Duration of Antimicrobial Therapy

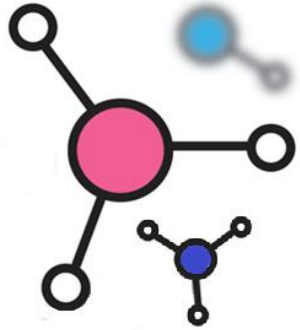
Kimberly D. Leuthner, PharmD, FIDSA

University Medical Center of Southern Nevada

August 15, 2017

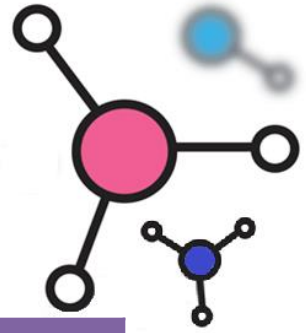
Thank you

Objectives



- Overview
- Generalized treatment concepts
- Disease specific
  - Pneumonia
  - Pyelonephritis
  - Intra-abdominal infection
- Summary

2008 Hospital Drug expenses

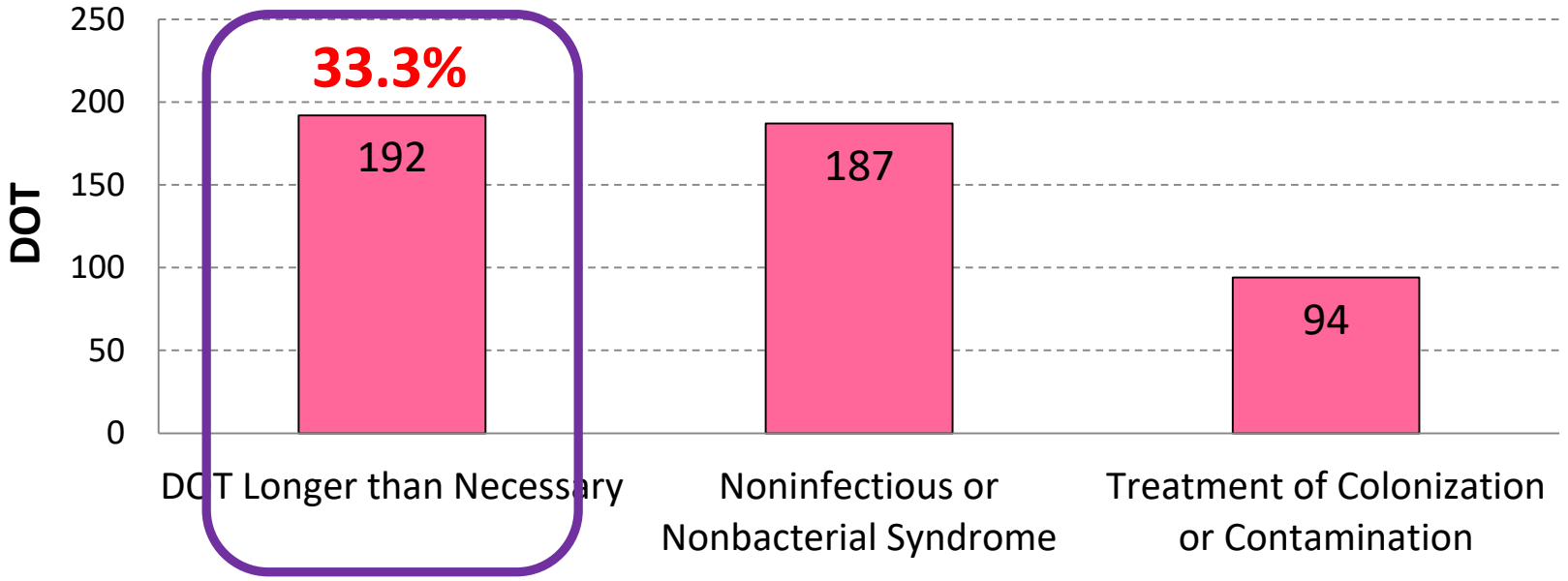


Drug Expenses	2008 Expenditures ($ Thousands)	% change from 2007
Antineoplastics	3,344,742	5.0
Hemostatic modifiers	3,459,980	6.6
Anti-infectives, systemic	3,188,596	7.3
Blood growth factors	2,196,040	-9.6
Hospital solutions	1,697, 024	17.5

Hoffman, JM, et al. Am J Health-Syst Pharm 2010;67:919-28

Unnecessary Use in Hospitals

- Prospective observational study conducted in adult inpatients over 2 weeks in August 2001
- 576 (30%) of 1941 total antimicrobial days of therapy (DOT) were deemed unnecessary



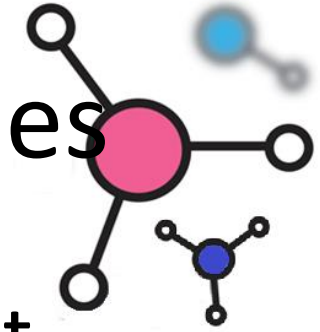
Hecker MT, et al. Arch Intern Med 2003;163:972-78

