Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Pharyngitis- Antibiotic Duration

Specific Care Question

In pediatric patients with group A streptococcal pharyngitis, is a 5–7-day course of antibiotics as effective as a 10-day course?

Rationale for Question Asked

The most current US guidelines for managing group A streptococcal (GAS) pharyngitis recommend 10 days of antibiotic therapy for patients with microbiologically confirmed diagnosis (Shulman et al., 2012). This recommendation is based on the theory that eradicating GAS from the pharynx may reduce the risk of developing rare but clinically significant complications of GAS, such as acute rheumatic fever, peritonsillar abscess, cervical lymphadenitis, and mastoiditis, among others, as well as limit the spread of the disease (Altamimi et al., 2012; Shulman et al., 2012). However, antibiotic administration is not without risk. Studies have reported that longer courses of antibiotics are associated with increased emergence of antimicrobial resistance (Principi et al., 2023; Spellberg, 2016), decreased adherence (Schwartz et al., 2004), and increased burden to families related to the cost and administration of medications (National Collaborating Centre for Primary Carel, 2009) when compared to shorter courses. Additionally, side effects such as diarrhea or allergic reactions may limit tolerability and require therapeutic intervention in some patients, regardless of the duration of therapy. Finally, practice guidelines from many European countries recommend a shorter course (5-7 days) of antibiotic therapy or no antibiotic therapy based on disease severity and stratification of risk factors (de Jongh & Opstelten, 2015; NICE, 2018; Pelucchi et al., 2012; Windfuhr et al., 2016). A literature search was conducted to determine if the current standard practice of providing 10 days of antibiotic therapy for microbiologically confirmed GAS pharyngitis should be continued.

Recommendations from the Pharyngitis Clinical Pathway Committee

The Pharyngitis Clinical Pathway Committee recommends continuing the current practice of providing a 10-day course of antibiotics for patients with microbiologically confirmed GAS pharyngitis in accordance with national guidelines, as 10 days of therapy was found to be superior to 5-7 days for the outcome of bacterial eradication, based on low certainty of evidence.

Overview and Certainty of Evidence

Three randomized controlled trials (RCTs; Kuroki et al., 2013; Sakata, 2008; Skoog Ståhlgren et al., 2019) from 2006-2023 compared short course (5-7 days) vs. long course (8-10 days) antibiotic therapy for the treatment of GAS pharyngitis. The outcomes of interest to the committee were bacterial eradication of GAS (generally measured 1-2 weeks after the completion of therapy), rate of relapse or recurrence (reported as symptomatic relapse within one month, with or without confirmation of the same serotype), and frequency of adverse events and/or complications. For the outcome of bacterial eradication, long-course therapy was superior to a short-course in achieving eradication of GAS, *OR* = 0.48; 95% CI [0.37, 0.77], *p-value* = 0.002. For the outcome of symptomatic relapse, no significant difference was seen between treatment groups, *OR* = 0.99; 95% CI [0.39, 2.52], *p-value* = 0.98.

In addition to the RCTs above, one retrospective cohort study (Salinas Salvador et al., 2022) reported adverse events and complications. Adverse events were self-reported via patient diaries or extracted via chart review and included diarrhea, nausea/vomiting, and rash. Generally, adverse events were balanced between treatment groups, with the exception of diarrhea being more frequent with amoxicillin/clavulanate (46.8%) vs. amoxicillin alone (12.8%; Kuroki et al., 2013) and rash occurring more frequently with penicillin (8%) vs. cephalosporins (0%; Sakata, 2008).

Complications reported in the included studies:

- Kuroki (2013) reported that urinalysis 1-2 weeks after completion of therapy did not show signs of abnormality or acute glomerulonephritis in any patient.

- Skoog Ståhlgren (2019) reported that four patients in the long-course group experienced complications possibly provoked by streptococci (peritonsillitis (3) and psoriasis (1)).
- Sakata (2008) reported that complications such as rheumatic fever or glomerulonephritis did not occur during the observation period.
- Salinas Salvador (2022) reported that no significant differences were found between groups in the development of scarlet fever, *OR* = 0.7; 95% CI [0.14, 3.4].

Certainty Of The Evidence For Bacterial Eradication of Group A Streptococcus (GAS). The certainty of the body of evidence was low. The body of evidence was found to have serious risk of bias due to concerns about randomization, allocation, missing outcome data, and lack of adherence reporting; serious indirectness due to concerns about included populations (mixed adult and pediatric studies), study setting (foreign countries), and differences in antibiotics used; and serious imprecision due to small sample sizes and wide confidence intervals.

Certainty Of The Evidence For Relapse or Recurrence. The certainty of the body of evidence was very low. The body of evidence was found to have serious risk of bias due to concerns about randomization, allocation, missing outcome data, and lack of adherence reporting; serious indirectness due to concerns about included populations (mixed adult and pediatric studies), study setting (foreign countries), and differences in antibiotics used; and serious imprecision due to very small numbers of events.

