# Shorter is (generally) better!

## - Updates on Duration guidelines for common pediatric infections

BCPS Children's Health Today Conference

November 8th 2024

Alastair McAlpine

## Conflicts of Interest

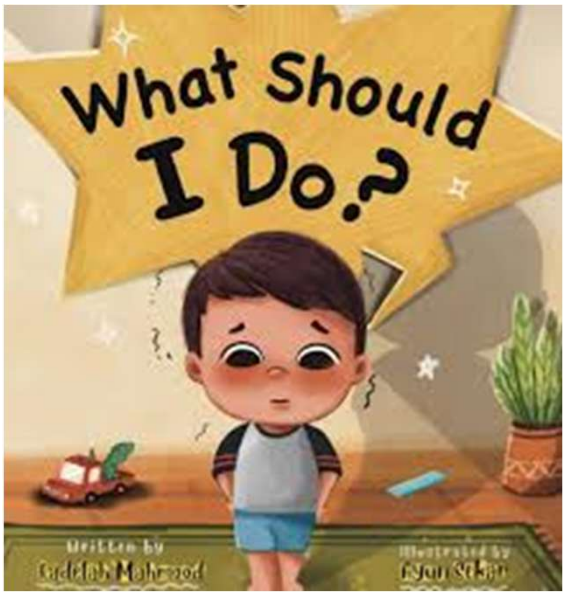
- None to declare

## Contents

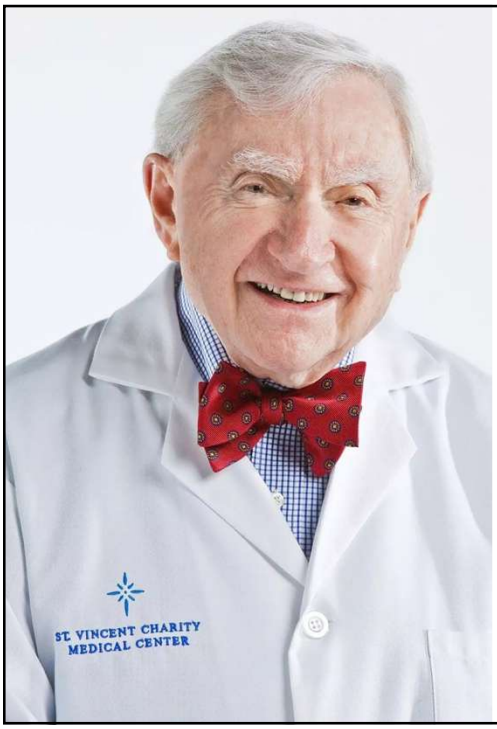
- Why should we care?
- History of antibiotic duration data
- IV vs PO
- Recommended durations
- Conclusion

# Rationale

- One of those most frequent questions for ID Team: “How long do we treat [X] for?”
- Evidence is frequently changing and none of us is fully up to date
- We all have our personal biases




# Why do some recommendations come from?




# Where do “old” guidelines come from?

## The times have changed!

| Myth | Truth |
| --- | --- |
| I can stop taking antibiotics when I start to feel better | If you are given an antibiotic you must finish the course. If you don't, you may increase your risk of developing drug-resistant bacteria. This means that antibiotics may not work for you when you really need them. |

HSC Public Health Agency

## Challenges

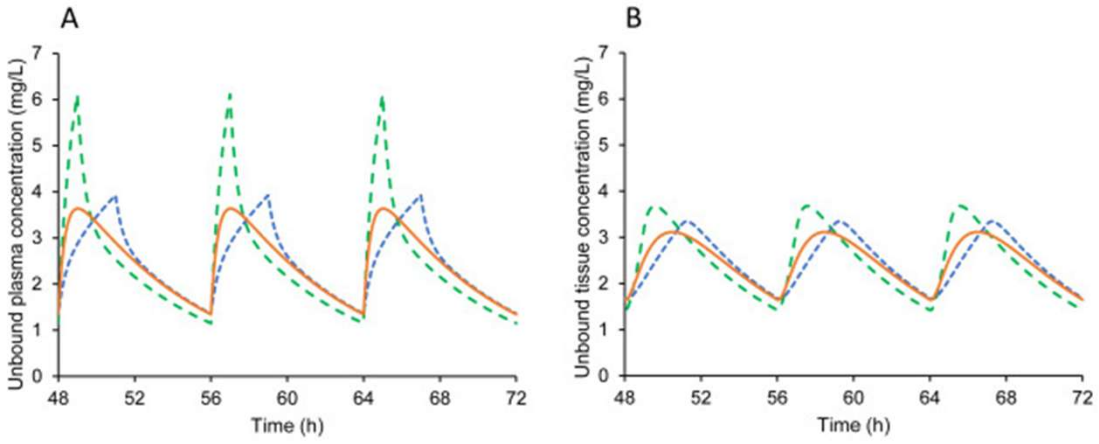
- Many “old” guidelines based on extremely weak (or no!) evidence
- From an era when antimicrobial resistance was not considered a major threat.
- Often cover “just in case.”
- Very difficult to overturn
  - The people want RCTs!

