Top Recent Articles from Infectious Disease Perspective

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October 5, 2017

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Disclosure

- I have no relevant financial relationships with the manufacturers of any commercial products or provider of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

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Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Baxter R, et al. *Pediatrics* May 2017;139(5):e20164091
- ACIP and Tdap with pregnancy
  - 2006 - administer Tdap in the immediate postpartum period
  - 2011 - Tdap during pregnancy for those who had not previously received Tdap
  - 2013 - Tdap during every pregnancy, preferably between 27-36 weeks gestation

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Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Retrospective cohort study of full term infants born at Kaiser Permanente Northern California from 2010 to 2015
- Mothers born before 1996 so that all mothers had received whole-cell rather than acellular pertussis
- Cases of pertussis were defined as being PCR positive
- Infants followed from birth to 12 months of age
- Vaccine efficacy determined for 0-2 months of age and 0-12 months of age

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Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Percentage of mothers who received Tdap during pregnancy increased from <1% in 2006-2008 to 11.9% in 2010 and to 87.4% by 2015
- The percentage of mothers who received the Tdap vaccine during postpartum days 0-14 peaked at 31.7% for infants born in 2010 and declined thereafter to 1.8% for infants born in 2015

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Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Study population consisted of 148,981 infants born from 2010, when KPNC began recommending Tdap vaccination in pregnancy, through 2015
  - mothers of 45.8% of the study population received Tdap vaccine during pregnancy at least 8 days before birth
- 17 infants (11.4 per 100,000 infants) tested positive for pertussis by 2 months of age
- 110 infants (73.8 per 100,000 infants) tested positive by 1 year of age
  - 103 included in the analyses after restricting to infants who followed the recommended DTaP schedule

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Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Maternal Tdap vaccination during pregnancy reduced pertussis risk by an estimated **91.4**% during the first two months of life
  - pertussis risk reduced by **69.0**% during the entire first year of life
  - no evidence for interference of Tdap during pregnancy with infant DTaP vaccination
- Maternal Tdap after pregnancy (cocooning) did not significantly reduce pertussis risk

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	VE, % (95% CI)	P-value
Tdap During Pregnancy Infant 0 DTaP	87.9 (42.4-97.5)	0.009
Tdap During Pregnancy Infant 1 DTaP	81.4 (42.5-94.0)	0.004
Tdap During Pregnancy Infant 2 DTaP	6.4 (-165.1-66.9)	0.901
Tdap During Pregnancy Infant 3 DTaP	65.9 (4.5-87.8)	0.041
Tdap After Pregnancy	24.1 (-28.5-55.1)	0.305
Tdap Before Pregnancy	55.6 (20.1-75.4)	0.007

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

- Georgiou R, et al. *Pediatrics* March 2017;139:e20163003
- Systematic review of the literature in December 2015
  - any study design reporting nonoperative treatment (NOT) for acute uncomplicated appendicitis (AUA)
    - NOT = antibiotic therapy without surgery
  - limited to studies of children (<18 years) and articles published in English
  - excluded studies that report NOT for complicated appendicitis (such as perforated or ruptured appendicitis, appendicitis with an abscess, or appendix mass)

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

- 727 records screened
- 20 full-text articles assessed for eligibility
- Ten articles (7 prospective, 3 retrospective) reporting NOT for AUA were included
  - Six, including one randomized controlled trial, compared NOT to appendectomy
  - Four reported outcomes of children receiving NOT without a comparison group
- 413 children were either randomized to or selected for NOT

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

- No study reported any adverse events related to NOT or concern over the safety of NOT
- NOT was successful as initial treatment in **97**% (95% CI 95.5-98.7)
- Adjusted incidence of recurrent appendicitis was 14% (95% CI 7-21)
- The long-term efficacy of NOT (those children who did not have an appendectomy by the final follow-up) was 82% (95% CI 77-87)

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

- In the six studies that compared NOT with appendectomy duration of initial hospital stay was reported in 4 studies
- Duration of hospital stay for children who had an appendectomy was shorter by a mean of 0.5 days (95% CI 0.2-0.8) compared to children who had NOT
- Total duration of hospital stay including during follow-up (initial plus readmissions) was similar between children initially treated with NOT and appendectomy
  - weighted mean difference 1.1 days (95% CI -1.2 to 3.5; P=.34)