Study characteristics. The search for suitable studies was completed on October 3, 2023 and returned 151 records. Dr. Katie Berg reviewed the 151 titles and/or abstracts found in the search and identified 23 studies believed to answer the question. Rana El Feghaly, MD reviewed the titles and/or abstracts for the 23 studies found in the search and identified 11 studies believed to answer the question. Citation searching yielded nine additional records. After an in-depth review of the full single studies, four were found to answer the question and report on at least one of the pre-specified outcomes of bacterial eradication, relapse or recurrence, or adverse events.

Table 1

Characteristics of Included Studies

Author (year)	Study Type	Population	N	Intervention	Control	Results
Kuroki et al., 2013 Japan	RCT	Children < 15 years with a positive rapid antigen test for GAS	*N* = 119	Amoxicillin/clavulanate x 3 days (*n* = 64) 96.4 mg/kg/day (90 mg/kg/day amox) in two divided doses	Amoxicillin x 10 days (*n* = 55) 30 mg/kg/day in three divided doses	**Bacterial eradication:** AMPC/CLAV x 3 days: 65.4% (34/52) AMPC x 10 days: 85.4% (35/41) ($p < .05$); *OR* = 0.32, 95% CI [0.11, 0.91] **Adverse Drug Reaction (ADRs):** The incidence of diarrhea was significantly higher in the CVA/AMPC group than in the AMPC group ($p < .01$). Urticaria and eruption (one case each) were noted in the CVA/AMPC group, and upper airway inflammation (one case) was seen in the AMPC group.

Sakata et al., 2008 Japan	RCT	Children 6 mos – 13 yrs with pharyngitis and positive for GAS from a culture of a pharyngeal swab	*N* = 250	Cefcapene/pivoxil (CFPN-PI) x 5 days (*n* = 82) x 10 days (*n* = 88) 9-10 mg/kg/day in three divided doses	Amoxicillin (AMPC) x 10 days (*n* = 80) 30-40 mg/kg/day in three divided doses	**Bacterial eradication:** CFPN-PI x 5 days: 93.8% (75/80) AMPC x 10 days: 91.7% (66/72) *OR* = 1.36, 95% CI [0.40, 4.67] **Clinical recurrence:** CFPN-PI x 5 days: 1.3% (1/77) AMPC x 10 days: 2.9% (2/69) *OR* = 0.44, 95% CI [0.04, 4.97] **ADRs:** Rash occurred in 6 patients in the AMPC group and none in the CFPN-PI group ($p <$ .01). Incidence of diarrhea was similar between groups.
Skoog-Stahlgren et al., 2019 Sweden	RCT	Children > 6 yrs with at least three Centor criteria (fever > 38.5, tender lymph nodes, inflamed tonsils, absence of cough) and positive rapid antigen test for GAS	*N* = 422 (< 18 yrs: *n* = 105; ≥ 18 yrs: *n* = 317)	Penicillin V x 5 days (*n* = 212) (< 18 yrs: *n* = 55; ≥ 18 yrs: *n* = 157) 10-20 kg: 250 mg/dose 20-40 kg: 500 mg/dose > 40 kg: 800 mg/dose administered four times daily	Penicillin V x 10 days (*n* = 210) (< 18 yrs: *n* = 50; ≥ 18 yrs: *n* = 160) 10-20 kg: 250 mg/dose 20-40 kg: 500 mg/dose > 40 kg: 1000 mg/dose administered three times daily	**Bacterial eradication:** Pen V x 5 days: 80.4% (156/194) Pen V x 10 days: 90.7% (165/182) *RD* = - 10.2, 95% CI [-17.8, -2.7] **Clinical relapse:** Pen V x 5 days: 4.5% (8/179) Pen V x 10 days: 3.9% (7/180) *RD* = 0.6, 95% CI [-4.1, 5.3] **ADRs:** Patients in the 5-day group reported fewer adverse events and shorter duration of adverse events. No statistical analysis was performed.
Salvador et al., 2022 Spain	Retro-spective Cohort	Children from a single primary care center with a diagnosis of streptococcal pharyngitis	*N* = 350 episodes of AP in 252 patients	Amoxicillin, penicillin, or other administered x 5-7 days (*n* = 224)	Amoxicillin, penicillin, or other administered x 8-10 days (*n* = 126)	**AP or scarlet fever w/in 3 months:** Short-course: 9.8% (22/224) Long-course: 9.5% (12/126) *OR* = 0.97, 95% CI [0.46, 2.03] **ADRs:** Short-course: 2.7% (6/224) Long-course: 0.9% (1/126) *OR* = 0.29, 95% CI [0.04, 2.44]

