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Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

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Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Specific Care Question
In pediatric patients diagnosed with group A streptococcal (GAS) pharyngitis, is amoxicillin per so (PO) once daily (QD) as effective as comparator treatments: amoxicillin PO BID, penicillin V PO BID, or penicillin intramuscular (IM)?

Rationale for Question Asked
GAS pharyngitis is treated to prevent rheumatic fever, reduce symptoms (e.g., pain, throat swelling, and fever), and curb infection spread (Armengol & Hendley, 2012; Shulman et al., 2012). Among the antibiotics proven effective in treating GAS pharyngitis, penicillin, and amoxicillin are preferred due to their efficacy, safety, and low cost (Diseases, 2012; Shulman, 2012). In children, amoxicillin is prescribed more frequently than penicillin, mainly due to the palatability of the amoxicillin oral suspension (Pichichero, 2023; Armengol & Hendley, 2012; Shulman et al., 2012). According to Shulman et al., 2012, amoxicillin has proven effective with QD dosing for a course of ten days. However, some practitioners continue to prescribe amoxicillin BID for a ten-day course. Before altering antibiotic prescribing practices, a review of the current literature was conducted to analyze dosing frequency recommendations for amoxicillin to ensure updated recommendations align with the best evidence.

Recommendations from the Pharyngitis Clinical Pathway Committee
Based on best evidence and a review of additional considerations (see Appendix), a conditional recommendation is made for amoxicillin provided once daily over a ten-day course based on the literature of very low certainty but with significantly increased feasibility of treatment administration.

Overview and Certainty of Evidence

Bacterial Eradication. Three randomized controlled trials (RCTs; Clegg et al., 2006; Lennon et al., 2008; Rimoin et al., 2011) and one observational study (Nakao et al., 2019) when reviewing literature from 2006 to 2023 compared amoxicillin QD to amoxicillin or penicillin V BID or penicillin V intramuscular (IM). The outcome of interest for the committee was determined to be bacterial eradication of GAS. In the presented studies, bacterial eradication data was collected via polymerase chain reaction (PCR) tests and/or cultures and described as treatment failure or success. No statistical difference was found in bacterial eradication between amoxicillin QD versus amoxicillin/penicillin V BID or penicillin IM, *OR* = 0.80; 95% CI [0.61, 1.04] for 12 - 21 days post-treatment; *OR* = 0.94; 95% CI [0.76, 1.16] for 22 - 36 days post-treatment.

Clinical Recurrence. Clinical recurrence was described in one RCT (Clegg et al., 2006) and defined as the recurrence of signs and symptoms associated with GAS (9.2% in amoxicillin QD versus 7.1% for amoxicillin BID in the 12–21 day post-treatment visit; 0.9% in both treatment groups for the 22–36-day post-treatment visit). No statistical difference was noted in clinical recurrence for 12-21 days or 22-36 days post-treatment, *OR* = 1.32; 95% CI [0.73, 2.40]; *OR* = 1.04; 95% CI [0.15, 7.46].

Adverse Events. Adverse events were reported in one RCT (Clegg et. al., 2006) as symptoms such as abdominal pain, diarrhea, nausea/vomiting, fever, or rash (nonspecific). No statistical difference was noted between amoxicillin QD versus amoxicillin BID, *OR* = 1.18; 95% CI [0.74, 1.88]. One RCT by Lennon et al., 2008, reported one child (1/177) with acute rheumatic fever in the amoxicillin QD treatment group. This study took place in New Zealand.

Certainty of the Evidence for Bacterial Eradication. The certainty of the body of evidence was very low (See Table 1, Figure 2). A review of the available evidence that answered the question demonstrated a low number of participants, concerns with the methodology in the blinding of participants and assessors, as well as comparing strains from different geographical areas with a potential variance of the streptococcal bacteria, resulting in an overall analysis of the certainty of the evidence as very low.

Study characteristics. The search for suitable studies was completed on October 04, 2023. Dr. K. Berg reviewed 186 titles and/or abstracts found in the search and identified 15 studies believed to answer the question. Drs. R. El Feghaly and K. Tilak reviewed the 15 abstracts found in the initial review and identified six single studies believed to answer the question. After an in-depth review of the single studies, four were found to answer the question.

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Table 1
Characteristics of Included Studies

