Antibiotic Stewardship 2023

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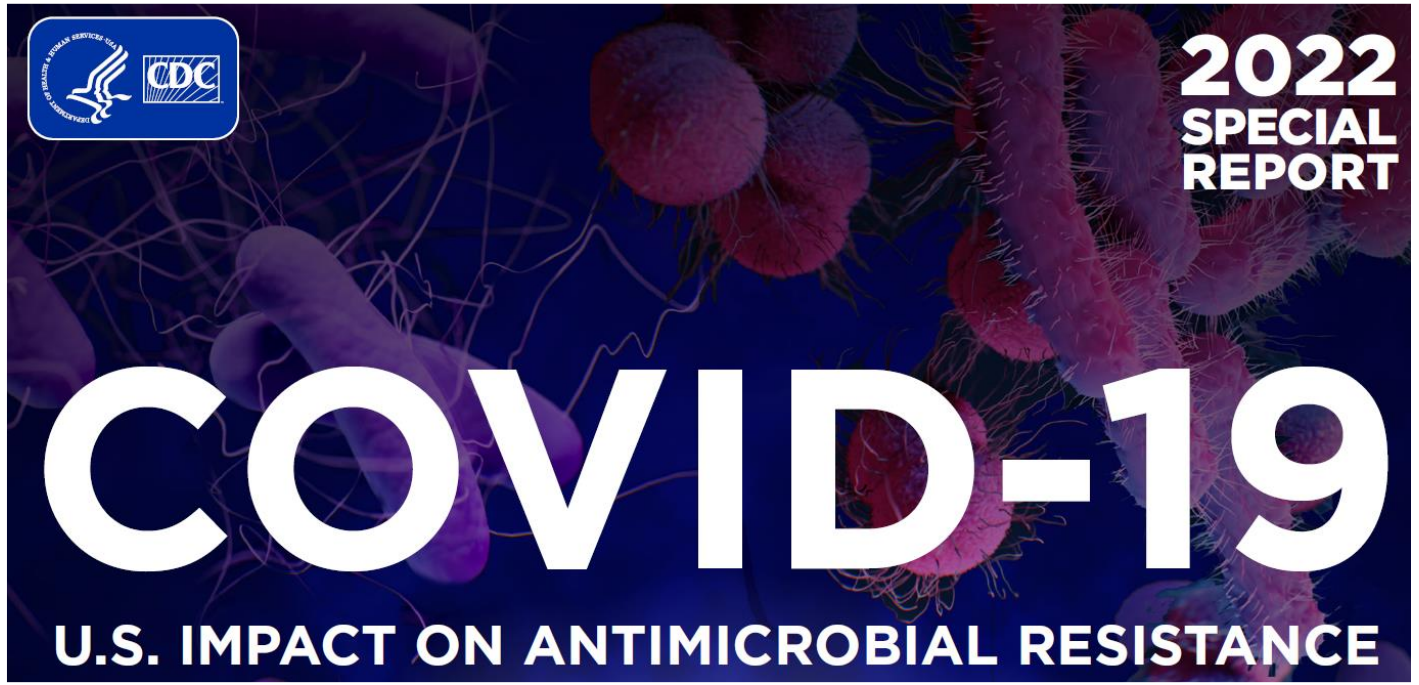
What is Antibiotic Stewardship?

- The right drug - …and sometimes, that means NO DRUG
- For the right **DURATION**
- At the right dose – and no, there's nothing magical about IV

No drug…
because it’s a virus!



Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↑13%)

https://www.cdc.gov/drugresistance/covid19.html

COVID-19 Impacts on

Antibiotic Use:

Improve the use of antibiotics wherever they are used and improve access

- 80% of hospitalized COVID-19 patients received an antibiotic
- Half of hospitalized patients received ceftriaxone
- Likely reflects problems in distinguishing COVID from CAP

https://www.cdc.gov/drugresistance/covid19.html

Impact of COVID-19 on Inpatient Antibiotic Use in the United States, Jan 2019-July 2022

- 4/2020 first major wave compared vs 4/2019 increases of
  - Total antibiotic use = 7%
  - Azithromycin = 64%
  - Ceftriaxone = 27%,
  - Piperacillin-tazobactam = 5%
- Antibiotic use again spiked, though less than in 2020, during 2021 peaks

O'Leary EN, et al. *Clin Infect Dis* 2023; https://doi.org/10.1093/cid/ciad453

Real-life Assessment of BioFire FilmArray (BFA) Pneumonia Panel in Adults Hospitalized With Respiratory Illness

- "Diagnostic uncertainly has led to unnecessary use of broad-spectrum antibiotics, with resultant side effects and spread of antimicrobial resistance…"
- 298 sputa tested
  - BFA vs sputum + standard of care testing = 91% vs 60%, $P < .0001$
- **Negative predictive value, 92% to 100%.**

Falsey AR, et al. *J Infect Dis* published online June 27, 2023

Open Forum Infectious Diseases

IDSA Infectious Diseases Society of America

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

The effect of rapid point-of-care respiratory pathogen testing on antibiotic prescriptions in acute infections – a systematic review and meta-analysis of randomized controlled trials

Ilari Kuitunen, MD, PhD ✉, Marjo Renko, MD, PhD ✉

Open Forum Infectious Diseases, ofad443, https://doi.org/10.1093/ofid/ofad443

Published: 18 August 2023 **Article history** ▾

- 754 abstracts screened - 10 studies included. Risk of bias only low in 4, and some concerns in 4 studies.
- 4 studies analyzed flu & RSV tests, 6 studies analyzed multiplex (viral and/or bacterial) testing
- RX rate = 48.2% (496/1029) in flu & RSV group - 48.7% (540/1109) in control (RR 0.97, CI 0.92-1.02; moderate quality evidence).
- RX rate in the multiplex testing group was 54.3% (1554/2859), and 57.3% (1336/2326) in the control group (RR 1.00, CI 0.96-1.04; moderate quality evidence).
- Moderate quality evidence: rapid point-of-care testing **does not decrease ABX prescriptions**

JAMA Internal Medicine | Original Investigation

Evaluation of Oseltamivir Used to Prevent Hospitalization in Outpatients With Influenza

A Systematic Review and Meta-analysis

- 2352 studies identified, 15 included.
- 6295 individuals with 54.7% prescribed oseltamivir (OTV)
- OTV did not reduce hospitalization in:
  - Overall. (mean age = 45.3: RR, 0.77; 95%CI, 0.47-1.27)
  - Older pts (mean age 65 years: RR, 0.99; 95%CI, 0.19-5.13)
  - Patients considered at greater risk (RR, 0.90; 95%CI, 0.37-2.17)
- OTV increased nausea (RR, 1.43) & vomiting (RR, 1.83)
- HOWEVER… no discussion of time to initiation of therapy

Hanula R et al. JAMA Intern Med 2023 Jun 12

A Statewide Quality Initiative to Reduce Unnecessary Antibiotic Treatment of Asymptomatic Bacteriuria (ASB)

- 14572 patients (pts) with + urine culture (median age, 75.8; 70.5% female)
- 28.4%(n = 4134) had ASB, of whom 76.8% (n = 3175) received antibiotics (abx).
- % of pts treated with abx who had ASB ↓ 29.1%(26.2%-32.2%) to 17.1%(14.3%-20.2%)
- % with a + urine culture with ASB ↓ from 34.1%(31.0%-37.3%) to 22.5% (19.7%-25.6%)
- % of pts with ASB who received abx = stable (82.0%(95%CI, 77.7%-85.6%) to 76.3% (68.5%-82.6%),
- Mean antibiotic duration = stable (6.38 (6.00-6.78) days to 5.93 (5.54-6.35)
- Over 3 years, ASB-related abx use ↓ & unnecessary urine cultures ↓

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2806966

No drug!
Prevention with vaccines

Influenza 2022-23

CDC estimates* that, from **October 1, 2022** through **April 30, 2023**, there have been:

27 – 54 million
flu **illnesses**

12 – 26 million
flu **medical visits**

300,000 – 650,000
flu **hospitalizations**

19,000 – 58,000
flu **deaths**

https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

van Heuvel et al.
Antimicrobial Resistance & Infection Control (2023) 12:70
https://doi.org/10.1186/s13756-023-01272-6

Antimicrobial Resistance
and Infection Control

REVIEW Open Access

The impact of influenza and pneumococcal vaccination on antibiotic use: an updated systematic review and meta-analysis

Lotte van Heuvel[1], John Paget[1*], Michel Dückers[1,2,3] and Saverio Caini[1]

- flu vaccine ↓ antibiotic (ABX) prescriptions & days of ABX (Ratio of Means (RoM) 0.71, 95% CI 0.62–0.83) more than pneumococcal vaccination (RoM 0.92, 95% CI 0.85–1.00).
- These studies also confirm a ↓ in the proportion of people receiving ABX post flu vaccine (Risk Ratio (RR) 0.63, 95% CI 0.51–0.79).
- "our data supports the use of influenza vaccination as an important public health intervention to ↓ antibiotic use and possibly control AMR."

Antimicrobial Resistance & Infection Control (2023) 12:70 published online July 14, 2023

The Right Drug…
“I’m allergic to…”

Penicillin “allergy”

- Reported in 10-15% of patients;
- <10% of patients who report an allergy have one
- Even severe reactions wane with time
- 55% (220 patients) were delabeled without testing or challenge
- Reasons for delabeling included: documented tolerance of penicillin antibiotic (64%), multiple reasons (25%)

Ham YY, et al. Allergy Asthma Proc 2021;42:153
Brown J, et al. J All Clin Immunol 2023;151:SAB40. Abstract #120

Evaluating the PEN-FAST Clinical Decision-making Tool to Enhance Penicillin Allergy Delabeling

- Clinical decision-making tool with high negative predictive value (NPV) that can identify patients with low-risk penicillin allergy who do not require skin testing prior to oral penicillin challenge.
- 120 patients
- Direct challenge for 16 patients (13.3%)
- Negative predictive value of **100%** in identifying patients with a low-risk penicillin allergy
- PEN-FAST is simple, useful for primary care clinicians, particularly in areas without easy access to allergists.

JAMA Intern Med 2023;183:883-885. doi: 10.1001/jamainternmed.2023.1572

Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial

- 377 patients in the analysis
- Most patients had a PEN-FAST score of 0 or 1.
- Primary outcome in 1 pt (0.5%) in intervention group & 1 pt (0.5%) in control group - RD of 0.0084 pp (90% CI, −1.22 to 1.24 pp).
- 5 days following challenge, 9 immune-mediated adverse events in intervention group & 10 in control group (RD, −0.45 pp; 95% CI, −4.87 to 3.96 pp).
- No serious adverse events occurred.

JAMA Intern Med. Published online July 17, 2023. doi:10.1001/jamainternmed.2023.2986

The right drug:
Bactrim doesn’t work for Streps

Beta Streps and Bactrim…

JAMA. 2016;316(3):325-337. doi:10.1001/jama.2016.8825

- Beta streps (Group A, B, C, G) = primary cause of cellulitis / non-purulent SSTIs
- "… trimethoprim-sulfamethoxazole … ***should not be used*… *not offer adequate streptococcal coverage*…"

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Less severe SSTI empiric

Non-purulent SSTIs
(β-hemolytic Streptococci)

- Penicillin
- Cephalosporins
- Dicloxacillin
- Clindamycin if severe β-lactam allergy

Purulent SSTIs
(*Staphylococcus aureus*)

- TMP/SMX
- Doxycycline

Clin Infect Dis 2014;59(2):e10-e52

Current Guidelines: TMP-SMX & Streptococci

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

- " The activity of doxycycline and SMX-TMP against β-hemolytic streptococci is not known"

- β-lactam + TMP-SMX recommended if MRSA and streptococci are a concern

Clin Infect Dis 2014;59(2):e10-e52

JCM
Journals.ASM.org

Is *Streptococcus pyogenes* Resistant or Susceptible to Trimethoprim-Sulfamethoxazole?

