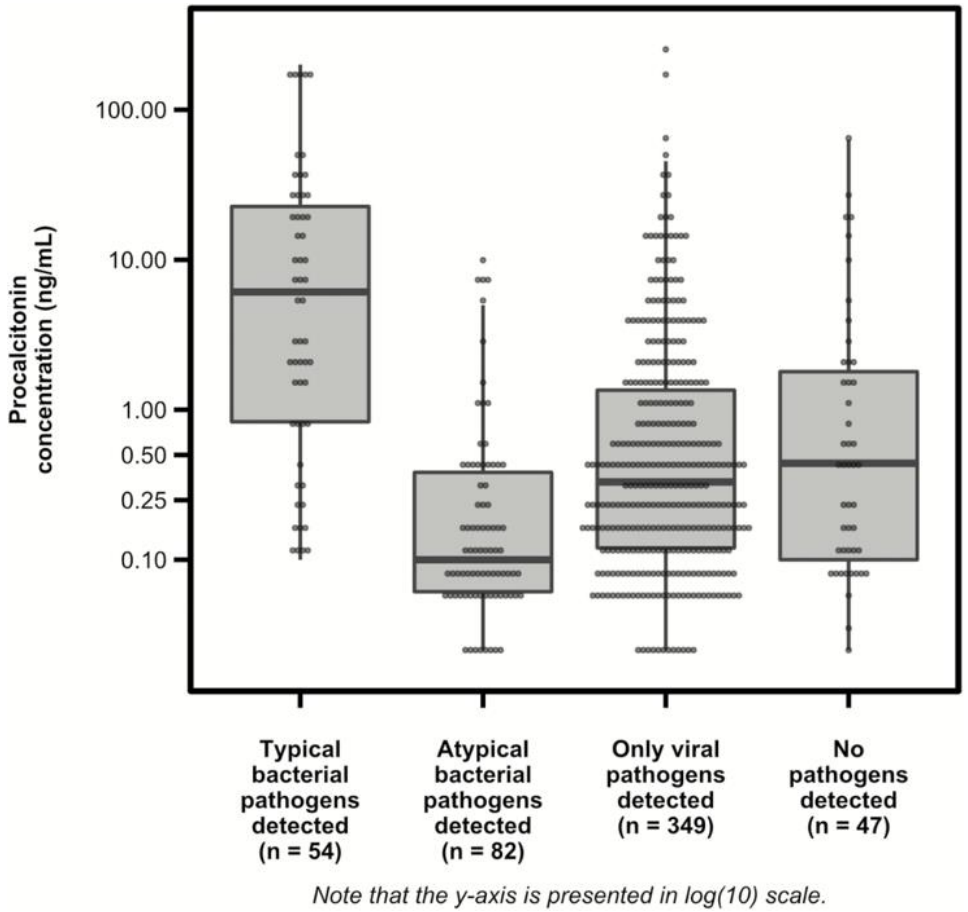
Pernica M, et al. JAMA Pediatrics March 2021

CAP, Hospitalized Children



66% viruses

EPIC study group, NEJM 2015



EPIC study group, JPIDS 2017

Duration per Guidelines, CAP

Guideline	Year	Duration
CAP, WHO	2009	3-5 days
CAP, Pediatric	2011	10 days, although shorter may be just as effective
Adults With Hospital-acquired and Ventilator-associated Pneumonia	2016	7 days
CAP, Adults	2019	5 days Use clinical stability; most achieve in 1st 48-72 hours, still minimum 5 days

Missing: empyema, lung abscess, necrotizing pneumonia

Duration in Practice

Condition	Guideline recommended duration	Median course duration in days
Pharyngitis	10 days (A,P)	10
Sinusitis	5-7 days (A), 10-14 days (P)	10
Acute otitis media	10 days (shorter courses for select children)	10
Community-acquired pneumonia	5 days (A, 2019) 10 days, shorter may be eff (P, 2011)	10
Cellulitis	5 days (A,P)	10
Abscess	5 days (A,P)	10
Acute cystitis	1- 7 days (F, 12-64 yrs)	7

King LM, et al. Clin Infect Dis 2020

What Went Wrong?

1945, Meads and Finland, 54 patients w pneumococcal pneumonia

"until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours…then given for another 2-3 days."

44/54 survived; 2/44 relapsed; 1 similar (24hr Rx) , 1 different serotype

Despite this remarkable success, these relapses weighed heavily on the authors, leading them to suggest:

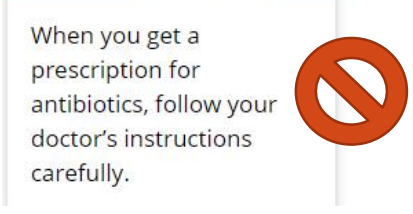
"The need for continuing treatment even after the fever and symptoms subside is suggested by the relapses that have occurred in this series."

What Went Wrong?

