Focused Stewardship Initiatives: Shorter is Better

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University of Nebraska Medical Center
Nebraska Medicine

Disclosures

- The speaker has no financial relationships or disclosures

Objectives

1. Discuss the historical precedent and evidence regarding antibiotic durations of therapy and antibiotic resistance

2. Review the evidence for shorter antibiotic durations for common infectious diseases

3. Demonstrate ways to incorporate shorter duration options into facility guidelines

Why we must, how we can

- “AMR is more than just a medical issue in the same way that climate change is more than just an atmospheric science issue”
  – Dr. Ramanan Laxminarayan

- "Improvements anywhere can lead to impacts everywhere“
  -Dr. Amanda Beaudoin

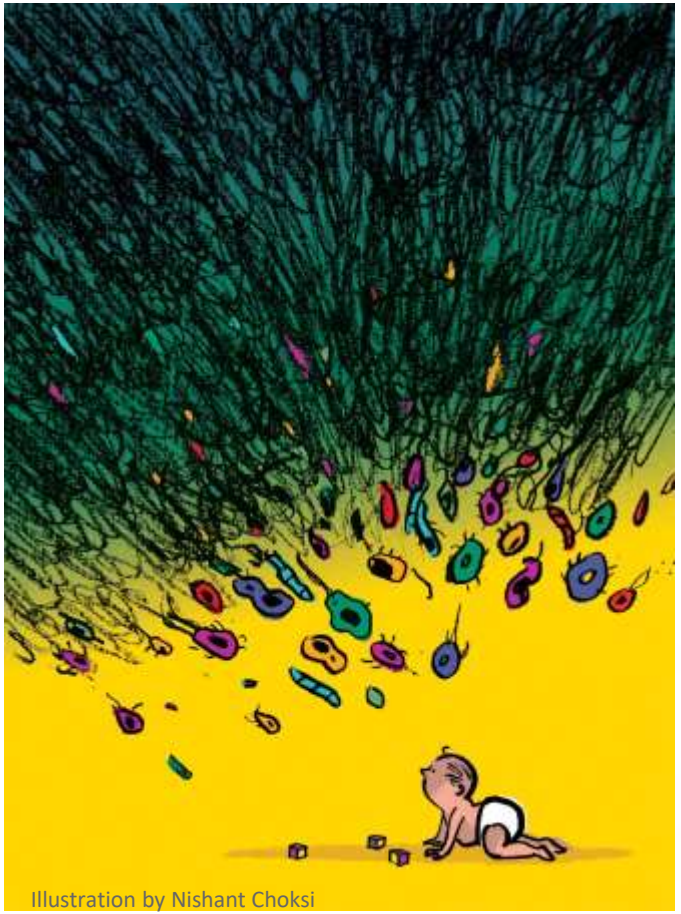


Illustration by Nishant Choksi

Laxminarayan R. Antimicrob Steward Healthc Epidemiol. 2023;3(1):e204.
Srinivasan A. Cleve Clin J Med. 2017;84(9):673-679

Group Question

Shorter courses of antibiotics for common infectious diseases are associated with which of the following?

a) Increased adverse events
b) Increased risk of antibiotic resistance
c) Decreased cure rates
d) Decreased risk of antibiotic resistance

Historically

~~"Always complete the full prescription, even if you feel better, because stopping treatment early could promote treatment failure and the growth of drug-resistant bacteria"~~

GET SMART
Know When Antibiotics Work
www.cdc.gov/getsmart

CDC circa 2000s

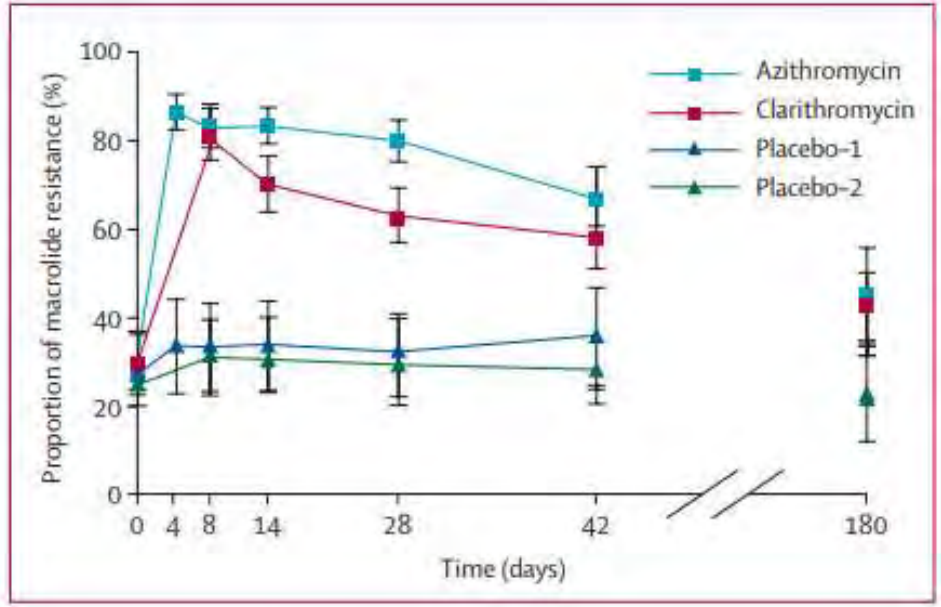
**While this is good advice when one wants to promote adherence and ensure patients take an adequate course to "maximally cure" an infection, it is poor advice for preventing resistance and adverse events.*

Llewelyn MJ. BMJ. 2017 Jul 26;358:j3418.
Rice LB. Clin Infect Dis. 2008 Feb 15;46(4):491-6

In Reality

Just 4 days of antibiotic therapy was enough to drive a **3-fold** increase in macrolide resistant *S. pneumoniae* in throat swabs

Changes in macrolide-resistant S. pneumoniae while on macrolides compared to placebo



Malhotra-Kumar S. Lancet. 2007 Feb 10;369(9560):482-90

What About Duration?

So, we know even a short duration of therapy is enough to create resistance, then why care about longer durations if resistance is going to happen regardless?