Identification of Studies

Search Strategy and Results (see Figure 1)

#8 NOT 'case report'/de
#7 AND ('Article'/it OR 'Article in Press'/it)
#5 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR 'child'/exp OR child OR 'children'/exp OR children OR 'pediatrics'/exp OR pediatrics OR 'pediatric'/exp OR pediatric OR 'paediatric'/exp OR paediatric)
#5 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)
#1 AND #2 AND #3 AND [2013-2023]/py
#1 AND #2 AND #3
('pharyngitis'/exp OR pharyngitis) AND ('group a streptococcal infection'/exp OR 'group a streptococcal infection' OR 'streptococcus group a'/exp OR 'streptococcus group a') OR 'streptococcal pharyngitis'/exp OR 'streptococcal pharyngitis'
'antibiotic agent'/exp OR 'antibiotic agent' OR 'antibiotic therapy'/exp OR 'antibiotic therapy' OR 'antibiotic'/exp OR antibiotic
'drug administration schedule' OR 'short course' OR 'short-course' OR 'long course' OR 'long-course' OR 'time'/exp OR time OR 'time factor'/exp OR 'time factor' OR 'treatment duration'/exp OR 'treatment duration' OR 'duration'/exp OR duration:ti,ab,kw OR course:ti,ab,kw OR days:ti,ab,kw OR short:ti,ab,kw OR long:ti,ab,kw

Search Dates: 2013-Current
Records identified through database searching: *n* = 11
Additional records identified through other sources back to 2006: *n* = 9 (search extended back to 2006 due to limited results over the past ten years and to establish consistency with concurrent Pharyngitis CAT for dosing frequency)

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Altamimi et al. (2012)	Wrong time frame; meta-analysis including articles written before 2006
Chiappini et al. (2017)	Wrong article type; consensus statement
Di Mario et al. (2021)	Wrong intervention; diagnosis not available
Falagas et al. (2008)	Wrong time frame; meta-analysis including articles written before 2006
Grant and Le Saux (2021)	Wrong article type; narrative review
Holm et al. (2020)	Wrong time frame; meta-analysis including articles written before 2006
McMurray et al. (2015)	Wrong article type; review article
Mustafa and Ghaffari (2020)	Wrong article type; narrative review
Oliveira Pereira (2013)	Wrong language; English translation unable to be retrieved
Principi et al. (2023)	Wrong article type; narrative review
Radetsky (2017)	Wrong article type; narrative review
Robinson (2021)	Wrong article type; narrative review
Schwartz et al. (2015)	Wrong outcome; return to school
Skoog et al. (2016)	Wrong article type; description of protocol design only (no data)
Tell et al. (2022)	Wrong intervention groups reported; subgroup analysis of already included article (duplicate data)

Windfuhr et al. (2016)	Wrong population; German guideline for management of tonsillitis

Question Originator

R. El Feghaly, MD and K. Tilak, MD

Findings from this review were presented with the question originator, Dr. R. El Feghaly, and the following pharyngitis committee members: C. Scoby, DO, K. Berg, MD, FAAP, J. Smith, BA, K. Hess, PharmD, and A. Melanson, OTD, OTR/L on December 19, 2023.

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Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)