Louis B. Rice and Brad Spellberg

"It is unclear how this confused desire to prevent reinfections subsequently transformed into the illogical dogma that antibiotic resistance could be prevented by continuing therapy beyond resolution of symptoms"

Center for Disease Control's "Get Smart" Web site



RCT, 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia JAMA 2003

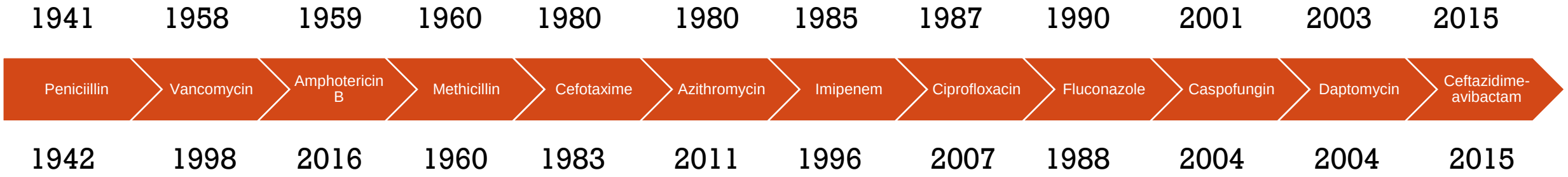
MDR pathogens emerged more frequently in those who received 15 vs 8 days, 62% vs 42% of pulmonary recurrences, p = .04

Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. Am J Respir Crit Care Med 2000

Antimicrobial resistance developed in 35% in standard therapy vs 15% of the patients in the shorter duration, p = 0.017

Antibiotic Discovery

YEAR ANTIBIOTIC APPROVED OR RELEASED



YEAR RESISTANCE IDENTIFIED

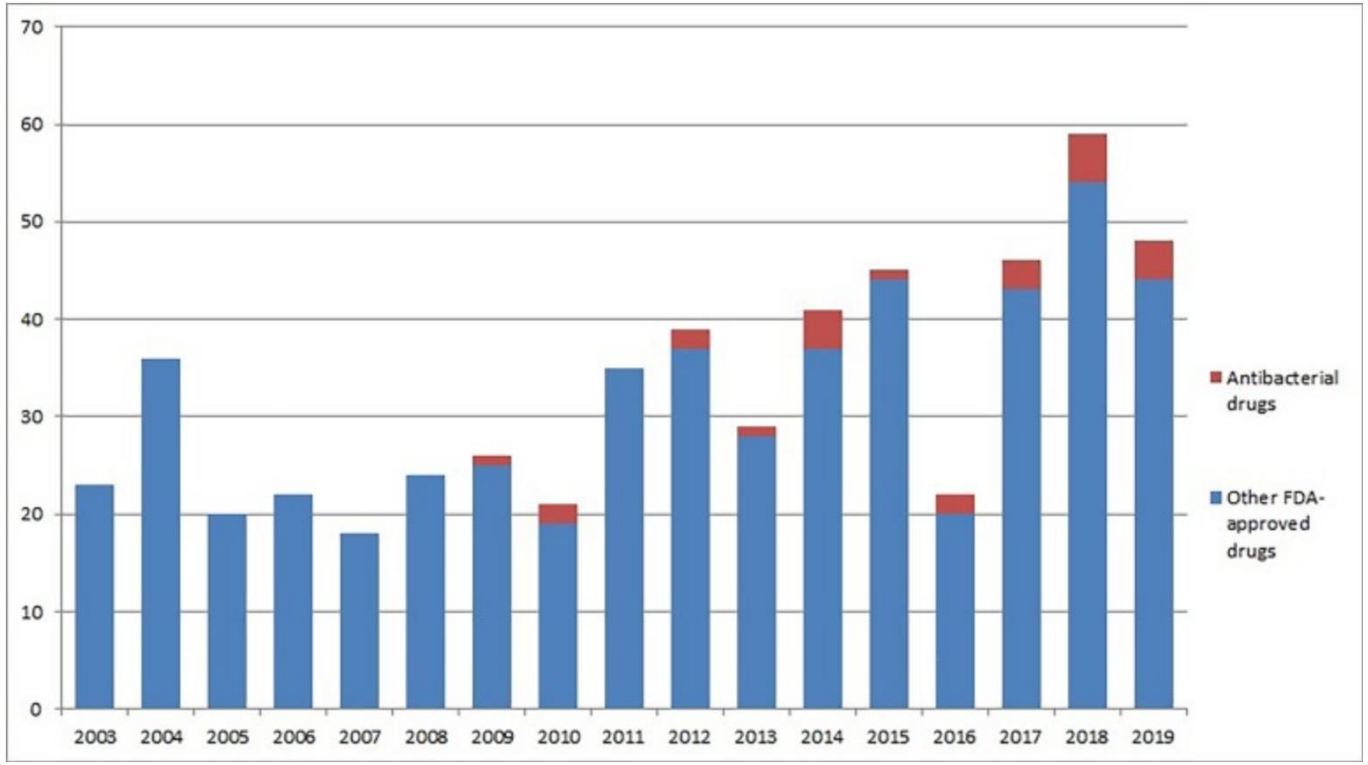
Adapted from CDC data

Table 1. Microbes versus humans.