- Its complicated…antibiotics have broad effects; resistance is multifactorial and differs in complexity based on the pathogen and drug involved.

- Generally, longer durations have been shown to increase selective pressure and the prevalence of resistance.

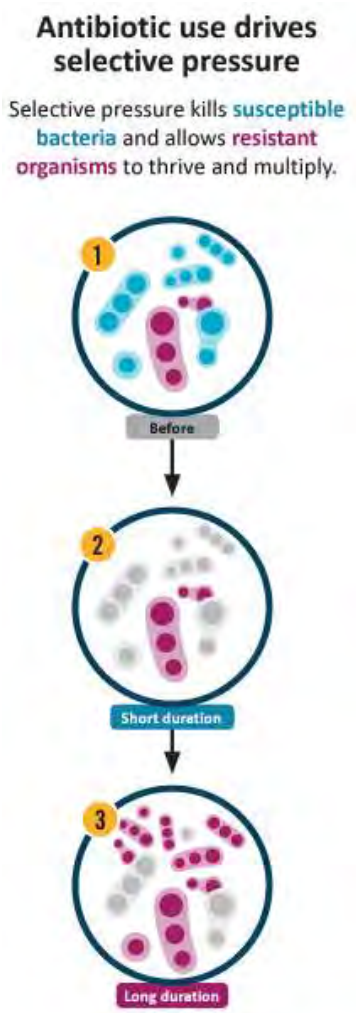


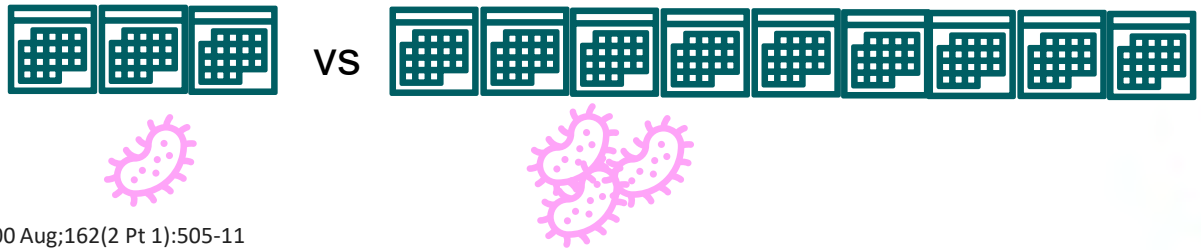
Image from: https://www.publichealthontario.ca/en/Health-Topics/Antimicrobial-Stewardship/Long-Term-Care
Rice LB. Clin Infect Dis. 2008 Feb 15;46(4):491-6
https://www.contagionlive.com/view/about-antibiotics-complete-the-course-or-stop-when-you-feel-better

Longer Durations = More Resistance

Ventilator and Hospital associated Pneumonia (VAP/HAP) antibiotics increased resistance **15%** (3 days) -> **35%** (10+ days) with no difference in mortality or length of ICU stay

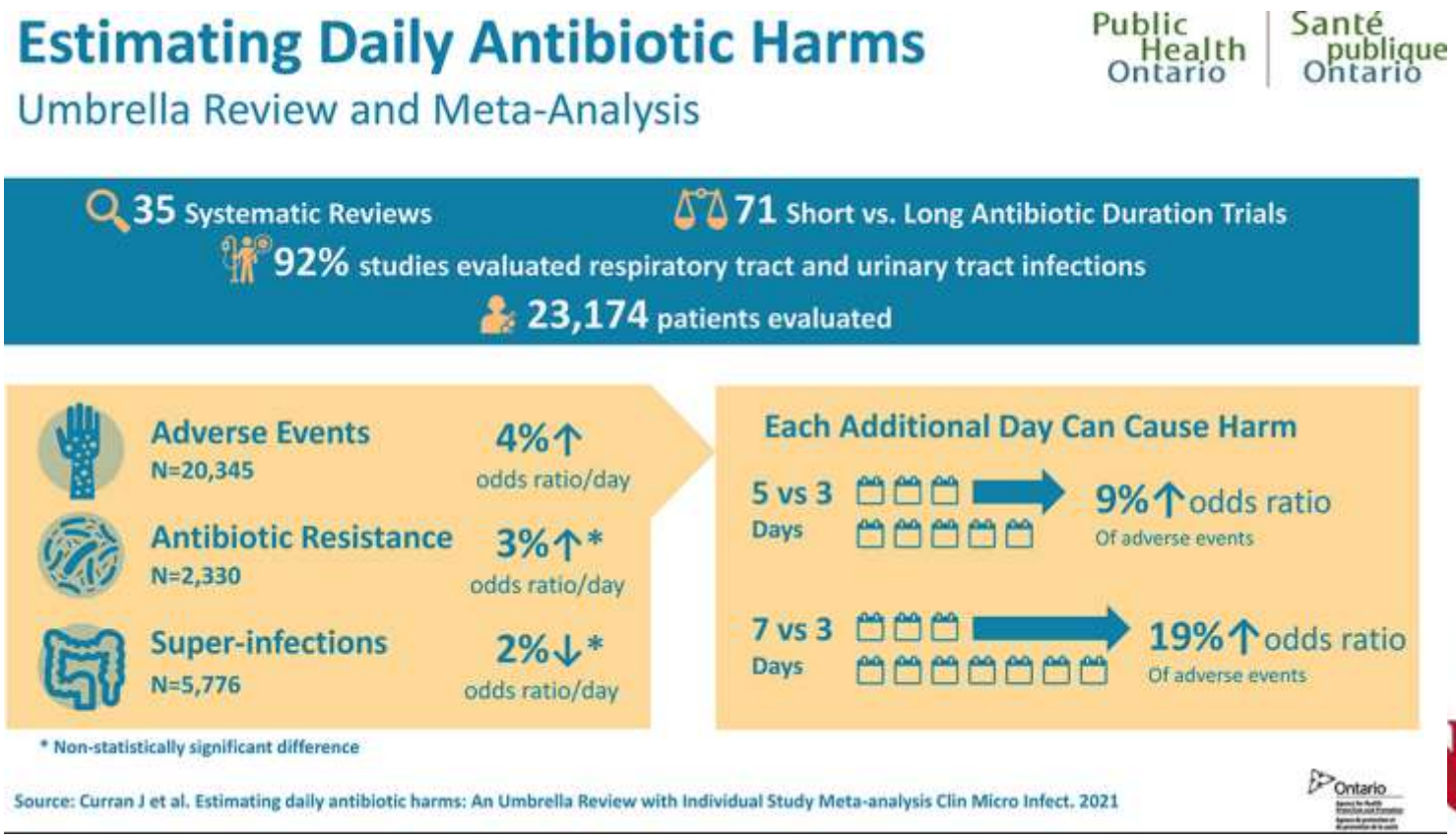
Ventilator associated pneumonia (VAP) antibiotics increased MDRO carriage **42.1%** (8 days) → **62%** (15 days) with equal cure