## Are IV antibiotics better than PO

# Is IV superior to oral?

- Early oral antibiotics were acid unstable or poorly absorbed
- Led to anecdotal reports of treatment failure on oral therapy
- Despite newer antimicrobials with better absorption, dogma persists.

## Different antibiotics at steady-state




Landersdorfer, Clin Micro, 2023

## When is IV appropriate?

- Life-threatening conditions when you need rapid concentrations in the blood (sepsis, meningitis, etc.)
- Early serious infections when you need rapid concentrations (bacteremia, endocarditis, etc.)
- Any concerns about GI absorption (Poor perfusion, diarrhea, vomiting, short gut, etc.)
- No PO option available (aminoglycosides, glycopeptides)

## Unnecessary antibiotic use – Short term

- Hospitalizing children is traumatic and harmful – particularly for >7d
  - Impacts on ECD
  - >20% have emotional disturbances lasting 6m
  - Boring AND traumatic
- Increased risk of *C. difficile* colitis
- Increase risk of allergic reaction
- Pain and trauma of IV therapy
- Social cost on families of long hospital stays for IV therapy

## Unnecessary antibiotic use - Long term

- Increased allergies in childhood (Zven, JAMA, 2019)
- Microbiome disruption - ?Effects (McDonnell, Gut Microbes, 2021)
- Associations with early childhood obesity (Ye, Nature, 2024)
- Associations with cognitive impairment (Liu, Front. Neuro, 2022)
- Associations with juvenile idiopathic arthritis (Duong, J Infect, 2022)
- Etc etc

## Cost

- England: excess duration - 1.3 million days of excess antimicrobial use
- US: In hospitalized patients 1/3 of unnecessary antibiotics were due to unnecessarily prolonged durations
- Observational study of patients with pneumonia: two thirds of patients had excess durations, with 93.2% of the excess being in the form of discharge antibiotics
- **Each excess day** associated with a 5% increase of patient having an antibiotic-associated adverse event

# Antimicrobial Resistance


- Recognized by WHO as one of the Top 10 threats to human health
- Responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths
- AMR puts many of the gains of modern medicine at risk.

# General trends: Shorter is better

- Antibiotic resistance one of the greatest threats to medicine and humans
- More antibiotics = more resistance
- If we want less resistance: we NEED to reduce antibiotic use
- Longer is NOT better:
  - multiple studies show: increased adverse events, increased antibiotic resistance, longer hospital stays and cost, worse outcomes.
- Using the optimal duration is best for patients, hospital, society

