MAKING THE CASE:

LIMITING ANTIBIOTIC TREATMENT DURATIONS

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Disclosure

I do not have any relevant financial relationships with any commercial interests.

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Learning Objectives

Discuss the potential benefit of reducing the length of antibiotic courses on antimicrobial resistance

Review clinical data and/or treatment guidelines that support shorter courses of antibiotic therapy

Identify opportunities for antimicrobial stewardship intervention to optimize durations of therapy

Explore potential outcomes and benefits of shorter antibiotic durations on the healthcare system

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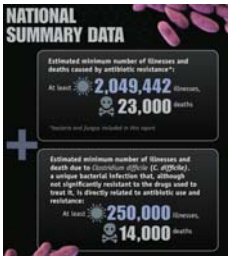
Antimicrobial Resistance

The ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive

A serious global threat that affects almost every bacterial species

Dynamics of antibiotic resistance are dependent on the host, environment, drug, and disease



CID 2007; 45: S129 – S136
www.who.int/mediacentre/factsheets/fs194/en/

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How does antimicrobial use drive resistance development?

a. Reduces the rate of bacteria eradication
b. Selects for resistant mutant subpopulations
c. Induces enzymes that degrade antibiotics
d. A and B
e. B and C

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Resistance Development

Antibiotic resistance can arise in several ways:

- Selection of pre-existing, resistant mutants occurring as minority subpopulations
- Selection of random or induced mutations
- Acquisition of resistant determinants (i.e. plasmids, phages, mosaic genes, transposons, transformation)
- Clonal spread of a pre-existing transmissable, resistant isolate
- Induction in the presence of an inducer (i.e. β–lactams)

Misuse and overuse of antimicrobials can accelerate this process

Journal of Applied Microbiology Symposium Supplement 2002; 92: 78S – 84S

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Target: Antimicrobial Exposure

Reduces selective pressure and rate of resistance development

Antimicrobial selective pressure can be reduced at three points:

- Before therapy begins – optimizing empiric prescribing
- During therapy – reducing the number and spectrum of antimicrobials
- At the end of therapy – limiting treatment durations

Timely initiation of antimicrobial therapy and encouragement of broad spectrum empiric coverage limits intervention

CID 2008; 46: 491 - 496

Antimicrobial Treatment Durations

- Community Acquired Pneumonia
- Hospital Acquired Pneumonia
- Ventilator-Associated Pneumonia
- Urinary Tract Infection
- Intra-abdominal Infection

Community Acquired Pneumonia

IDSA/ATS Guidelines recommend that patients with CAP should be treated for a minimum of 5 days

Recommendations largely based on empiric therapy

Most patients clinically stable by 3 – 7 days

Longer durations of therapy rarely necessary

Exceptions:

- *Pseudomonas aeruginosa*
- *Burkholderia pseudomallei*
- Endemic fungi

Duration of Antibiotic Therapy

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)
33. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

Criteria for clinical stability defined as temperature ≥37.8°C, heart rate ≤100 beats/min, respiratory rate ≤24 breaths/min, systolic blood pressure ≥90 mm Hg, arterial oxygen saturation ≥90% or pO_2 ≥60 mm Hg on room air, ability to maintain oral intake, and normal mental status

CID 2007; 44: S27 – S72

High-Dose, Short-Course Levofloxacin for CAP

Study Design:

Randomized, double-blind, active treatment-controlled, noninferiority study

Study Population:

≥18 years of age with mild to severe CAP and radiographic evidence of acute PNA

Intervention:

Levofloxacin 750 mg/day IV/PO for 5 days versus levofloxacin 500 mg/day IV/PO for 10 days

Table 3. Evaluability of clinical and microbiologic efficacy of levofloxacin regimens in the intent-to-treat population.

Class of efficacy, evaluability status	No. (%) of patients: 750-mg group[a] (n = 256)	500-mg group[b] (n = 272)
Clinical efficacy		
Evaluable	198 (77.3)	192 (70.6)
Not evaluable, by reason		
Inappropriate posttherapy visit date	22 (8.6)	24 (8.8)
Deviation from protocol dosing regimen	14 (5.5)	26 (9.6)
Other protocol violation	9 (3.5)	9 (3.3)
Unconfirmed clinical diagnosis	8 (3.1)	12 (4.4)
Lost to follow-up[c]	3 (1.2)	5 (1.8)
Effective concomitant therapy	2 (0.8)	4 (1.5)
Microbiologic efficacy		
Evaluable	103 (40.2)	92 (33.8)
Not evaluable, by reason		
Infection not bacteriologically proven	123 (48.1)	139 (51.1)
Unconfirmed clinical diagnosis	8 (3.1)	12 (4.4)
Deviation from protocol dosing regimen	8 (3.1)	10 (3.7)
Inappropriate bacteriologic culture	6 (2.3)	11 (4.0)
Other protocol violation	6 (2.3)	6 (2.2)
Lost to follow-up[c]	2 (0.8)	1 (0.4)
Receipt of effective concomitant therapy	0 (0.0)	1 (0.4)