Variable	Microbes	Humans	Factor
No. on earth	5×10^{31}	6×10^{9}	$\sim 10^{22}$
Mass, metric tons	5×10^{16}	3×10^{8}	$\sim 10^{8}$
Generation time	30 min	30 years	$\sim 5 \times 10^{5}$
Time on earth, years	3.5×10^{9}	4×10^{6}	$\sim 10^{3}$

Spellberg B, et al. *Clin Infect Dis* 2008

Antibiotic Discovery Pipeline



Andrei S, et al. *Discoveries* 2019

Drug Shortages

FDA Drug Shortages

Current and Resolved Drug Shortages and Discontinuations Reported to FDA

Azithromycin Tablets	***Resolved***
Cefazolin Injection	***Currently in Shortage***
Cefepime Injection	***Resolved***
Cefotaxime Sodium Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cefoxitin for Injection, USP	***Currently in Shortage***
Ceftazidime and Avibactam (AVYCAZ®) for Injection, 2 grams/0.5 grams	***Currently in Shortage***
Ceftolozane and Tazobactam (Zerbaxa) Injection	***Currently in Shortage***

The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

"In AD 321, Roman Emperor Constantine the Great codified that there would be 7 days in a week.
Even in the modern era of evidence-based-medicine, this remains a primary reference for duration of antibiotic therapy: it leads physicians to treat infections in intervals of 7 days"

"Had Constantine chosen a 4-day week, providers would likely routinely prescribe 4-8 day courses of therapy"

Short Course Antibiotic Therapy- Replacing Constantine Units with "Shorter is Better"

Noah Wald-Dickler, MD and Brad Spellberg, MD

JAMA *Internal MedicineB*2016
Clin Infect Dis 2019

"coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including **dosing, duration of therapy, and route** of administration"

Clin Infect Dis 2016

RETHINKING ROUTE

Rethinking Route

- Early transition of IV to PO
- Start with PO

Drug	Oral bioavailability
Clindamycin	90%
Linezolid	100%
Ciprofloxacin	80%
Levofloxacin	100%
TMP-SMX	95%
Doxycycline	>90%
Rifampin	90%
Fluconazole	95%
Voriconazole	95%
Isavuconazonium sulfate	95%

Source: idstewardship.com

Oral/IV[a]	Cost[b]
Ciprofloxacin	¢/$
Levofloxacin	¢/$
Metronidazole	¢/¢
TMP-SMX	¢/$$$
Doxycycline	¢/$$
Linezolid	$/$$
Azithromycin[c]	¢/$

UCLA ASP

Step-down to Bactrim PO

Indication requires high-dose IV Bactrim

Credit @idstewardship

Early Conversion IV to PO, Randomized Controlled Trails

Bone/Joint Infections

Bone or joint infection
N=1054

: Min 7 days from start or sx

Rx failure	14.6%	13.2%
Catheter complication	9.4%	1.2%

OVIVA trial, U.K.NEJM 2019

Endocarditis

L-sided endocarditis
N=400
Strep, E. faecalis, S. aureus, CoNS

: Min 10 days

Primary composite outcome	12.1%	9%

*composite of all-cause mortality, unplanned cardiac surgery, embolic events, relapse of bacteremia with the primary pathogen- x 6months

POET Trial, Denmark, NEJM 2019

Ped Septic Arthritis

Cx + septic arthritis
3 mnths-15 yrs
N=130, 10 vs 30 days

: 2-4 days

	30d	10d
Relapse	0	0
Late-onset reinfection	2	0

Clin Infect Dis 2009

Early switch to oral antibiotics has similar outcomes with less catheter-related adverse events