High-dosed amoxicillin nasopharyngeal PCN-resistant *S. pneumoniae* carriage increased **24%** (5 days) → **32%** (10 days)



Singh N. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):505-11
Chastre J. JAMA. 2003 Nov 19;290(19):2588-98.
Schrag SJ. JAMA. 2001 Jul 4;286(1):49-56.

Longer Durations = More Side Effects



Curran J. *Clin Microbiol Infect*. 2022;28(4)

The History of Durations

1940s Early CAP duration studies

"in general, the results were satisfactory with penicillin dosed 1.5-2 days"

"Most were treated for 3-4 days"

1950s-1990s Antibiotic Golden Era of Use & Abuse

FDA Director of Abx involved in large scandal w/ Pharma promoting abx

Industry promoted heavy use – minimal to no evidence for durations of therapy

1990s-2000s Guidelines question durations

"We are not aware of any controlled trials that have specifically addressed how long PNA should be treated"

"1 day appears to be equally effective to 3 days for traveler's diarrhea"

Meningitis… 7-21 days "duration based more on tradition than evidence"

2008 IDSA Conference on AMR

"The most reasonable strategy is to stop irritating the bacteria…reduce our use of abx to the bare minimum to safely treat patients in the hope that this will reduce selective pressure and thereby reduce resistance" – Dr. Rice

2000-Present 20+ years of duration studies

>120 RCTs to suggest short durations for UTI, GNR BSI, CAP, VAP, SSTI, OM, SA, sinusitis, NF, malaria, etc

Slide adapted from Kellie Wark, MD

Rice LB. Clin Infect Dis. 2008 Feb 15;46(4):491-6

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Short-course Antibiotic Therapy—Replacing Constantine Units With "Shorter Is Better"

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

courses [2]. And the modern week has 7 days in it because the Roman Emperor Constantine the Great said so in 321 CE [2]. Had Constantine chosen a 4-day week, providers would likely routinely prescribe 4- to 8-day courses of therapy.

*"I understood why I needed to complete the full course, what I didn't understand was why a full course took precisely **7 days**. Why not six, eight or nine and a half? Did the number seven correspond to some biological fact about the human digestive tract or the life cycle of bacteria?"*

https://blogs.jwatch.org/hiv-id-observations/index.php/how-to-figure-out-the-length-of-antibiotic-therapy/2010/10/22/
Wald-Dickler N. Clin Infect Dis. 2019 Oct 15;69(9):1476-1479.
Spellberg B. Clin Microbiol Infect. 2023 Feb;29(2):141-142

The Shorter is Better Mantra

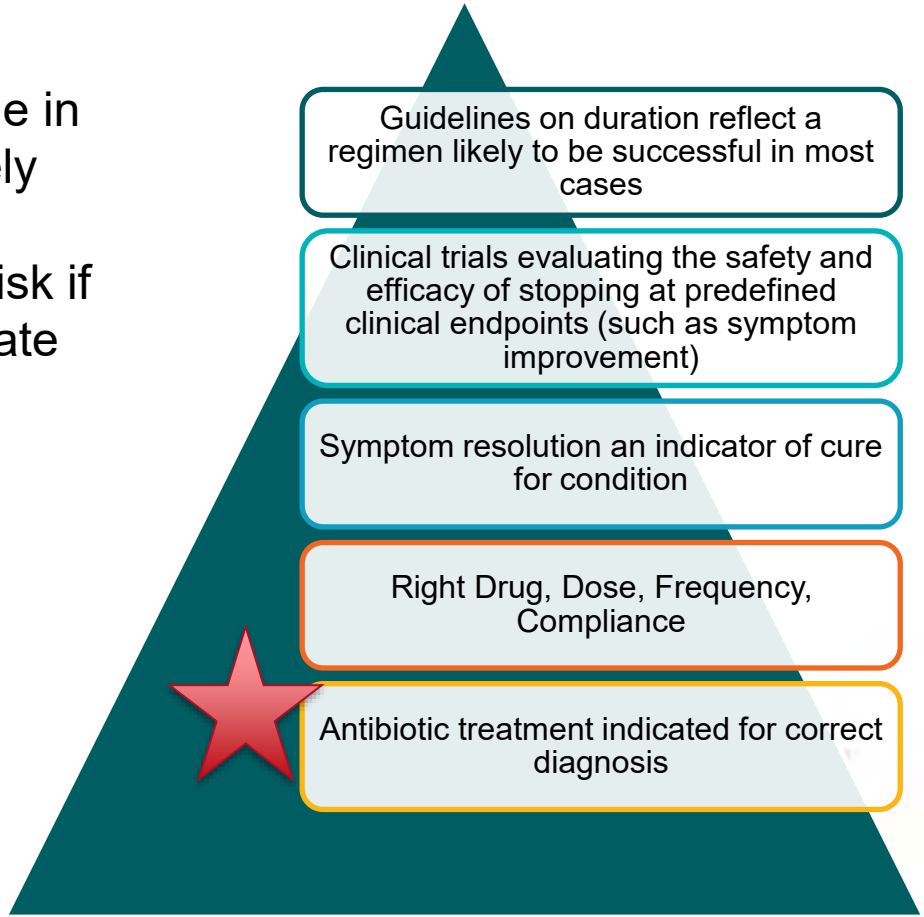
From Fear of Undertreatment to Harm from Overtreatment

- Modern trials are needed to challenge historical dogma, establishing **a new standard of care** for durations of antimicrobial therapy
  - "We're looking for that Goldilocks amount and duration of antibiotics that treats the infection but does not overtreat it so that we can avoid side effects and changes to the healthy germs that are there"- Buddy Creech, MD

https://pids.org/2023/02/08/in-the-news-shorter-is-better-mantra-begins-to-change-antibiotic-prescribing/
https://www.bmj.com/content/358/bmj.j3418

Can You Stop When You Feel Better?