Duration of Antimicrobial Therapy

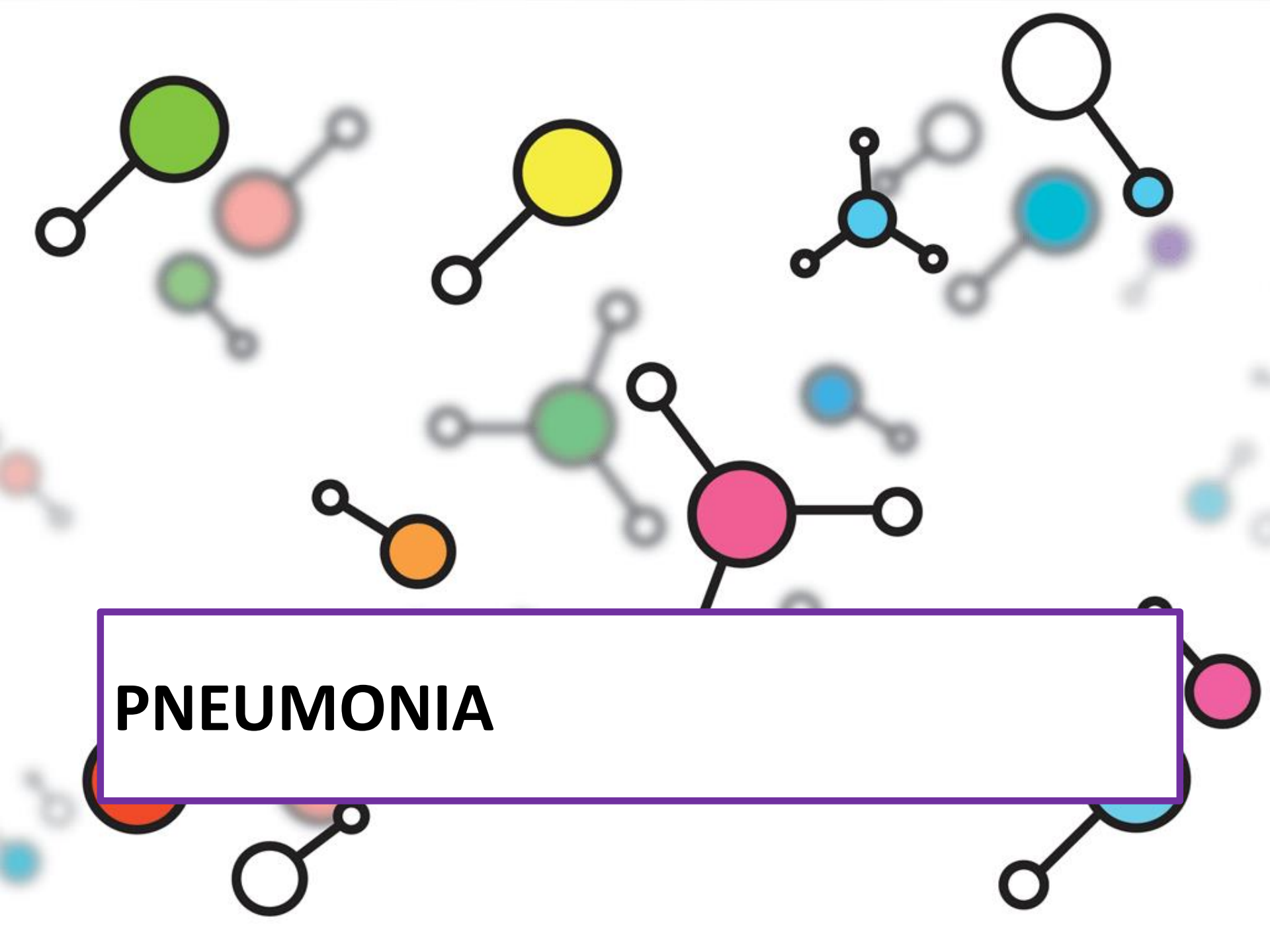
"Among available strategies to reduce use, reductions in length of antimicrobial regimens are the safest and are likely to be the most palatable to practicing clinicians."

Rice LB: *Clin Infect Dis* 2008; 46:491

General treatment duration Issues



- Duration depends on individual patient response
  - Quicker the response ➡ shorter the duration
- Source control extremely important
  - Drain abscesses
  - Remove lines or urinary catheters
- Empirical treatment important
  - Need to get it correct up front so knowing local susceptibility patterns vital



PNEUMONIA

Clinical Infectious Diseases 2007; 44:S27–72

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Lionel A. Mandell,[1,a] Richard G. Wunderink,[2,a] Antonio Anzueto,[3,4] John G. Bartlett,[7] G. Douglas Campbell,[8] Nathan C. Dean,[9,10] Scott F. Dowell,[11] Thomas M. File, Jr.[12,13] Daniel M. Musher,[5,6] Michael S. Niederman,[14,15] Antonio Torres,[16] and Cynthia G. Whitney[11]

[1]McMaster University Medical School, Hamilton, Ontario, Canada; [2]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [3]University of Texas Health Science Center and [4]South Texas Veterans Health Care System, San Antonio, and [5]Michael E. DeBakey Veterans

Clinical Infectious Diseases

IDSA GUIDELINE

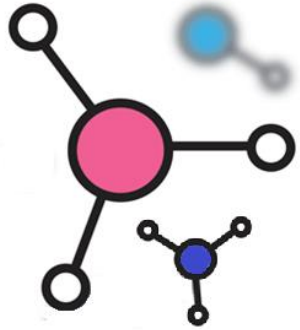
Clinical Infectious Diseases® 2016;63(5):e61–111

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha; [2]Division of Pulmonary and Critical Care Medicine, University of Connecticut

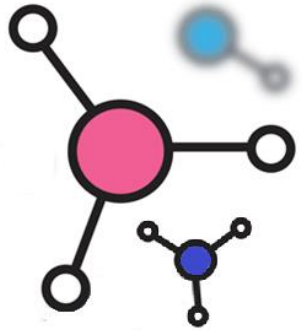
CAP: Length of Therapy



- Minimum of 5 days
- Before discontinuation of therapy:
  - Afebrile for 48 – 72 hrs
  - ≤ 1 CAP-associated sign of clinical instability
- Longer duration usually indicated with Legionella, Chlamydophila, MRSA

Mandell LA et al. CID 2007;44:S27-72
File TM and Niederman MS. Infect Dis Clin North Am. 2004;18(4):993-1016

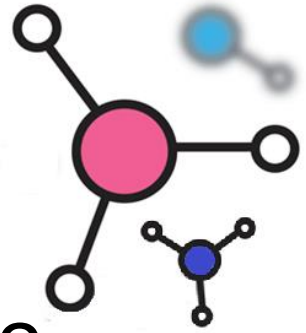
CAP: Criteria for Clinical Stability



- Temperature < 37.8°C
- Heart rate < 100 beats/min
- Respiratory rate < 24 breaths/min
- Systolic blood pressure > 90 mmHg
- Arterial O_2 sat > 90% or pO2 > 60 mmHg RA
- Ability to maintain oral intake
- Normal mental status

Mandell LA et al. CID 2007;44:S27-72

Duration for CAP Clinical Trial



- Randomized, multicenter clinical trial to confirm IDSA duration recommendations
  - Intervention group
    - 5 days minimum
    - Stopped when temperature ≤ 37.8° for 48h, and ≤ 1 CAP stability sign
  - Control group
    - Duration determined by physician

Uranga A et al. JAMA Int Med 2016;176(9)1257:1265

Results

Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Class[a]

PSI Class	No. (%) of Participants		P Value
	Control Group	Intervention Group	
Clinical Success at Day 10			
PSI classes I-III			
Intent to treat	41/86 (47.7)	58/101 (57.4)	.18
Per protocol	39/80 (48.8)	58/94 (61.7)	.09
PSI classes IV-V			
Intent to treat	30/60 (50)	32/59 (54.2)	.64
Per protocol	28/53 (52.8)	28/50 (56)	.75
Clinical Success at Day 30			
PSI classes I-III			
Intent to treat	83/88 (94.3)	93/102 (91.2)	.41
Per protocol	80/82 (97.6)	89/95 (93.7)	.29
PSI classes IV-V			
Intent to treat	49/61 (80.3)	54/58 (93.1)	.04
Per protocol	46/54 (85.2)	47/49 (95.9)	.10