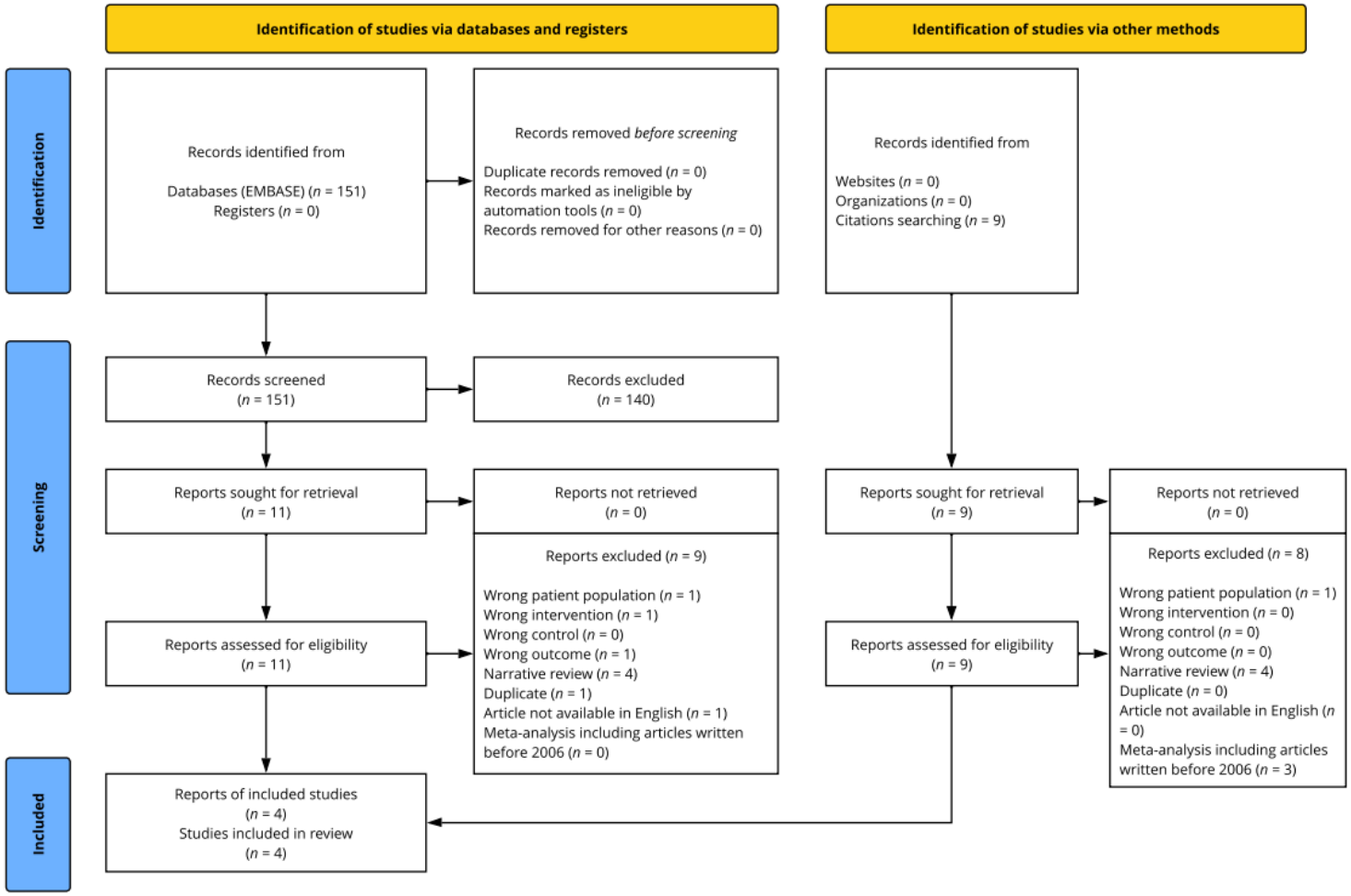
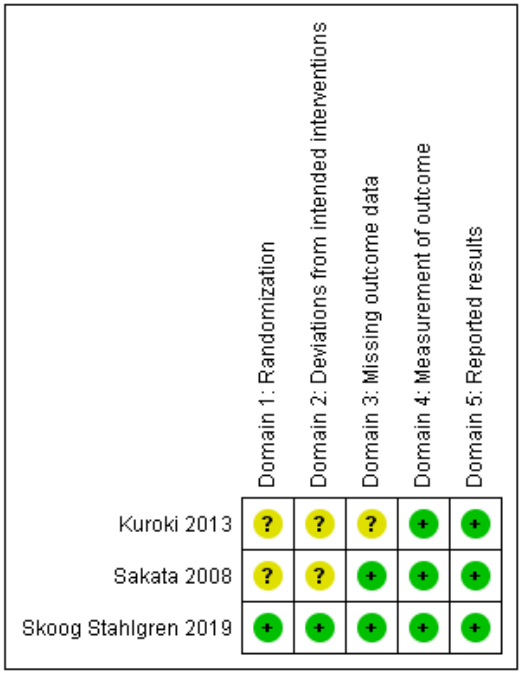


Figure 2

Risk of Bias Summary for outcome of bacterial eradication



Summary of Findings Table

Table 2

Summary of Findings Table: Long vs. Short Course Antibiotic Use

Certainty assessment							Summary of findings				
							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (5-7 days) of antibiotics	Long course (10 days) of antibiotics	Relative (95% CI)	Absolute (95% CI)	Certainty
Bacterial eradication (5-7 days post-treatment)											
3	randomised trials	serious[a,b,c,d]	not serious	serious[e,f,g]	serious[h]	none	265/326 (81.3%)	266/295 (90.2%)	**OR 0.48** (0.30 to 0.77)	**87 fewer per 1,000** (from 168 fewer to 26 fewer)	⨁⨁◯◯ Low CRITICAL
Symptomatic relapse within one month											
2	randomised trials	serious[a,b,c,d]	not serious	serious[e,f,g]	serious[h,i]	none	9/256 (3.5%)	9/249 (3.6%)	**OR 0.99** (0.39 to 2.52)	**0 fewer per 1,000** (from 22 fewer to 50 more)	⨁◯◯◯ Very low

Notes

a. Concerns about randomization methods
b. Concerns about allocation sequence
c. Significant number of patients lost to follow up without reasons given
d. Adherence data unclear
e. Concerns about setting (European and Asian countries vs. US which may have different strains of GAS or higher rates of sequelae)
f. Adult patients included in analysis
g. Not all studies compared the same drugs in short course vs. long course
h. Low number of participants
i. Low number of events