- Testing in the mid 1940s reported resistance in GAS, but…
- However, the perception remained
- Thymidine in agar antagonizes sulfa activity against streps
- Reports of tmp/smx resistance in GAS are prior to 2006…
- When thymidine content in agar was standardized

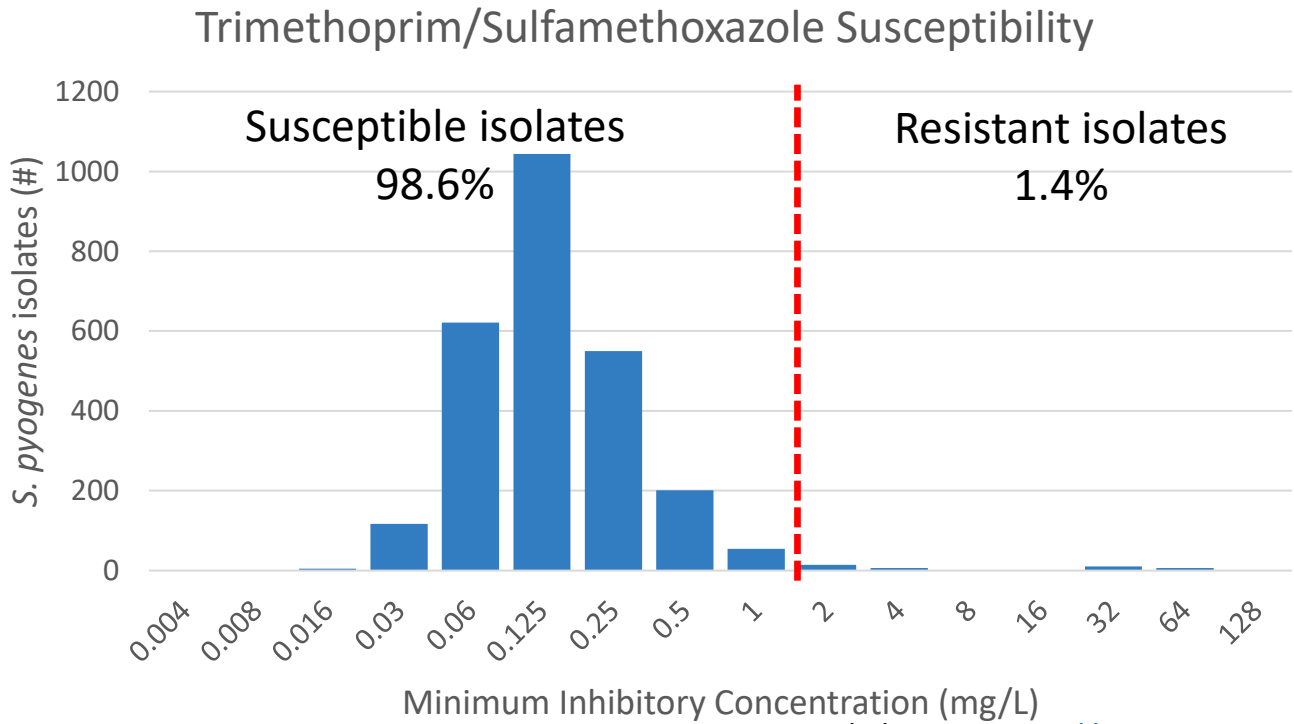
Bowen AC, et al. *J Clin Microbiol* 2012; 50:4067

Modern *in vitro* data

- 2012 *in vitro* study
- 100 clinical *Streptococcus pyogenes* isolates
- TMP-SMX susceptibility performed

- **100/100 (100%) isolates susceptible**

- European susceptibility database
- 2,629 *S. pyogenes* isolates w/ TMP-SMX susceptibility results