Uranga A et al. JAMA Int Med 2016;176(9)1257:1265

HAP/VAP guidelines

- 7 day course of antibiotics
  - Depending upon response of the patient

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

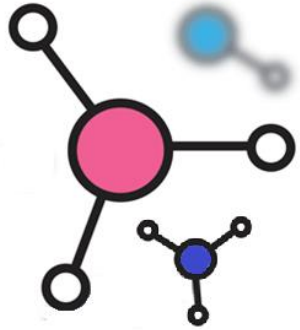
Clinical Infectious Diseases® 2016;63(5):e61–111

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha; [2]Division of Pulmonary and Critical Care Medicine, University of Connecticut

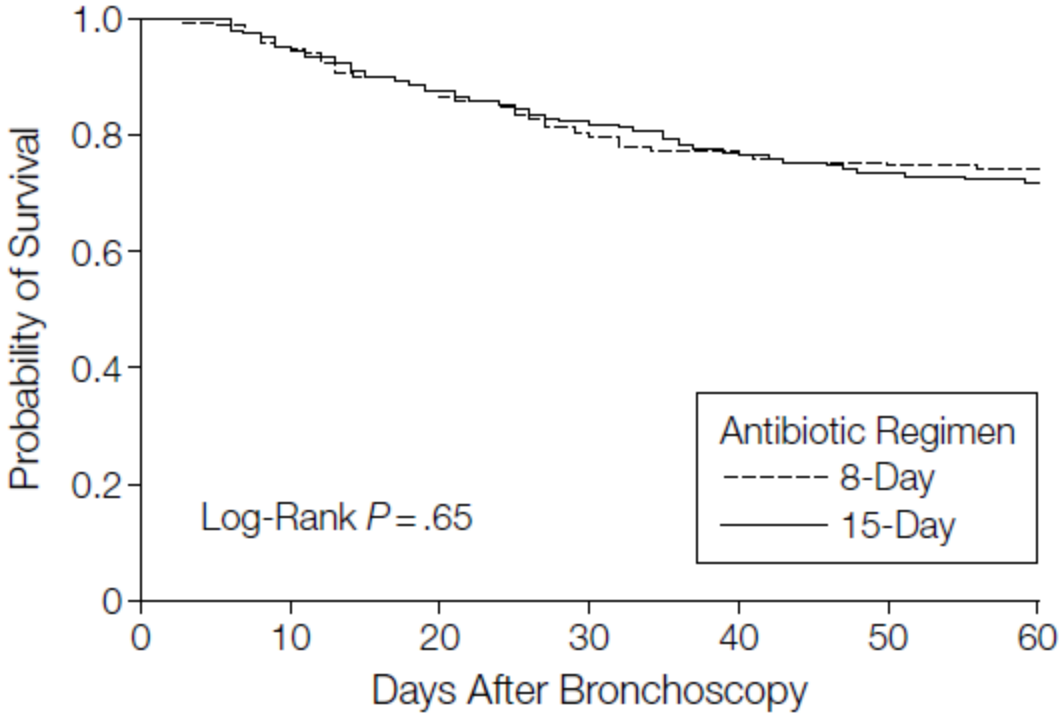
8 vs. 15d for VAP



- Randomized, double blind trial for VAP
- 51 ICUs
  - VAP confirmed by quantitative, BAL culture
- Randomized to either 8 days vs. 15 days of antibiotics
- Primary outcomes (at day 28 post BAL)
  - Death (any cause)
  - Microbiological reoccurrence

Chastre et al. JAMA 2003;290(19):2588-2598

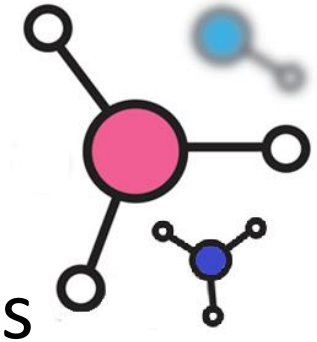
Probability of survival



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

Chastre et al. JAMA 2003;290(19):2588-2598

Results

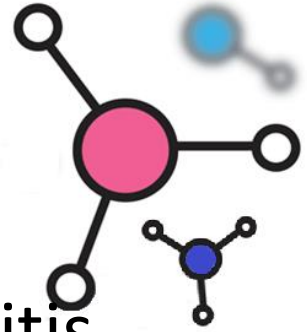


	8 days (n=197)	15 days (n=204)
Mortality	18.8%	17.2%
Recurrent infection	28.9%	26.0%
Antibiotic free days	13.1 days	8.7 days
Antimicrobial resistance	42.1%	62.0%
Recurrence rate: Non-fermenting GNB	40.6%	25.4%