Meta-analysis(es)

Figure 3

Comparison: Long vs. Short Course Antibiotic Use, Outcome: Bacterial eradication

Study or Subgroup	Short course Events	Total	Long course Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kuroki 2013	34	52	35	41	26.4%	0.32 [0.11, 0.91]
Sakata 2008	75	80	66	72	8.5%	1.36 [0.40, 4.67]
Skoog Stahlgren 2019	156	194	165	182	65.1%	0.42 [0.23, 0.78]
Total (95% CI)		**326**		**295**	**100.0%**	**0.48 [0.30, 0.77]**
Total events	265		266			

Heterogeneity: Chi² = 3.48, df = 2 (P = 0.18); I² = 42%

Test for overall effect: Z = 3.05 (P = 0.002)

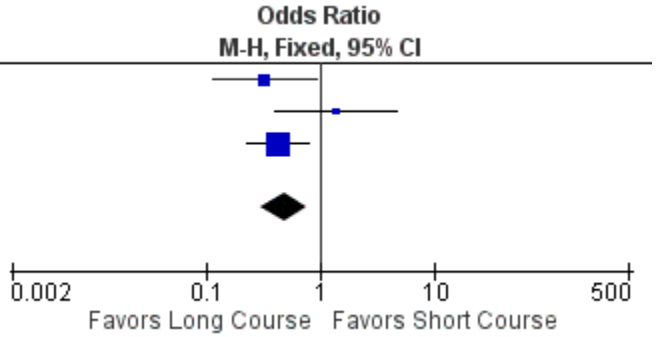


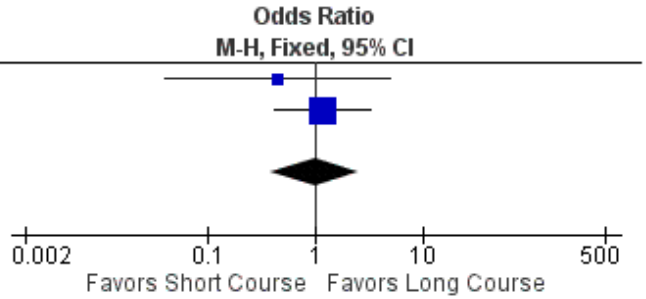
Figure 4

Comparison: Long vs. Short Course Antibiotic Use, Outcome: Symptomatic relapse within one month*

Study or Subgroup	Short course Events	Total	Long course Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sakata 2008	1	77	2	69	23.8%	0.44 [0.04, 4.97]
Skoog Stahlgren 2019	8	179	7	180	76.2%	1.16 [0.41, 3.26]
Total (95% CI)		**256**		**249**	**100.0%**	**0.99 [0.39, 2.52]**
Total events	9		9			

Heterogeneity: Chi² = 0.51, df = 1 (P = 0.47); I² = 0%

Test for overall effect: Z = 0.03 (P = 0.98)



*Relapse was reported differently in these two studies. Sakata (2008) confirmed relapse microbiologically, while Skoog Stahlgren (2019) was based on reappearance of symptoms only.

Characteristics of Intervention Studies

Kuroki et al., (2013)

Methods	Randomized Control Trial
Participants	**Participants:** Children with pharyngolaryngitis or tonsillitis, aged less than 15 years, who tested positive on the instantaneous GAS infection diagnosis kit between November 2009 and May 2011. **Setting:** Seven medical facilities in Chiba Prefecture, Japan **Randomized into study:** *N* = 119 • **Group 1, Clavulanate/Amoxicillin (CVA/AMPC) group:** *n* = 64 • **Group 2, Amoxicillin (AMPC) group:** *n* = 55 **Completed Study:** *N* = 96 • **Group 1:** *n* = 54 • **Group 2:** *n* = 42 **Gender, males (as defined by researchers):** • **Group 1:** *n* = 25 (46.3%) • **Group 2:** *n* = 22 (51.2%) **Race / ethnicity or nationality (as defined by researchers):** • Not reported **Age, mean (range) in years** • **Group 1:** 5.6 (2-13) • **Group 2:** 5.3 (1-9) **Inclusion Criteria:** • Children less than 15 years • Children with pharyngolaryngitis or tonsillitis • Children who tested positive on the instantaneous GAS infection diagnosis kit **Exclusion Criteria:** • Not reported **Power Analysis:** Not reported.
Interventions	• **Group 1:** 3-day treatment with combined CVA/AMPC preparation at dose level of 96.4 mg/kg/day in two divided doses • **Group 2:** 10-day treatment with AMPC at a dose level of 30 mg/kg/day in 3 divided doses

Outcomes	**Primary outcome(s):**
	• Clinical efficacy
	  ○ Measured using the Criteria for Judgment in Clinical Studies of Antimicrobial Drugs in the Field of Pediatrics and rated using four categories: markedly effective, effective, slightly effective, or ineffective
	
	Secondary outcome(s)
	• Bacteriological efficacy of Group A Streptococcus after treatment completion*
	  ○ Reported as either eradicated or detected.
	
