

Short Is In: Update on Antimicrobial Duration of Therapy

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Conflict of Interest

- Speaker's Bureau
 - Merck, Tetrphase
- Grant Funding
 - Merck, ALK Abello
- Consulting
 - Merck

Objectives

- Review potential adverse effects associated with prolonged durations of antimicrobial therapy
- Assess data to support shorter antibiotic courses for selected infectious diseases

Where we are currently in ID

- *At least 30-50%* of antibiotic usage is unnecessary
- Antimicrobial prescribing is often more behavioral than scientific
- Fewer infectious diseases players in antibiotic research and development
- Duration of therapy has been largely made up for many infections
- Constantine in 321 A.D. decreed 7 days as a week
 - Hence how we have come to 7-14 days of therapy for many infections

What are the risks of prolonged, unnecessary therapy?

- *C. difficile* infection
 - Adverse effects
 - Resistance emergence
 - Microbiome alteration
 - Increased costs
-
- Bottom line: Defining appropriate DOT is an important antimicrobial stewardship issue. Many times zero is the right DOT...

Does One Extra Day Matter? Surgical Prophylaxis

- Multicenter, national retrospective VA study over 5 years
- Various surgeries including colorectal, cardiac, orthopedic
- <24h, 24-<48h, 48-<72h, >72h exposure groups
- Nearly 80,000 patients mean age of 65
- NNH for AKI were 9,6, and 4 for 24-<48h, 48-<72h, greater than 72h
- NNH for CDI was 2000, 90, and 50 for same three groups
- Vanc independently associated risk factor for AKI
 - Both cardiac and non-cardiac surgeries
 - Evaluate PCN “allergy”

Branch-Elliman W. et al. *JAMA Surg.*
2019;154:590-98.

Discharge Rx Effect on DOT

- 3 centers
- ~45,000 inpatients admissions
- Discharge Rxs made up nearly 40% of total therapy
- Nearly 8 in 10 patients who received discharge Rx exceeded 7-day duration for most commonly seen infections
- Patients with discharge Rxs had longer DOT than those who received all ABX inpatient

- We need transitions of care stewardship!

Dyer A. et al. *Infect Control Hosp Epidemiol.* 2019;40:847-54.

Summary of Disease States where Short Is In

Stewardship: Shorter = Better

Diagnosis	Short (d)	Long (d)	Result	#RCTs
CAP	3 or 5	7-14	Equal	9
VAP	8	15	Equal	2
Pyelo	7 or 5	14 or 10	Equal	6
Intra-abd	4	10	Equal	2
GNB Bacteremia	7	14	Equal	1*
AECB	≤5	≥7	Equal	>20
Cellulitis	5-6	10	Equal	4*
Chronic Osteomyelitis	42	84	Equal	2
Septic Arthritis	14	28	Equal	1
Ortho Implant w/removal	28	42	Equal	1
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
<i>P. vivax</i> Malaria	7	14	Equal	1

*GNB bacteremia in UTI/cIAI studies too; 3 cellulitis studies found no diff, 1 (low dose oral flucox) had ↑relapses; references at www.bradspellberg.com 14

<https://twitter.com/BradSpellberg/status/1191016978208608257>

STOP-IT

- Open-label, multicenter, randomized trial involving complicated intrabdominal infections (cIAI) in 518 patients (NIH study)
- Short course (4 days +/- 1 day) vs. longer course (cIAI with **definitive source control** + 2 days ABX post resolution of symptoms up to 10 days)
- Primary composite outcome: SSI, recurrent IAI, 30-day mortality
- Secondary outcomes: DOT and Rates of subsequent infections
- No difference in outcomes
 - Short course (4 days) vs. Standard course (8 days)
 - 21.8% vs. 22.3% for Primary outcome ; 95% CI (-7 to 8.0); P=0.92

Gram-negative Bacteremia

- Randomized, multicenter, open-label noninferiority trial
- Patient who were afebrile and hemodynamically stable for ≥ 48 h before day 7 of hospitalization received 7 or 14 days of effective ABX therapy
 - **All patients had definitive source control**
- Primary composite outcome at 90 days:
 - All-cause mortality
 - Relapse, suppurative, or distant complications
 - Readmission or hospitalization ≥ 14 days

Gram-negative Bacteremia: Patients

Baseline Characteristic	Value
Average Age	71 years
Charlson comorbidity score	2
Malignancy	~30%
Central Catheters at Baseline	~30%
Hospital-acquired	~25-30%
SOFA Score at Presentation	2
Most Common Source of Infection	Urinary (68%)
Most Common Organism	<i>E. Coli</i> (60-65%)
MDR Organisms	~20%

Gram-negative Bacteremia: Results

- Three centers in Italy/Israel over 4.5 years with 604 patients
- No difference in outcomes (45.8% vs. 48.3%; P=0.527)
 - High % in both groups driven by readmissions
 - Significant functional capacity decrease in both groups but greater in longer ABX group (51.4% vs. 57.2%; P=0.031 {NS})
- Total antibiotic days from culture collection to day 90 post randomization
 - 10 days versus 16 days (P=0.001)
- *C. difficile* infection rates no different between groups
- Very few nonfermenters such as *Pseudomonas aeruginosa*