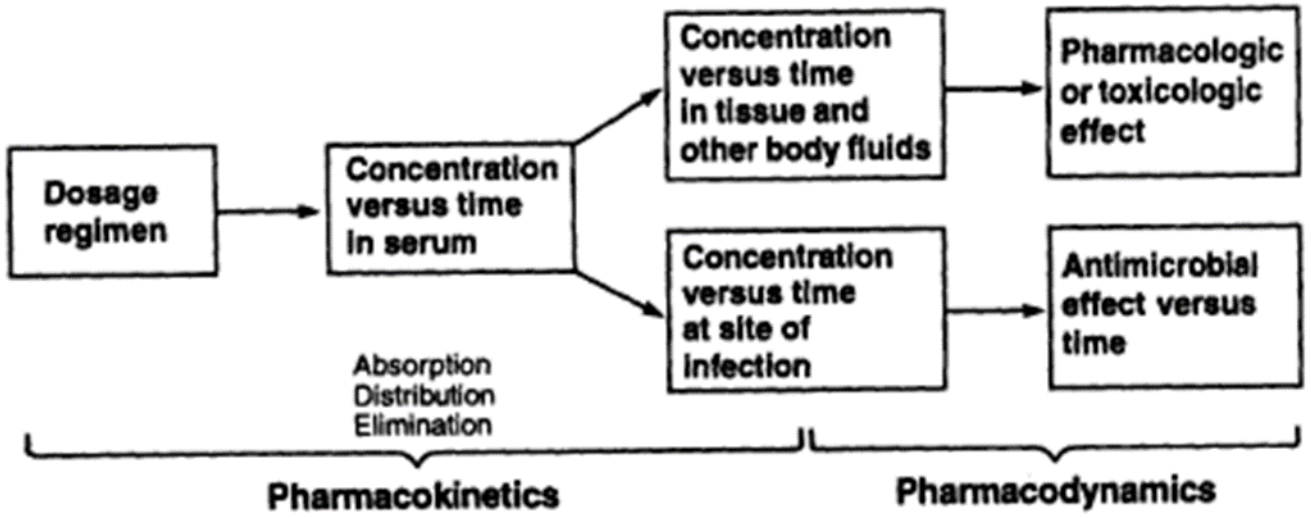
Early IV to PO, Bacteremia

- Several retrospective studies in adults (gram negative and *S. aureus*)
- Pediatrics- we win, right?
  1. Young infants with bacteremic urinary tract infections (transient)
     - Multicenter retrospective cohort study; ≤60 days old; 11 children's hospitals; 2011-16[1]
       - N=115; 50% ≤7d of IV antibiotics (2-24d); no difference in recurrent UTIs or hospital reutilization (2v4)
  2. *S. aureus* bacteremia (SAB) in the setting of musculoskeletal infection (transient)
     - Clinical Management of SAB in Neonates, Children, and Adolescents[2]
       - Children with SAB and acute osteoarticular infection: may switch to oral therapy after a minimum of 3 days of IV therapy

[1]Samir SS, et al. *Pediatrics* 2019
[2]McMullan BJ, et al. *Pediatrics* 2020

RETHINKING DOSING

Pharmacokinetics and Pharmacodynamics (PK/PD)

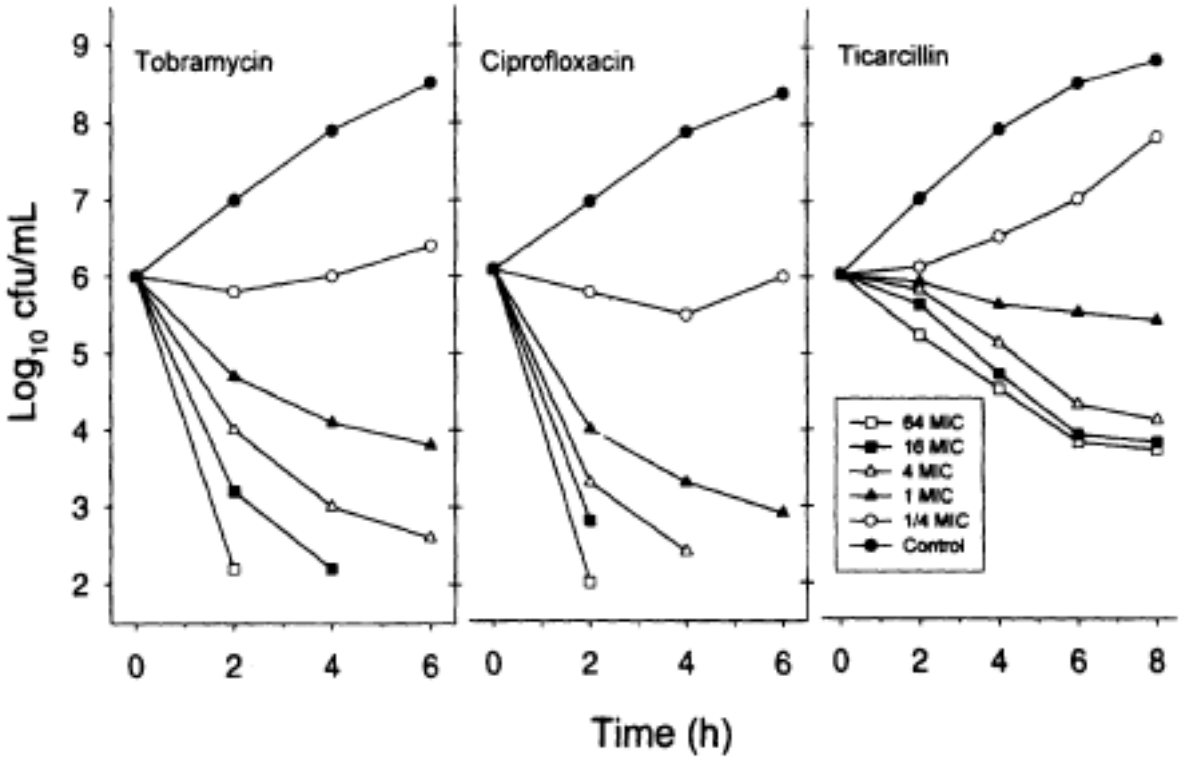


Craig WA. Clin Infect Dis. 1998

PK/PD Profiles of Antibiotics

Concentration-dependent Killing
↑ concentration = ↑ bactericidal (rate + extent)
aminoglycosides + fluoroquinolones