Author (year)	Study Type	Population	N	Intervention	Control	Results
Clegg et al. (2006)	RCT	Children 2 – 18 years of age with signs and symptoms of GAS in the United States.	*N* = 652	Amoxicillin QD for 10 days (*n*=326) <40kg = 750 mg/dose **OR** ≥40kg = 1000 mg/dose	Amoxicillin BID for 10 days (*n*=326) <40kg = 375 mg/dose **OR** ≥40kg = 500 mg/dose	**Visit 2** (14-21 days post-treatment: Failure rates = 31% (91 of 294) for QD 23.9% (71 of 296) for BID **Visit 3** (28-35 days post-treatment): Failure rates = 4.6% (10 of 216) for QD 13.3% (30 of 225) for BID
Lennon et al. (2008)	RCT	Children 5 – 12 years of age were assessed for GAS and treated at school in New Zealand.	*N* = 353	Amoxicillin QD for 10 days (*n*=177) ≤30 kg = 750mg/dose **OR** >30kg = 1500mg/dose	Penicillin V BID for 10 days (*n*=176) ≤20kg = 250mg/dose **OR** >20kg = 500mg/dose	**Visit 3** (12 -16 days post-treatment): Failure rates = 12.7% (20/158) amoxicillin QD 11.9% (19/159) penicillin V BID **Visit 4** (26-36 days post-treatment): Failure rates = 10.7% (17/159) amoxicillin QD 11.3% (18/159) penicillin V BID
Nakao et al. (2019)	Cohort, Retrospective	Children older than 3 years with suspected acute pharyngitis from GAS in Japan.	*N* = 34	Amoxicillin QD for 10 days (*n*=12) 40-50mg/kg/day *upper limit of 1000mg/day for all treatment groups*	Amoxicillin BID for 10 days (*n*=15) Amoxicillin 3x/day for 10 days (*n*=7)	**Visit 3** (9-11 days post-treatment): Treatment Success (Rate of negative PCR) = 58.3% (7/12) amoxicillin QD 67.6% (10/15) amoxicillin BID 100% (7/7) amoxicillin 3x/day
Rimoin et al. (2011)	RCT	Children 2-12 years of age with a positive test for GAS in Egypt or Croatia.	*N* = 507	Amoxicillin QD for 10 days (*n*=261) 750mg/dose for all weights	Penicillin IM (*n*=246) <27kg = 600,000 units/dose ≥27kg= 1.2 million units/dose	**F/U visit** (21-28 days post-treatment): Treatment Success = 46% (121/261) amoxicillin QD 54% (132/246) penicillin IM

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Identification of Studies

Search Strategy and Results (see Figure 1)

'streptococcal pharyngitis'/exp OR 'streptococcal pharyngitis' OR ('pharyngitis'/exp OR pharyngitis) AND ('group a streptococcal infection'/exp OR 'group a streptococcal infection' OR 'streptococcus group a'/exp OR 'streptococcus group a') AND 'amoxicillin'/exp OR 'amocillin' OR 'penicillin v'/exp OR 'penicillin v' AND [2006-2023]/py 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) AND ('Article'/it OR 'Article in Press'/it) NOT 'case report'/de

Search Dates: 2006-Current (search extended back to 2006 due to limited results over the past ten years).
Records identified through database searching *n* = 15
Additional records identified through other sources *n* = 0

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Armengol & Hendley (2012)	Wrong comparison: Combined amoxicillin QD/BID vs cephalexin
Bar-Yishay et al. (2022)	Wrong intervention: No dosing frequency included
Casey et al. (2007)	Wrong article type: Review article
Casey et al. (2008)	Wrong comparison: Compared oral penicillin V, IM benzathine penicillin, and amoxicillin as a group to cephalosporin
Casey & Pichichero (2007)	Wrong comparison: Compared dosing of BID instead of QD for the intervention
Del Mar et al. (2008)	Wrong article type: Summary of another article
Dona et al. (2018)	Wrong intervention: Review of a pre vs. post-intervention of a clinical pathway
Eslami et al. (2014)	Wrong outcome: Various clinical manifestations
Gerber et al. (2009)	Wrong article type: Scientific statement: not a study
Gidengil et al. (2013)	Wrong comparison: Compared amoxicillin or penicillin to cephalexin
Schulman et al. (2012)	Wrong article type: Clinical practice guideline

Question Originator

R. Elfeghaly, 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.

Medical Librarian Responsible for the Search Strategy

K. Swaggart, MLIS, AHIP

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Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)

