

Controversies in the antibiotic treatment of young infants with first febrile UTI

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Over past 2 decades 'less is more' in UTI management

Less antibiotics

Less imaging

MORE IS NOT **ALWAYS** BETTER

The same is true for medical tests and treatments. Talk to your doctor about what you need, and what you don't. To learn more, visit www.choosingwisely.ca



Objectives

To discuss controversies in the antibiotic treatment of young infants with first febrile UTI:

- 1. Initial route antibiotic treatment oral vs. IV?
- 2. Early transition to oral antibiotics short vs. long IV duration?
- 3. Total duration of antibiotic treatment 5 vs. 10 days?

UTI Common & Expensive

Figure 1. Volume and Cost of Encounters for the 25 Highest-Cost Medical Conditions Among Children With Inpatient Encounters in Ontario, Canada, From 2014 to 2019



- 18th most common and expensive inpatient condition in Ontario
- 8th most common inpatient condition in US

Gill et al. JAMA Network Open 2022

First Febrile UTI in infants <2 years: CPS and AAP UTI guidelines

CPS Guidelines, 2014

- Clean Catch \geq 100,000 CFU/ml (\geq 10⁸ CFU/L)
- Catheter \geq 50,000 CFU/ml (\geq 5x10⁷ CFU/L)
- SPA any growth

AAP Guidelines, 2011

- Clean Catch not specified
- Catheter ≥ 50,000 CFU/mI
- SPA ≥ 50,000 CFU/mI



No bag specimens for culture

New role of voiding stimulation methods

Are oral antibiotics effective and safe for treatment of young infants with first febrile UTI?

Jackie is a 5 week old term infant with first febrile UTI. She is feeding well and looks well otherwise. The urinalysis is positive for leukocytes and nitrites. Should you treat her with oral antibiotics? Should she be admitted with short (2 days) or longer course IV antibiotics (5 days)? Total duration of antibiotics?



First Febrile UTI: Less vs. More Antibiotics

LESS: SHORTER/NO IV ABx TREATMENT

- \downarrow Need for repeated PIVs or PICC \downarrow LOS
- \downarrow Abx adverse events, microbiome
- \downarrow Harms of hospitalization
- \downarrow Health system impact, cost
- ?bioavailability in young infants

MORE: LONGER IV Abx TREATMENT

 \downarrow reduce risk of treatment failure



CPS and AAP UTI guidelines

CPS Guidelines, 2014

Most experts recommend initial treatment with oral antibiotics for febrile UTIs in nontoxic children with no known structural urological abnormality, assuming that they are likely to receive and tolerate every dose.

There is no evidence that children with UTIs and documented bacteremia who have a rapid clinical response to antibiotics require intravenous antibiotics or a longer course of antibiotics. However, all such children need to be assessed by a physician the day that the blood culture is known to be positive.

AAP Guidelines, 2011

When initiating treatment, the clinician should base the choice of route of administration on practical considerations. Initiating treatment oral or parenterally is equally efficacious.



Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

Robert H. Pantell, MD, FAAP,^a Kenneth B. Roberts, MD, FAAP,^b William G. Adams, MD, FAAP,^c Benard P. Dreyer, MD, FAAP,^d Nathan Kuppermann, MD, MPH, FAAP, FACEP,^e Sean T. O'Leary, MD, MPH, FAAP,^f Kymika Okechukwu, MPA,^g Charles R. Woods Jr, MD, MS, FAAP^h SUBCOMMITTEE ON FEBRILE INFANTS

PEDIATRICS Volume 148, number 2, August 2021:e2021052228

Initial Antibiotic Route

8-28 days: well appearing, positive urinalysis – initial treatment with IV antibiotics

29-60 days: well appearing, positive urinalysis – initial oral or IV antibiotics depending on inflammatory marker results

Antibiotic Route transition in hospitalized infants

29-60 days: UTI (positive urine culture): discharge hospitalized patients on oral antibiotics if blood culture negative, CSF (if obtained) is negative, infant is well and improving, no other reasons for hospitalization

Position Statement

Management of <u>well-appearing</u> febrile young infants aged ≤90 days

Brett Burstein MDCM, PhD, MPH, Marie-Pier Lirette MBChB, Carolyn Beck MD, Laurel Chauvin-Kimoff MD, Kevin Chan MD, MPH