	Safety outcome(s):
	• The onset of any adverse event (disease, symptom, lab abnormality)
	*Outcomes of interest to the CMKC clinical pathway development team

Notes	**Results** • Clinical efficacy – In the 3-day CVA/AMPC group the drug was markedly effective in 50 cases (92.6%) vs 37 cases (88.1%) in the 10-day AMPC group. • Bacteriological efficacy – The GAS eradication rate following treatment was significantly higher in the 10-day AMPC group, 35 (85.4%), than the 3-day CVA/AMPC group, 34 (65.4%), ($p < .05$) **Limitations** • Study was unblinded. • Exclusion criteria not mentioned. • Patients excluded post hoc due to lack of follow-up were not included in the final analysis for clinical and bacterial efficacy. • Study agents were different between treatment groups.

Sakata et al., (2008)

Methods	Randomized Control Trial

Participants	**Participants:** Children ages 6 months to 13 years with signs and symptoms of acute pharyngitis.
	
	Setting: Asahikawa, Japan, 12 pediatric clinics, between June 2006 and February 2007.
	
	Randomized into study: *N* = 250
	• **Group 1, Cefcapene-pivoxil (CFPN-PI) 5 days:** *n* = 82
	• **Group 2, Cefcapene-pivoxil (CFPN-PI) 10 days:** *n* = 88
	• **Group 3, Amoxicillin (AMPC) 10 days:** *n* = 80
	
	Completed Study: *N* = 221
	• **Group 1:** *n* = 77
	• **Group 2:** *n* = 75
	• **Group 3:** *n* = 69
	
	Gender, males (%):
	• **Group 1:** 54.8%
	• **Group 2:** 56.1%
	• **Group 3:** 57.1%
	
	Race / ethnicity or nationality (as defined by researchers):
	• The study was conducted in Japan. The authors did not note race, ethnicity or nationality of the participants.
	
	Age, mean/median in years ± SD
	• **Group 1:** 5.5 ± 2.3
	• **Group 2:** 5.6 ± 2.5
	• **Group 3:** 5.7 ± 2.4
	
	Inclusion Criteria:
	• Diagnosis of pharyngitis based on the presence of
	  ○ Sore throat
	  ○ Inflammation and erythema of the uvula and pharynx or tonsils, frequently with fever.
	  ○ Positive GAS culture from pharyngeal swab.
	
	Exclusion Criteria:
	• Known allergy to β-lactams.
	• Systemic antibiotic treatment in the 48 hours before study entry.
	• Azithromycin therapy in the week before enrollment.
	• Known GAS carrier status.
	• A deep tissue infection of the upper respiratory tract.
	• Gastrointestinal conditions that affect enteric antibiotic absorption.
	• Significant renal or hepatic impairment.
	• Severe concurrent illness.
	
	Power Analysis: Not reported.

Interventions	A complete medical history was taken and a confirmatory pharyngeal swab culture was done on all patients. Antibiotic administration was initiated on the day of the first visit. All patients were scheduled for four follow up visits, at specified intervals. An additional swab

	culture was obtained on the second visit and urinalysis on the third visit. All patients had access to additional visits as needed. • **Group 1:** Oral CFPN-PI, 9-10 mg/kg/day in three divided doses for five days. • **Group 2:** Oral CFPN-PI, 9-10 mg/kg/day in three divided doses for 10 days. • **Group 3:** Oral AMPC 30-40 mg/kg/day in three divided doses for 10 days.
Outcomes	**Primary outcome(s):** • Clinical cure within 3 days (defined as resolution of signs and symptoms) • GAS eradication on second visit* (no GAS isolated on follow-up culture) • Relapse after treatment* (defined as recurrence of signs and symptoms) **Safety outcome(s):** • Adverse events: diarrhea, rash* • Complications: rheumatic fever or glomerulonephritis* *Outcomes of interest to the CMKC clinical pathway development team