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

- Total complications were reported in 5 of the 6 comparative studies
- Risk of complications was similar
  - Risk difference 2% (95% CI 0-1; P=.1)
    - 1/175 with NOT (surgical site infection in child who failed initial NOT and had appendectomy)
    - 9/239 with appendectomy

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Related Study

- Prospective nonrandomized study of NOT for acute appendicitis with appendicolith compared to appendectomy
  - Mahida JB, et. *Journal of Pediatric Surgery* 2016;51:908-911
  - Recruitment of the study was halted after enrollment of 14 patients (5 nonoperative, 9 surgery) due to high failure rate (3/5) in the nonoperative group

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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Shah SS, et al. *Pediatrics* Dec 2016;138:e20161692
- Multicenter retrospective cohort study with propensity score modeling and matching
- Children ≥2 months and <18 years discharged with complicated pneumonia (pleural effusion, empyema) between 2009 and 2012
  - Used data from the Pediatric Health Information System (PHIS) affiliated with the Children's Hospital Association

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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Main exposure variable was PICC or oral discharge antibiotic administration and primary outcome was treatment failure
  - treatment failure was defined as an ED revisit or rehospitalization that resulted in extension or change of antibiotic therapy or performance of pleural drainage
- Propensity score matching incorporated age, race, insurance, length of stay in days, blood culture results (negative or positive), ICU admission, and timing and route of pleural drainage

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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- 2123 subjects in final cohort from 36 hospitals
  - 1842 received oral antibiotics and 281 received antibiotics via PICC
  - PICC use post discharge varied across hospitals, ranging from 0% to 71%
- Pleural fluid drainage was performed in 43.9% of children
- Pathogen was identified in blood or pleural fluid culture in 305 (N= 14.4%) of children
  - 175 *Streptococcus pneumoniae*, 77 *Staphylococcus aureus* (56 MRSA, 72.7%), 21 *Streptococcus pyogenes*, 9 *Streptococcus milleri* group

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TABLE 1 Study Population Characteristics Pre- and Postmatch

Characteristic[a]	Prematch		Postmatch[b]	
	Oral	PICC	Oral	PICC
n	1842	281	1842	281
Age <5 y	56.0	61.6	61.1	61.6
White race	57.7	65.5	62.4	65.5
Government payer	54.0	36.3	35.3	36.3
Length of stay (d)	7.2	9.1	9.2	9.1
Culture positive	12.4	24.6	23.9	24.6
ICU admission	18.1	26.3	27.0	26.3
Drainage procedure				
No drainage	61.0	24.6	24.5	24.6
Late surgical drainage	11.7	15.3	14.8	15.3
Early surgical drainage	14.9	19.2	21.4	19.2
Late chest tube drainage	4.6	15.3	12.1	15.3
Early chest tube drainage	7.9	25.6	27.2	25.6

[a] Values presented as percentages except for length of stay, for which mean values are presented.
[b] Percentages are weighted.

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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Treatment failure before matching occurred in 57 (2.7%) overall
  - 3.2% with PICC antibiotic and 2.6% with oral (P>.2)
- No treatment failures occurred among the 77 patients with *Staph aureus*
- Among children discharged with oral therapy for culture-negative infection, treatment failure occurred in 1.4% discharged with amoxicillin and 1.9% of those discharged anti-MRSA antibiotics

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TABLE 2 Outcomes of Children With Complicated Pneumonia

Outcome	Unadjusted Rates, % (*n*)	Matched OR (95% CI)[a]	*P*	Adjusted Rates, %[b]	Matched Risk Difference (95% CI)[c]	*P*
Treatment failure						
PICC	3.2 (9)	1.26 (0.54 to 2.94)	>.2	3.2	1.8% (−0.4 to 3.9)	.1
Oral	2.6 (48)	—	—	1.4	—	—
PICC Complications						
PICC	7.1 (20)	—	—	—	—	—
Oral	N/A	N/A	N/A	N/A	N/A	N/A
Adverse drug reaction						
PICC	3.2 (9)	19.1 (4.2 to 87.3)	<.001	3.2	3.1% (0.01 to 5.2)	.003
Oral	0.2 (4)	—	—	0.01	—	—
Other related revisits						
PICC	6.1 (17)	3.27 (1.85 to 6.48)	.001	6.0	4.4% (1.5 to 7.4)	.003
Oral	3.0 (56)	—	—	1.6	—	—
All related revisits						
PICC	17.8 (50)	4.71 (2.97 to 7.46)	<.001	17.8	14.8% (10.1 to 19.3)	<.001
Oral	5.8 (106)	—	—	3.1	—	—

N/A, not applicable; —, X.