- No difference in outcomes with short course (8-day) treatment

Chastre et al. JAMA 2003;290(19):2588-2598

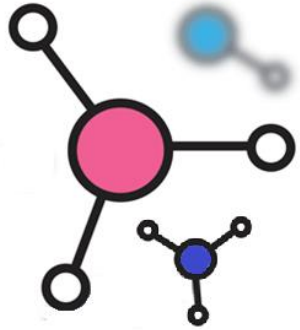
Aspiration Pneumonia



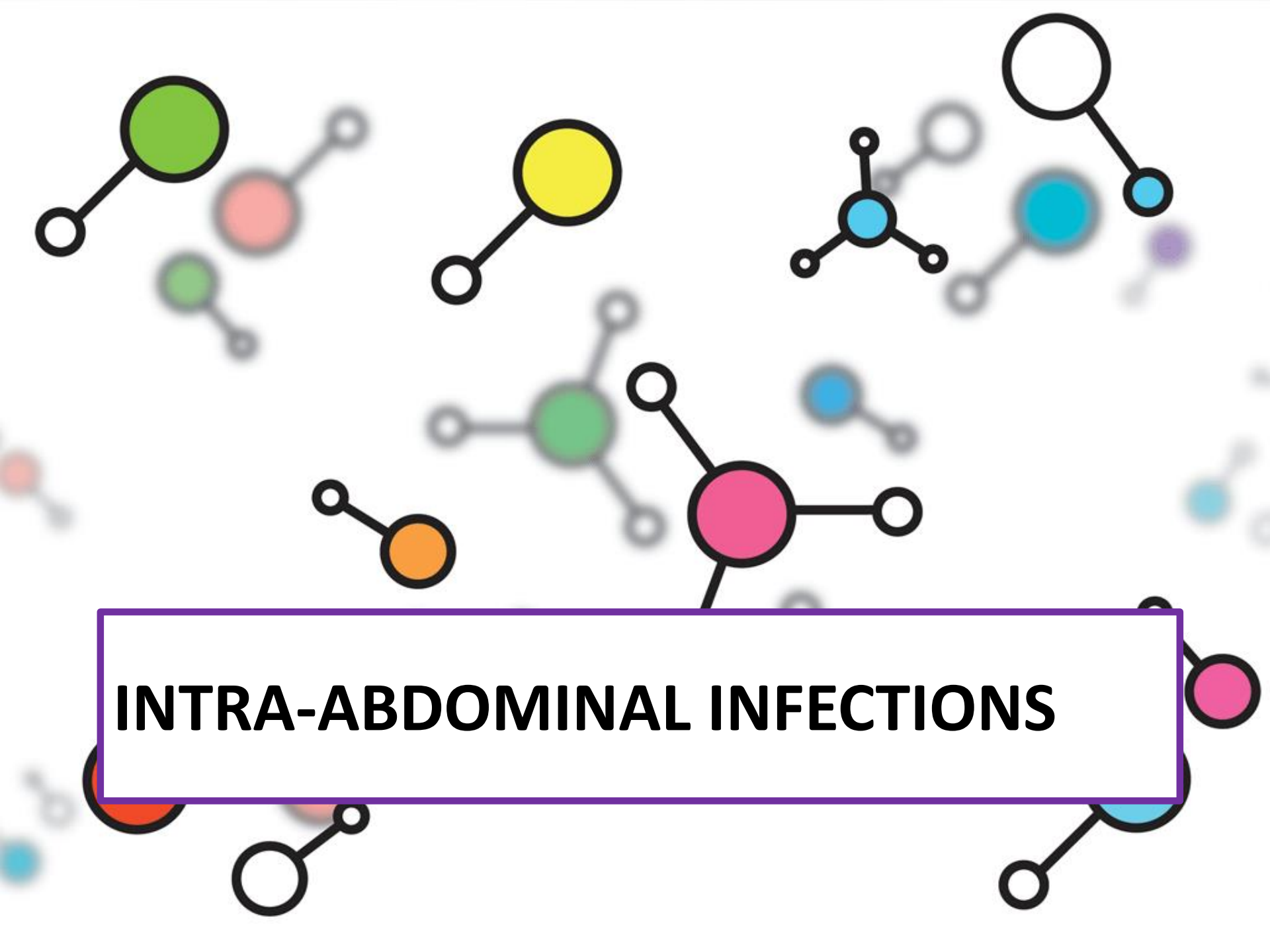
- Aspiration syndrome vs. chemical pneumonitis
  - Defined for patients intubated for > 48h
    - Temperature ≥ 38.5°C or ≤ 35.5°C
    - WBC ≥ 10,000/mm or ≤ 4,000/mm
    - New infiltrate
    - Purulent aspirate
- Randomized, prospective observational
- No differences in mortality, LOS or
- Empirical antibiotics – even with witnessed aspirations – not warranted unless clinical syndrome
  - Antibiotics stopped if appropriately obtained cultures negative

Lascarrou JB et al. Crit care Med 2017;45:1268-1275

Recommendations

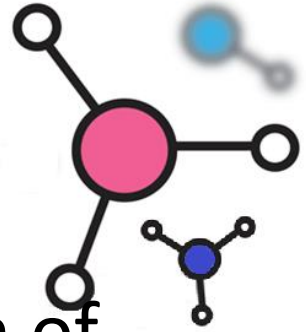


- CAP
  - 5 days
  - Hospitalized patients may need to extend duration until ≤ 1 CAP clinical stability marker
- HAP/VAP
  - Short course (7 days) appropriate for most
  - May need longer duration for non-fermenting gram negatives
- Aspiration pneumonia
  - Unless clinical signs/symptoms antibiotics not warranted
  - Antibiotics discontinued if cultures negative



INTRA-ABDOMINAL INFECTIONS

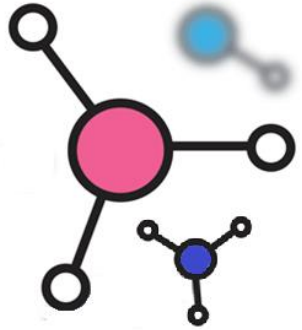
Uncomplicated Intra-abdominal



- Generally involve transmural inflammation of a portion of the GI tract or its appendages
  - No extension of the infection beyond the hollow viscus
  - Microorganisms cannot be cultured from peritoneal or other surrounding fluid
- If untreated, there is a substantial probability of these infections progressing to a complicated intra-abdominal infection

Solomkin JS, et al: *Surg Infect* 2010; 11:79; *Clin Infect Dis* 2010; 50:133

Complicated Intra-abdominal



- Growth of pathogenic microorganisms in a normally sterile region of the abdominal cavity
- Usually refers to secondary or tertiary peritonitis or an intra-abdominal abscess arising from a perforated viscus:
  - Appendix
  - Colon or small bowel
  - Stomach or duodenum
  - Gallbladder
  - Postoperative

Solomkin JS, et al: *Surg Infect* 2010; 11:79; *Clin Infect Dis* 2010; 50:133

IDSA GUIDELINES

Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America

Joseph S. Solomkin,[1] John E. Mazuski,[2] John S. Bradley,[3] Keith A. Rodvold,[7,8] Ellie J. C. Goldstein,[5] Ellen J. Baron,[6] Patrick J. O'Neill,[9] Anthony W. Chow,[16] E. Patchen Dellinger,[10] Soumitra R. Eachempati,[11] Sherwood Gorbach,[12] Mary Hilfiker,[4] Addison K. May,[13] Avery B. Nathens,[17] Robert G. Sawyer,[14] and John G. Bartlett[15]

Clinical Infectious Diseases 2010; 50:133–64

Sartelli *et al. World Journal of Emergency Surgery* (2017) 12:22
DOI 10.1186/s13017-017-0132-7

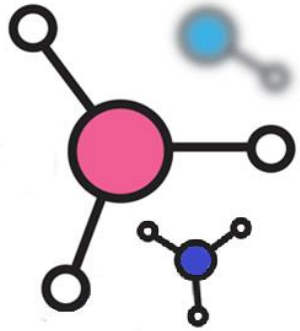
World Journal of Emergency Surgery

REVIEW Open Access

Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference

Massimo Sartelli[1*], Fausto Catena[2], Fikri M. Abu-Zidan[3], Luca Ansaloni[4], Walter L. Biffl[5], Marja A. Boermeester[6],