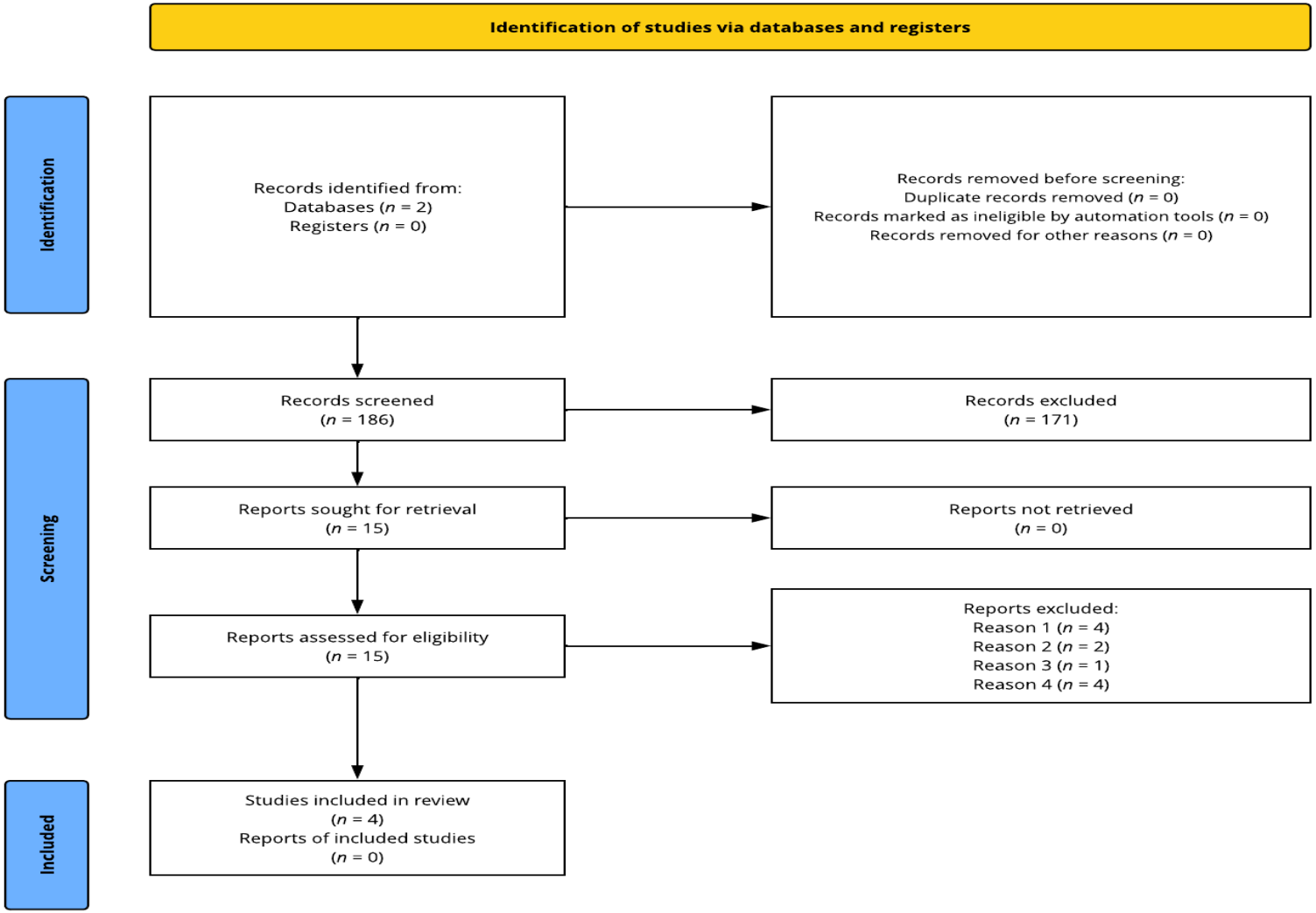

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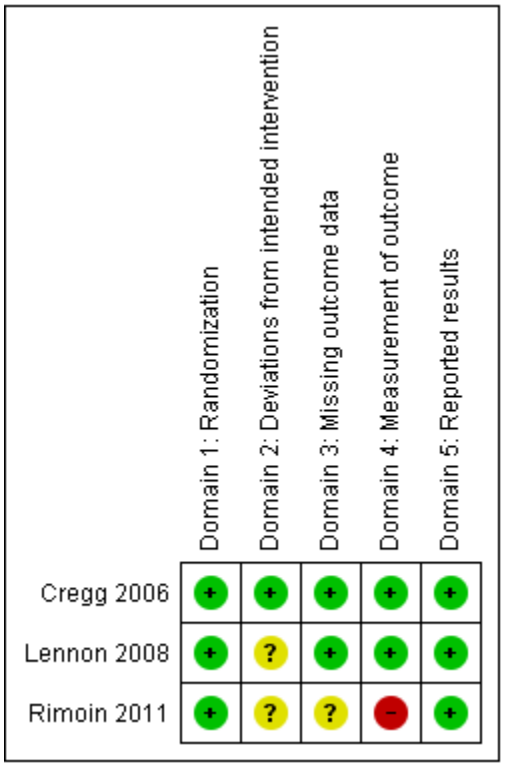
Figure 2

Risk of Bias Summary for outcome of bacterial eradication



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Summary of Findings Table

Table 2
Summary of Findings Table: Bacterial Eradication

Certainty assessment							Summary of findings				
							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amoxicillin daily	amoxicillin twice a day or penicillin V	Relative (95% CI)	Absolute (95% CI)	
Treatment Success 9-11 days post-treatment											
1	observational studies	not serious	not serious	not serious	serious[a]	none	7/12 (58.3%)	10/15 (66.7%)	**OR 0.70** (0.18 to 1.91)	**121 fewer per 1,000** (from 436 fewer to 204 more)	⨁◯◯◯ Very low
Treatment Success 12-21 days post-treatment											
2	randomized trials	serious[b]	not serious	not serious[c]	not serious	none	339/503 (67.4%)	362/502 (72.1%)	**OR 0.80** (0.61 to 1.09)	**38 fewer per 1,000** (from 109 fewer to 8 more)	⨁⨁◯◯ Low
Treatment Success 22-36 days post-treatment											
3	randomized trials	very serious[d]	not serious	not serious[e]	not serious	none	469/764 (61.4%)	471/748 (63.0%)	**OR 0.94** (0.76 to 1.16)	**15 fewer per 1,000** (from 66 fewer to 34 more)	⨁◯◯◯ Very low