[a] ORs estimated from condition logistic regression stratified by the matched sets. An OR >1 means that the PICC route has a higher risk for the adverse outcome.

[b] Rates are standardized by weighting matched sets by the number of PICC patients and analyzed using weighted logistic regression with robust variance estimates translated to probabilities and their differences.

[c] Estimated using weighted logistic regression. A risk difference of greater than 0 means that the PICC route has the higher risk for the adverse outcome.

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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Conclusions
  - Treatment failure rates did not differ between PICC and oral postdischarge antibiotic administration
  - Adverse events were more frequent with PICC
  - Children with complicated pneumonia should preferentially be discharged with an oral antibiotic

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Quinolone Ear Drops After Tympanostomy Tubes and the Risk of Eardrum Perforation: A Retrospective Cohort Study

- Alrwisan A et al. *Clinical Infectious Diseases* April 2017;64:1052-1-58.
- A cell culture study showed that treatment of TM fibroblasts with ciprofloxacin led to marked cytotoxicity and depression in collage synthesis
- Retrospective cohort study using Medicaid encounter and pharmacy billing data from 29 US states between 1999 and 2006.
- Children <18 years old without predisposing factors for perforation requiring tympanoplasty entered the cohort after TT placement and first dispensing of antibiotic ear drops (within one year of TT placement).
  - Included ear drops were quinolones (ofloxacin, ciprofloxacin plus hydrocortisone, or ciprofloxacin plus dexamethasone) or neomycin plus hydrocortisone
- Analysis adjusted for age, sex, race, adenoidectomy, TT reinsertion, calendar year of tube insertion, number of ear drop prescriptions, and time to first ear drop initiation

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Quinolone Ear Drops After Tympanostomy Tubes and the Risk of Eardrum Perforation: A Retrospective Cohort Study

- 96,595 children entered the study cohort
  - 18,320 received neomycin
  - 78,275 received quinolone
- Each year increase in patient's age was associated with a 21% increase in the hazard of perforation (95% CI 18%-24%)
- An increased frequency of ear drop prescriptions was also associated with higher risk of perforation (HR 1.14; 95% CI 1.11-1.17)

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Exposure	No. of Patients	No. of Cases	Incidence per 10,000 person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Neomycin	18320	42	11.4	Reference	
All Quinolones	78275	322	17.3	1.44 (1.04-2.00)	1.61 (1.15-2.26)
Ofloxacin	50163	207	16.3	1.35 (0.96-1.89)	1.49 (1.05-2.09)
Cipro/HC	11649	79	25.2	2.17 (1.48-3.61)	1.94 (1.32-2.85)
Cipro/Dex	16463	36	12.7	0.87 (0.55-1.39)	2.00 (1.18-3.41)

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Quality of Life after Surgery for Recurrent Otitis Media in a Randomized Controlled Trial

- Kujala T, et al. *The Pediatric Infectious Disease Journa*l July 2014;33:715-719.
- Evaluated the effect of tympanostomy tubes (TT) with and without adenoidectomy for improving the quality of life (QOL) in young children with recurrent acute otitis media (RAOM)
- Myringotomy with tympanostomy tube placement is the most common ambulatory surgery performed on children in the United States
  - 667,000 children <15 years of age underwent TT placement in 2006

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Quality of Life after Surgery for Recurrent Otitis Media in a Randomized Controlled Trial