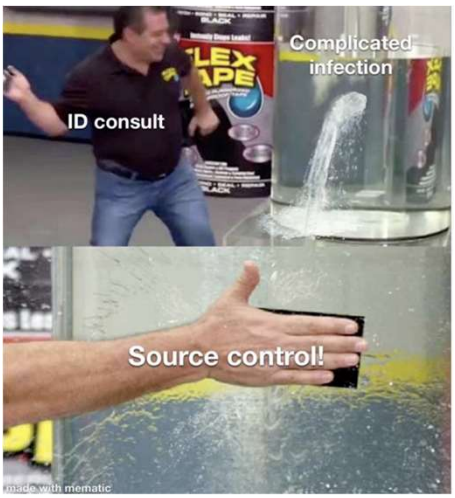
## Shorter Is Better

| Diagnosis | Short (d) | Long (d) | Result | #RCT |
|---|---|---|---|---|
| CAP | 3-5 | 5-14 | Equal | 14 |
| Atypical CAP | 1 | 3 | Equal | 1 |
| Possible PNA in ICU | 3 | 14-21 | Equal | 1* |
| VAP | 8 | 15 | Equal | 2 |
| cUTI/Pyelonephritis | 5 or 7 | 10 or 14 | Equal | 9** |
| Intra-abd Infection | 4 | 10 | Equal | 2 |
| Complex Appendicitis | 2 | 5 | Equal | 1 |
| GNB Bacteremia | 7 | 14 | Equal | 3† |
| Cellulitis/Wound/Abscess | 5-6 | 10 | Equal | 4‡ |
| Osteomyelitis | 42 | 84 | Equal | 2 |
| Osteo Removed Implant | 28 | 42 | Equal | 1 |
| Debrided Diabetic Osteo | 10-21 | 42-90 | Equal | 2φ |
| Septic Arthritis | 14 | 28 | Equal | 1 |
| AECB & Sinusitis | ≤5 | ≥7 | Equal | >25 |
| Neutropenic Fever | AFx72h/3 d | +ANC>500/9 d | Equal | 2 |
| Post Op Prophylaxis | 0-1 | 1-5 | Equal | 55Ψ |
| Erythema Migrans (Lyme) | 7 | 14 | Equal | 1 |
| *P. vivax* Malaria | 7 | 14 | Equal | 1 |
| Total: 18 Conditions | | | | >125 RCTs |

*Infiltrate on CXR but low CPIS score (≤6), both ventilated and non ventilated, likely CAP, HAP, and VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; φall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

## Caveats

- These are guidelines, NOT protocols
- Clinician discretion takes precedence at all times
- ONLY applies to immune-competent children, with normal anatomy, in whom the clinical course is progressing as expected
- PO switch assumes they can tolerate and absorb PO meds
- Does NOT replace the need for an ID consult when needed
- Does NOT specify WHICH antibiotics are to be used



## Where can you find these?

Firstline

## Where else?

Provincial Health Services Authority

Home | Document Index | Links and Resources | About | Contact

**PHSA Shared Health Organizations Portal (SHOP)**

SHOP is the central access point for PHSA policies and decision support tools, such as guidelines, procedures, protocols and standards. Enter keywords in the 'Search Bar' below to get started.

Click the "Links and Resources" tab above for frequently referenced materials (e.g. Micromedex). Learn more about the benefits of SHOP on POD or visit the SHOP FAQ page.

**NOTE:** Creating a "one-stop SHOP" is our goal, however not all policies and DSTs are available on SHOP at this time. Ensure that you are familiar with the location of other clinical resources including unit-specific documents before coming on shift. In an emergent situation, check with your unit/work area for the location of these documents.

Please press CTRL + F5 on your keyboard after opening a document to ensure you have the most up-to-date version.

SHOP
SHARED HEALTH ORGANIZATIONS PORTAL
Search for documents for all Health Organizations: SHOP
For Health Organization specific documents:
PHC SHOP VCH SHOP

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

EVIDENCE-BASED GUIDELINES FOR DURATION OF THERAPY FOR COMMON PEDIATRIC INFECTIONS - COMMON LIST
Guideline

Appointments: Filling Short Notice Appointments
Procedure

CMMS Downtime Protocol: Biomedical Engineering
Standard Operating Procedures

**CNS INFECTIONS**

| Infection | Duration | IV to Oral switch | References |
|---|---|---|---|
| Meningitis: | | | |
| - *N. meningitidis* | 5-7 days IV | No oral switch | Tunkel, Clin Inf Dis, 2004[5] McMullan, Lancet, 2016[6] |
| - *H. influenzae* | 7-10 days IV | No oral switch | Tunkel, Clin Inf Dis, 2004[5] McMullan, Lancet, 2016[6] |
| - *S. pneumoniae* | 10-14 days IV | No oral switch | Tunkel, Clin Inf Dis, 2004[5] McMullan, Lancet, 2016 |
| - Group B streptococcus | 14-21 days IV | No oral switch | Singhi, J Trop Pediatr, 2002[7] Martin, Infection, 1990[8] McMullan, Lancet 2016[6] |
| - Gram-negative bacteria | 21 days IV | No oral switch | |
| - *Listeria monocytogenes* | 21 days IV | No oral switch | McMullan, Lancet 2016[6] Mylonakis, Medicine (Baltimore), 1998[9] |