Canadian Paediatric Society, Acute Care Committee, Ottawa, Ontario, Canada



1. Initial antibiotic treatment route in infants with first febrile UTI?

Antibiotics for acute pyelonephritis in children (Review)

Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC



- 4 RCTs: Oral (10-14 d) vs. Short IV (3-4 d) followed by Oral Antibiotics
- > 1 month age
- NO DIFFERENCE in:
 - Duration of fever (2 studies, 808 children: MD 2.05 hrs, 95% CI -0.84-4.94)
 - Persistent UTI at 72 hours (2 studies, 542 children: RR 1.01, 95% CI 0.07-17.41)
 - Persistent kidney damage at 6-12 months (4 studies, 943 children: RR 0.82, 95% CI 0.59-1.12)

2. Early transition to oral antibiotic treatment in infants with first febrile UTI?



Antibiotics for acute pyelonephritis in children (Review)

Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC



- 6 RCTs: <u>Short IV (3-4d) followed by Oral Antibiotics vs. Long IV (7-14 days)</u>
- > 1 month age
- No DIFFERENCE in:
 - Persistent bacteriuria at end of treatment (4 studies, 305 children: RR 1.10, 95% CI 0.07-17.41)
 - Persistent kidney damage at 6-12 months (4 studies, 726 children: RR 1.01, 95% CI 0.80-1.29)

Length of Intravenous Antibiotic Therapy and Treatment Failure in Infants With Urinary Tract Infections

AUTHORS: Patrick W. Brady, MD,^{a,b,c} Patrick H. Conway, MD, MSc,^{a,b,c} and Anthony Goudie, PhD^{b,c}

- Retrospective cohort study, 24 US children's hospitals
- Of 12,333 infants, < 6 mo age: 240 (1.9%) experienced treatment failure
 - ≤3 days initial IV Antibiotics 1.6%
 - ≥ 4 days initial IV Antibiotics 2.2 %
- After propensity score adjustment, no significant association between long vs. short course IV antibiotics and treatment failure (OR 1.02, 95% CI 0.77-1.35)

Characteristics	Proporti	Р	
	Short Therapy $(N = 5414)$	Long Therapy $(N = 6919)$	
Gender			
Male	45.8 (2479)	56.5 (3906)	<.0001
Female	54.2 (2935)	43.5 (3013)	
Age			
<1 mo (neonates)	19.2 (1042)	33.8 (2341)	<.0001
\geq 1 and $<$ 2 mo	27.4 (1484)	27.5 (1902)	
\geq 2 and $<$ 3 mo	22.0 (1190)	17.2 (1188)	
\geq 3 and $<$ 4 mo	14.0 (757)	9.5 (657)	
\geq 4 and $<$ 5 mo	10.3 (557)	7.2 (499)	
\geq 5 and $<$ 6 mo	7.1 (384)	4.8 (332)	
Race			
White	65.3 (3534)	63.8 (4413)	.003
Black	15.9 (862)	18.3 (1263)	
Other	18.8 (1018)	18.0 (1243)	
Ethnicity			
Hispanic	23.1 (1248)	30.7 (2126)	<.0001
Not Hispanic or unknown	76.9 (4166)	69.3 (4793)	
Bacteremia			
Known	0.5 (26)	0.8 (55)	.03
Unknown or not present	99.5 (5388)	99.2 (6864)	
Genitourinary abnormalities			
Known	10.2 (551)	19.9 (1379)	<.0001
Unknown or not present	89.8 (4863)	80.1 (5540)	
Primary payer			
Medicaid	49.9 (2699)	50.1 (3467)	<.0001
Private insurance	27.8 (1504)	20.2 (1395)	
Self-pay	3.9 (212)	3.7 (253)	
Other	18.5 (999)	26.1 (1804)	

TABLE 1 Patient Characteristics for Short and Long Intravenous Antibiotic Therapy Groups

