

Short Duration of Antibiotic Therapy in Common Infections

October 9, 2019

Enterobacteriaceae bacteremia

Study	Design	Population	Findings
Swamy et al.	Retrospective cohort (≤ 7 days, 8-14 days, >14 days)	Uncomplicated gram negative bloodstream infections	<ul style="list-style-type: none"> Similar clinical and microbiological response rates between all groups No specific factors influenced outcome
Chotiprasitsakul et al.	Retrospective cohort (6-10 days, 11-16 days)	Gram negative bloodstream infections	<ul style="list-style-type: none"> Similar 30-day mortality rates (9.6% vs. 10.1%) No difference in recurrence rates, CDI, or emergence of resistance
Yahav et al. (n=604)	Prospective RCT (7 days, 14 days)	GNR bacteremia, controlled source, afebrile & hemodynamically stable for 48h	<ul style="list-style-type: none"> Similar 90-day mortality, relapse, readmission, CDI, resistance Faster return to baseline for short duration

Enterobacteriaceae bacteremia

Criteria for short duration:

- No ongoing focus of infection
- For at least 48 hours:
 - Hemodynamically stable
 - Afebrile

*Urinary source most commonly evaluated in studies

*Short duration not well studied in non-lactose fermenting GNRs (ex: *Pseudomonas aeruginosa*)

*Most common oral antibiotic – fluoroquinolone

Recommended duration:

- 7 days

Community-acquired pneumonia

- IDSA/ATS guidelines: updated Oct 2019

Question 15: In Outpatient and Inpatient Adults with CAP Who Are Improving, What Is the Appropriate Duration of Antibiotic Treatment?

Recommendation. We recommend that the duration of antibiotic therapy should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities [heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature], ability to eat, and normal mentation), and antibiotic therapy should be continued until the patient achieves stability and for no less than a total of 5 days (strong recommendation, moderate quality of evidence).

Community-acquired pneumonia

- Multicenter, noninferiority randomized controlled trial
 - Inclusion: adult inpatients w/ CAP diagnosis (new infiltrate on CXR + 1 symptom compatible with PNA)
 - Exclusion: HIV, chronic immunosuppression, nursing home, admit to hospital in past 14 days, antibiotics in past 30 days, uncommon pathogens (*P. aeruginosa*, *S. aureus* etc.), extrapulmonary infxn, ICU
- 5 days (body temperature, $\leq 37.8^{\circ}\text{C}$ x 48h & no more than 1 CAP-associated sign of clinical instability: hypoxia, hypotension, tachycardia, tachypnea) vs. duration determined by physicians
- Similar demographics: mean age ~65, 15% COPD, 16% diabetes, 40% PSI IV-V

Community-acquired pneumonia

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	P Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%) ^a			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD) ^b			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%) ^a			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD) ^b			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

Community-acquired pneumonia

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis^a

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	P Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure ^b	2 (1.5)	3 (2.1)	>.99
Respiratory failure ^c	26 (19.0)	31 (21.2)	.64
Severe sepsis ^d	7 (5.1)	8 (5.5)	.89
Renal failure ^e	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

Community-acquired pneumonia

Criteria for short duration:

- Afebrile for 48 hours
- No more than 1 sign of clinical instability
 - SBP < 90mm Hg
 - HR > 100/min
 - RR > 24/min
 - Arterial O₂ <90% or PaO₂ <60 mmHg at room air

Recommended duration:

- 5 days

Hospital-acquired & ventilator-associated pneumonia

XXI. Should Patients With VAP Receive 7 Days or 8–15 Days of Antibiotic Therapy?

Recommendation

1. For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration (*strong recommendation, moderate-quality evidence*).

Remarks: There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

XXII. What Is the Optimal Duration of Antibiotic Therapy for HAP (Non-VAP)?

Recommendation

1. For patients with HAP, we recommend a 7-day course of antimicrobial therapy (*strong recommendation, very low-quality evidence*).