P. aeruginosa

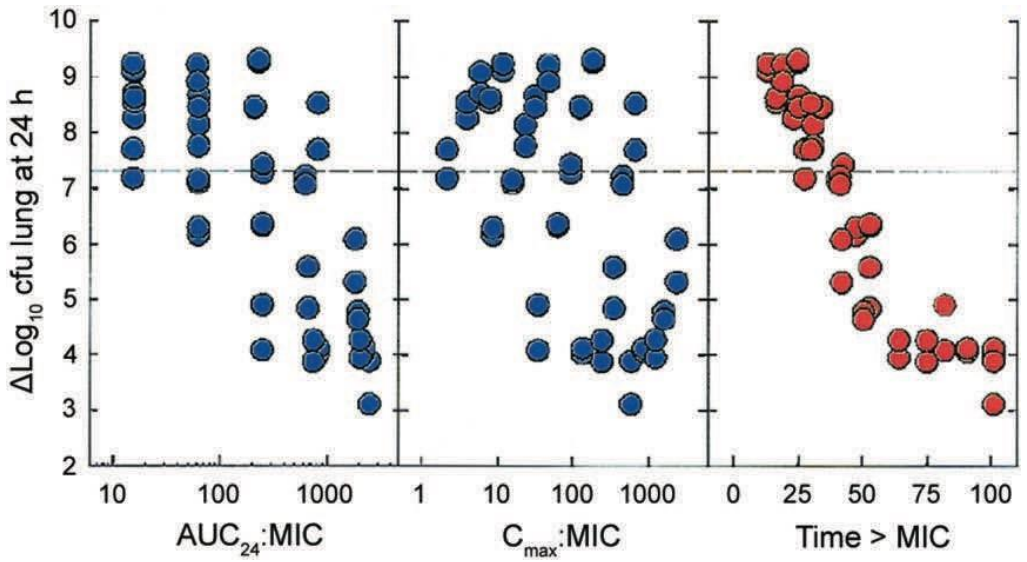


Shah et al. 1976; Vogelman and Craig 1986

PK/PD Profiles of Antibiotics

Time-dependent Killing
Minimal concentration dependent killing Saturation of killing rate at low multiples of MIC (4-5x) Extent of killing largely dependent on time of exposure
β-lactams

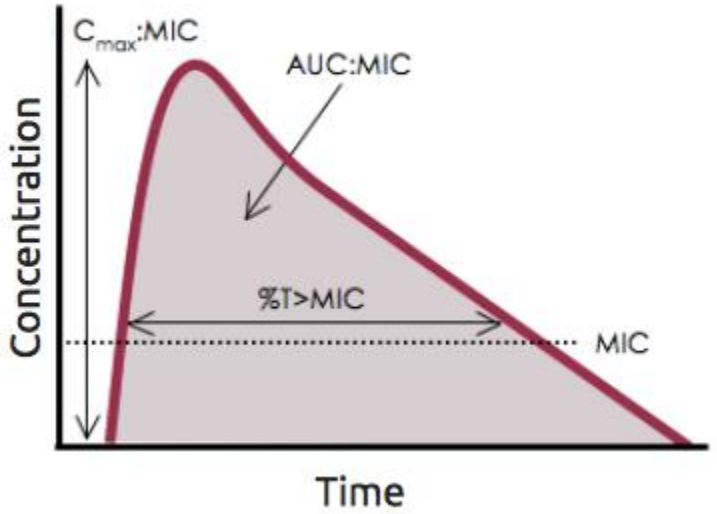
Cefotaxime vs *K. pneumoniae* mouse model