Treatment of UTIs in Infants <2 Months: A Living Systematic Review

Nassr Nama, MD, MSc, FRCPC, FAAP,^{a,b} Robine Donken, PhD,^c Colleen Pawliuk, MLIS,^d Leire Leache, PharmD, PhD,⁵ Manish Sadarangani, BM, BCh, DPhil,^{a,b,c} Matthew Carwana, MD, FRCPC^{a,b,d} THE INSIGHTSCOPE TEAM • Main comparison: \leq 3 days vs. > 3 days IV

- Studies which included infants < 2 months
- All observational studies (retrospective)
- UTI recurrence: 1.7% (1.3,2.2) ≤ 3 days vs.
 2.4% (1.8,3.2) > 3 days IV

HOSPITAL PEDIATRICS Volume 11, Issue 9, September 2021

				Anticipated Absolute Effects		
Outcomes, Follow-up	No. Participants (No. Observational Studies)	Certainty of the Evidence, GRADE	Relative Effect, OR (95% Cl)	Risk With Long Parenteral Antibiotics (>3 d)	Risk Difference With Short Parenteral Antibiotics (≤3 d) ^a	
UTI recurrence follow- up, range: 14–90 d	5451 (10)	⊕⊕ LOW	1.02 (0.64 to 1.61)	24 per 1000	0 fewer per 1000 (8 fewer to 14 more)	
Subgroup Analyses						
UTI recurrence (0—1 mo) follow-up, range 14—90 d	2275 (7) ^b	⊕⊕ LOW	1.17 (0.66 to 2.08)	19 per 1000	3 more per 1000 (6 fewer to 20 more)	
UTI recurrence (1—2 mo) follow-up, 30 d	2715 (5) ^c	⊕⊕ LOW	0.90 (0.44 to 1.88)	26 per 1000	3 fewer per 1000 (14 fewer to 22 more)	
UTI recurrence (bacteremic) follow- up, range: 14—30 d	358 (4) ^d	\oplus VERY LOW ^e	0.91 (0.22 to 3.80)	49 per 1000	4 fewer per 1000 (38 fewer to 115 more)	
UTI recurrence (nonbacteremic) follow-up, range: 14–90 d	4731 (7) ^d	⊕⊕ LOW	1.07 (0.66 to 1.73)	18 per 1000	1 more per 1000 (6 fewer to 12 more)	

TABLE 2 Summary of Findings Table

Bacteremia?



Parenteral Antibiotic Therapy Duration in Young Infants With Bacteremic Urinary Tract Infections

Cohort study, 11 US centres, ED presentation

115 infants \leq 60 days with bacteremic UTI, 32 (28%) ill appearing, excluded those with meningitis

Short course defined as \leq 7 days IV and long course > 7 days IV

- 58 (50%) received short-course IV antibiotics (range 2-24 days)
- 60 (52%) ≤ 28 days age: 42% short-course IV, 58% long-course
 Propensity score weighting

No significant difference in UTI recurrence or hospital reutilization

Outcome	Short-Course IV/ IM Antibiotics (n = 58)	Long-Course IV/IM Antibiotics (n = 57)	Adjusted Relative Risk (95% Cl) ^a	Percent Adjusted Risk Difference (95% Cl) ^a	Adjusted Mean Difference (95% CI) ^a	No adverse
Recurrent UTI, n (%)	2 (3)	4 (7)	1.9 (0.3 to 11.6)	3 (—5.8 to 12.7)	_	readmission,
Recurrent UTI with same organism, <i>n</i> (%)	2 (3)	2 (4)	1.1 (0.1 to 8.4)	0.2 (-7.8 to 8.3)		neurologic sequelae
All-cause reutilization, <i>n</i> (%)	6 (10)	9 (16)	1.2 (0.4 to 3.9)	3 (-14.5 to 20.6)	_	
LOS, d, adjusted mean (95% CI)	4.5 (4.4 to 4.6)	10.8 (10.7 to 10.9)	—		6 (4.0 to 8.8)	

TABLE 2 Outcomes of Infants With Bacteremic UTI

^a IPW was conducted by using propensity scores to achieve covariate balance in patient clinical and demographic characteristics. Marginal structural models were applied to the weighted population to obtain adjusted estimates.