Remarks: There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

Criteria for short duration:

- Clinical response to treatment
- No abscess or empyema

Recommended duration:

- 7 days

Aspiration

- Aspiration pneumonia: No data addressing duration of therapy. Based on CAP & HAP/VAP studies, experts recommend a 5-7 day course
- Aspiration pneumonitis:
 - Antibiotics not recommended initially, usually re-consider if persistent hypoxia/imaging suggestive of pneumonia
 - Retrospective cohort study, prophylactic abx (n=76) vs supportive care only (n=124) w/ diagnosis of aspiration pneumonitis
 - Included: Adult inpatient, witnessed aspiration, new infiltrate on CXR. Excluded: Ventilator, patients on abx
 - Prophylaxis grp w/ similar rates of mortality, transfer to ICU, more escalation of abx, & fewer abx free-days

Aspiration

Pneumonia:

- Use CAP or HAP/VAP criteria depending on setting of acquisition

Recommended duration:

- 5-7 days

Pneumonitis vs pneumonia (if initiated in critically ill patient):

- Re-evaluate antibiotic need based on clinical improvement & imaging/lab/micro studies

Recommended duration:

- ≤ 48 hours

3 day course for pneumonia?

Study	Design	Population	Findings
El Moussaoui, et al.	MC, DB, RCT - amoxicillin (3 days (n=56), 8 days (n=63))	Adult inpatients, diagnosis of CAP, PSI score ≤ 110	<ul style="list-style-type: none"> • Similar clinical success at Days 10 & 30 • Small sample size
Klompas, et al.	Retrospective cohort (≤ 3 days (n=259) vs. > 3 days (n=1,031))	Adult ventilated patients on empiric abx for possible VAP with minimal and stable ventilator settings*	<ul style="list-style-type: none"> • No difference in duration of mechanical ventilation, length of stay, mortality

* Daily PEEP ≤ 5 cm H₂O & daily FiO₂ $\leq 40\%$

COPD & chronic bronchitis exacerbation w/ suspected bacterial etiology

Chronic obstructive pulmonary disease

Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies

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Journal of Antimicrobial Chemotherapy (2008) **62**, 442–450

doi:10.1093/jac/dkn201

Advance Access publication 8 May 2008

JAC

Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis

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Cystitis, no urologic abnormalities or systemic signs & symptoms

- IDSA/ESCMID: last update 2010
 - 1 day – Fosfomycin
 - 3 days - TMP/SMX & levofloxacin
 - 5 days – Nitrofurantoin
 - 5-7 days – Beta-lactam
- Goodley KJ, et al. (2018) – 1 x dose of aminoglycoside
 - Systematic review, 13 articles (1978-1991), 1 study in elderly (mean age: 74), mostly female (79%), duration of f/up (48h – 3 yrs), comparator arm (fosfomycin, TMP/SMX, or beta lactam), most studies with lower cystitis (2 included pyelonephritis)
 - Overall cure rate of 94%, microbiologic cure > 85%, pts w/ anatomical abnormalities less likely to have microbiologic cure

Complicated cystitis & pyelonephritis

- Levofloxacin: 5 days
 - MC, DB, RCT (n=506) levofloxacin 5 days vs. ciprofloxacin 10 days; 60% female, 40% > 65 years old, 30% pyelonephritis
 - No difference in microbiologic cure or clinical success (resolution of signs & symptoms w/o additional tx); 45 day post-evaluation
- IV beta-lactam: 7 days
 - ASPECT-cUTI study (n=1083)– IV zerbaxa vs. IV levaquin 7 day fixed duration (80% pyelonephritis); 21-42 day follow-up
 - ZEUS study (n=465)– IV Fosfomycin vs. IV zosyn 7 day fixed duration (50% pyelonephritis); 19-21 day follow-up
- Meta-analysis of RCTs: ≤ 7 days or longer treatment
 - Similar except subgroup of studies in patients w/urogenital abnormalities

Peterson J, et al. Urology 2008;71(1):17-22.

Wagenlehner FM, et al. Lancet 2015; 385(9981):1949-56

Kaye KS, et al. Clin Infect Dis 2019; [Epub ahead of print].