Shah et al. 1976; Vogelman and Craig 1986

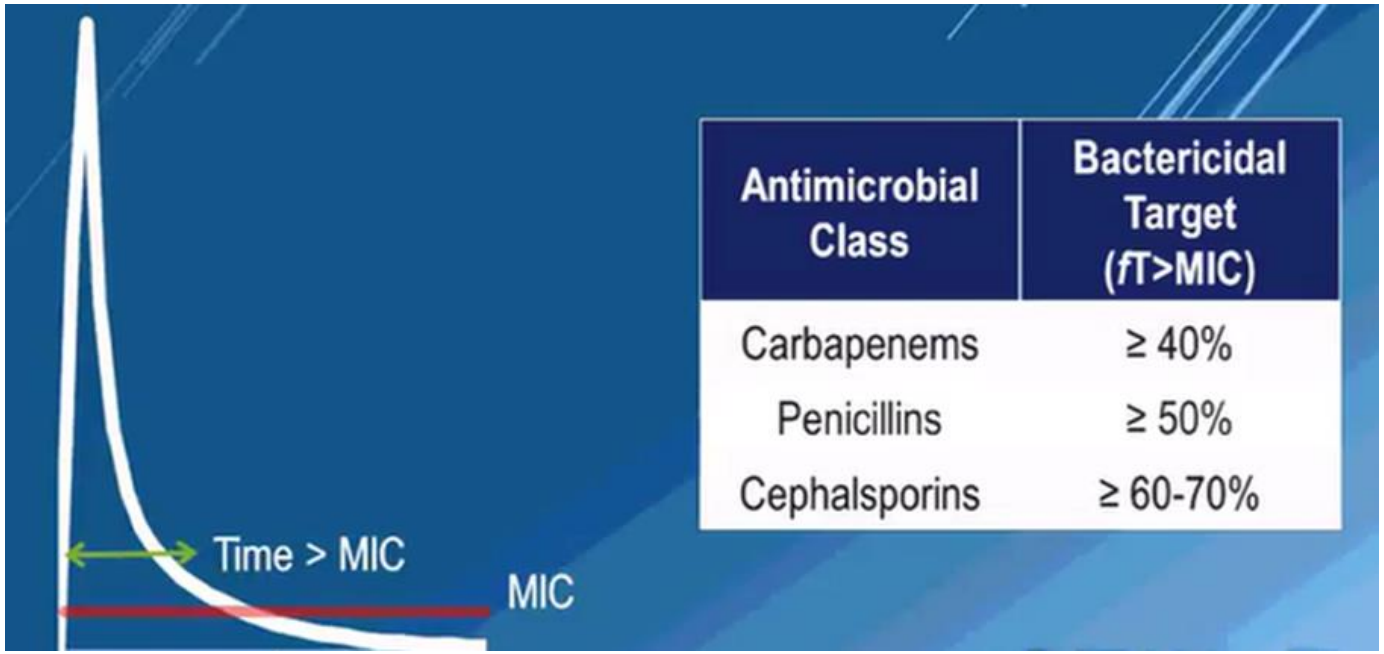
PK/PD Indices of Antibiotics

Figure 2. The PK-PD indices associated with antibacterial activity

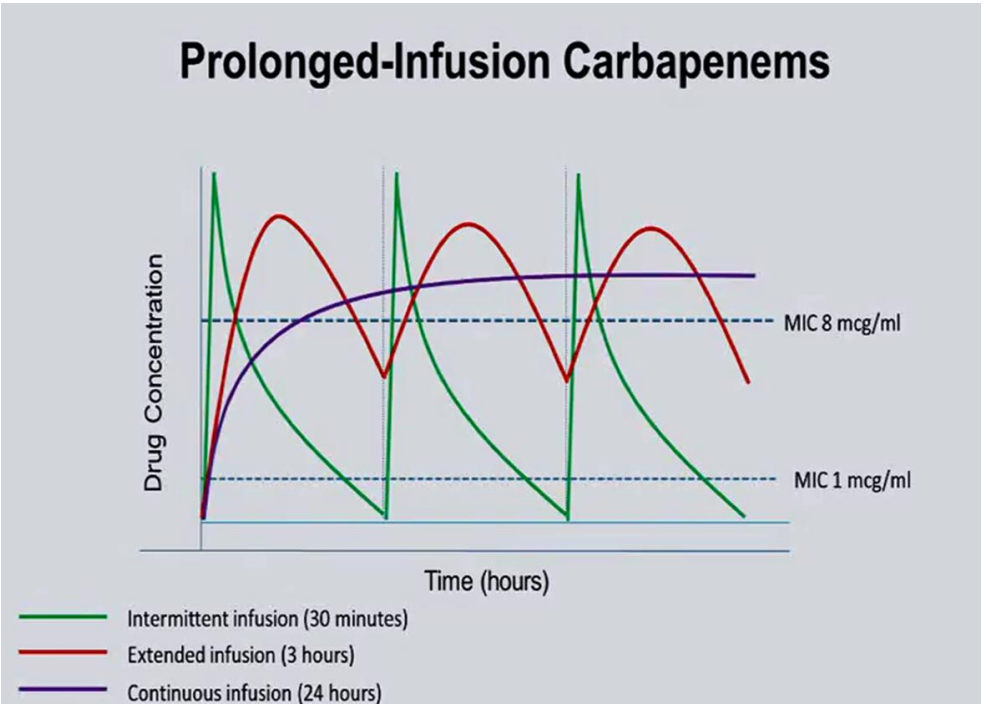


Source: idstewardship.com

Time>MIC and Extended Infusions



Antimicrobial Class	Bactericidal Target (*f*T>MIC)
Carbapenems	≥ 40%
Penicillins	≥ 50%
Cephalsporins	≥ 60-70%