Bowen AC et al. J Clin Microbiol 2013;50(12):4067

EUCAST MIC Distribution database. Accessed 11/3/2022. https://www.eucast.org/

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 19, 2015 VOL. 372 NO. 12

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections

Design / Context	Treatments	Results	Notes

• RCT, blinded, multicenter
• Adults & pediatrics
• Uncomplicated skin & soft tissue infections
  • Abscess (30%)
  • Cellulitis (53%)
  • Both (16%)
	1) TMP/SMX 2 DS BID
	
	2) Clindamycin 300mg TID
	
	Both treatments oral & x 10 days
		Cure 7 – 10 days after treatment (cellulitis ± abscess subgroup, n = 362):
		
		TMP-SMX: **77%%**
		Clindamycin: **81%**
		CI (-13.5% to 4.8%)
			"…not powered …. in the subgroup of patients with cellulitis, but the data suggest that if there is a difference in outcome it is probably small."

Miller LG et al. N Engl J Med 2015; 372:1093

Stewardship: The right duration

"Traditional stewardship strategies targeting patients who don't need antibiotics don't help patients who do need antibiotics but receive treatment for longer than necessary. In contrast, treating for shorter periods of time helps both patients who do and do not need antibiotics but receive them for long durations."

Spellberg B. *Clin Micro Infect* 2023;29:141

Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia	3-5	7-10
Nosocomial pneumonia	≤8	10-15
Pyelonephritis	5-7	10-14
Intraabdominal infection	4	10
AECB & COPD	≤5	>7
Acute bacterial sinusitis	5	10
Cellulitis	5-6	10
Chronic osteomyelitis	42	84

Spellberg B. Clin Micro Infect 2022. DOI:https://doi.org/10.1016/j.cmi.2022.04.005

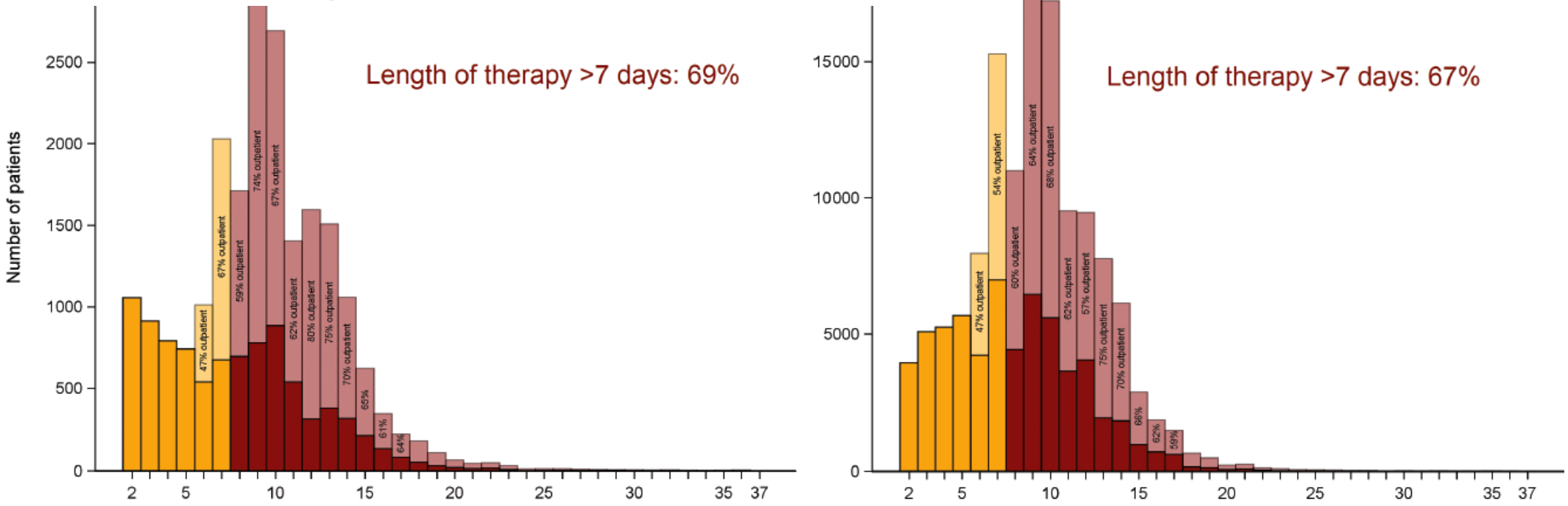
Clinical Infectious Diseases

MAJOR ARTICLE

Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States

Sarah H. Yi, Kelly M. Hatfield, James Baggs, Lauri A. Hicks, Arjun Srinivasan, Sujan Reddy, and John A. Jernigan

Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia



CID 2018;66:1333

Intravenous to Oral Antibiotic Switch Therapy Among Patients Hospitalized With Community-Acquired Pneumonia

- 642 US hospitals 2010 – 2015. Early switch = change by day 3
- 378041 CAP patients, 21784 (6%) early switch, usually to fqs
- Early switch = shorter inpatient abx tx, shorter LOS, and lower $$$
- No excesses in 14d mortality or late ICU admission
- Higher mortality risk = less likely to be switched.
- <15% of very low–risk pts switched early.
- Early switch = equivalent outcomes, shorter LOS, fewer abx days

Clin Infect Dis 2023;77:174-85. https://doi.org/10.1093/cid/ciad196

Dogmas of Stewardship: For your consideration

"It is hard to convince doctors not to prescribe antibiotics at all. It is easier to convince doctors to prescribe for a duration of therapy shown to be effective in RCTs."

Spellberg B. *Clin Micro Infect* 2023;29:141

Dogmas of Stewardship: For your consideration

"Traditional durations of antimicrobial therapy in medicine are **not** based on controlled investigations. Therefore, RCTs are adequate to contravene historical dogma, establishing a new standard of care for durations of antimicrobial therapy."

Spellberg B. *Clin Micro Infect* 2023;29:141

Treatment recommendations in the IDSA guidelines

Quality of Evidence	Strength of Recommendation	
	Weak	Strong
High	2 (0.3)	54 (7.6%)
Moderate	29 (4.1%)	204 (28.7%)
Low	117 (16.5%)	238 (33.5%)
Very Low	32 (4.5%)	35 (4.9%)
Total	**180 (25.3%)**	**531 (74.7%)**

Miles KE, et al. *Open Forum Infect Dis* 2021 Jan 21;8(2):ofab033

Google: “how long does it take a new randomized trial to impact medical practice”

REVIEW

The answer is 17 years, what is the question: understanding time lags in translational research

*J R Soc Med 2011: **104**: 510–520. DOI 10.1258/jrsm.2011.110180*

Dogmas of Stewardship: For your consideration

"The idea that prolonging therapy somehow prevents resistance by eradicating every last bacterium that could result in a future relapse, now caused by resistant strains, is neither evidence based, nor rational."

"That idea is rather based on urban legend. The longer patients and the environment are exposed to antibiotics, the greater the selective pressure driving resistance."

Spellberg B. *Clin Micro Infect* 2023;29:141

Clinical Infectious Diseases

INVITED ARTICLE

REVIEWS OF ANTI-INFECTIVE AGENTS: Louis Saravolatz, Section Editor

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

- First – remember how these definitions work
- 56 trials since 1985 comparing "cidal" vs "static"
- 49 no show no difference
- In 6, the static agent looked better
- 1 – the cidal looked better… but it was imi vs **tigecycline**…

Clin Infect Dis 2018;66:1470, https://doi.org/10.1093/cid/cix1127

How about for MRSA pneumonia?

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

For high-risk patients who are not in septic shock, but who are treated in an ICU where >25% of the *S. aureus* respiratory isolates in their ICU are MRSA, an agent with coverage for this pathogen should be added to initial empiric therapy. This involves choosing between vancomycin and linezolid.