Notes	**Results:**
	• There were no significant differences in eradication rate, clinical cure rate, and relapse rate between the three treatment groups.
	  ○ Bacterial Eradication
	  ▪ (CFPN-PI) x 5 days: 93.8%
	  ▪ (CFPN-PI) x 10 days: 96.2%
	  ▪ (AMPC) x 10 days: 91.7%
	  ○ Relapse
	  ▪ (CFPN-PI) x 5 days: 1.3%
	  ▪ (CFPN-PI) x 10 days: 4%
	  ▪ (AMPC) x 10 days: 2.9%
	• Adverse events:
	  ○ Diarrhea
	  ▪ (CFPN-PI) x 5 days: 3.8%
	  ▪ (CFPN-PI) x 10 days: 4.9%
	  ▪ (AMPC) x 10 days: 4%
	  ○ Rash
	  ▪ (CFPN-PI) x 5 days: 0%
	  ▪ (CFPN-PI) x 10 days: 0%
	  ▪ (AMPC) x 10 days: 8%
	• Twenty-nine patients were excluded from analysis due to
	  ○ Medication non-compliance, described as taking less than 80% of the prescribed doses
	  ○ Adverse effect leading to treatment cessation
	  ○ Mistiming of second or third follow up visits
	• The study was not powered for secondary outcomes
	
	Limitations:
	• Study was unblinded.

Salinas Salvador et al., (2022)

Methods	Retrospective Observational Cohort
Participants	**Participants:** Patients diagnosed with acute pharyngitis **Setting:** Two pediatric caseloads from the Jose Ramon Munoz Fernandez Primary Care Center in Zaragoza, Spain, between 2016 and April 2020. **Number enrolled into study:** *N* = 350 care episodes (252 patients) • **Group 1, Conventional course of antibiotic therapy (8-10 days):** *n* = 224 • **Group 2, Short course of antibiotic therapy (5-7 days):** *n* = 126 **Gender, males (%) (as defined by researchers):** • **Group 1:** *n* = 107 (48%) • **Group 2:** *n* = 68 (54%) **Race / ethnicity or nationality (as defined by researchers):** • Not reported **Age, mean in years (SD)** • **Group 1:** 7.26 (2.7) • **Group 2:** 7.22 (2.8) **Inclusion Criteria:** • Diagnosis of acute pharyngitis • Positive rapid antigen detection test (RADT) or throat swab culture for GAS **Exclusion Criteria:** • Diagnosis of acute pharyngitis without testing for GAS • Absence of records of the dispensation of the prescribed antibiotic in the pharmacy management system • Scarlet fever • Immunosuppression due to illness or medication **Covariates Identified:** • Patients enrolled after 2018 were impacted by new treatment guidelines and differences in seasonal distribution due to COVID lockdown (general decrease in all respiratory infections)

Interventions	**Both:** Authors collected epidemiological data (sex, age and date of diagnosis) and data on the prescribed antibiotic therapy course (antibiotic, days of treatment and, if a change was required, the second prescribed antibiotic) from the health records of all included patients. Amoxicillin was the most frequently prescribed, followed by penicillin. Other antibiotics included josamycin, clindamycin, cefadroxil, and cefuroxime.
	
	• **Group 1: 8-10 days antibiotic therapy**
	  ○ Amoxicillin (*n* = 178)
	  ○ Penicillin (*n* = 35)
	  ○ Other (*n* = 11)
	• **Group 2: 5-7 days antibiotic therapy**
	  ○ Amoxicillin (*n* = 98)
	  ○ Penicillin (*n* = 27)
	  ○ Other (*n* = 1)

Outcomes	**Primary outcome(s):** • Rate of reinfection in the 3 months following the studied episode ○ Acute pharyngitis or scarlet fever*

	○ Other infections of possible streptococcal etiology (pneumonia, otitis media, sinusitis, streptococcal perineal disease, and septic arthritis) **Safety outcome(s):** • *Adverse events *Outcomes of interest to the CMKC clinical pathway development team
Results	**Results:** • 22 patients in group 1 (9.8%) vs 12 patients in group 2 (9.5%) developed a microbiologically confirmed episode of AP or scarlet fever within 3 months of the initial episode (*OR* = 0.97, 95% CI [0.46, 2.03])* ○ When patients with scarlet fever were analyzed separately, the study also found no significant differences between groups (*OR* = 0.7, 95% CI [0.14, 3.4]) • There were no significant differences between groups in other infections of possible streptococcal origin: 4% (n = 9) in group 1 and 2.4% in group 2 (n = 3) (*OR* = 0.58, 95% CI [0.15, 2.19]) • There were no significant differences between groups in adverse events, with an incidence of 2.7% (n = 6) in group 1 versus 0.8% (n = 1) in group 2 (*OR* = 0.29, 95% CI [0.04, 2.44]) **Limitations:** • Retrospective design • Information was obtained from health records on the prescribed duration of treatment, but authors were unable to verify if patients took their medication as prescribed • Duration of antibiotics in the two groups (5-7 days vs. 8-10 days) varied slightly from the clinical question of 5 vs. 10 days

Skoog-Stahlgren et al., (2019)