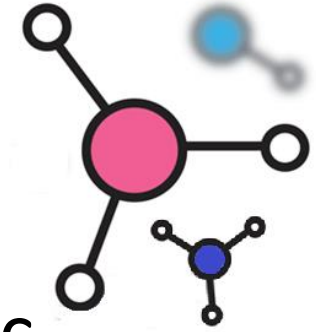
Guideline recommendations



- Uncomplicated intra-abdominal infections
  - Surgical interventions and antibiotics ≤ 24 h
- Complicated Intra-abdominal infection
  - 4 to 7 days **UNLESS UNABLE** to achieve adequate source control
- Bowel injuries due to penetrating, blunt or iatrogentic trauma
  - ≤ 24 hours if repaired within 12h
- Acute appendicitis without evidence of perforation, abscess or local peritonitis
  - ≤ 24 hours

Solomkin JS, et al: *Clin Infect Dis* 2010; 50:133
Sartelli M et al. World Journal of Emergency Surgery 2017;12:22

Why Source Control?

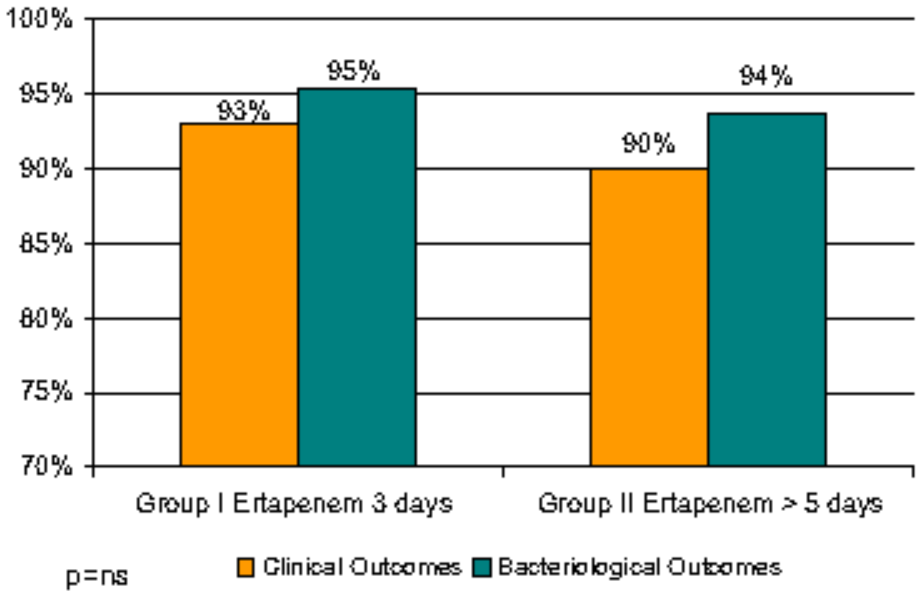


- Risk factors for mortality in 108 bacteremic patients with intra-abdominal infections.
- Overall mortality was 27.8%
- Source control ≤ 24h: 74/101 patients (73.3%)
  - Mortality 9.5% adequate source control
  - Mortality 33.3% inadequate source control
- In the multivariate logistic regression analysis, inadequate source control was highly associated with mortality (P = 0.011)

Tellor B, et al: *Crit Care Med* 2012; 40[Suppl]:680

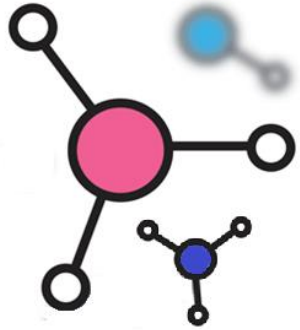
Duration of Antimicrobial Therapy

- Prospective trial of 3 vs. > 5 days of antimicrobial therapy in 90 patients with low severity intra-abdominal infections
  - 50% with perforated appendicitis



Basoli A, et al: *J Gastrointest Surg* 2008; 12:592

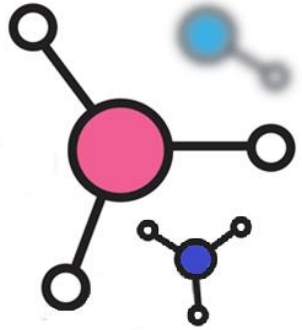
SIS STOP-IT trial



- Randomized, open-label trial
  - Control: antibiotics until 2d post SIRS resolution (max 10d)
  - Experimental: antibiotics for 4 days
- Primary outcome: composite endpoint
  - Surgical site infection
  - Recurrent intra-abdominal infection
  - Death