- “There is no risk, and every advantage in stopping antibiotic therapy immediately after a bacterial infection has been excluded or is unlikely; and minimal risk if signs and symptoms of a mild/moderate infection have improved or resolved”



https://bpac.org.nz/bpj/2015/june/symptoms.aspx#:~:text=Traditionally%2C%20clinicians%20and%20health%20authorities,the%20development%20of%20antibiotic%20resistance

Criticisms

- "Response to therapy is likely to depend on a range of host-, pathogen-, and drug-specific factors. Prospective trial-based set durations, even if reassuringly short, oversimplify real-world data…"

- "…clinicians should appreciate the sometimes-limited inclusion criteria when incorporating clinical trial data into their practice…"

"We are not advocating for fixed short durations for all, but for a cultural change away from arbitrarily long fixed durations, utilizing the **best available evidence to offer individualized patient care**"

JOURNAL ARTICLE

Short-course Antibiotic Therapy: A Bespoke Approach Is Required FREE

Stephen Hughes ✉, Pegah Kamranpour, Malick M Gibani, Nabeela Mughal, Luke S P Moore

Clinical Infectious Diseases, Volume 70, Issue 8, 15 April 2020, Pages 1793–1794, https://doi.org/10.1093/cid/ciz711

Published: 17 September 2019 **Article history** ▾

JOURNAL ARTICLE

Reply to Hughes et al FREE

Cesar I Fernandez-Lazaro, Bradley J Langford, Kevin L Schwartz ✉

Clinical Infectious Diseases, Volume 70, Issue 8, 15 April 2020, Pages 1795–1796, https://doi.org/10.1093/cid/ciz713

Published: 17 September 2019 **Article history** ▾

JOURNAL ARTICLE

Reply to Hughes et al FREE

Brad Spellberg ✉, Noah Wald-Dickler

Clinical Infectious Diseases, Volume 70, Issue 8, 15 April 2020, Pages 1794–1795, https://doi.org/10.1093/cid/ciz712

Published: 17 September 2019 **Article history** ▾

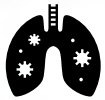
Cesar I Fernandez-Lazaro. *Clinical Infectious Diseases*, Volume 70, Issue 8, 15 April 2020, Pages 1795–1796
Brad Spellberg. *Clinical Infectious Diseases*, Volume 70, Issue 8, 15 April 2020, Pages 1794–1795
Stephen Hughes. *Clinical Infectious Diseases*, Volume 70, Issue 8, 15 April 2020, Pages 1793–1794

Common Shorter is Better Conditions

Table. Summary of the ACP Best Practice Advice on Appropriate Use of Short-Course Antibiotics in Common Infections

Condition	Patient Population	Available Guidelines and Evidence*	Best Practice Advice
Acute bronchitis	Adults with COPD	GOLD guideline (18) Meta-analysis of 21 studies comparing ≤5 vs. >5 days (19)	Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).
Community-acquired pneumonia	All adults who are not immunocompromised†	IDSA/ATS guideline (20)	Clinicians should prescribe antibiotics for community-acquired pneumonia for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.
Urinary tract infection: uncomplicated bacterial cystitis	Nonpregnant adult women†	IDSA/ESCMID guideline (21)	In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, TMP-SMZ for 3 days, or fosfomycin as a single dose.
Urinary tract infection: uncomplicated pyelonephritis	Nonpregnant adults†	IDSA/ESCMID guideline (21) Recent systematic review (22) 3 recent RCTs (23-25)	In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP-SMZ (14 days) based on antibiotic susceptibility.
Nonpurulent cellulitis	All adults	IDSA guideline (26) NICE guideline (27) 1 recent RCT (28)	In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.

≤ 5 days for AECOPD



≤ 5 days for CAP

3-5 days for UTI

5-14 for pyleo days based on abx

5-6 days for cellulitis

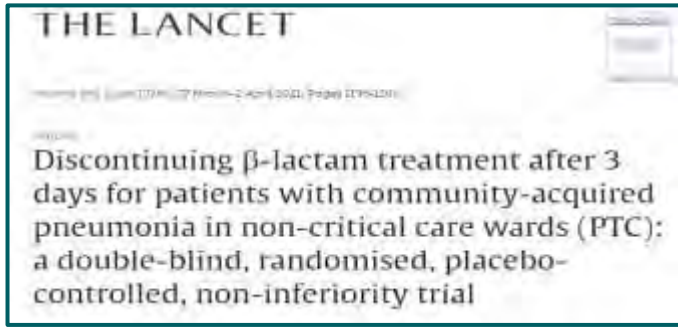
Lee RA. *Ann Intern Med*. 2021;174(6):822-827.