Bacteraemic urinary tract infection: management and outcomes in young infants

Multi-centre retrospective cohort study across 11 US children's hospitals in infants \leq 90 days with bacteremic UTI (no meningitis)

- 251 infants with bacteremic UTI
- Median age 35 d (17-58 d), 19 (7.6%) ill appearance
- Mean duration of IV antibiotic therapy was 7.8 days (+/- 4 days)
- No infants had a relapsed bacteremia
- 6 (2.4%) infants had relapsed UTI
 - Duration of IV antibiotics did not differ between infants with and without a relapse (8.2 vs. 7.8 days)

Summary: Initial oral antibiotic route and early transition to oral?

- In neonates (≤ 28 days): well appearing with non-bacteremic UTI and no concern for meningitis, short-course (≤ 3-4 days) IV antibiotics with early conversion to oral antibiotics may be considered with follow-up
- In young infants (29-60 days): well appearing, normal IM, initial oral antibiotic treatment may be considered with follow-up; if hospitalized for initial IV antibiotics, non-bacteremic, short-course (≤ 3-4 days) IV antibiotics with early conversion to oral antibiotics with follow-up
- 3. In **young infants (<90 days),** with **bacteremic UTI** and well appearing, shorter course IV antibiotics (≤7 days) with early conversion to oral antibiotics may be considered

3. Antibiotic treatment duration of infants with first febrile UTI?

Antibiotic Treatment Duration: CPS and AAP UTI guidelines

CPS Guidelines, 2014

• 7 to 14 days

AAP Guidelines, 2011

• 7 to 10 days

Short-Course Therapy for Urinary Tract Infections in Children The SCOUT Randomized Clinical Trial

Theoklis Zaoutis, MD; Nader Shaikh, MD; Brian T. Fisher, DO; Susan E. Coffin, MD; Sonika Bhatnagar, MD; Kevin J. Downes, MD; Jeffrey S. Gerber, MD; Timothy R. Shope, MD; Judith M. Martin, MD; Gysella B. Muniz, MD; Michael Green, MD; Jennifer P. Nagg, RN; Sage R. Myers, MD; Rakesh D. Mistry, MD; Shawn O'Connor, BS; Walter Faig, PhD; Stephen Black, MS; Elizabeth Rowley, PhD; Kellie Liston, BA; Alejandro Hoberman, MD

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MULTICENTRE, NONINFERIORITY RCT

Outcome assessment at 2 visits day 11-14 and 24-30



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MULTICENTRE, NONINFERIORITY RCT

Outcome assessment at 2 visits day 11-14 and 24-30

	Children, No. (%)		
Characteristic	Standard-course therapy (n = 328)	Short-course therapy (n = 336)	All children (n = 664)
Age group	. ,		
2-23 mo	60 (18)	64 (19)	124 (19)
2-6 у	183 (46)	202 (60)	385 (58)
7-10 у	85 (26)	70 (21)	155 (23)
Sex			
Female	316 (96)	323 (96)	639 (96)
Male	12 (4)	13 (4)	25 (4)
Race ^b			
Black	73 (22)	83 (25)	156 (23)
Multiracial	23 (7)	25 (7)	48 (7)
White	217 (66)	210 (63)	427 (64)
Other ^c	14 (4)	18 (5)	32 (5)
Unknown	1 (0)	0 (0)	1 (0)
Ethnicity ^b			
Hispanic	33 (10)	27 (8)	60 (9)
Non-Hispanic	295 (90)	309 (92)	604 (91)
Febrile at presentation			
Yes	122 (37)	128 (38)	250 (38) ^d
No	206 (63)	208 (62)	414 (62)
Medication			
Amoxicillin-clavulanate	4 (1)	2 (1)	6 (1)
Cefdinir	183 (56)	185 (55)	368 (55)
Cefixime	2 (1)	1 (0)	3 (0)
Cephalexin	103 (31)	112 (33)	215 (32)
Trimethoprim-sulfamethoxazole	36 (11)	36 (11)	72 (11)
Study site			
Children's Hospital of Philadelphia	143 (44)	152 (45)	295 (44)
UPMC Children's Hospital of Pittsburgh	185 (56)	184 (55)	369 (56)
Infecting organism			
Escherichia coli	296 (90)	301 (90)	597 (90)
Proteus mirabilis	20 (6)	22 (7)	42 (6)
Klebsiella pneumoniae	5 (2)	4 (1)	9 (1)
Other	7 (2)	9 (3)	16 (2)