Notes
a. Low number of participants
b. Concerns with study personnel analyzing the data vs. lab personnel
c. Comparison of strains from different geographical areas with a potential variance of the streptococcal bacteria (US vs New Zealand)
d. Concern with assessors' awareness of intervention received by the participant
e. Comparison of strains from different geographical areas with a potential variance of the streptococcal bacteria (US, New Zealand, Croatia, Egypt)

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Meta-analysis(es)
Figure *2*
Comparison: Amox QD versus Amox BID, Outcome: Bacterial Eradication

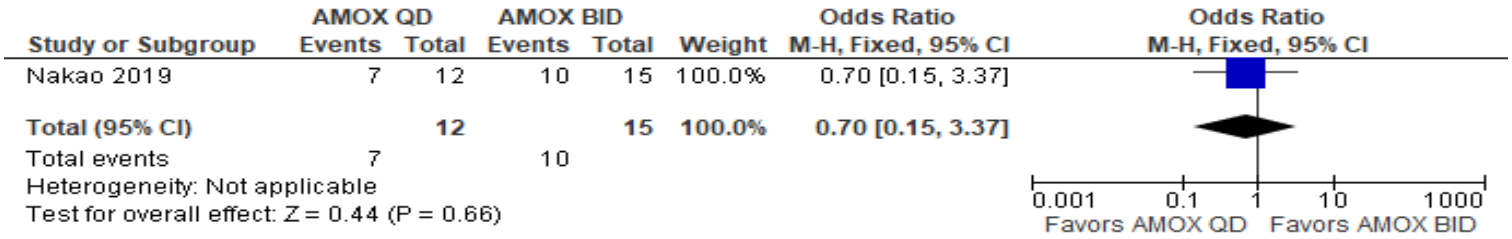


Figure 3
Comparison: Amox QD versus Amox or Pen V BID, Outcome: Bacterial Eradication

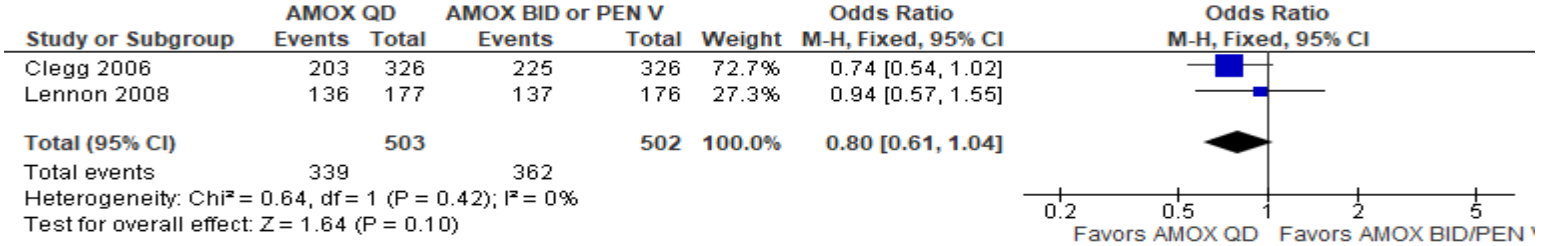
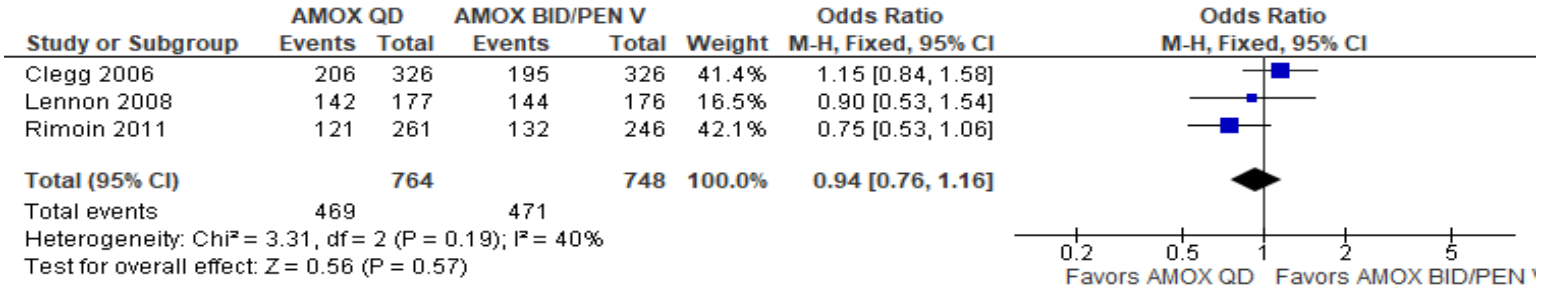