Shorter is Better: CAP

Adults + Pediatrics

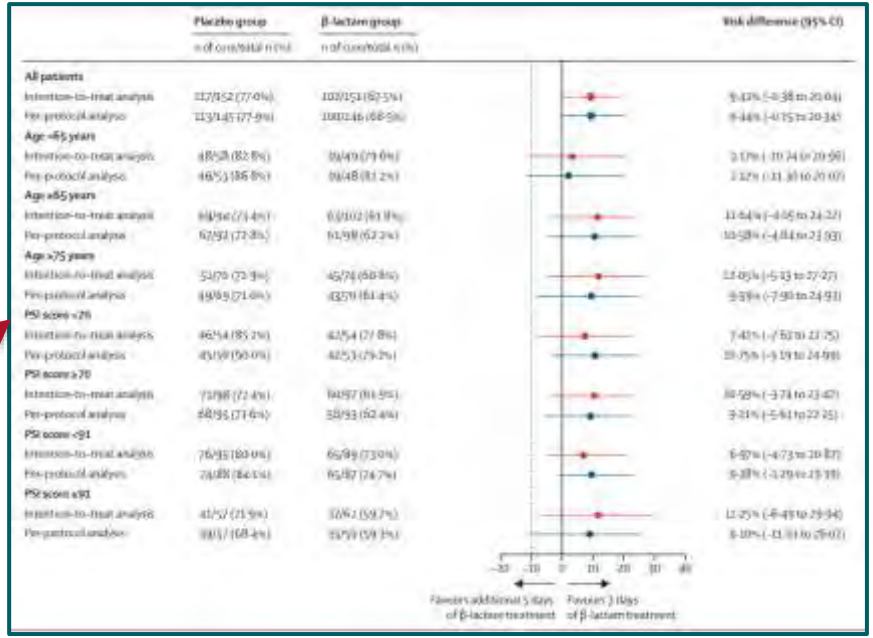
- 14 randomized controlled trials including >8000 patients
- 3-5 days (short) noninferior to 5-14 days (long) of treatment

3 days non-inferior to 5 days in adult patients who met clinical stability criteria by day 3 (afebrile, sx improved)) across severity groups


THE LANCET

Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial

Primary outcome of cure at day 15



Source: https://www.bradspellberg.com/shorter-is-better
Dinh A, Lancet. 2021 Mar 27;397(10280):1195-1203.

Shorter is Better: UTI

Adults + Pediatrics

- 11 randomized controlled trials of >2600 patients
- Complicated UTI: 5-7 days antibiotics non-inferior to 10-14 days
- Pyelonephritis: 5-7 days non-inferior to 10-14 days

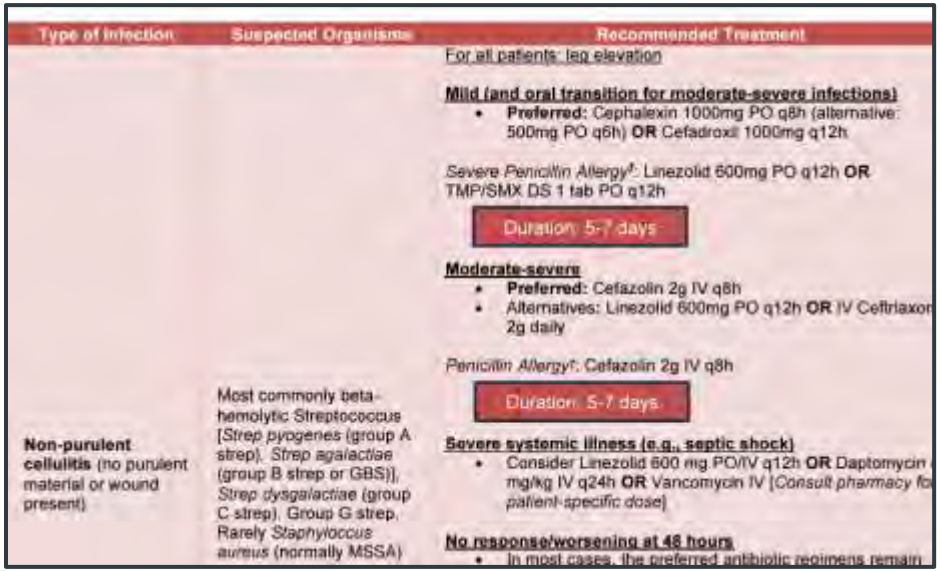
Source: https://www.bradspellberg.com/shorter-is-better

Elajouz B, *Antimicrob Steward Healthc Epidemiol*. 2022;2(1):e171. Published 2022 Oct 21.
Goodlet KJ. Antimicrob Agents Chemother. 2018 Dec 21;63(1):e02165-18..

Shorter is Better: SSTI

Adults

- Four randomized controlled trials of >1400 patients
  - 1 maybe not non-inferior (DANCE, but had several limitations)
- Generally, 5-6 days antibiotics non-inferior to 10 days for cellulitis



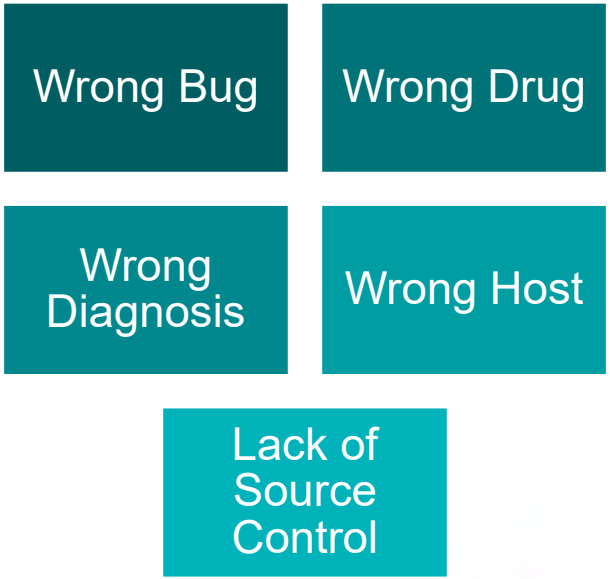
Type of Infection	Suspected Organisms	Recommended Treatment
Non-purulent cellulitis (no purulent material or wound present)	Most commonly beta-hemolytic Streptococcus [*Strep pyogenes* (group A strep), *Strep agalactiae* (group B strep or GBS)], *Strep dysgalactiae* (group C strep), Group G strep. Rarely *Staphylococcus aureus* (normally MSSA)	For all patients: leg elevation **Mild (and oral transition for moderate-severe infections)** • **Preferred:** Cephalexin 1000mg PO q8h (alternative: 500mg PO q6h) **OR** Cefadroxil 1000mg q12h *Severe Penicillin Allergy*[†]: Linezolid 600mg PO q12h **OR** TMP/SMX DS 1 tab PO q12h Duration: 5-7 days **Moderate-severe** • **Preferred:** Cefazolin 2g IV q8h • Alternatives: Linezolid 600mg PO q12h **OR** IV Ceftriaxon 2g daily *Penicillin Allergy*[†]: Cefazolin 2g IV q8h Duration: 5-7 days **Severe systemic illness (e.g., septic shock)** • Consider Linezolid 600 mg PO/IV q12h **OR** Daptomycin mg/kg IV q24h **OR** Vancomycin IV [*Consult pharmacy fo patient-specific dose*] **No response/worsening at 48 hours** • In most cases, the preferred antibiotic regimens remain

https://www.bradspellberg.com/shorter-is-better
https://shea-online.org/the-new-antibiotic-mantra-shorter-is-better-but-is-longer-better-for-cellulitis/
https://www.unmc.edu/intmed/_documents/id/asp/clinicpath-ssti.pdf

Lack of Clinical Improvement with Appropriate Duration?