# The Guidelines


# Newborns in NICU

| Infection | Duration | IV to Oral switch |
|---|---|---|
| **SEPSIS** | | |
| **Early-onset (<72h post-partum)** | | |
| - **Culture-proven bacteremia** | 7-10 days IV | No oral switch |
| - **Culture-negative** | ≤ 5 days IV (Consider discontinuing earlier if no source found) | No oral switch |
| **Late-onset (>72h post-partum)** | | |
| - **Culture-proven bacteremia** | 7-10 days IV | No oral switch |
| - **Culture-negative** | ≤ 5 days IV (Consider discontinuing earlier if no source found) | No oral switch |
| **Necrotizing enterocolitis** | | |
| - **Stage I** | 3 days IV | No oral switch |
| - **Stage II** | 5-7 days IV | No oral switch |
| - **Stage III** | 10-14 days IV | No oral switch |

# Bacteremia

| Infection | Duration | IV to Oral switch |
|---|---|---|
| **Gram-negative bacteremia with enterobacterales (assumes source control)** | **7 days IV** | **?** |
| **Gram-negative bacteremia with urogenital source and source control achieved** | As for complicated UTI | As for complicated UTI |
| **S. aureus bacteremia with no source (uncomplicated)** | 14 days IV from 1st negative culture | N/A |
| **S. aureus bacteremia associated with acute osteomyelitis/septic arthritis** | As per acute osteomyelitis/SA recommendations | As for acute osteomyelitis/SA recommendation |
| **S. pneumoniae bacteremia associated with pneumonia** | As for pneumonia | N/A |

# Bacteremia

- Most gram-negative infections with source control: 7 days IV (AMMI 2020)
- Havey (2011): Meta-analysis of 24 Trials.
  - Patients receiving shorter (5-7 days) versus longer (7-21 days) therapy: no significant difference detected for clinical cure, microbiologic cure, and survival
- Yahav (2019): Randomized, multicenter, open label trial in adults
  - "Hospitalized patients: 7 days was noninferior to 14 days."
- Turjeman (2023): Meta-analysis and SR.
  - For hemodynamically stable patients, 7 days non-inferior to 14 days
- Exceptions include: Pseudomonas, other resistant or atypical bacteria
- Bacteremia with S. aureus and no source: unchanged (14 days IV from first negative culture)

## Bacteremia with a focus

- Bacteremia with urogenital source: treat as per pyelonephritis (CPS 2014/2020)
- Bacteremia with osteoarticular infection: treat as per osteoarticular infection guidelines (CPS 2018)
- Bacteremia with *S. pneumoniae* and pneumonia: treat as for pneumonia (AMMI 2020)

## Cardiac

| Infection | Duration | IV to Oral switch | |
|---|---|---|---|
| Infective endocarditis in childhood | 4-6 weeks (Depends on bacteria, risk factors, surgery. Consult ID) | All IV | Refer to American Heart Association Guidelines on Endocarditis 2015 |

# CNS infections

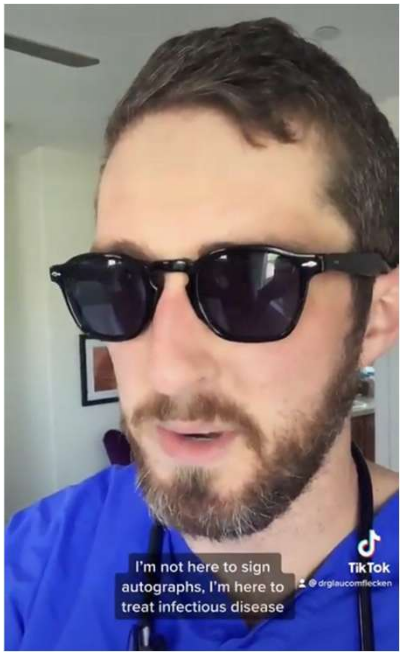
- Meningitis and HSV encephalitis recommendations unchanged:

| Infection | Duration | IV to oral switch |
|---|---|---|
| - N. meningitidis | 5-7 days IV | No oral switch |
| - H. influenzae | 7-10 days IV | No oral switch |
| - S. pneumoniae | 10-14 days IV | No oral switch |
| - Group B streptococcus | 14-21 days IV | No oral switch |
| - Gram-negative bacteria | 21 days IV | No oral switch |
| - Listeria monocytogenes | 21 days IV | No oral switch |
| - HSV encephalitis | 21 days IV (need –ve PCR) | No oral switch |