Figure 4
Comparison: Amox QD versus Amox/Pen V BID or Pen IM, Outcome: Bacterial Eradication



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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Characteristics of Intervention Studies

Clegg et al. (2006)

Methods	**Randomized Control Trial**
Participants	**Participants:** Children ages 3 to 18 years with symptoms and signs of GAS pharyngitis **Setting:** Single pediatric practice in USA, October through May, for two consecutive years (2001 - 2003) **Randomized into the study:** *N* = 652 • **Group 1,** *Amoxicillin QD: n* = 326 • **Group 2,** *Amoxicillin BID: n* = 326 **Completed Study:** *N* = 590 (visit 2); 441 (visit 3) • **Group 1:** *n* = 294 (visit 2); *n* = 216 (visit 3) • **Group 2:** *n* = 296 (visit 2); *n* = 225 (visit 3) **Gender, females (as defined by researchers):** • **Group 1:** *n* = 164 (50.3%) • **Group 2:** *n* = 162 (49.7%) **Race/ethnicity or nationality (as defined by researchers):** • **Group 1:** White = 299; Black = 21; Hispanic/other = 6 • **Group 2:** White = 283; Black = 33; Hispanic/other = 10 **Age, mean in years, (SD):**

	Group 1		Group 2	
	< 40 kg	≥40 kg	< 40 kg	≥ 40kg
Mean ± SD	6.9 ± 2.2	12.1 ± 2.0	6.8 ± 2.2	12.1 ± 2.6
Median	6.6	11.8	6.5	12.1
Range	2.9-13.6	7.9-17.3	3.0-13.1	7.0-18.0

Inclusion Criteria:
- Children aged 3 to 18 years
- Signs and symptoms of GAS pharyngitis (fever, sore throat, pain on swallowing, pharyngeal erythema, tonsillar exudate, soft palate petechiae, tender cervical nodes)
- Absence of findings making viral illness more likely (primary symptoms of cough, coryza and hoarseness, diarrhea, conjunctivitis, viral exanthem/enanthem)
- Positive rapid test for GAS (and confirmed by conventional culture positive for GAS)

Exclusion Criteria:
- History of penicillin or amoxicillin allergy
- Treatment with an oral antimicrobial in the past week
- Treatment with a long-acting parenteral penicillin in the past 4 weeks
- Three or more culture-confirmed episodes of GAS pharyngitis in the previous year
- Known streptococcal carriage
- Known immune suppression

Power Analysis: Assumed dropout rate of 20%, power of 90%, and the use of 2-sided testing with the 90% confidence interval for the difference in efficacy between treatment groups. A sample size of 650 patients was estimated based on an expected bacteriologic failure rate of 15%

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Interventions	**Both:** Patients with a positive rapid test for GAS were stratified by weight (<40 kg or ≥40kg); both groups were asked to come back at 14 - 21 days (visit 2) and again at 28 - 35 days (visit 3), adverse events were described, and adherence was evaluated by review of returned daily logs and dosage bottles. • **Group 1(QD) :** Received 750mg QD (patient weight < 40kg) or 1000mg (patient weight ≥ 40 kg) of amoxicillin for 10 days • **Group 2 (BID):** Received 375mg BID (patient weight < 40 kg) or 500mg (patient weight ≥ 40kg) of amoxicillin for 10 days
Outcomes	**Primary outcome(s):** • *Bacteriologic failure at visit 2 • *Clinical recurrence at visit 2 (clinical cure defined as resolution of symptoms and signs of GAS pharyngitis) **Secondary outcome(s)** • *Bacteriologic failure at visit 3 • Clinical recurrence visit 3 **Safety outcome(s):** • *Adverse events - study log filled out by caregiver/patient was reviewed at visit 2 *Outcomes of interest to the CMKC CAT development team
Notes	**Results:** • Bacteriologic failure rates at visit 2 were 20.1% for the amoxicillin QD group and 15.5% for the amoxicillin BID group • Bacteriologic failure rates at visit 3 were 2.8% for the amoxicillin QD group and 7.1% for the BID amoxicillin group • Clinical recurrence occurred in 9.2% of the QD group and 7.1% of the BID group at visit 2 • Clinical recurrence occurred at 0.9% for both groups at visit 3 • Gastrointestinal and other adverse events occurred in the QD group at a comparable rate to the BID group (17% vs 14 %, respectively) **Limitations:** • Amoxicillin QD was not directly compared with the standard comparator (penicillin), typically provided TID • Stratification of patients by weight for dosing did not reflect standard practice for the use of amoxicillin for GAS pharyngitis • Study subjects were recruited from a single pediatric practice, which could limit the generalizability of findings • The study was not powered for subgroup analysis

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Lennon et al. (2008)