Table 1. Selected Demographic and Clinical Characteristics of Children With Data on Primary Outcome According to Treatment Group^a

Treatment failure was up to 5.5% greater with short-course

LOW TREATMENT FAILURE IN BOTH GROUPS

NNT to for standard-course therapy was 28, i.e. 28 children would need to be treated with an additional 5 days to prevent 1 treatment failure. For febrile UTI, NNT was 67

Table 2. Primary and Secondary Outcomes

Children, No./total No. (%)				Difference of	
Standard-course therapy	Short-course therapy	All children	P value	proportions, % (95% CI)	No. needed to treat ^a
2/328 (0.6)	14/336 (4.2)	16/664 (2.4)	<.01	3.6 (≤5.5) ^b	28
12/326 (3.7)	13/322 (4.0)	25/648 (3.9)	.97	0.4 (-2.6 to 3.3)	с
11/328 (3.4)	32/336 (9.5)	40/664 (6.0)	<.01	6.2 (2.5-9.9)	17
30/328 (9.1)	41/336 (12.2)	71/664 (10.7)	.25	3.1 (–1.6 to 7.7)	c
15/328 (4.6)	42/336 (12.5)	47/664 (7.1)	<.01	7.9 (3.7-12.1)	13
23/298 (7.7)	28/310 (9.0)	51/608 (8.4)	.66	1.3 (–3.1 to 5.7)	с
	Children, No./tota Standard-course therapy 2/328 (0.6) 12/326 (3.7) 11/328 (3.4) 30/328 (9.1) 15/328 (4.6) 23/298 (7.7)	Children, No./total No. (%) Standard-course therapy Short-course therapy 2/328 (0.6) 14/336 (4.2) 2/328 (0.6) 14/336 (4.2) 12/326 (3.7) 13/322 (4.0) 11/328 (3.4) 32/336 (9.5) 30/328 (9.1) 41/336 (12.2) 15/328 (4.6) 42/336 (12.5) 23/298 (7.7) 28/310 (9.0)	Children, No./total No. (%) Standard-course therapy Short-course therapy All children 2/328 (0.6) 14/336 (4.2) 16/664 (2.4) 2/328 (0.6) 14/336 (4.2) 16/664 (2.4) 12/326 (3.7) 13/322 (4.0) 25/648 (3.9) 11/328 (3.4) 32/336 (9.5) 40/664 (6.0) 30/328 (9.1) 41/336 (12.2) 71/664 (10.7) 15/328 (4.6) 42/336 (12.5) 47/664 (7.1) 23/298 (7.7) 28/310 (9.0) 51/608 (8.4)	Children, No./total No. (%) Short-course therapy Short-course therapy All children P value 2/328 (0.6) 14/336 (4.2) 16/664 (2.4) <.01	$\begin{array}{c c c c c c c c } \hline Children, No./total No. (\%) & Difference of proportions, flerapy & All children & P value & Difference of proportions, % (95% CI) & Difference of Difference of Difference of the characteristic definition of the char$

Adverse events similar between groups

Table 3. Adverse Events According to Study Group

	Children, No. (%)					
Characteristic	Standard-course therapy (n = 328)	Short-course therapy (n = 336)	All children (n = 664)	P value		
Participants with adverse events	155 (47.3)	147 (43.8)	302 (45.5)	.10		
Most frequently reported adverse events						
Diarrhea	43 (13.1)	34 (10.1)	77 (11.6)	.41		
Cough	21 (6.4)	26 (7.7)	47 (7.1)	.28		
Pyrexia	17 (5.2)	18 (5.4)	35 (5.3)	.60		
Vomiting	11 (3.4)	20 (6.0)	31 (4.7)	1.00		
Rhinorrhea	13 (4.0)	16 (4.8)	29 (4.4)	.16		
Other	115 (35.1)	111 (33.0)	226 (34.0)	.75		
Severity of adverse event						
Mild	107 (32.6)	117 (34.8)	224 (33.7)	.64		
Moderate	47 (14.3)	26 (7.7)	73 (11.0)	.61		
Severe	1 (0.3)	4 (1.2)	5 (0.8)	.37		
Serious	2 (0.6)	4 (1.2)	6 (0.9) ^a	.69		

SCOUT Trial Interpretation?