# Additional CNS Infections

- Brain abscess, tuberculomas, more complicated infections…

  Call ID



# ENT/Ocular/Dental

- Not many changes – recommendations as per CPS
- AOM

| Infection | Duration | IV to Oral switch |
|---|---|---|
| - Mild illness >6m | 0 days | All oral |
| - Mod-severe illness <2 years | 10 days | All oral |
| - Mod-severe illness >2 years | 5 days | All oral |
| Associated with perforation | 10 days | All oral |

# Mastoiditis

| Infection | Duration | IV to Oral switch |
|---|---|---|
| Mastoiditis | 12-21 days | 5 days IV (+/- surgery) then switch based on clinical improvement |

- McMullan (2016): 4 low quality studies
  Average of 4-7 days IV, rest PO

- Moore (2006): No difference in rate of readmission to hospital between intravenous and oral outpatient treatment after mastoidectomy was found

# Sinusitis and cervical lymphadenitis

| Infection | Duration | IV to Oral switch |
|---|---|---|
| Bacterial sinusitis (uncomplicated) | 0 days (mild)<br><br>5 days - 7 days post resolution of symptoms (severe) | All oral<br><br>All oral |
| Cervical lymphadenitis<br><br>- Uncomplicated acute bacterial (presumed)<br><br>- Atypical mycobacteria | 0 days (most)<br><br>7 days<br><br>0-180 days (consult ID) | <br><br>0 days IV (+/- surgery)<br><br>0 days IV (+/- surgery) |

# Sinusitis

- Most mild sinusitis is viral and does not respond to antibiotic therapy (Garbett, Pediatrics 2001 and Kristo, Acta Pediatr 2005)
- Evidence for durations is scant, multiple confounders
- Severe or progressive sinusitis represents a risk of intracranial disease

- Mild sinusitis can be watched
- Progressive or severe sinusitis should be treated

# Pre-septal and orbital cellulitis

| Infection | Duration | IV to Oral switch |
|---|---|---|
| **Pre-septal cellulitis** | **7-10 days** | **May be all oral** |
| **Orbital cellulitis** | 10-14 days | IV initially then switch to oral when clinical improvement |

# Orbital cellulitis

- Previous guidelines recommended long therapy (14-21 days)
- Anosike (2022): Retrospective study 220 children: “Treatment failure uncommon in patients who received ≤ 2 weeks of therapy.”

- Emmett Hurley (2012): Retrospective cohort study of 42 children: Treated with a median of 4 days IV therapy. 41 not readmitted.
  - “The duration of IV therapy associated with successful nonsurgical management of appropriately selected children with OC is considerably shorter than that recommended in current pediatric infectious disease literature.”

# Preseptal cellulitis

- Pre-septal cellulitis is a milder infection which can be managed with a 7-10 day course of oral antibiotics
- IV therapy recommended if any concern about orbital cellulitis, patient clinically unwell, or inability to tolerate oral medications

# Respiratory

| Infection | Duration | IV to Oral switch |
|---|---|---|
| **Community-Acquired Pneumonia**<br>- **Mild (outpatient)**<br>- **Moderate/Severe (admitted)** | **3-5 days**<br>**5-7 days** | **All Oral**<br>**IV for 1-2 days or until clinical improvement** |
| **Empyema** | 2-6 weeks | IV until clinical improvement |
| **Hospital-acquired pneumonia/ ventilator-acquired pneumonia** | 5-7 Days | ? |
| **Aspiration pneumonia** | 5-7 days | May be all oral – Patient-dependent |
| **Aspiration pneumonitis** | 0 days | N/A |

# Community-Acquired Pneumonia

- Old dogma: 7-10 days
- New suggestion:
  - Uncomplicated, outpatient: 3-5 days
  - Admission: 5-7 days