Torres A, et al. *Eur Respir J* 2017;50:1700582

The Magic Isn't in the IV – Its in the PK

- Can you get enough drug into the blood
- Challenges of oral beta-lactams
- Are the PK-PD targets hit?
- IV linezolid = Oral linezolid,
- Other good oral options not fully investigated?
  - Moxifloxacin – Resistance concerns?
  - Delafloxacin – New drug, limited data, limited experience
  - Clindamycin – Extensive experience in pediatrics
  - Trimethoprim-Sulfamethoxazole: Concerning data?
  - Minocycline/Doxycycline – PK/PD concerns

ELEVEN years ago…: 7 vs 14 Days of Ciprofloxacin (Cip) for Pyelonephritis

	Cip 7 days	Cip 14 days	Difference (90% CI)	Non-Inferiority test P value
Cure	93%	93%	-0.3% (-7.4 to 7.2)	0.015
Clinical failure or recurrent UTI symptoms	7%	7%	-	-

- 22% of patients bacteremic in the 7 day arm
- 32% in the 14 day arm
- The take home: pyelo = 7 days with quinolones!
- Even bacteremic pyelo!
- Questions when using non-quinolone agents

ALL ORAL THERAPY!

Sandberg T, et al. *Lancet* 2012;380:484-90.

Clinical Infectious Diseases
MAJOR ARTICLE

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

- 604 patients – 306 Intervention vs 298 control
- 2013-2017 3 centers in Israel & Italy
- Afebrile & hemodynamically stable for at least 48h, source control
- 411 (68%) urinary source
- 90% Enterobacteriaceae

Yahav et al. *Clin Infect Dis* 2019;69:1091

Clinical Infectious Diseases
MAJOR ARTICLE

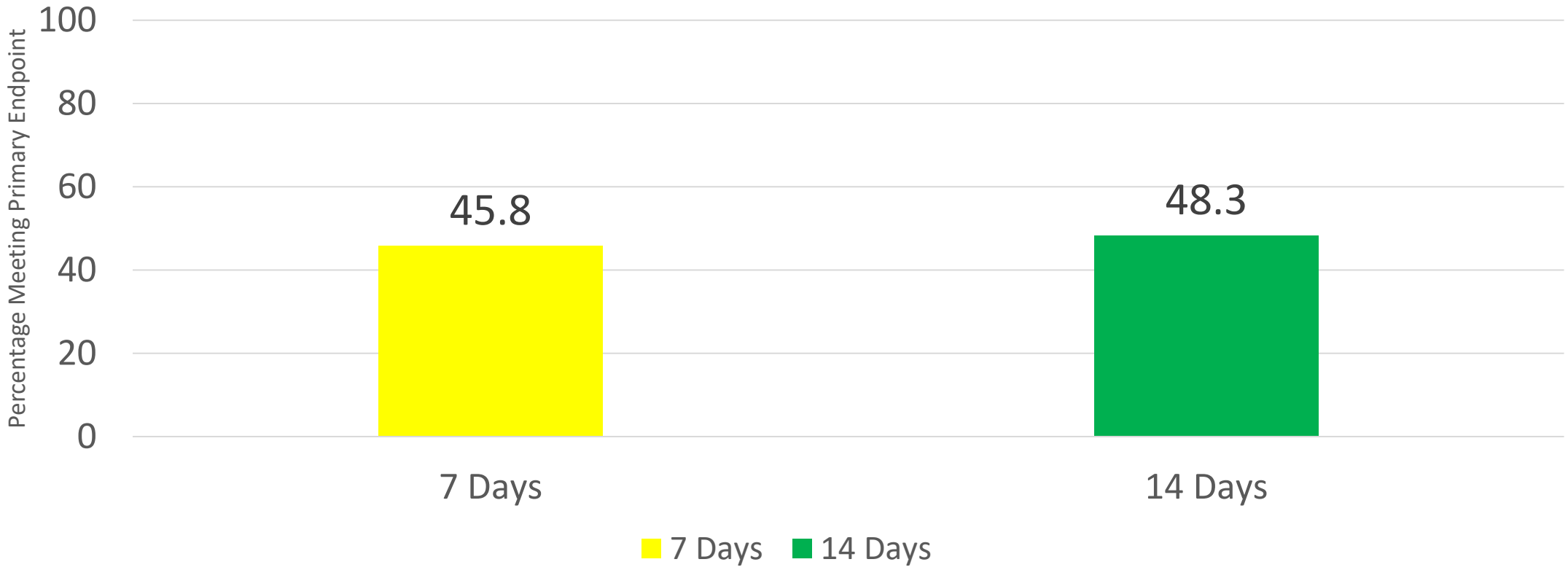
Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