Included children age 2 mo to 10 years with uncomplicated UTI, fUTI and cystitis

- Authors make the argument that given low treatment failure rate, 5 days of antibiotics a reasonable option and shared decision making with parents should be used
- Others
 - For cystitis, given low treatment failure in study 5 days reasonable
 - For fUTI, 10 days still advisable given possibility of long term complications

Are oral antibiotics effective and safe for treatment of young infants with first febrile UTI?

Jackie is a 5 week old term infant with first febrile UTI. She is feeding well and looks well otherwise. The urinalysis is positive for leukocytes and nitrites. Should you treat her with oral antibiotics? Should she be admitted with short (2 days) or longer course IV antibiotics (5 days)? Total duration?



Summary

Initial oral antibiotic route and early transition to oral?

- In neonates (≤ 28 days): well appearing with non-bacteremic UTI and no concern for meningitis, short-course (≤ 3-4 days) IV antibiotics with early conversion to oral antibiotics may be considered with follow-up
- In young infants (29-60 days): well appearing, normal IM, initial oral antibiotic treatment may be considered with follow-up; if hospitalized for initial IV antibiotics, non-bacteremic, short-course (≤ 3-4 days) IV antibiotics with early conversion to oral antibiotics with follow-up
- 3. In **young infants (<90 days),** with **bacteremic UTI** and well appearing, shorter course IV antibiotics (≤7 days) with early conversion to oral antibiotics may be considered

Duration of treatment?

- 1. Total duration in non-bacteremic UTI:
 - a) (<2 months): uncertainty, 7-14 days
 - b) (>2 months) 5 days vs. 10 days shared decision-making

Evidence Based Clinical Decisions





© Canadian Paediatric Society. Source: Management of well-appearing febrile young infants aged ≤90 days, Acute Care Committee, October 12, 2023. Available at www.cps.ca

Are oral antibiotics effective and safe for treatment of young infants with first febrile UTI?

In **neonates** (\leq 28 days): well appearing with **non-bacteremic UTI** and no concern for meningitis, short-course (\leq 3-4 days) IV antibiotics with early conversion to oral antibiotics may be considered with follow-up

In **young infants (29-60 days):** well appearing, normal IM, initial oral antibiotic treatment may be considered with follow-up; if hospitalized for initial IV antibiotics, non-bacteremic, short-course (\leq 3-4 days) IV antibiotics with early conversion to oral antibiotics with follow-up

In **young infants (<90 days),** with **bacteremic UTI** and well appearing, shorter course IV antibiotics (≤7 days) with early conversion to oral antibiotics may be considered

Total duration in non-bacteremic UTI: short course 5 days vs. 10 days – shared decision-making in >2 months; uncertainty for <2 months, 7-14 days



Summary

Are oral antibiotics safe & effective for treatment of young infants?

Role for initial oral antibiotic and early transition to oral antibiotics and based on age, presentation, and follow-up.

Total treatment duration based on age, presentation, 7-14 days in <2 months; 5 vs 7-10 days in >2 months



How things have changed!

ResearchClinical Practice GuidelinesQIChange in Practice & Patient Outcomes



Support for the Use of a New Cutoff to Define a Positive Urine Culture in Young Children

Nader Shaikh, MD, MPH,^a Sojin Lee, PhD,^a Janina A. Krumbeck, PhD,^b Marcia Kurs-Lasky, MS^a

PEDIATRICS Volume 152, number 4, October 2023:e2023061931

- Results support the use of urine cultures with threshold of >10,000 CFU/ml for the population (febrile, urinary inflammation, suspected UTI, urinary cath)
- Results may not apply to collection methods with more contamination (e.g. bag urine)
- More studies to elucidate threshold for non-Ecoli UTI

SOUNDING BOARD

THE CASCADE EFFECT IN THE CLINICAL CARE OF PATIENTS

THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 20, 1986

Cascade: a process that, once started, proceeds stepwise to its full, seemingly inevitable, conclusion.