- Evidence is STRONG that 5 days is enough for most out-patients and reasonable for in-patients, with some advising 7 days
- Emerging evidence that 3 days for uncomplicated pneumonia in outpatients is sufficient
- Complicated infections (underlying lung disease, empyema, effusion, necrosis) need a longer course

| REFERENCE, YEAR | DURATION |
|---|---|
| Up-To-Date, Oct 2022 | 5 days uncomplicated CAP<br>Hospitalized: 5-7 days |
| Redbook, 2022 | 5 days for uncomplicated CAP improving during that time |
| Bugs & Drugs, 2022 | 5 days, treat until clinically well and afebrile |
| Canadian Pediatric Society, 2018 | Outpatient: 5 days<br>Hospitalized: 7-10 days |
| SCOUT-CAP, 2022 (USA) | Non-severe PNA, Outpatient: 5 days was superior to 10 days |
| AMMI | 7 days |
| CAP-IT trial, 2021 (UK, Ireland) | Outpatient and patients admitted to hospital for < 48 hours: 3 days non-inferior to 7 days<br>(Note: possible numerous viral pneumonias being treated in study) |
| SAFER, 2021 (Canada) | Outpatient: 5 day vs. 10 day comparable clinical cure rates in both groups |
| Marques et al. , 2022 (Meta-analysis) | 6 months-10 years uncomplicated outpatient PNA: no statistical difference between 5 vs. 10 days. Recommend 5 days |
| Dinh A. et al, 2021 PTC study group (Hospitalized Adults) | 3 days was noninferior to 8 days in adults hospitalized with moderate to severe CAP in non-critical wards who achieved clinical stability by day 3 |
| Kuitinen et al, 2022 | 3-5 days same as 7-10 in high-income setting |

# Do all kids with pneumonia need Abx?

**Original Investigation** | Pediatrics

October 29, 2024

**Outpatient Antibiotic Use and Treatment Failure Among Children With Pneumonia**

Daniel J. Shapiro, MD, MPH[1]; Matt Hall, PhD[2]; Mark I. Neuman, MD, MPH[3]; et al

» Author Affiliations | Article Information

*JAMA Netw Open.* 2024;7(10):e2441821. doi:10.1001/jamanetworkopen.2024.41821

- 103,000 kids with CAP in ambulatoray settings
- 20% did not receive Abx
- Treatment failure uncommon, regardless of the group
- Severe outcomes unrelated to group

# CAP requiring admission

- Up to date: Recommends 7 days but says 5 may be effective
- Same et al (JPIDS 2021): Comparative study 439 kids at Johns Hopkins.
  - No differences between patients who received short-course (6d) vs prolonged-course antibiotic (10d) therapy.
- Adult colleagues treating in-patient CAP with 3 days of antibiotics

## Complicated pneumonia

- Difficult to make firm recommendations as spectrum is wide (mild effusion to loculated empyema)
- Generally:
  2-3 weeks for effusion
  2-4 weeks for empyema
  4-6 weeks for abscess
- Key is source control
- Range from 2-6 weeks total, with IV therapy until clinical improvement

## Hospital/Ventilator-Acquired Pneumonia

- Low-quality evidence for HAPs and VAPs in children
- Data in adults suggests short courses (7-8 days) as effective as longer courses (15 days)
- European societies and IDSA recommend ≤ 7 days in adults
- In cases where pseudomonas proven, can consider longer

# Urinary Tract Infections

- Old dogma:

Complicated <2m: 10-14 days, all IV

Complicated >2m: 7-14 days, ?IV ?PO


# Urinary Tract infectionn

| Infection | Duration | IV to oral switch |
|---|---|---|
| **UTI <28d** | 10d | Minimum 72h IV |
| **UTI 28-60d** | 10d | Minimum 24h IV |
| **UTI >60d** | 7-10d<br>(7 recommended) | Can be all PO |
| **Uncomplicated cystitis** | 2-4d | All PO |
| **Aspiration pneumonitis** | 0 days | N/A |

## Urinary Tract Infections

- Infants <60 days:

  Desai 2019: Multicenter retrospective cohort study:
  - "Young infants with bacteremic UTI who received ≤7 days of parenteral antibiotics did not have more frequent recurrent UTIs or hospital reutilizatiom"

- Lewis-de Los Angeles 2017: "Proportion of infants ≤60 days old receiving long IV treatment (>4 days) decreased substantially from 2005 to 2015 without an increase in hospital readmissions. "

## Complicated UTI >60 days

- Boquet 2012: Randomized trial of 171 children. "… supports the use of an oral antibiotic treatment of primary episodes of acute pyelonephritis in infants and young children."