Methods	Randomized Control Trial
Participants	**Participants:** Children aged ≥ 6 years meeting three or four Centor criteria between September 2015 and February 2018 **Setting:** Seventeen primary healthcare centers in urban and rural regions of Sweden (Skåne, Kronoberg, Västra, Götaland, and Södermanland) **Randomized into study:** *N* = 433 • **Group 1, Penicillin V 800 mg:** *n* = 215 ○ *n* = 212 (modified intention to treat) • **Group 2, Penicillin V 1000 mg:** *n* = 218 ○ *n* **=** 210 (modified intention to treat) **Completed Study:** *N* = 397 (test of cure), 359 (1-month follow-up), 387 (3-month follow-up) • **Group 1:** *n* = 202 (test of cure), 179 (1-month follow-up), 180 (3-month follow-up) • **Group 2:** *n* = 195 (test of cure), 180 (1-month follow-up), 189 (3-month follow-up) **Gender, males (as defined by researchers):** • **Group 1:** *n* = 74 (35.9%) • **Group 2:** *n* = 78 (37.1%) **Race/ethnicity or nationality (as defined by researchers):** • Not reported **Age, median in years, (IQR)** • **Group 1:** 30.0 (6 – 73) • **Group 2:** 31.0 (3 – 67) **Inclusion Criteria:** • Children ≥ 6 years of age with three or four of the following Centor criteria: ○ Fever > 38.5° C ○ Tender lymph nodes ○ Coatings of the tonsils (for children, inflamed tonsils) ○ Absence of cough • Positive rapid antigen detection test for GAS **Exclusion Criteria:** • Children demonstrating signs of serious illness • Hypersensitivity to penicillin • Receiving immunomodulating treatment corresponding to at least 15 mg of prednisolone • Having received antibiotics for pharyngotonsillitis in the past month (relapse) • Having received any antibiotic treatment within 72 hours **Power Analysis:** A clinical recovery of 90% was assumed in both groups, as was a power of 85%, a level of significance of 5%, two-sidedness, and a non-inferiority margin of 10%. Assuming that the primary outcome could not be evaluated in 25% of patients, 432 needed to be included in the study.
Interventions	The dosages for children up to 40 kg were adjusted according to weight (10 – 20 kg: 250 mg per dose, 20 – 40 kg: 500 mg per dose, irrespective of treatment arm). The physicians prescribed penicillin V, and the patients or their guardians obtained the

	prescription from the pharmacy. Patients were asked to complete a patient diary until the test of cure visit based on the last dose. Follow-up telephone calls were completed by regional nurses one month and three months after completion of the antibiotic treatment. Throat symptoms, potential relapses or new tonsillitis, and complications were monitored. • **Group 1, Penicillin V 800 mg:** Administered four times daily for five days. • **Group 2, Penicillin V 1000 mg:** Administered three times daily for 10 days.
Outcomes	**Primary outcome(s):** • Clinical cure (complete recovery without major residual symptoms or clinical findings) five to seven days after the end of antibiotic treatment at the test of cure visit* • Bacterial eradication at test of cure visit* (throat culture) **Secondary outcome(s)** • Frequency of relapses one month after first diagnosis (given clinical cure at test of cure visit)* • Frequency of complications and new pharyngotonsillitis during the three-month study period* **Safety outcome(s):** • Patterns of adverse events* *Outcomes of interest to the CMKC clinical pathway development team
Notes	**Results:** • Clinical cure at test of cure evaluation was 89.6% (181/202) in the five-day group and 93.3% (182/195) in the 10-day group; *RD* = -3.7, 95% CI [-9.7, 2.2] • Bacterial eradication at test of cure evaluation was 80.4% (156/194) in the five-day group and 90.7% (165/182) in the 10-day group; *RD* = - 10.2, 95% CI [-17.8, -2.7] • Relapse within one month (*n* = 359) was 4.5% (8/179) in the five-day group and 3.9% (7/180) in the 10-day group; *RD* = 0.6, 95% CI [-4.1, 5.3] • Complications by three-month follow-up (*n* = 387) were found only in the 10-day group 2.1% (4/18); *RD* = - 2.1. 95% CI [-4.7, 0.5]; three were peritonsillitis and one was psoriasis • New tonsillitis diagnosis by three-month follow-up (*n* = 386) was 3% (6/197) in the five-day group and 6.9% (13/189) in the 10-day group; *RD* = -3.8, 95% CI [-8.7, 1.0] • Adverse events recorded, as assessed by physicians, were assessed to be mild in intensity for 73% (97/132) in the five-day group and 61% (104/170) in the 10-day group, or moderate in intensity for 23% (31/132) in the five-day group and 33% (56/170) in the 10-day group. • Adverse events according to patient diary included diarrhea, nausea/vomiting, vaginal discharge or itching, and rash **Limitations**: • The study was not double-blinded (doctors and patients were aware of their treatment arm) and theoretically could have affected how they reported on an outcome. • The study was not powered for secondary outcomes.

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