[a] Levofloxacin, 750 mg q.d. iv or po for 5 days.
[b] Levofloxacin, 500 mg q.d. iv or po for 10 days.
[c] Patient did not return for posttherapy visits for reason other than clinical failure.

CID 2003; 37: 752 – 760

Additional RCTs on Antimicrobial Duration in CAP

Investigator (year, reference)	Type of infection	Regimen of shorter course treatment	Regimen of comparator	N	Outcome
Siegel et al (1999, [10])	CAP	Cefuroxime 750mg q8h IV, 2d, then cefuroxime axetil 500mg q12 PO, 5d, 7d in total	Cefuroxime 750mg q8h IV, 2d, then cefuroxime axetil 500mg q12 PO, 8d, 10d in total	52	No difference in clinical cure
Leophonte et al (2002, [11])	CAP	Ceftriaxone 1g IV qd, 5d	Ceftriaxone 1g IV qd, 10d	244	No difference in clinical cure
Dunbar et al (2003, [12])	CAP	Levofloxacin 750mg IV/PO qd, 5d	Levofloxacin 500mg IV/PO qd, 10d	528	No difference in clinical cure and bacteriological outcome
Dunbar et al (2004, [13])	CAP atypical	Levofloxacin 750mg IV/PO qd, 5d	Levofloxacin 500mg IV/PO qd, 10d	149	Noninferiority in clinical cure and bacteriological outcome
Leophonte et al (2004, [14])	CAP	Gemifloxacin 320mg qd, 7d	Amoxicillin/clavulanate 1000/125mg, 10d	320	No difference in clinical, bacteriological, and radiological efficacy
Tellier et al (2004, [15])	CAP	Telithromycin 800mg PO qd, 5d	Telithromycin 800mg PO qd, 7d	378	No difference in clinical cure and bacteriological outcome
Tellier et al (2004, [15])	CAP	Telithromycin 800mg PO qd, 5d or 7d	Clarithromycin 500mg PO bid, 10d	559	No difference in clinical cure and bacteriological outcome
El Moussaoui et al (2006, [16])	CAP	Amoxicillin 1g IV q8h, 3d	Amoxicillin 1g IV q8h, 3d, then amoxicillin 750mg PO q8h, 5d, 8d in total	119	Noninferiority in clinical and radiological success
File et al (2007, [17])	CAP	Gemifloxacin 320mg PO qd, 5d	Gemifloxacin 320mg PO qd, 7d	510	Non-inferiority in clinical, bacteriological, and radiological efficacy

CID 2011; 52: 1232 – 1240

A more recent look…

Study Design: A multi-center, noninferiority RCT designed to validate the IDSA/ATS guidelines for duration of therapy

Study Population: Enrolled 312 patients age ≥18 years diagnosed with CAP at 4 teaching hospitals in Spain

Randomized at day 5 to intervention or control group

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

JAMA Internal Medicine 2016; 176: 1257 - 1265

If recommended treatment durations are evidence-based and guideline driven they should not be modified to extend the duration of use.

a. True
b. False

Extending Treatment Durations - CAP

6% - 15% of hospitalized patients with CAP do not respond to initial antibiotic therapy

Treatment failure should be considered with failure to improve, clinical deterioration or pneumonia progression, and/or nonresponse

Longer durations of therapy warranted in the following cases:

- Initial therapy not active against the isolated pathogen
- Extrapulmonary infection identified (eg, meningitis or endocarditis).
- Pneumonia caused by *P. aeruginosa*, *S. aureus*, or *Legionella* spp or pneumonia caused by some unusual and less common pathogens (eg, *Burkholderia* spp., fungus).
- Necrotizing pneumonia, empyema, or lung abscess

CID 2007; 44: S27 – S72

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

IDSA/ATS guidelines recommend a 7 day treatment course for patients with HAP/VAP

Conventional treatment typically 14 – 21 days and is largely empirical

Concern for MDR pathogens and increased risk of relapse with shorter treatment courses

XIII. 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.

XII. 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.

CID 2016; 63: e61 – e111

Comparison of 8 vs 15 days in VAP

Study Design:

Randomized, double-blind trial among two parallel groups in 51 ICUs in France conducted between May 1999 and June 2002

Study population:

≥18 years with clinical suspicion for VAP and positive quantitative cultures initiated on appropriate empiric antibiotics therapy within 24 hours of bronchoscopy (N= 402)

Intervention:

Treatment duration of 8 vs 15 days with antibiotic selection at prescribers discretion

JAMA 2003; 290: 2588 - 2598

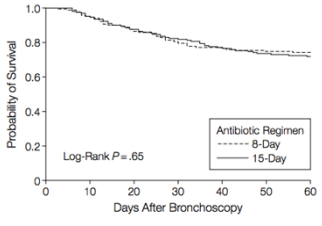
Primary Outcomes

Table 4. Primary Study Outcomes 28 Days After Bronchoscopy as a Function of Duration of Antibiotic Administration

Event	No./Total (%) 8-Day Regimen (n = 197)	No./Total (%) 15-Day Regimen (n = 204)	Between-Group Risk Difference (95% CI), %
Death from all causes*			
All patients	37/197 (18.8)	35/204 (17.2)	1.6 (–3.7 to 6.9)
Nonfermenting GNB†	15/64 (23.4)	19/63 (30.2)	–6.7 (–17.5 to 4.1)
MRSA	6/21 (28.6)	5/21 (23.8)	4.8 (–13.9 to 23.4)
Other bacteria	16/112 (14.3)	11/120 (9.2)	5.1 (–0.7 to 10.9)
Pulmonary infection recurrence*			
All patients	57/197 (28.9)	53/204 (26.0)	2.9 (–3.2 to 9.1)
Superinfection‡	39/197 (19.8)	39/204 (18.6)	1.2 (–4.3 to 6.6)
Relapse‡	33/197 (16.8)	23/204 (11.3)	5.5 (0.7 to 10.3)
Nonfermenting GNB†	26/64 (40.6)	16/63 (25.4)	15.2 (3.9 to 26.6)
Superinfection‡	13/64 (20.3)	8/63 (12.7)	7.6 (–1.1 to 14.2)
Relapse‡	21/64 (32.8)	12/63 (19.0)	13.8 (7.8 to 19.7)
MRSA	7/21 (33.3)	9/21 (42.9)	–9.5 (–30.1 to 11.1)
Superinfection‡	6/21 (28.6)	5/21 (23.8)	4.8 (–8.8 to 18.3)
Relapse‡	3/21 (14.3)	4/21 (19.0)	–4.8 (–9.9 to 0.4)
Other bacteria	24/112 (21.4)	28/120 (23.3)	–1.9 (–9.5 to 5.6)
Superinfection‡	20/112 (17.9)	25/120 (20.8)	–3.0 (–8.2 to 2.2)
Relapse‡	9/112 (8.0)	7/120 (5.8)	2.2 (–1.3 to 5.7)
	Mean (SD)		Mean Difference (95% CI), %
No. of antibiotic-free days*			
All patients	13.1 (7.4)	8.7 (5.2)	4.4 (3.1 to 5.6)
Nonfermenting GNB†	12.0 (7.4)	7.5 (5.4)	4.5 (2.2 to 6.7)
MRSA	12.9 (7.0)	4.9 (5.7)	8.0 (4.6 to 12.1)
Other bacteria	13.7 (7.5)	10.0 (4.6)	3.7 (2.1 to 5.3)

JAMA 2003; 290: 2588 - 2598

Probability of Survival



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

JAMA 2003; 290: 2588 - 2598

Short-course versus prolonged-course antibiotic therapy in HAP

Meta-analysis of RCTs assessing a fixed 'short' duration of antibiotic therapy with a ' prolonged' course for HAP (including patients with VAP) in critically ill adults

Six relevant studies involving 1088 participants

Primary outcomes:

- 28-day mortality
- Recurrence of pneumonia (diagnosed on the basis of clinical and/or microbiological criteria)
- 28-day antibiotic-free days.