Sawyer R, et al: *NEJM* 2015;372;21:1999-2005

Results

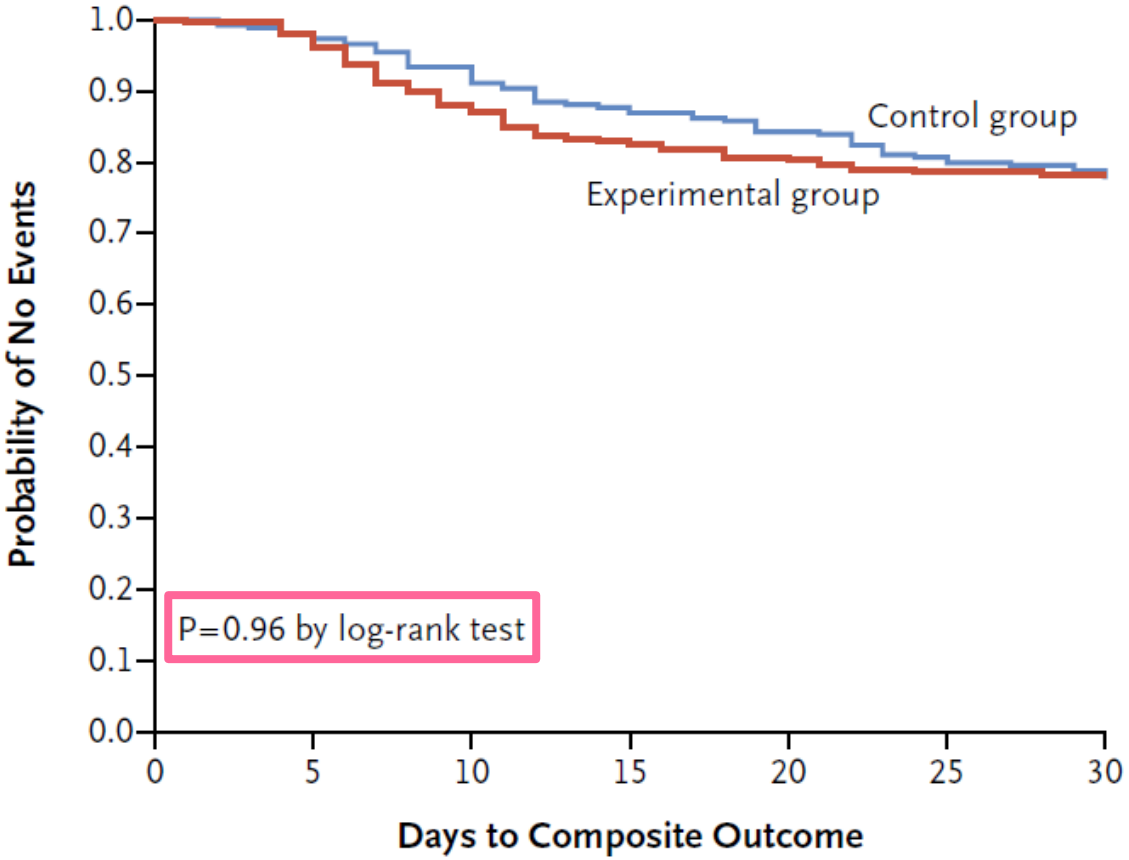


- 260 patients control vs. 257 experimental
- Similar baseline characteristics
  - Similar surgical interventions/source control
  - APACHE II score = 10

	Standard (N=260)	4 day (N=257)	P value
Surgical site infection; n(%)	23 (8.8)	17 (6.6)	0.43
Recurrent intra-abd infection; n(%)	36 (13.8)	40 (15.6)	0.67
Death; n(%)	2 (0.8)	3 (1.2)	0.99
Composite ; n(%)	58 (22.3)	56 (21.8)	0.92

Sawyer R, et al: *NEJM* 2015;372;21:1999-2005

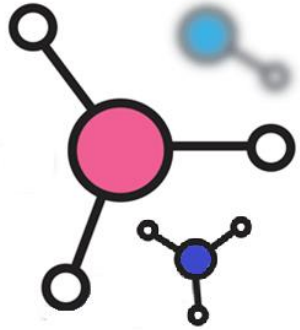
Time to Primary Outcome



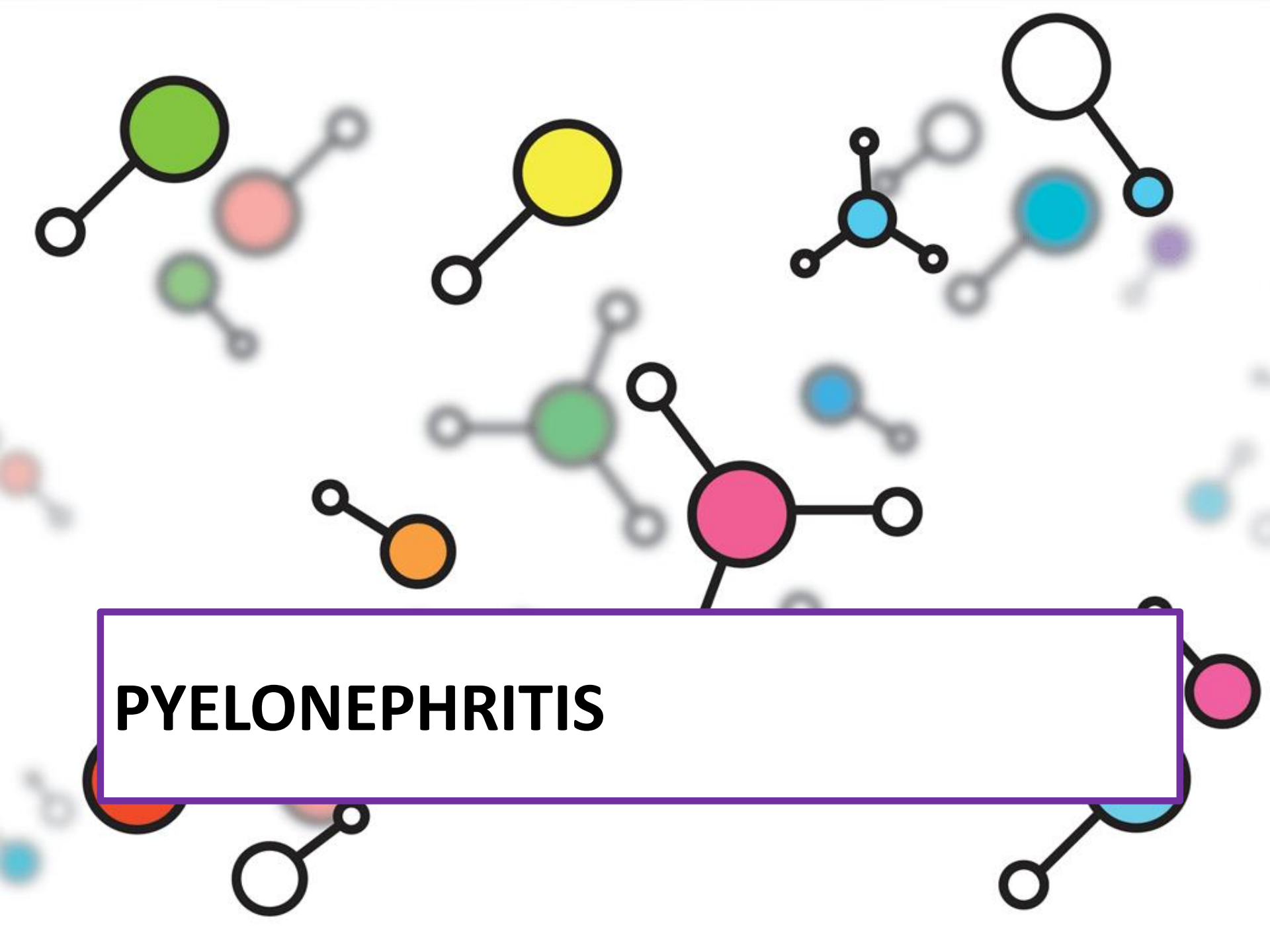
No. at Risk							
Control group	260	255	243	228	219	210	205
Experimental group	258	253	227	214	208	203	202

Sawyer R, et al: *NEJM* 2015;372;21:1999-2005

Recommendations



- Studies support guideline recommendations of shorter durations
  - Certain patients as few as 3 days
  - Most patients between 4 to 7 days
- Source control is still integral to the treatment of most patients with intra-abdominal infections
  - Duration of treatment without adequate source control not well defined