Eliakim-Raz N, et al. J Antimicrob Chemother 2013;68(10):2183-91

Catheter-associated UTI

Criteria for short duration:

- Catheter removed
- Prompt symptom resolution
- No upper-UTI
- Women <65 years of age – based on one study w/ single dose TMP/SMX vs. 10 days that suggested single dose less effective in women >65 years old (89 vs. 62% clinical cure)

Recommended duration:

- 3-5 days

Intra-abdominal infection

Guideline	Biliary tract infection/appendicitis
IDSA (2010)	24h post cholecystectomy with acute cholecystitis contained in gallbladder viscera
SIS (2017)	24h post-op in nonperforated cholecystitis
	4 days w/ adequate source control
	5-7 days if no source-control procedure and reassess for source control prevention in patients who do not respond to antibiotic therapy
WSES (2017)	Post-op antimicrobial therapy unnecessary in definitive source control
TG18 (2018)	24h post cholecystectomy for community-acquired grades I-II cholecystitis
	4-7 days for perforation, emphysema, or necrosis of gallbladder noted during cholecystectomy, and for grades I-III cholangitis with source control

Intra-abdominal infection

Guideline	Complicated IAI
IDSA (2010)	24h for stomach & proximal jejunum perf when source control within 24h & traumatic bowel perf repaired within 12h
	4-7 days
SIS (2017)	24h for traumatic bowel perf operated on within 12h & for gastroduodenal perf operated on within 24h
	4 days (96 h) with adequate source-control procedure
	5-7 days if no source-control procedure
	7 days for secondary bacteremia w/ source control and patient no longer bacteremic
WSES (2017)	3-5 days with adequate source-control procedure
	Diagnostic investigation for uncontrolled infection or treatment failure w/ signs of peritonitis/systemic infection beyond 5-7 days of antimicrobial treatment

Intra-abdominal infection

- STOP-it Trial: Prospective, RCT in complicated intrabdominal infection s/p adequate source control, 4 +/- 1 days of abx vs. until 2 days after resolution of fever, leukocytosis & ileus (max 10 days).

Variable	Control Group (N = 260)	Experimental Group (N = 258)
Age — yr	52.2±1.0	52.2±1.0
Male sex — no. (%)	145 (55.8)	144 (55.8)
Characteristics of index infection		
APACHE II score‡	9.9±0.4	10.3±0.4
Maximum white-cell count — per mm ³	15,600±0.4	17,100±0.7
Maximum body temperature — °C	37.8±0.1	37.7±0.1
Organ of origin — no. (%)		
Colon or rectum	80 (30.8)	97 (37.6)
Appendix	34 (13.1)	39 (15.1)
Small bowel	31 (11.9)	42 (16.3)

Variable	Control Group (N = 260)	Experimental Group (N = 258)
Source-control procedure — no. (%)		
Percutaneous drainage	86 (33.1)	86 (33.3)
Resection and anastomosis or closure	69 (26.5)	64 (24.8)
Surgical drainage only	55 (21.2)	54 (20.9)
Resection and proximal diversion	27 (10.4)	37 (14.3)
Simple closure	20 (7.7)	12 (4.7)
Surgical drainage and diversion	3 (1.2)	4 (1.6)

Variable	Control Group (N = 260)	Experimental Group (N = 257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99
Time to event — no. of days after index source-control procedure			
Diagnosis of surgical-site infection	15.1±0.6	8.8±0.4	<0.001
Diagnosis of recurrent intraabdominal infection	15.1±0.5	10.8±0.4	<0.001
Death	19.0±1.0	18.5±0.5	0.66
Secondary outcome			
Surgical-site infection or recurrent intraabdominal infection with resistant pathogen — no. (%)	9 (3.5)	6 (2.3)	0.62
Site of extraabdominal infection — no. (%)			
Any site†	13 (5.0)	23 (8.9)	0.11
Urine	10 (3.8)	13 (5.1)	0.65
Blood	3 (1.2)	5 (1.9)	0.71
Lung	3 (1.2)	3 (1.2)	0.99
Area of skin other than surgical site	1 (0.4)	4 (1.6)	0.36
Vascular catheter	0 (0)	2 (0.8)	0.47
<i>Clostridium difficile</i> infection — no. (%)	3 (1.2)	5 (1.9)	0.71
Extraabdominal infection with resistant pathogen — no. (%)	6 (2.3)	2 (0.8)	0.29
Duration of outcome — days			
Antimicrobial therapy for index infection			<0.001
Median	8	4	
Interquartile range	5–10	4–5	
Antimicrobial-free days at 30 days			<0.001
Median	21	25	
Interquartile range	18–25	21–26	
Hospitalization after index procedure			0.48
Median	7	7	
Interquartile range	4–11	4–11	
Hospital-free days at 30 days			0.22
Median	23	22	
Interquartile range	18–26	16–26	