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Cochrane Database of Systematic Reviews 2015; 8: 1 - 61

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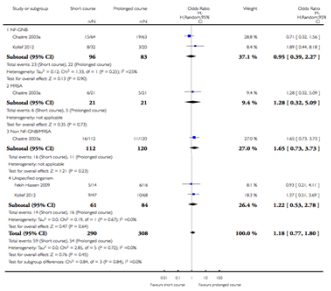
28-Day Mortality



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Cochrane Database of Systematic Reviews 2015; 8: 1 - 61

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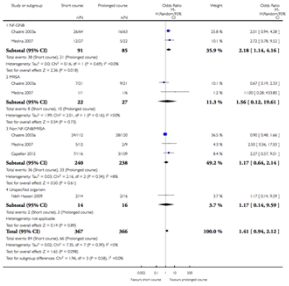
Recurrence of Pneumonia



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Cochrane Database of Systematic Reviews 2015; 8: 1 - 61

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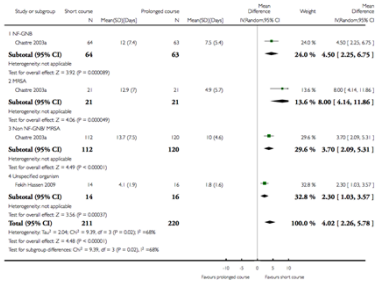
28-Day Antibiotic-Free Days



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Cochrane Database of Systematic Reviews 2015; 8: 1 - 61

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Uncomplicated Cystitis

One of the most common indications for antimicrobial use

Numerous clinical studies supporting limited durations of therapy

Optimal agent and treatment duration dependent on multiple factors (i.e. allergy history, local resistance patterns, availability)

Treatment Regimens and Expected Early Efficacy Rates:

Drug (dosage)	Estimated clinical efficacy	Estimated microbiological efficacy
Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 – 7 days)	93 (84-95)	88 (86-92)
Trimethoprim-sulfamethoxazole (160/800 mg twice daily for 3 days)	93 (90-100)	94 (91-100)
Fosfomycin trometamol (3 g single-dose sachet)	91	80 (78-83)
Fluoroquinolones (dose varies by agent; 3-day regimen)	90 (85-98)	91 (81-98)
β-lactams (dose varies by agent; 3 – 5 day regimen)	89 (79-98)	82 (74-98)

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CID 2011; 52: e103 – e120

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Acute Uncomplicated Pyelonephritis – 7 Days vs 14 Days

Study Design:

Randomized, double-blind comparative trial of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days)

Patient Population:

Women aged ≥18 years with clinical diagnosis of acute uncomplicated pyelonephritis

Primary Outcomes:

Study drug efficacy based on continued bacteriologic and clinical cure

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JAMA 2000; 283: 1583 - 1590

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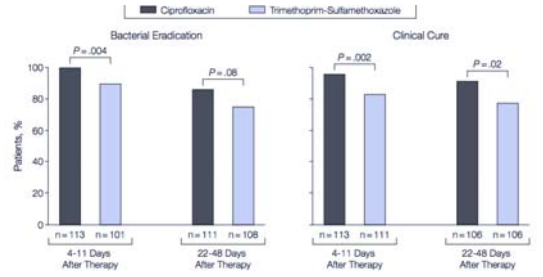
Continued Bacteriologic and Clinical Cure Rates



JAMA 2000; 283: 1583 - 1590

Acute Uncomplicated Pyelonephritis

RCTs on Antimicrobial Duration in Acute Pyelonephritis:

Gleckman et al (1985, [20])	AP	Gentamicin or Tobramycin 1.5–1.75mg/kg q8h IV, 48-72h, then TMP-SMX 160/800mg bid PO, 7-8d, 9-11d in total	Gentamicin or Tobramycin 1.5–1.75mg/kg q8h IV, 48-72h, then TMP-SMX 160/800mg bid PO, 18-19d, 20-22d in total	54	No difference in clinical cure rate
Stamm et al (1987, [21])	AP	Ampicillin 500mg q6h PO, 2 weeks	Ampicillin 500mg q6h PO, 6 weeks	27	No difference in clinical cure rate
Stamm et al (1987, [21])	AP	TMP-SMX 160/800mg q12h PO, 2 weeks	TMP-SMX 160/800mg q12h PO, 6 weeks	33	No difference in clinical cure rate
Jernelius et al (1988, [22])	AP	Pivampicillin/Pivmecillinam 500/400mg tid PO, 7d	Pivampicillin/Pivmecillinam 500/400mg tid PO, 7d, then 250/200mg tid PO, 14d, 21d in total	77	Bacteriological success: 28% vs. 69% ($P = .04$)
De Gier et al (1995, [23])	AP	Fleroxacin 400mg qd, 7d	Fleroxacin 400mg qd, 14d	54	No difference in clinical cure rate
Talan (2000, [24])	AP	Ciprofloxacin 500mg bid, 7d	TMP-SMX 160/800mg bid, 14d	255	Clinical cure rate: 96% vs. 83% ($P = .02$)
Klausner et al (2007, [25])	AP	Levofloxacin 750mg qd, 5d	Ciplofloxacin 500mg bid, 10d	192	No difference in clinical cure and microbiological eradication
Peterson et al (2008, [26])	AP	Levofloxacin 750mg qd, 5d	Ciplofloxacin 500mg bid, 10d	1109	Noninferiority in clinical cure rate and microbiological eradication