Reassess

- Initial therapy not active against isolated pathogen or dose/frequency of drug is insufficient
- Wrong diagnosis (e.g. – CHF exacerbation/pulm edema vs CAP)
- Lack of source control:
  - CAP - extrapulmonary infection, empyema/lung abscess, large pleural effusion
  - UTI – infected stones, perinephric abscess, altered anatomy/obstruction, bacteremia
  - SSTI – undrained abscess, wrong drug (dose)/bug



JAMA Internal Medicine | Original Investigation

Inappropriate Diagnosis of Pneumonia Among Hospitalized Adults

Ashwin B. Gupta, MD; Scott A. Flanders, MD; Lindsay A. Petty, MD; Tejal N. Gandhi, MD; Michael S. Pulia, MD, PhD; Jennifer K. Horowitz, MA; David Ratz, MS; Steven J. Bernstein, MD, MPH; Anurag N. Malani, MD; Payal K. Patel, MD, MPH; Timothy P. Hofer, MD, MSc; Tanima Basu, MA, MS; Vineet Chopra, MD, MSc; Valerie M. Vaughn, MD, MSc

~1 in 8 w/ inappropriate dx (most received full course of abx and had associated AEs)

Original Investigation | Infectious Diseases

March 13, 2024

Bacteremia From a Presumed Urinary Source in Hospitalized Adults With Asymptomatic Bacteriuria

Sonali D. Advani, MBBS, MPH[1]; David Ratz, MS[2]; Jennifer K. Horowitz, MA[3]; et al

~7 in 10 with ASB received abx (<2% risk of bacteremia)

CrossMark

TOP 10 MYTHS REGARDING THE DIAGNOSIS AND TREATMENT OF CELLULITIS

Erin K. McCreary, PHARMD, BCPS,* Melissa E. Heim, PHARMD, BCCCP,† Lucas T. Schulz, PHARMD, BCPS (AQ-ID),* Robert Hoffman, MD,‡ Jeffrey Pothof, MD,§ and Barry Fox, MD||

~40% of cellulitis is misdiagnosed

"The debate around stopping antibiotics early is basically about ensuring that antibiotics are started appropriately in the first place"

https://bpac.org.nz/bpj/2015/june/symptoms.aspx#:~:text=Traditionally%2C%20clinicians%20and%20health%20authorities,the%20development%20of%20antibiotic%20resistance

When Longer Durations are Needed

- There are situations when stopping with resolution of symptoms is not appropriate, such as when eradication of the bacteria is the aim
  - Note that curing an infection does not always mean microbiological eradication for common conditions

- Early stopping of treatment in these conditions can increase the risk of relapse and poor outcomes
  - Deep seated infections (endocarditis, osteomyelitis)
  - Infections with certain invasive organisms – e.g. *S. aureus*
  - Complex, difficult to treat infections – mycobacterial, fungal, etc.
  - Critical illness with complex etiology
  - Infections with insufficient source control

Often requires discussion between the prescriber and patient for tailored approach and plan to care

Stewardship Initiatives to Improve Durations

- The most effective interventions in changing antibiotic prescribing behavior are multifaceted!
  - EHR
  - Audit and Feedback
  - **Guidelines** and incorporation into clinical decision support

Guidelines, Care Standards, and Expected Practices

- Help shift the sense of medical/legal responsibility from the provider to the institution and provide psychological reassurance when standards change
- Help serve as the backbone for many other interventions:
  - Education
  - Prospective audit and feedback interactions
  - Clinical decision support systems (checklists)


Editorial ONLINE FIRST

April 19, 2024

Harnessing the Electronic Health Record to Improve Empiric Antibiotic Prescribing

Having and adhering to guidelines is also a regulatory requirement!

Yadav K. Open Forum Infect Dis. 2018 Dec 3;6(1):ofy319.
https://www.cms.gov/files/document/qso-22-20-hospitals.pdf
Malani AN, *JAMA.* Published online April 19, 2024.