Intra-abdominal Infections

- SBP: 5 days (Runyon BA, et al. Gastroenterology 1991;100(6):1737)
- Ischemic colitis: 7 days (Brandt, et al. Am J Gastroenterol 2015;111:18-44)

Table 6. Classification of disease severity and management

Disease severity	Criteria	Treatment
Mild	Typical symptoms of CI with a segmental colitis not isolated to the right colon and with none of the commonly associated risk factors for poorer outcome that are seen in moderate disease	Observation Supportive care
Moderate	Any patient with CI and up to three of the following factors:	Correction of cardiovascular abnormalities (e.g., volume replacement) Broad-spectrum antibiotic therapy Surgical consultation
	Male gender	
	Hypotension (systolic blood pressure <90mmHg)	
	Tachycardia (heart rate >100beats/min)	
	Abdominal pain without rectal bleeding	
	BUN >20mg/dl	
	Hgb <12g/dl	
	LDH >350U/l	
	Serum sodium <136mEq/l (mmol/l)	
	WBC >15 cells/cmm ($\times 10^9/l$)	
	Colonic mucosal ulceration identified colonoscopically	
Severe	Any patient with CI and more than three of the criteria for moderate disease or any of the following:	Emergent surgical consultation Transfer to intensive care Correction of cardiovascular abnormalities (e.g., volume replacement) Broad-spectrum antibiotic therapy
	Peritoneal signs on physical examination	
	Pneumatosis or portal venous gas on radiologic imaging	
	Gangrene on colonoscopic examination	
	Pancolonic distribution or IRCI on imaging or colonoscopy	

The optimal duration of antimicrobial therapy is unclear and studies to date have not addressed this issue. Once therapy has been initiated, this guideline recommends that antimicrobials be continued for at least 72 h, at which time the patient's clinical status should be reevaluated. If the patient has not clinically improved, one should consider consultation with an infectious disease expert to help define the antimicrobial regimen. If the patient is symptomatically improved after 72 h, a 7-day course of therapy should be considered.

Intra-abdominal infections

- Cholecystitis or appendicitis s/p source removal (no perforation). Gastroduodenal perf repaired within 24h & traumatic bowel perf repaired within 12h
 - Duration: 24 hours post-surgery
- Cholecystitis or appendicitis s/p source removal (perforation). Complicated peritoneal infection w/ good source control
 - Duration: 4 days
- Cholecystitis or complicated intra-abdominal infection w/ no source-control
 - Duration: 4-7 days
- SBP: 5 days
- Ischemic colitis (moderate to severe disease): 7 days

Uncomplicated cellulitis (no abscess or ulcer)

- IDSA Guideline (2014)

ORIGINAL INVESTIGATION

Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis

- Prospective, DB, RCT; N=87; levofloxacin 5 vs. 10 days
- Excluded: bacteremia, severe sepsis & septic shock, deep tissue infection, infection requiring debridement, animal or human bite, diabetic foot infection, neutropenia, chronic cellulitis (>2 weeks)
- Primary outcome: cellulitis resolution at 14 days with absence of relapse by 28 days (98% in both arms; no difference)

IV. What Is Appropriate for the Evaluation and Treatment of Erysipelas and Cellulitis?

Recommendations

15. The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (strong, high).
16. Elevation of the affected area and treatment of predisposing factors, such as edema or underlying cutaneous disorders, are recommended (strong, moderate).



Osteomyelitis s/p surgery w/ no residual infected bone or tissue

- IDSA Diabetic Foot Infection (2012)
 - 36. When a radical resection leaves no remaining infected tissue, we suggest prescribing antibiotic therapy for only a short duration (2–5 days) (weak, low). When there is persistent infected or necrotic bone, we suggest prolonged (≥ 4 weeks) antibiotic treatment (weak, low).
- Mostly expert opinion

Stopping antibiotics after surgical amputation in diabetic foot and ankle infections—A daily practice cohort

- 482 amputated DFI episodes followed for a median of 2.1 years
- In 109 cases (25%), antibiotics were stopped immediately after surgery
- Median duration of antibiotics admin 7 days (IQR, 1-16 days)
 - Clinical failure in 90 cases (17%) at anatomical site within 1 year (similar to 15-19% reported in literature)
 - Multivariate adjustment evaluating potential factors related to failure: none found

Thank You!