Methods	**Randomized Control Trial**

Participants	**Participants:** Children aged 5 – 12 years
	Setting: A school-based clinic in New Zealand from May 1996 to November 1998
	Randomized into the study: *N* = 353
	• **Group 1,** oral amoxicillin QD for 10 days: *n* = 177
	• **Group 2,** oral penicillin V BID for 10 days: *n* = 176
	
	Completed Study: *N* = 335
	• **Group 1:** *n* = 166
	• **Group 2:** *n* = 169
	
	Gender, males (as defined by researchers):
	• **Group 1:** *n* =177 (52%)
	• **Group 2:** *n* = 176 (49 %)
	
	Race/ethnicity (as defined by researchers):
	• **Group 1:** Maori 50%, Pacific Islander 30%, Other 19%
	• **Group 2:** Maori 50%, Pacific Islander 33%, Other 17%
	
	Age, median in years, (IQR)
	• **Group 1:** 8.7 (7.1 – 10.2)
	• **Group 2:** 8.5 (6.7 – 9.9)
	
	Inclusion Criteria:
	• Signs and symptoms indicative of acute pharyngitis or tonsillitis, including a sore throat and at least one of the following:
	  ○ Core temperature > 38°C
	  ○ Headache
	  ○ Nausea or abdominal pain
	  ○ Difficulty swallowing
	  ○ Inflamed or infected throat
	  ○ Tender glands in the neck
	Exclusion Criteria:
	• Hypersensitivity to penicillin
	• Likely to require treatment with other antimicrobials during the study period or had received antimicrobial therapy within 72 hours prior to study entry
	• History of acute rheumatic fever, cardiac disease, or kidney disease
	• Rash suggestive of scarlet fever or mononucleosis
	• Immunocompromised
	• Neoplastic disease
	• Terminal illness or neutropenia (absolute neutrophil count <1.5 x10/9 cells/l)
	• Previously been included in this study within the current school term (approximately 12 weeks in duration)
	
	Power Analysis: With no difference in treatment effect in the two arms of the trial and assuming 85% eradication, 155 evaluable subjects per treatment group would have 80% power to demonstrate non-inferiority (defined as the upper 95% confidence limit (CL) of the treatment effect difference of < 10%).

Interventions	**Group 1:** Received amoxicillin 1500 mg (or 750 mg for children with bodyweight ≤ 30 kg) administered orally QD for 10 days. **Group 2:** Received penicillin V 500 mg (or 250 mg for children with bodyweight ≤ 20 kg) administered orally BID for 10 days.

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Outcomes	**Primary outcome(s):** • Bacteriologic failure (including relapse) at visit 3.

Notes	**Results:**
	• Adherence to antibiotics was similar in both groups:
	  ○ Group 1 (QD): 97%
	  ○ Group 2 (BID): 98%
	• Twelve to sixteen days following antibiotic treatment, there was no difference in relapse rate (Group 1: 7.6% and Group 2: 7.6%).
	• Twenty-six to thirty-six days post-antibiotic treatment, there were no significant differences in treatment failure (1.9% in both groups).
	Limitations:
	• Amoxicillin QD was compared to penicillin V BID, but no further amoxicillin dosage recommendations or length of treatment was studied.
	• The study was conducted in one school with unique demographics, which could limit the overall generalization of the findings.

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Nakao et al. (2019)

Methods	Cohort, prospective
Participants	**Participants:** Children aged older than 3 years with suspected acute pharyngitis due to GAS infection between October 2015 and September 2016 **Setting:** Two pediatric medical institutions in Japan **Number enrolled in the study**: *N* = 34 • **Cohort 1, Amoxicillin QD:** *n* = 12 • **Cohort 2, Amoxicillin BID:** *n* = 15 • **Cohort 3, Amoxicillin thrice a day dosing (TID):** *n* = 7 **Gender, males (as defined by researchers):** • **Cohort 1:** *n* = 12 (100%) • **Cohort 2:** *n* = 10 (66.7%) • **Cohort 3:** *n* = 6 (85.7%) **Race/ethnicity or nationality:** • Not specified; the study was conducted in Japan **Age, mean/years, (standard deviation)**: • **Cohort 1:** 7.3 (± 3.1) • **Cohort 2:** 5.0 (± 1.4) • **Cohort 3:** 7.7 (± 1.3) **Inclusion Criteria:** • Children ≥ 3 years of age • Suspected acute pharyngitis due to GAS infection (clinical diagnosis made based on symptoms – fever, sore throat, malaise, and headache with acute onset, whereas physical findings include prominent pharyngeal redness, tonsil swelling with exudate, and cervical lymphadenopathy) **Exclusion Criteria:** • Patients with a history of penicillin allergies • Patients who received antibacterial drugs within the past 4 weeks **Covariates Identified:** • None Identified
Interventions	**Both:** Patients underwent rapid antigen testing with ImunoAce StrepA using a throat swab and isolation culture tests, in which GAS was detected. Patients received amoxicillin at 40 to 50 mg/kg/day; the maximum dose was 1000 mg/day. Antibiotic duration was 10 days. Patient families determined when (time of day) the doses would be administered. The clinical course was evaluated following treatment during outpatient visits. Patients were educated on the symptoms of relapse and complications. Patients were advised to seek re-evaluation if symptoms were suspected. • **Cohort 1:** Received amoxicillin QD for 10 days • **Cohort 2:** Received amoxicillin BID for 10 days • **Cohort 3:** Received amoxicillin TID for 10 days
Outcomes	**Primary outcome(s):** • Rate of negative GAS PCR in throat swabs collected after the start of treatment. • Number of GAS copies determined by polymerase chain reaction (PCR) in throat swabs collected after the start of treatment.* **Secondary outcome:** • None Identified **Safety outcome:**