- Part of a larger study looking at reduction in episodes of AOM for children undergoing tympanostomy tubes, tympanostomy tubes plus adenoidectomy, or neither that was published in 2012
- Children aged between 10 months and 2 years of age who had at least 3 AOM episodes in the previous 6 months and had been referred to Otolaryngology Dept.
- A disease-specific QOL questionnaire (Otitis Media-6) completed by the principal caregiver at entry (time of surgery or no surgery) and 4 and 12 months later
  - divided into 6 subsets of physical suffering, emotional distress, caregiver concern, activity limitations, hearing loss, and speech impairment

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Quality of Life after Surgery for Recurrent Otitis Media in a Randomized Controlled Trial

- 159 children were randomized and 123 completed the study and analyzed
  - 42 TT, 46 TT with adenoidectomy, 35 no surgery
  - no significant differences in baseline characteristics (e.g., age, number of episodes of AOM, age of first AOM episode, daycare, duration of breastfeeding)
- A remarkable improvement in ear-related QOL between entry and 12-month followup was seen in all 3 groups, **with no difference between groups**

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Quality of Life after Surgery for Recurrent Otitis Media in a Randomized Controlled Trial

- The number of AOM episodes did not show any correlation with QOL in any of the OM-6 subsets at entry to the study.
- 12 children in the no surgery group (34%) had a failure of treatment (2 AOM episodes in 2 months or 3 in 6 months)
  - 9 failures in the TT group (21%) and 8 in the TT plus adenoidectomy group (17%)

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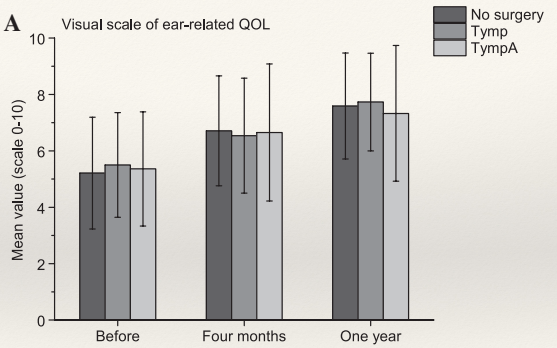

Global ear-related QOL running from 0 (worst possible) to 10 (best possible)

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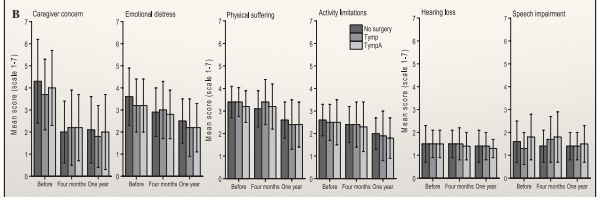

Outcome measures of QOL scale running from 1 (no problem/not present) to 7 (severe problems)

Significant improvements during the 12-month followup for subsets of caregiver concern, emotional distress, and physical suffering, but no significant differences between treatment groups in any of the six subsets.

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Tonsillectomy versus Watchful Waiting for Recurrent Throat Infection: A Systematic Review

- Morad A et al. *Pediatrics* February 2017;139:e20163490
- Objective was to compare sleep, cognitive, behavioral, and health outcomes of tonsillectomy vs watchful waiting in **children** with recurrent throat infections
- Recurrent or severe tonsillitis has been defined as ≥7 episodes of sore throat in the preceding year, or ≥5 episodes in each of the preceding 2 years, or ≥3 episodes in each of the preceding 3 years

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Tonsillectomy versus Watchful Waiting for Recurrent Throat Infection: A Systematic Review

- Searched Medline (PubMed), Embase, and Cochrane Library from January 1980 to June 2016
  - also hand-searched the reference lists of included articles and recent reviews addressing tonsillectomy in children to identify potentially relevant articles
- Principal outcomes of interest included the number and severity of recurrent throat infections, quality of life, and health care utilization (number of clinician visits or contacts, number of courses of antibiotics)
- Significant heterogeneity in outcomes reported precluded meta-analysis
  - synthesized studies qualitatively and reported descriptive statistics in summary tables
- Strength of evidence (insufficient, low, medium, high) was assessed to reflect the confidence in the stability of the treatment effects in the face of future research