Community-Acquired Pneumonia

- Over 4.5 million outpatient/ED visits annually
- Second most common cause of hospitalization and most common infectious cause of death
- 1.5 million unique CAP hospitalizations annually
- Early data with PCNs in 1940's titrated DOT based on clinical response
 - Average DOT 1.5-4 days with high cure rates
- DOT has been 10-14 days minimum anecdotally for many years
 - Even 2007 CAP guidelines stated 5 days minimum appropriate but lots of caveats for "clinical stability"
- Remember...shortest duration of therapy is zero
 - Pharmacists opportunity for pneumococcal vaccination

DOT in CAP

- Randomized, multicenter noninferiority trial in Spain over ~2 years
- Patients randomized at Day 5
 - Intervention Group: If body temp < 37.8°C for ≥ 48 hours and ≤ 1 sign of clinical instability: STOP
 - Control group: *Determined by treating physician*
- Primary outcomes
 - Clinical success at day 10 and 30
 - CAP-related symptoms at day 5 and 10 (Questionnaire)

DOT in CAP: Baseline Characteristics

Characteristic	Control Group	Intervention Group
Mean Age	66.2	64.7
Current Smoker	21.3%	22.6%
COPD	14%	16.7%
Charlson Comorbidity Index	1	1
PSI Class I-III	59.3%	63%
PSI Class IV-V (No ICU patients)	40.7%	37%
Mean PSI Score	83.7	81.8

DOT in CAP: Results

- Vast majority of patients got FQ-based therapy (~80%)
- Most isolated organism: *S. pneumoniae*
- Clinical success not different at day 30 (88.6% vs. 91.9%; P=0.33)
- CAP symptom questionnaire scores not different (18.6 vs. 17.9; P=0.69)
- Readmission by day 30 favored shorter course (6.6% vs. 1.4%; P=0.02)
 - Per Protocol analysis
- Shorter course data has been demonstrated for amoxicillin and ceftriaxone as well in other studies

Uranga A. et al. *JAMA Internal Med.* 2016;176:1257-65.

Leophante P. et al. *Med Mal Infect.* 2992;32:360-81.

El Moussaoui R. et al. *BMJ* 2006;332:1355.

VAP 8 vs. 15 DOT

- Prospective, randomized, double-blind trial in 51 ICUs
- Approximately 400 patients
- Antibiotic regimens chosen by treating physician
- Primary outcomes
 - Death from any cause
 - Microbiologically documented recurrence
 - Antibiotic free days

PneumA

Summary

No clinical advantage of 15-day regimen over 8-day regimen

Average number of antibiotic-free days 50% higher for patients randomized to 8-day regimen

Multiresistant pathogens more frequent in patients with infection recurrence who had received 15-day course

No fermenting causes of VAP (i.e. *Pseudomonas* species) had greater infection recurrence

-Newest HAP/VAP guidelines recommend 7 days still

Pneum A: Summary

- No clinical advantage of 15-day regimen over 8-day regimen
- Average number of antibiotic-free days 50% higher for patients randomized to 8-day regimen
- MDR pathogens more frequent in 15-day course group with recurrence
- Non-fermenting GNR (*Pseudomonas* species) had greater infection recurrence in 8 day group (40.6% vs. 25.4%)
 - 2016 HAP/VAP guidelines still recommend short courses...

Acute Exacerbations of Chronic Bronchitis

- Lead to significant resource utilization and cost to health care system
- Mean costs of ~\$4000 annually specific to COPD
 - \$6000 for ≥ 2 or more exacerbations
- Remember the shortest course should be ZERO
 - Vaccination opportunities abound
 - Not all COPD exacerbations require antibiotic therapy
 - Especially mild exacerbations

Pasquale MK et al. *Int J Chron
Obstruct Pulmon Dis.*
2012;7:757-764.
GOLD Guidelines 2019

Acute Exacerbations of Chronic Bronchitis: Meta Analysis

- Retrospective meta analysis of double-blind studies
 - Short course (≤ 5 days) vs. Longer course (≥ 5 days)
- MEDLINE, EMBASE, Cochrane central register to July 2006
- Inclusion criteria
 - Adults with COPD exacerbation or chronic bronchitis
 - No ABX at time of diagnosis
 - Random assignment to short or long course
- Primary outcome: Clinical Cure at follow-up on ITT

Results

- 21 studies with 10,698 patients
- Quality of studies high at 3.9 (5 being most robust: Jadad score)
- Odds ratio for clinical cure with short vs. conventional treatment
 - 0.99 (95% CI 0.90-1.08)
- Late follow-up summary odds ratio clinical cure
 - 1.0 (95% CI 0.91-1.10)
- Late follow-up summary odds ratio bacteriologic cure
 - 1.05 (95% CI 0.87-1.26)
- Short is In (and has been in for a long time...)