- **Primary Outcome** - at 90 days from randomization composite of:
  - All cause mortality
  - Clinical failure
    - either relapse of bacteremia, local suppurative complications, or distant complications
  - Readmission or extended hospital stay (>14 days)

Clinical Infectious Diseases

MAJOR ARTICLE

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial



Oral antibiotics utilized

Type of antibiotics [a]	Short arm (196 patients)	Long arm (242 patients)*
Quinolones	151 (77.0)	172 (71.1)
Beta-lactams	28 (14.3)	50 (20.7)
Trimethoprim-Sulfamethoxazole	17 (8.7)	20 (8.3)

Data are presented as numbers (percentage)

65% of patients in the short duration arm received oral antibiotics

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D.,

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2

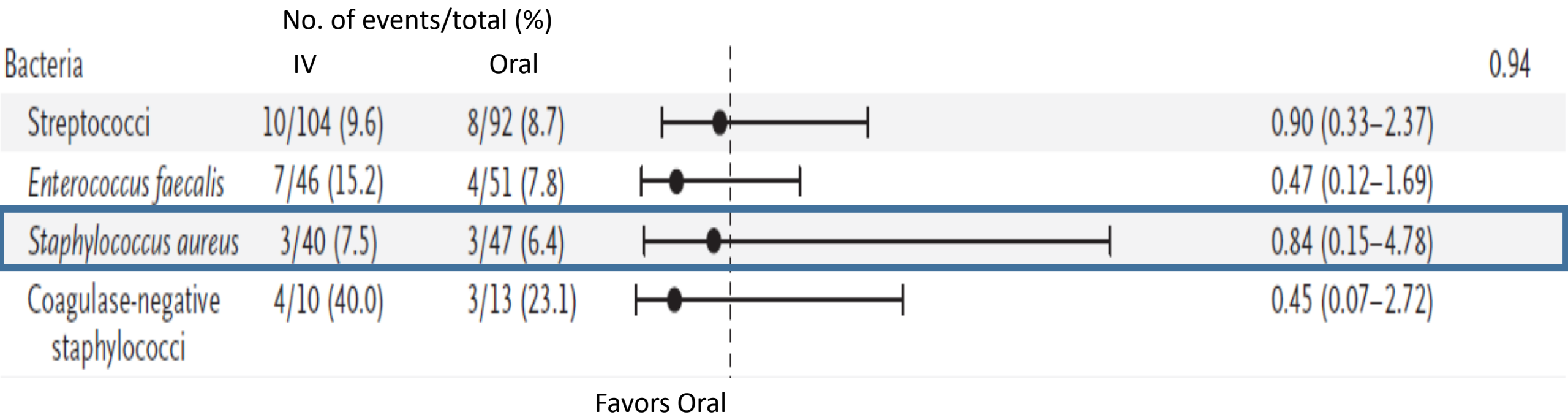
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2

3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2

4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

N Engl J Med 2019; 380:415-424

Poet: Outcomes by bug IV vs Oral – "But there was no MRSA!"



N Engl J Med 2019; 380:415-424

IV to PO switch – Anybody have enough nurses?

- Time motion study of nurses giving IV and oral ABX doses
- Mean administration duration of 22 minutes 5 seconds for IV
- Mean of 80 seconds for oral dose
- You switch one IV antibiotic that has to be given 3x/d
- You free up 1 hour of nursing time…

Jenkins A. *J Antimicrob Chemother* 2023; https://doi.org/10.1093/jac/dkad239

Conclusions: Antibiotic Stewardship is…

- Right drug (which is sometimes none)
- Right duration (probably shorter than what you were taught)
- Right dose and route (there is nothing magic about IV)
- Vaccines prevent antibiotic use and = stewardship
- “Antibiotic Allergies” often aren’t and fixing them is good stewardship