Extended Infusions-β-lactams

Clinical outcomes

- Prolonged versus short-term IV infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomized trials. *Lancet* 2018
  - lower all-cause mortality (risk ratio 0·70, 95% CI 0·56-0·87)

Pharmacologic target optimization

- Probability of target attainment higher

Ease of administration outpatient

UCLA Change of Practice: β-lactams Extended Infusions

NEW! Extended Infusion Antibiotics:
Meropenem, Cefepime, & Piperacillin-Tazobactam 4.5g

- Meropenem, cefepime, and piperacillin-tazobactam 4.5g will be orderable in CareConnect as an order panel with the first dose (bolus) being given over 30 min. and subsequent doses infused over 4 hours
- Dosing recommendations will be available through the CareConnect ordering sidebars, as well as in the UCLA Spectrum Mobile App
- **Go-live dates for CareConnect provider order entries to become available:**
  4/19/2021: Meropenem **5/3/2021**: Cefepime, Piperacillin-tazobactam 4.5g
- **Rationale:** Extended infusion is the preferred method for this antibiotic class. Studies have shown extended infusion beta-lactams improves patient outcomes such as lower mortality rates and shorter length of hospital stay.
- If extended-infusion is not feasible for your patient (i.e. line access, incompatibilities, etc.), contact pharmacy for assistance.

UCLA Change of Practice: Vancomycin PK/PD Target

- Traditional practice: trough monitoring as surrogate of AUC:MIC
- New practice: target AUC:MIC for MRSA, ≥400:1
- When: Summer-fall, 2021
- Why: 2020 Vancomycin therapeutic monitoring guideline

Am J Health-Syst Pharm.2020

Vancomycin AUC monitoring, Data

- Accepted PK/PD index: AUC:MIC ratio of ≥400:1, range 400-600
- Using Bayesian software programs
- Clinical outcomes
  - Several retrospective, single-center studies, MRSA infections (BSI, pneumonia, endocarditis)
  - Prospective, multicenter, observational study of 265 hospitalized adults with MRSA BSI
- Acute kidney injury (AKI)
  - Lower with AUC-based monitoring
  - Median values a/w AKI: trough, 15.7 mg/L and AUC, 625 mg·h/L
  - Same study- lower frequent blood sampling, earlier target attainment, shorter length of stay

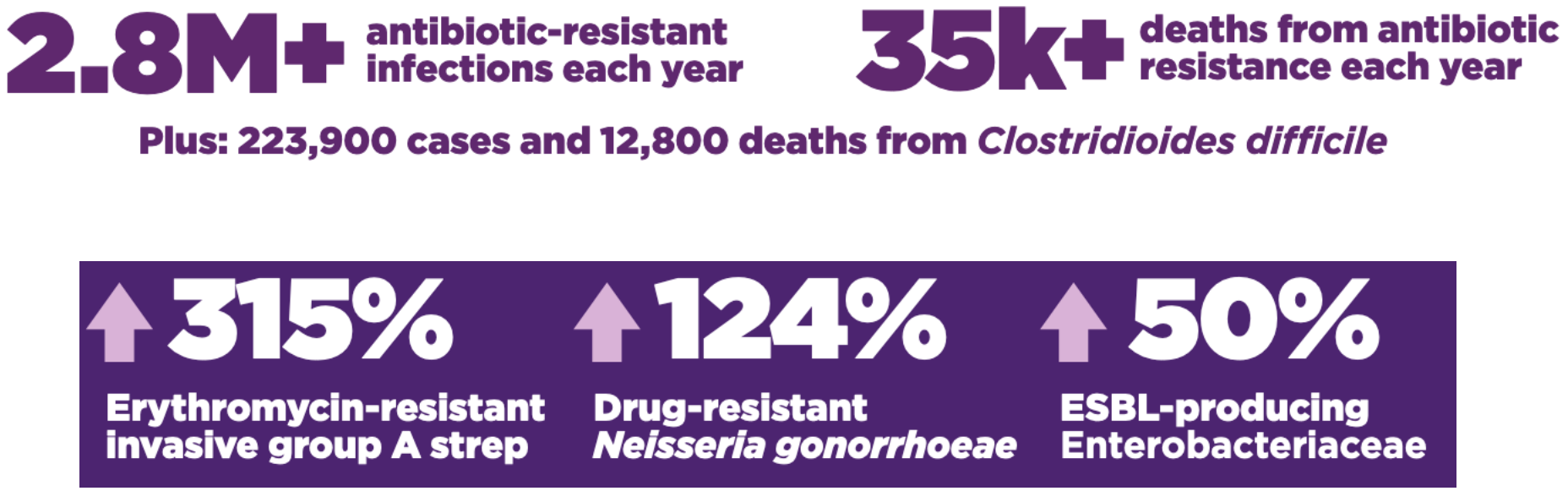
Neely, M. et al. *Antimicrob Agents Chemother* 2018