PYELONEPHRITIS

Clinical Infectious Diseases 2011;52(5):e103–e120

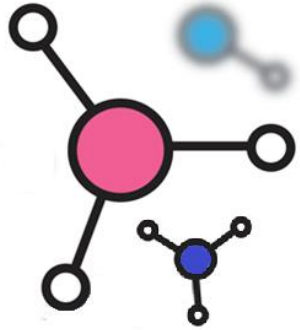
IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Kalpana Gupta,[1] Thomas M. Hooton,[2] Kurt G. Naber,[9] Björn Wullt,[10] Richard Colgan,[3] Loren G. Miller,[4] Gregory J. Moran,[5] Lindsay E. Nicolle,[8] Raul Raz,[11] Anthony J. Schaeffer,[6] and David E. Soper[7]

[1]Department of Medicine, Veterans Affairs Boston Health Care System and Boston University School of Medicine, Boston, Massachusetts; [2]Department of Medicine, University of Miami Miller School of Medicine, University of Miami, Miami Florida; [3]Department of Family and Community Medicine, University

Guideline recommendations



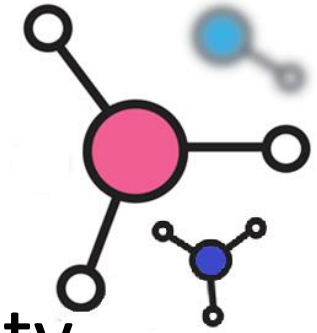
- Pyelonephritis
  - 7 days with fluoroquinolone
    - Only if resistance rates < 10%
  - 14 days with TMP/SMX
  - 10-14 days with B-lactam

UMCSN outpatient resistance > 25%

Guidelines published in 2011 – anything new?

Gupta K et al. Clinical Infectious Diseases 2011;52(5):e103-120

Ciprofloxacin 7 vs. 14 days



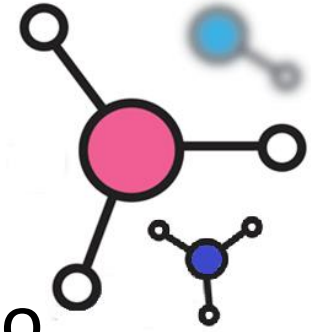
- Randomized, prospective non-inferiority

	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p value
Short-term efficacy	73	83		
Cure	71 (97%)	80 (96%)	−0·9% (−6·5 to 4·8)	0·004
Clinical failure or recurrent symptomatic urinary tract infections	2 (3%)	3 (4%)	..	
Cumulative efficacy	73	84		
Cure	68 (93%)	78 (93%)	−0·3% (−7·4 to 7·2)	0·015
Clinical failure or recurrent symptomatic urinary tract infections	5 (7%)	6 (7%)	..	

Data are number (%), unless otherwise indicated.

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

Duration Re-evaluation



- Meta-analysis of RCT comparing ≤ 7 days to longer therapy
  - Not specific for which antibiotics included
- Primary outcome
  - Clinical failure at EOT longer treatment arm
- Secondary outcomes
  - Clinical failure at end of follow-up
  - Microbiological failure
  - All cause mortality
  - Resistance development

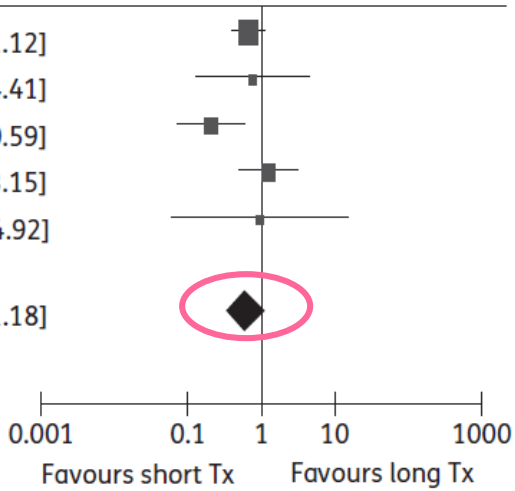
Eliakim-Raz N et al. Antimicrob Chemother 2013;68:2183-2191

End of therapy

Study or subgroup	Short Events	Short Total	Long Events	Long Total	Weight	RR M-H, Random, 95% CI
Peterson 2008	23	265	31	241	38.9%	0.67 [0.41–1.12]
Sandberg 2012	2	73	3	83	10.3%	0.76 [0.13–4.41]
Talan 2000	4	113	19	111	21.5%	0.21 [0.07–0.59]
de Gier 1995	7	18	5	16	24.5%	1.24 [0.49–3.15]
Klausner 2007	1	80	1	76	4.8%	0.95 [0.06–14.92]
Total (95% CI)		549		527	100.0%	0.63 [0.33–1.18]
Total events	37		59			

Heterogeneity: $\tau^2 = 0.20$; $\chi^2 = 6.83$, df = 4 ($P = 0.15$); $I^2 = 41\%$

Test for overall effect: $Z = 1.45$ ($P = 0.15$)

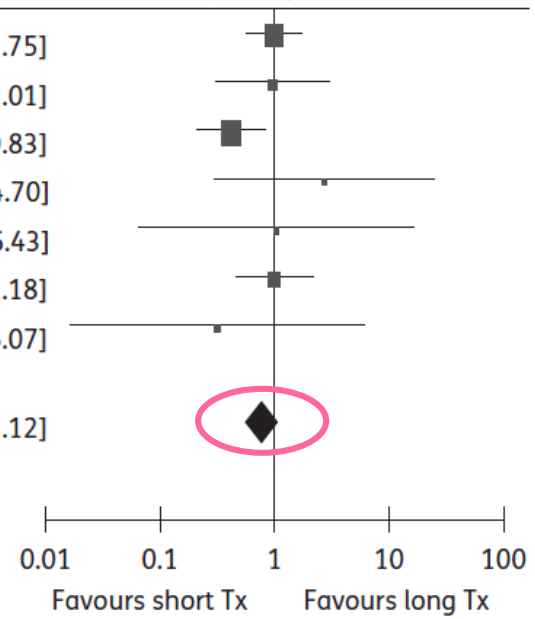


End of Follow-up

Study or subgroup	Short Events	Short Total	Long Events	Long Total	Weight	RR M-H, Fixed, 95% CI
Peterson 2008	23	265	21	241	32.8%	1.00 [0.57–1.75]
Sandberg 2012	5	73	6	84	8.3%	0.96 [0.31–3.01]
Talan 2000	10	106	24	106	35.8%	0.42 [0.21–0.83]
Jernelius 1988	3	32	1	29	1.6%	2.72 [0.30–24.70]
Klausner 2007	1	94	1	98	1.5%	1.04 [0.07–16.43]
Mensa 1999	12	123	11	113	17.1%	1.00 [0.46–2.18]
Ode 1980	0	13	2	21	2.9%	0.31 [0.02–6.07]
Total (95% CI)		706		692	100.0%	0.79 [0.56–1.12]
Total events	54		66			