Pyelonephritis DOT

- Significant data supporting cystitis short course therapies
 - Nitrofurantoin 100mg PO BID X 5 days
 - FQ X 3 days
 - TMP/SMX X 3 days
- Pyelonephritis however often treated for 10-14 days
 - Especially if bacteremia detected and beta-lactam required
- Remember the shortest duration is zero!
 - Asymptomatic bacteriuria should rarely be treated outside of pregnancy
- Can we shorten the duration of therapy?

Acute Uncomplicated Pyelonephritis: Shorter DOT is in for FQs!

FQ Regimen	Days of Therapy Studied	Clinical cure	Microbiologic cure
Ofloxacin or Levofloxacin	5 or 10 days	93.3% vs. 94.7%	87% vs. 80%
Cipro vs. Cipro	7 vs. 14 days	97% vs. 96%	95.9% vs. 96.4%
Levo vs. Cipro	5 vs. 10 days	79.8% vs. 77.5%	88.3% vs. 86.7%

Dinh A. et al. *European Journal of Clinical Microbiology and Infectious Diseases*.

2017;36:1443-1448.

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

Peterson J. et al. *Urology*. 2008;71:17-22.

Septic Arthritis

- Optimal therapy for postsurgical antibiotics unknown
- Prospective, unblinded, randomized, noninferior study
- Native joint bacterial arthritis (wrist/hand)
- Surgical lavage completed in all patients
- Patients randomized to 14 or 28 days post surgery
- Important exclusions
 - Implant-related infections or follow-up < 2 months
- Primary outcome: Complete remission of infection at minimum of 2 months
 - Clinical, Laboratory, Radiologic

Septic Arthritis: Results

- 77 patients in each arm
- *S. aureus* most common pathogen (Zero MRSA)
- Oral ABX highly variable but Amox/Clav most common agent
- Median length of IV ABX: 1 and 2 days in short and long respectively
- Patients receiving 2 week therapy similar outcomes to 4 week
 - 99% vs. 97%
- Adverse effects similar
- Median LOS 4 vs. 6 days favoring shorter DOT (P=0.01)

Neutropenic Fever

- Open-label, randomized, superiority, controlled study in heme malignancies or heme stem-cell transplant recipients evaluating empirical antimicrobial therapy (EAT)
- Objective: Determine if clinical approach regardless of neutrophil recovery would optimize duration of therapy of EAT
- Investigators masked only prior to randomization
- EAT with monotherapy or dual therapy initiated by local protocols and international guidelines
- Experimental group: EAT d/c after 72 hours afebrile with clinical improvement
- Control group: EAT d/c after neutrophil recovery (ANC 500+)

Neutropenic Fever: Results

- Three year study with 157 episodes among 709 patients
- Mean number of EAT-free days higher in experimental group
 - 16.1 vs. 13.6; $p=0.026$
- Adverse effects similar between groups
 - Mucositis, Diarrhea, N/V
 - Severe more common in control group
- Mortality low overall in both groups (not outcome of interest)
- Take Home Message: High risk population with less DOT of EAT possible using clinical criteria independent of ANC

What can we do to help?

- Educate, Educate, Educate
 - Education has really short half-life
- Be involved in transitions in care
 - Antibiotic DOT can be lengthened at many touchpoints in care
- Be the glue among prescribers

- This is low hanging fruit with tremendous benefit!

Stewardship Near Time of Discharge

- Single center retrospective study
- Stewardship team of pharmacist and ID physician reviewed HER of patients discharged on oral antibiotics from VA twice weekly
- Evaluated choice and *total duration of therapy*
- Cases discussed prn with pharmacist and prescribing service
- ~10% of patients required intervention (1 in 12)
- Most common intervention: You guessed it! (Stop the ABX)
- Most common disease state: COPD
- Most common ABX stopped: Azithromycin

Conclusion

- Shorter is definitely in...for a lot of disease states
- The number of disease states is continuously growing
- Pharmacists can have a tremendous impact on implementing these goals of shorter duration of therapy

Assessment Question

- Which of the following is correct regarding duration of antibiotic therapy?
 - A. Discharge antibiotic prescriptions contribute minimally to overall excessive duration of therapy
 - B. Patient reported adverse events decrease with each excessive day of therapy
 - C. Excessive duration of therapies is confined to antibiotic treatment and not prophylaxis
 - D. Stewardship review and prospective audit/feedback of discharge medications can significantly decrease duration of therapy

Assessment Question

- Which of the following infection are amenable to a shorter course of therapy (5-7 days) compared to a longer course of therapy (10-14 days)?
 - A. Osteomyelitis
 - B. Community-acquired pneumonia
 - C. MRSA endocarditis
 - D. Pulmonary Aspergillosis

Assessment Question

- A 25-year-old female with *E. coli* bacteremia secondary to pyelonephritis is being treated with levofloxacin and has clinically responded after 48 hours. Which of the following is the most appropriate treatment duration based on recent data?
 - A. 2 days
 - B. 7 days
 - C. 14 days
 - D. 28 days