Vancomycin AUC monitoring, What to Expect

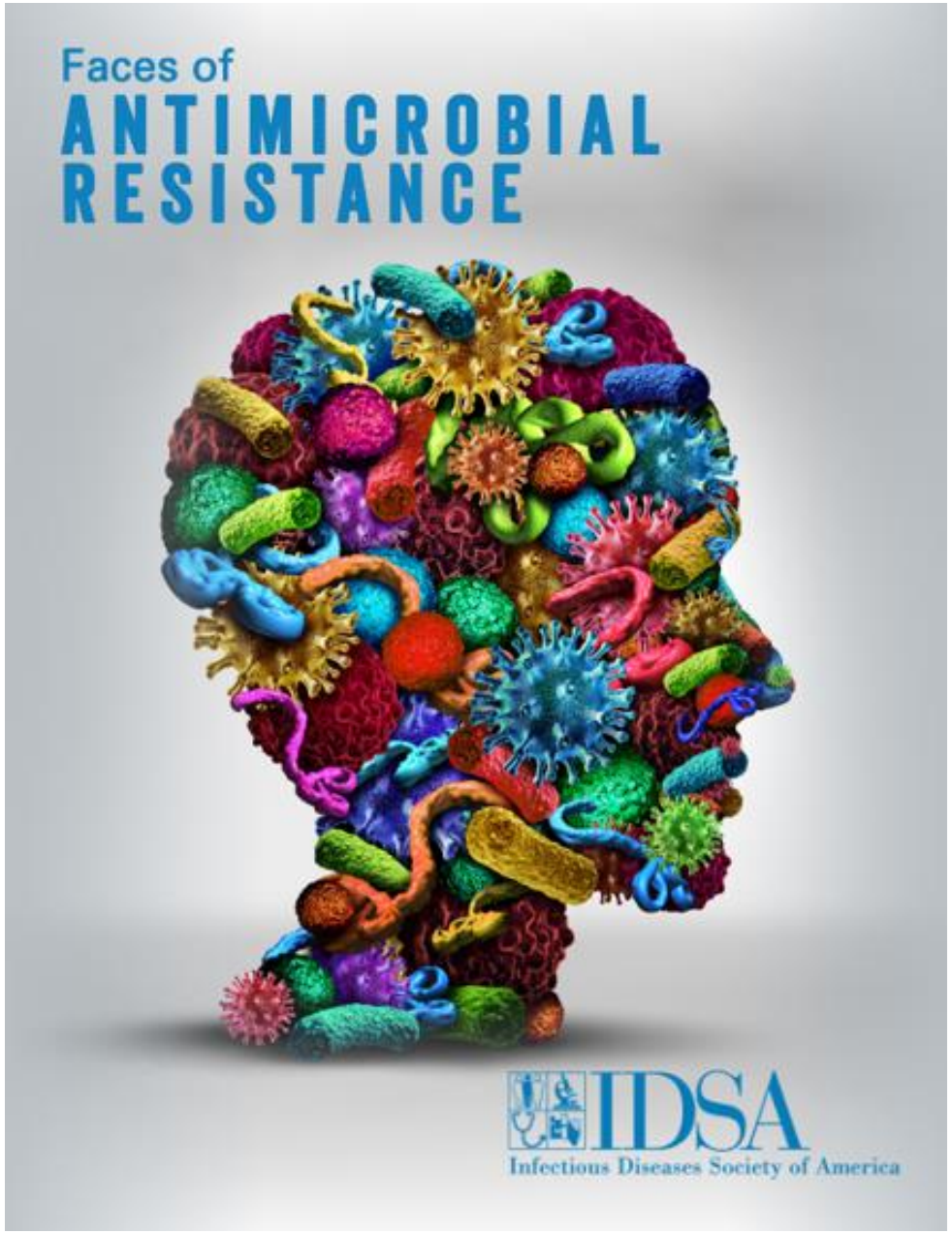
- AUC based monitoring will be implemented soon
- Continuous infusions
  - *Earlier target attainment, less variability in serum concentrations, ease of drug level monitoring, lower risk of AKI*
  - Higher steady state concentrations on continuous infusions
  - Not troughs, but steady state concentrations (Css)
  - Css 17-25 corresponding to AUC 400-600
  - Overall daily dose is lower in many cases

Am J Health-Syst Pharm.2020

Time to Act is Now.



2019 CDC Antimicrobial Resistance Threat Report



Stop referring to a coming post-antibiotic era—it's already here!

It is time to rethink the use of this limited resource

It is time to adopt the mantra- shorter is better!