CID 2011; 52: 1232 - 1240

Intra-abdominal Infection

Previous guidelines recommended a duration of therapy no greater than 1 week with adequate source control

Typical durations of 7 – 14 days observed in clinical practice

Ability to shorten therapy limited by 20% rate of clinically significant infectious complications after treatment

SIS-IDSA guidelines recommendation that antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control.

CID 2010; 50: 133 - 164

Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Study design:

Open-label, multi-center trial comparing fixed-duration antibiotic therapy (4 days) after source control to antimicrobial therapy until 2 days after the resolution of SIRS

Study population:

≥16 years old with complicated intra-abdominal infection and adequate source control

Primary outcome:

A composite of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days after the index source-control procedure

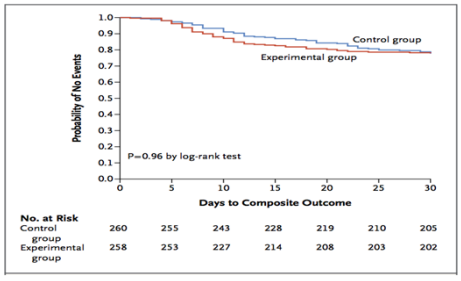
NEJM 2015; 372: 1996 - 2005

Primary Outcome

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

NEJM 2015; 372: 1996 - 2005

Kaplan-Meier Time-to-Event Curves for Composite Primary Outcome



NEJM 2015; 372: 1996 - 2005

Limiting Antimicrobial Treatment Durations in Clinical Practice

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Which of the following are antimicrobial stewardship strategies to limit antibiotic treatment durations?

a. Education
b. Post-prescription antibiotic review
c. Antibiotic time out procedures
d. Development of local guidelines
e. All of the above

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Direct Feedback

Education
- Increases knowledge of evidence-based guideline recommendations
- Supports multi-disciplinary antimicrobial stewardship initiatives

Post-prescription antibiotic review
- Opportunity to provide real-time, case specific recommendations
- One-on-one education of prescribers

Antibiotic time out
- Opportunity to reassess antimicrobial therapy at 48 – 72 hours
- Ability to establish treatment durations and order stop dates for active antimicrobial therapy

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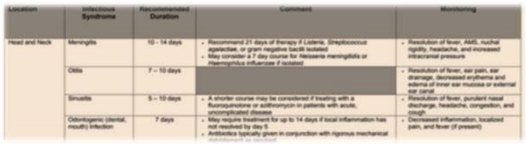
Treatment Duration Guidelines

An educational tool used to summarize treatment duration recommendations for key indications

Serves as a quick reference and guide for prescribers and pharmacists; format varies

Should present recommendations which are evidence-based and developed with consensus from Infectious Disease Specialists (if possible)



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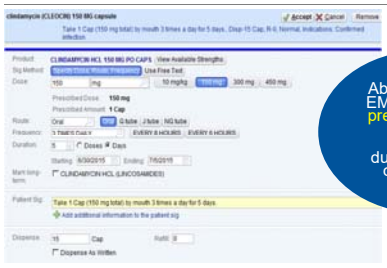
Incorporation Into the EMR



Ability in multiple EMR platforms to pre-select and/or pre-specify treatment durations based on indication

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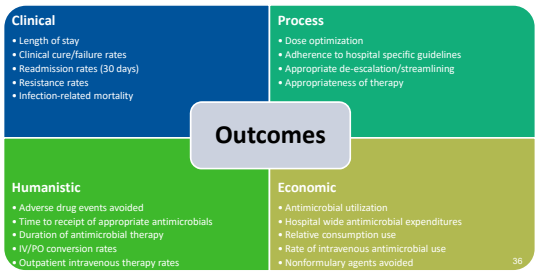
CID 2013; 57: 1005 - 1013

Outcome Measures



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Summary

- Misuse and overuse of antimicrobials can increase antimicrobial resistance development
- Antimicrobial treatment duration is a feasible target to reduce overall antimicrobial exposure
- Clinical evidence supports shorter antimicrobial treatment courses for a number of common infectious diseases
- Limiting treatment durations in clinical practice can potentially improve key outcome measures

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Questions?

"Antibiotic resistance: no action today, no cure tomorrow."

WHO

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