- Fox 2022: Retrospective observational study 791 children. No difference in those who received 8 vs 11 days for pyelonephritis

# Skin/Bone/Joint

- Osteoarticular infections

| Infection | Duration | IV to Oral switch |
|---|---|---|
| Acute osteomyelitis/ acute septic arthritis | 3-4 weeks (Hip/vertebrae - 6 weeks) | IV until clinical improvement |
| Chronic osteomyelitis | 6-12w<br>Depends on surgery, organism, severity.<br><br>Surgical debridement strongly advised | IV until clinical improvement.<br>May be full oral if mild. |

# Cellulitis + necrotizing fasciitis

| Infection | Duration | IV to Oral switch |
|---|---|---|
| Cellulitis<br>- Mild | 5-7 days | All oral |
| - Moderate-Severe | 5-10 days | IV 1-3 days then switch to oral with clinical improvement |

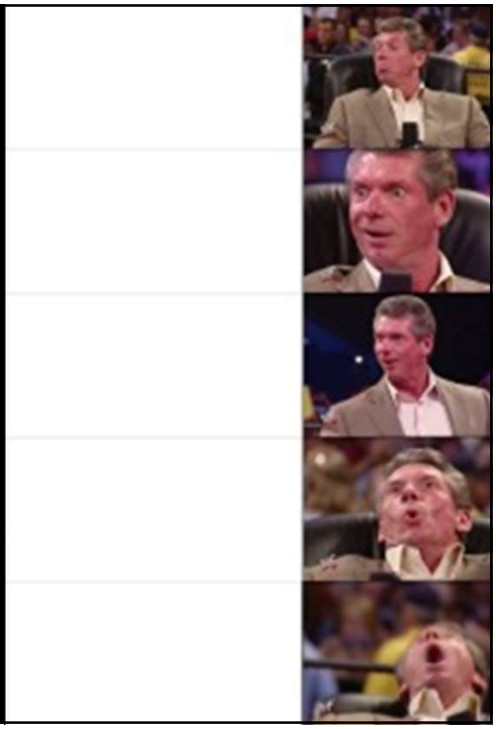
| | | |
|---|---|---|
| Necrotizing fasciitis | No recommendation | N/A |

## Gastrointestinal

| | | |
|---|---|---|
| **Primary peritonitis** | **5-7 days** | **Varies** |
| **Secondary peritonitis** | No recommendation | N/A |
| **Ascending cholangitis** | No recommendation | N/A |
| **Clostridium difficile infection** | 10-14 days | All oral unless fulminant infection |
| **Intra-abdominal collection** | If source control: 5-7 days<br><br>If no source control: No recommendation | IV until clinical improvement |

## The Future?

- Oral switch for bacteremia?
- Shorter courses (3d) for stable F&N?
- Shorter course of uncomplicated CAP (3d)?
- Single dose therapy for atypical pneumonia?



THE LANCET
Child & Adolescent Health

This journal Journals Publish Clinical Global health Multimedia Events About

ARTICLES · Volume 8, Issue 9, P625-635, September 2024

Oral versus intravenous empirical antibiotics in children and adolescents with uncomplicated bone and joint infections: a nationwide, randomised, controlled, non-inferiority trial in Denmark

Allan Bybeck Nielsen, MD [a,c] · Mette Holm, PhD [d] · Morten S Lindhard, PhD [f] · Jonathan P Glenthøj, MD [g] · Luise Borch, PhD [h,i] · Ulla Hartling, MD [j] · et al. Show more

- 248 children with OM randomized
- "In children and adolescents with uncomplicated BJIs, initial oral antibiotic treatment was non-inferior to initial intravenous antibiotics followed by oral therapy."

# Conclusion

- Existing duration guidelines outdated and based on poor evidence
- Generally: shorter is better!

- IV is not superior to PO
- Earlier IV to PO switches are usually safe

- General trends are for shorter durations and more rapid IV to PO switches (I see this continuing)

# Thank you!

- Questions?