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	• None Identified *Outcomes of interest to the CMH Clinical Pathway development team
Notes	**Results:** • Differences were observed in the age (p = 0.02) and sex (p = 0.047) of the subjects in the QD and BID groups • Analysis revealed a higher initial bacterial load in the QD group (1.4×10^6 [2.2×10^5 - 4.3×10^6]) compared to the BID group (8.2×10^5 [2.4×10^5 – 1.6×10^6]) • There were no significant differences in the rate of negative PCR results and quantitative parameters between QD and BID dosing at repeated visits after the antibiotic course (Visit 1: not estimable; Visit 2: p = 0.21; Visit 3: p = 0.52; Overall effect: p = 0.17) **Limitations:** • There was a small number of samples to assess the outcome of eradication

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Rimoin et al. (2011)

Methods	**Randomized Control Trial**

Participants	**Participants:** Children 2-12 years of age with complaint of sore throat
	Setting: Two urban outpatient clinics in Cairo, Egypt, and Zagreb, Croatia
	Randomized into study: *N* = 558 (Croatia: *n* = 166, Egypt *n* = 392)
	• **Group 1, IM Benzathine Penicillin G (BPG):** *n* = 275
	  ○ Croatia: *n* = 84; Egypt: *n* = 191
	• **Group 2, Oral Amoxicillin QD:** *n* = 283
	  ○ Croatia: *n* = 82; Egypt: *n* = 201
	
	Completed Study: *N* = 272 (Croatia *n* = 111, Egypt *n* = 161)
	• **Group 1:** *n* = 181
	  ○ Croatia: *n* = 57; Egypt: *n* = 124
	• **Group 2:** *n* = 91
	  ○ Croatia: *n* = 54; Egypt: *n* =37
	
	Gender, % male (as defined by researchers):
	• **Group 1,** Croatia: *n* = 65.5; Egypt: *n* = 60.2
	• **Group 2,** Croatia: *n* = 56.1; Egypt: *n* = 55.7
	
	Race/ethnicity or nationality (as defined by researchers):
	• **Group 1,** Croatian: *n* = 84, Egyptian: *n* = 191
	• **Group 2,** Croatian: *n* = 82, Egyptian: *n* = 201
	
	Age, mean (SD) in years
	• **Group 1,** Croatia: 5.6 (2.6); Egypt: 5.3 (2.6)
	• **Group 2,** Croatia: 5.7 (2.4); Egypt: 5.4 (2.5)
	
	Inclusion Criteria:
	• Children aged 2-12 years
	• Presented to an outpatient clinic with a complaint of sore throat
	• Patients with a positive rapid antigen test and positive throat culture
	Exclusion Criteria:
	• If parent reported:
	  ○ Oral antibiotic use in the past 3 days
	  ○ Injectable penicillin in the past 28 days
	• History of rheumatic fever
	• History of rheumatic heart disease
	• Required hospitalization at the time of enrollment
	• Previously enrolled in the study
	• Known hypersensitivity to penicillin
	• Likely to require treatment with other antimicrobials during the study period
	• Positive rapid antigen detection test and negative throat culture
	
	Power Analysis: It was estimated that a sample size of 154 patients per treatment arm would have 80% power to demonstrate non-inferiority (defined as the upper 95% confidence limit of the treatment effect difference of ≤10%). Thus, if the treatment success for benzathine penicillin G (BPG) IM was 90.0%, amoxicillin success would fall between 80.0% and 90.0% to be considered non-inferior. They were unable to reach the estimated sample size in each country, thus possibly not having the power to detect differences between treatment groups between countries.