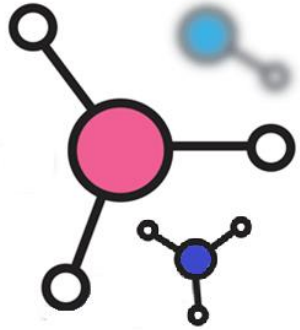
Heterogeneity: $\chi^2 = 6.06$, df = 6 ($P = 0.42$); $I^2 = 1\%$

Test for overall effect: $Z = 1.32$ ($P = 0.19$)



Summary

- No differences in any outcomes
  - Clinical failure at EOT or EOF
  - Microbiological
  - Adverse events

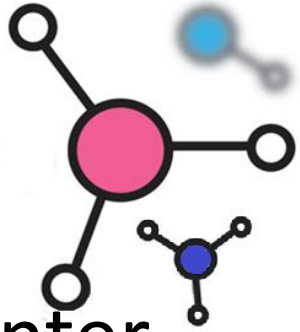


Conclusion

- Shorter courses for the treatment of acute pyelonephritis appropriate
- If patient has urogenital abnormalities, longer durations may be warranted

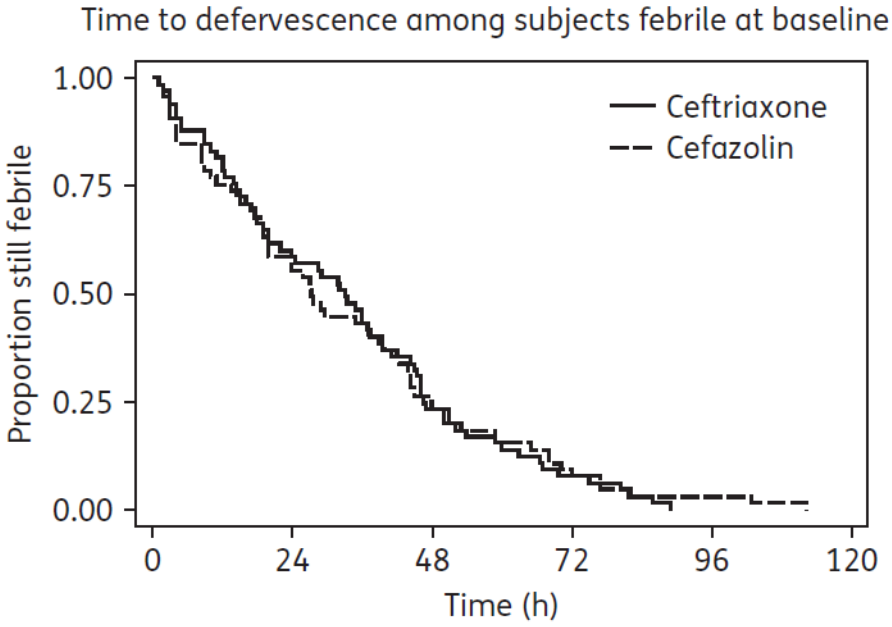
Eliakim-Raz N et al. Antimicrob Chemother 2013;68:2183-2191

B-lactams for pyelonephritis



- Retrospective, non-inferiority, multi-center cohort for cefazolin vs. ceftriaxone
  - Included for clinical signs/symptoms of pyelonephritis
  - Microbiological susceptibilities not required
- Primary outcome
  - If cefazolin non-inferior to ceftriaxone

Hobbs ALV et al. J Antimicrob Chemother 2016;71:1665-1671

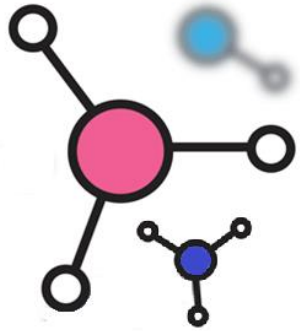


No different between groups

	Cefazolin ($N=92$)	Ceftriaxone ($N=92$)	P
β-Lactam	60 (65.2)	50 (54.3)	0.13
Fluoroquinolone	16 (17.4)	31 (33.7)	0.01
Sulfamethoxazole/trimethoprim	12 (13.0)	2 (2.2)	0.01
Nitrofurantoin	2 (2.2)	2 (2.2)	1
No antibiotics	2 (2.2)	7 (7.6)	0.12
Duration of therapy (days), mean (SD)	8.4 (4.2)	7.2 (3.3)	0.02[a]

Hobbs ALV et al. J Antimicrob Chemother 2016;71:1665-1671

Summary



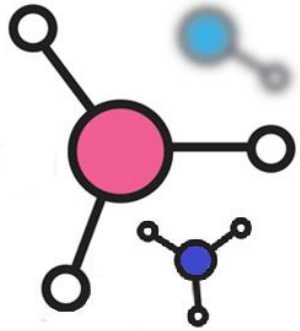
- Retrospective study
- No differences clinical response
  - 87.0% cefazolin vs. 85.9% ceftriaxone
- Cefazolin was non-inferior to ceftriaxone

Demonstrates

- Shorter courses even for B-lactam antibiotics may be appropriate
- Treatment outcomes were independent of susceptibilities

Hobbs ALV et al. J Antimicrob Chemother 2016;71:1665-1671

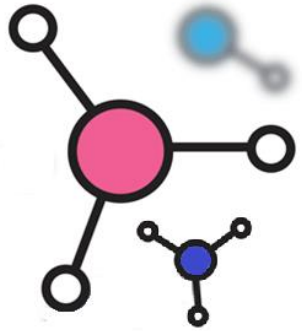
Recommendations



- Guidelines suggest 10-14 days
- Newer studies show shorter duration appropriate
  - ≤ 7 days
  - Does not appear to matter which antimicrobial
- Important to know local susceptibilities to ensure appropriate empirical therapy
  - Duration may have to be extended due to non-response if initial therapy not susceptible

Hobbs ALV et al. J Antimicrob Chemother 2016;71:1665-1671

Overall Summary



- Studies supporting shorter courses regardless of diagnosis

Disease	Treatment days	
	Short	Long
Community acquired pneumonia	3 – 5	7 – 10
VAP/HAP pneumonia	≤ 8	10 – 15
Aspiration pneumonia	3 – 7	7 – 10
Intra-abdominal infection	4	10
Pyelonephritis	5 – 7	10 – 14

- Duration should be individualized to patient response

Spellberg, B. JAMA Int Med 2016;176(9)1254:1255

Questions?