Incorporate Shorter is Better into Local Guidelines

IDSA
Infectious Diseases Society of America

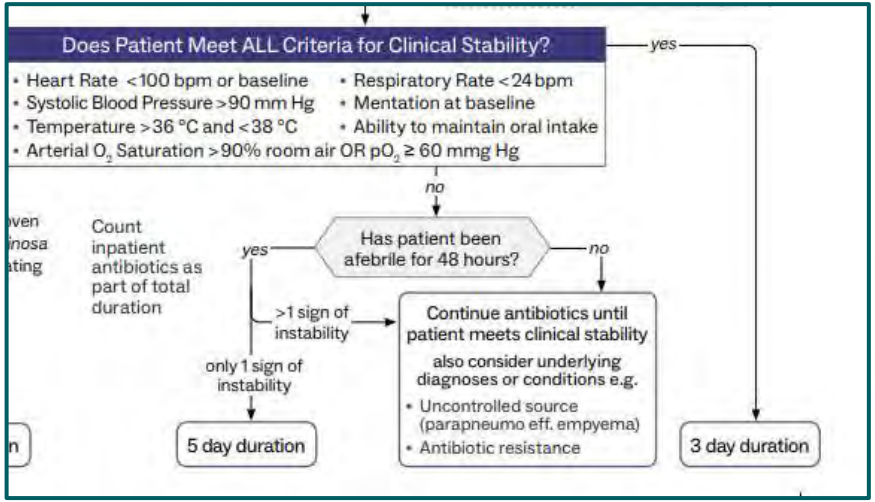
CAP CLINICAL PATHWAY

Treatment Considerations	Assess for adverse drug events
	Assess for clinical stability; patient afebrile with at least 5 signs of CAP stability criteria listed above or return to baseline
	Assess for ability to tolerate oral therapy, oral de-escalation options: • No MDRO risk factors (choose one): – Amoxicillin (500mg) + clavulanate (125mg) PO TID, or Amoxicillin (875 mg or 2000mg) + clavulanate (125mg) PO BID – Cefpodoxime 200mg PO BID – Cefuroxime 500mg PO BID • MDRO Risk Factors: – Levofloxacin 750mg PO q24h – If Legionella-negative or alternative etiology identified, discontinue azithromycin after 1500mg total
Discharge Considerations	Consider duration of antibiotics administered: (no more than 3-5 days total in the ED and inpatient) if clinically stable by day 3.[4]
	Ensure post-discharge follow-up including insurance coverage and availability at outpatient pharmacy
	Consider vaccination (pneumococcal, influenza, COVID-19, and RSV in eligible populations)). If relevant, provide smoking cessation counselling/medications and ensure patient is on proper therapy to enhance control of chronic conditions (e.g., COPD, CHF)
	Educate patients and caregivers[7]: • Planned antibiotic course (if needed) and instructions for follow-up medical care • Signs and symptoms of worsening infection, and sepsis • Signs and symptoms of antibiotic-associated adverse events, including *Clostridioides difficile* infection

Care Process Model MARCH 2024

Diagnosis and Management of
Community-Acquired Pneumonia in Adults 2024 Update
Intermountain Canyons and Desert Regions

This evidence-based Care Process Model has been developed by a multidisciplinary team at Intermountain Health consisting of representatives from Pulmonary, Infectious Disease, and Antibiotic Stewardship. Based on national guidelines, it can serve to guide Emergency Departments and Clinics in diagnosis, risk assessment, and treatment of community-acquired pneumonia in adults.



https://intermountainhealthcare.org/ckr-ext/Dcmnt?ncid=520102603
https://www.idsociety.org/practice-guideline/community-acquired-pneumonia-cap-in-adults/#References
https://www.unmc.edu/intmed/_documents/id/asp/clinicpath-cap-guidance-2020-revision-final-updated.pdf

UTI Guidelines – Amb Care Focused

Recommendations for Management of Uncomplicated UTI

First-line agents:
• Nitrofurantoin monohydrate/microcrystal 100mg BID **x 5 days** o Do not use if CrCL <30
Second-line agents (in order of preference):
• Trimethoprim-sulfamethoxazole 160/800mg (one DS tablet) BID **x 3 days** **OR** • Cephalexin 500mg BID **x 5-7 days** **OR** • Fosfomycin tromethamine 3g x **single dose**

Recommended Regimens for Management of Complicated UTI

First-line agents:
• Levofloxacin* 750mg daily **x 5-7 days** **OR** • Trimethoprim/sulfamethoxazole 160/800mg (one DS tablet) BID **x 7 days**
Second-line agents:
• Amoxicillin-clavulanate 875/125mg BID **x 7 days PLUS** Ceftriaxone 1g IM **x 1 dose**
Most cUTI will be managed inpatient; stable patients can be managed outpatient. Empiric therapy should be guided by recent treatment and urine culture data if available. If fluroquinolone prescribed in last 12 months, or history of resistance use an alternative agent until culture available. Adjust therapy as needed based on urine culture results. *Ciprofloxacin 500mg BID is an alternative

https://www.unmc.edu/intmed/_documents/id/asp/clinicpath-nm-uti-executive-summary_final.pdf

Group Question

Shorter courses of antibiotics for common infectious diseases are associated with which of the following?

a) Increased adverse events
b) Increased risk of antibiotic resistance
c) Decreased cure rates
d) Decreased risk of antibiotic resistance

Group Question

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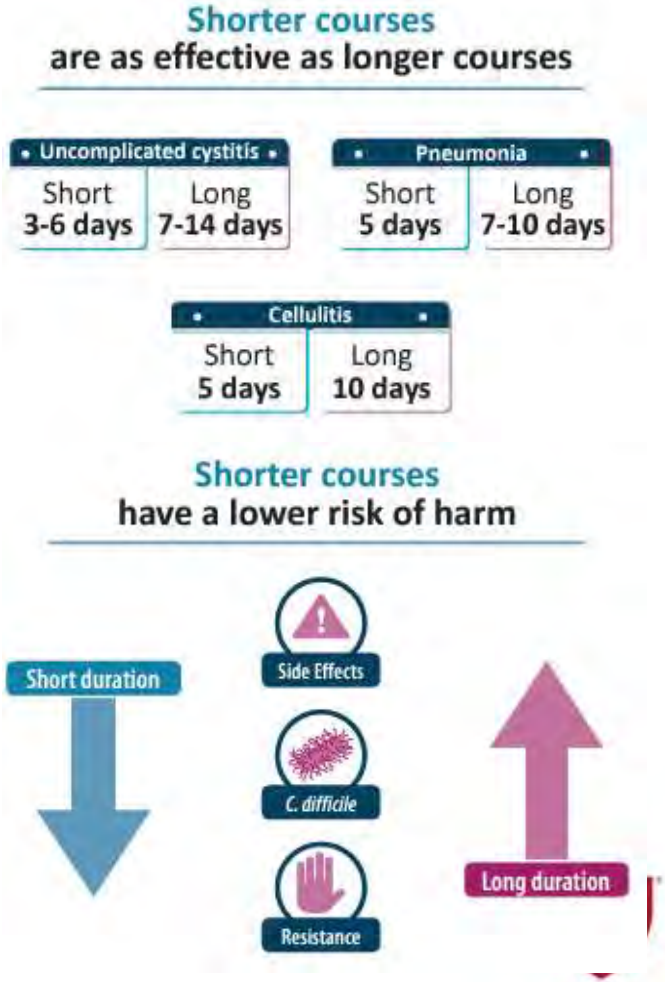
Conclusions