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Interventions	**Group 1:** Single dose of intra-muscularly administered BPG (600 000 units if body weight <27 kg; 1.2 million units if body weight ≥ 27 kg) **Group 2:** Oral amoxicillin suspension (750 mg QD for all weight categories) given 10 for days

Outcomes	**Primary outcome(s):**
	• **Bacteriologic treatment success***
	  ○ Defined as eradication of GAS from the pharynx at the follow-up visit. Eradication was defined as no GAS present on the throat culture.
	• **Compliance**
	  ○ Parents/guardians were given a Whatman no. 3 filter paper strip and asked to dip it into the child's urine once on the seventh day of treatment, allow it to air dry, place it in an envelope, and bring it back to the clinic at the follow-up visit. Compliance was measured by antimicrobial activity in the urine filter paper strips.
	Secondary outcome(s):
	• None reported
	Safety outcome(s):
	• None reported
	*Outcomes of interest to the pharyngitis clinical pathway development committee

Notes	**Results:** • Patients with negative throat culture results from the initial visit were excluded from the final result analysis (9 in Croatia, 20 in Egypt), and patients with loss to follow-up were excluded from the final result analysis (18 in Croatia and 47 in Egypt). Both intention-to-treat (ITT) and per-protocol (PP) analyses were reported. • For treatment success in Croatia, ITT and PP treatment rates were comparable for IM BPG and amoxicillin (2.5% difference vs 1.1% difference, respectively). • For treatment success in Egypt, amoxicillin was not comparable with IM BPG in ITT analysis (15.1% difference) but was comparable in PP analysis (−9.3% difference). **Limitations:** • Unable to conduct M protein gene (emm) typing to identify GAS subtypes before and after therapy. Thus, it is possible that some patients who may have been reinfected after successful eradication of the initial infection were misclassified as treatment failures. • Unable to conduct serologic analyses that would have allowed us to classify those patients who failed treatment as carriers. However, both carriers and those who reacquired GAS after successful treatment should have been equally distributed between the two treatment groups. Therefore, the observed treatment difference between regimens should not have been affected. • Although a randomized, controlled design was used, patients and clinicians were aware of the study assignments. • Both study drugs were obtained locally rather than from a central source, which could have resulted in differences in the microbiologic efficacy of either treatment regimen between countries.

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

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Critically Appraised Topic (CAT): Amoxicillin QD vs BID or Penicillin V to Treat Pediatric Pharyngitis

Appendix

Evidence to Decision Assessment for Amoxicillin QD versus Amoxicillin/Penicillin V BID or Penicillin IM

QUESTION

In pediatric patients diagnosed with pharyngitis, is Amoxicillin QD as effective as Amoxicillin BID or Penicillin V?	
POPULATION:	Children and adolescents 2 to 18 years of age with acute pharyngitis due to GAS
INTERVENTION:	Amoxicillin QD
COMPARISON:	Amoxicillin/penicillin V BID or Pen IM
MAIN OUTCOMES:	**Bacterial eradication** (treatment success), bacteriologic failure, clinical recurrence, adverse events (e.g., vomiting, fever) Only one patient in 4 studies was reported to develop acute rheumatic fever.

ASSESSMENT

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	For dosing frequency, the certainty of the evidence is very low. A review of the available evidence that answered the question demonstrated a low number of participants and concerns with the methodology in the blinding of participants and assessors, resulting in an overall analysis of the certainty of the evidence as very low.	

Resources required
How large are the resource requirements (costs)?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Amoxicillin is a generically available, relatively low-cost, and narrow-spectrum antibiotic that presents a useful therapeutic alternative to penicillin V (Lennon et al., 2008).	No difference in side effects was reported with taking the full dose once a day compared to spreading the dose over 2-3 times daily.

Equity
What would be the impact of the intervention on health equity?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

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○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Availability – generic availability contributes to reducing the burden of the disease (Massell et al., 1988). Continuing with once-daily dosing does not impact access to the medication.	This continues today (December 2023) with current price comparisons and availability throughout community pharmacies.

Acceptability
Is the intervention acceptable to key stakeholders (including patients and families)?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Clinician acceptability - Patients with acute GAS pharyngitis should be treated with an appropriate dose for a duration likely to eradicate the organism from the pharynx (usually ten days). Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin is the recommended drug of choice for those non-allergic to these agents (Shulman, 2012; recommendation #8)	Parents prefer giving medication at once-a-day intervals rather than several times a day.

Feasibility
Is the intervention feasible to implement?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Stakeholders report that the reduction in dosing to once a day will be an easily accepted change to clinical practice based on the literature and guideline reviewed, as well as considerations discussed above in the evidence-to-decision tool.	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

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Recommendation
The Pharyngitis Clinical Pathway Committee makes a conditional recommendation for dosing of amoxicillin once daily over a ten-day course based on the literature and significantly increased feasibility of treatment administration.
Implementation considerations
The update will be included in the new clinical pathways and shared with various departments considered the first access points for assessing, testing, and prescribing antibiotics for GAS pharyngitis. These include the Emergency Department, Urgent Care Clinics, Primary Care Clinics, Inpatient Units, and community pediatricians. Power plans will be updated to reflect the preferred medication and dosing. Confirmation to continue with once-daily dosing for amoxicillin will be included in email announcements to clinicians at Children's Mercy and in a newsletter sent to community pediatricians.
Monitoring and evaluation
Each department will monitor and encourage change in practice to once-daily dosing of amoxicillin over ten days. The education to confirm standard practice for amoxicillin will provide clinicians with sound, evidence-based reasoning to ensure this re-education will not compromise the well-being of children being treated for GAS pharyngitis.

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