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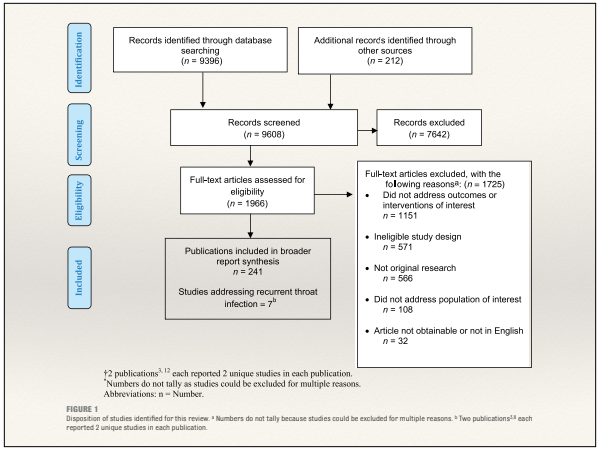

†2 publications[3, 12] each reported 2 unique studies in each publication.
[a]Numbers do not tally as studies could be excluded for multiple reasons.
Abbreviations: n = Number.

FIGURE 1
Disposition of studies identified for this review. [a] Numbers do not tally because studies could be excluded for multiple reasons. [b] Two publications[2,3] each reported 2 unique studies in each publication.

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Tonsillectomy versus Watchful Waiting for Recurrent Throat Infection: A Systematic Review

- Seven studies including children with ≥3 infections in the previous 1-3 years were analyzed
- In studies reporting baseline data, the number of infections/sore throats decreased from baseline in both groups
  - in the short term (<12 months) there were greater decreases in sore throat days, clinician contacts, diagnosed group A streptococcal infections, and school absences in children who had a tonsillectomy
    - there were 1.19 fewer mean episodes of sore throat with tonsillectomy compared to no surgery in the first post surgical year based on two RCTs
    - benefits did not persist over time
- Quality of life was not markedly different between groups at any time point (3 studies)

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Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, and Adenitis) Syndrome after Tonsillectomy

- Identified children who had tonsillectomy (+/- adenoidectomy) between 1990 and 2007 with a history of regularly recurring fever episodes at least 5 times
  - Oulu University Hospital in Finland
- 132 patients met the inclusion criteria and postoperative follow-up data was collected on 119 patients
  - divided patients into those who met current diagnostic criteria for PFAPA and those who did not
- Main outcome measure was the effectiveness of tonsillectomy in patients who did and did not meet the current criteria for PFAPA

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Table I. Thomas criteria for diagnosis of PFAPA

I	Regularly recurring fevers with an early age of onset (<5 y of age)
II	Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs: Aphthae Cervical lymphadenitis Pharyngitis
III	Exclusion of cyclic neutropenia
IV	Completely asymptomatic interval between episodes
V	Normal growth and development

Incomplete PFAPA

- Patients ≥5 years old at onset of fever episodes, or
- Patients who did not have aphthous stomatitis, cervical lymphadenitis, and pharyngitis at the onset of fever episodes

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PFAPA

- In 1987, Marshall et al (*J Pediatric* 1987;110:43-46) described a syndrome of periodic fever, pharyngitis, and aphthous stomatitis of unknown etiology
  - the acronym of PFAPA was introduced 2 years later
- the most common pediatric inflammatory fever syndrome
  - incidence of 2.3 per 10,000 children up to 5 years of age from Norwegian study
- Long-term (12-21 years) follow-up (Wurster VM et al, *Journal of Pediatrics* 2011) showed 50 of 59 patients had complete resolution with mean symptom duration of 6.3 years (95% CI, 5.4-7.3 years)
- Multiple randomized trials and Cochrane systematic review (Burton MJ et al, 2014) have shown effectiveness of tonsillectomy

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Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, and Adenitis) Syndrome after Tonsillectomy

- Mean age of patients was 2.7 years at the onset of symptoms, 4.3 years at the time of tonsillectomy, and 13.2 years at the time of study visit or telephone interview
- Data collected 2-20 years (mean 8.9 years) after tonsillectomy
- The duration of fever episodes and time between fever episodes was similar in the two groups

Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, and Adenitis) Syndrome after Tonsillectomy

- In the group that met Thomas criteria for PFAPA, 97% (56/58) had complete resolution of fever episodes after tonsillectomy
- In the group that did not meet Thomas criteria, 50/50 had complete resolution of fever episodes after tonsillectomy