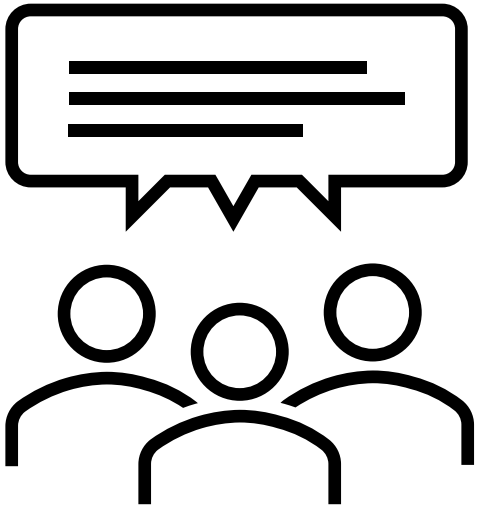
- For common bacterial infections, no evidence exists that stopping antibiotic treatment early increases risk of resistant infection

- One of the most impactful stewardship interventions that we can make is shortening (or in some cases stopping) antibiotic therapy, when appropriate, based on modern trials, to decrease the risk of resistance and harm from antibiotic associated adverse events



https://www.publichealthontario.ca/en/Health-Topics/Antimicrobial-Stewardship/Long-Term-Care

Questions/Comments



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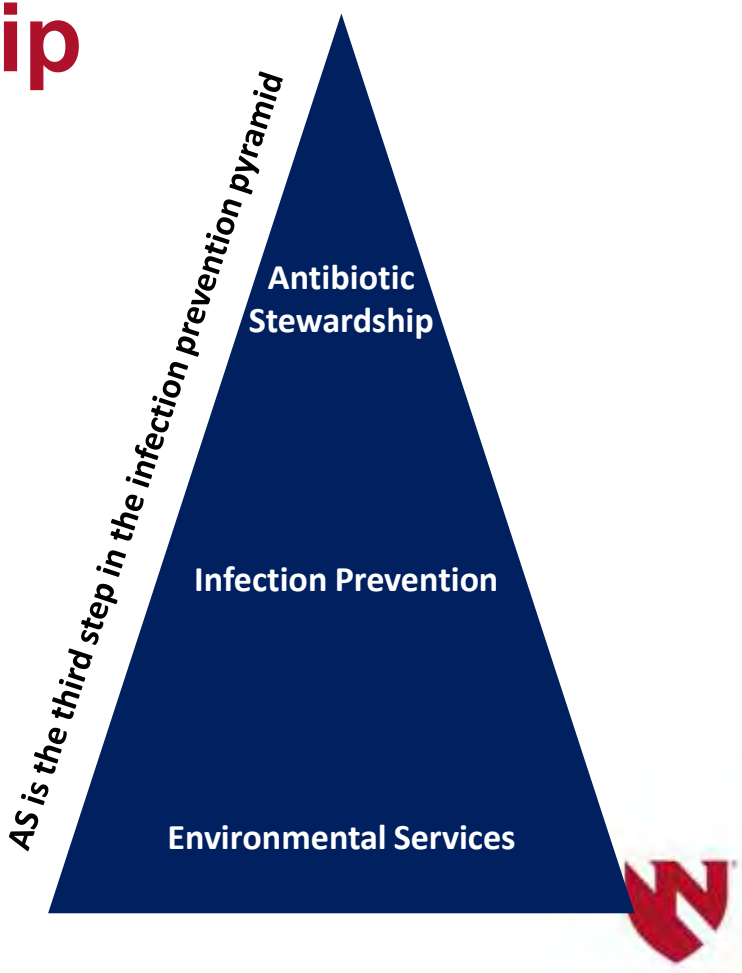
University of Nebraska Medical Center

Nebraska Medicine

Antibiotic Stewardship

- Improve the culture of safety
- Provide tools and support for frontline staff
- Strive to reduce preventable harm by identifying problems that cause harm to patients
  - Problems can be behavioral, technical, or both



The Dogma

OCTOBER 22ND, 2010

How to Figure Out the Length of Antibiotic Therapy

One thing we ID doctors know — that other clinicians simply don't — is how long to treat a patient with antibiotics.

I was reminded of this special power by these recent events:

- An excellent fellow from the hospital's Critical Care program rotated through our division recently. When asked about what she wanted learn from the elective, the first thing she said was figuring out — finally — how long an antibiotic course should be.

"In this highly data-driven exercise, it is important also to note the number of rules — seven, as in days of the week.

That did not occur by chance." – Paul Sax, MD – 2010

1. Choose a multiple of 5 (fingers of the hand) or 7 (days of the week).

2. Is it an outpatient problem that is relatively mild? If so, choose something less than 10 days. After application of our multiples rule, this should be 5 or 7 days.

3. Is it *really* mild, so much so that antibiotics probably aren't needed at all but clinician or patient are insistent? Break the 5/7 rule and go with 3 days. Ditto uncomplicated cystitis in young women.

4. Is it a serious problem that occurs in the hospital or could end up leading to hospitalization? With the exception of community-acquired pneumonia (5 or 7 days), 10 days is the minimum.

5. Patient not doing better at the end of some course of therapy? Extend treatment, again using a multiple of 5 or 7 days.

6. Does the infection involve a bone or a heart valve? Four weeks (28 days) at least, often 6 weeks (42 days). Note that 5 weeks (35 days) is not an option — here the 5's and 7's cancel each other out, and chaos ensues.

7. The following lengths of therapy are inherently weird, and should generally be avoided: 2, 4, 6, 8, 9, 11, 12, 13 days. Also, 3.14159265 days.

https://blogs.jwatch.org/hiv-id-observations/index.php/how-to-figure-out-the-length-of-antibiotic-therapy/2010/10/22

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The Shorter Is Better movement: past, present, future

Brad Spellberg • Louis B. Rice

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The fundamental principles of Shorter Is Better:

1) 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.
2) 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.
3) 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.
4) 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.