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Review article

PFAPA syndrome in children: A meta-analysis on surgical versus medical treatment

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ABSTRACT

Objective: To compare the range of medical and surgical therapies for children with PFAPA syndrome.
Methods: A literature search was performed using Medline, Embase, Ovid and Cochrane databases for studies between 1987 and 2010 that compared PFAPA treatment in children (surgical versus medical). Random-effect meta-analytical techniques were conducted for the outcome measures.
Results: The use of antibiotics and cimetidine in PFAPA syndrome are ineffective. However, there is evidence that the use of steroids is effective in the resolution of symptoms. Tonsillectomy (+/− adenoidectomy) as a treatment of PFAPA was found to be an effective intervention for resolution of symptoms ($P < 0.00001$). Meta-analysis of surgery versus cimetidine and surgery versus antibiotics demonstrated that surgery is a significantly more effective treatment for PFAPA syndrome. A comparison of treatment with steroids or surgery did not show any statistically significant difference, confirming the effectiveness of both therapies for the resolution of PFAPA syndrome ($P = 0.83$).
Conclusions: The most effective non-surgical therapy is corticosteroids. However, they do not prevent future fever cycles. The results of this meta-analysis showed that tonsillectomy (+/− adenoidectomy) is the most effective intervention for long-term resolution of PFAPA syndrome symptoms.

Contents

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1. Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome was first described in 1987 by Marshall et al. [1] and is characterized by recurrent episodes of fever (>39 °C) lasting 3–6 days every 3–8 weeks with an early age onset (<5 years of age); absence of upper respiratory tract infection with at least one of the following clinical signs: aphthous stomatitis, pharyngitis, cervical adenitis; completely asymptomatic intervals between episodes; and normal growth and development [2–4]. The exact etiology of PFAPA syndrome is still unknown, and no evidence linking geographical, microbial or ethnic factors have been found [3]. As specific laboratory abnormalities have not been shown, PFAPA syndrome is defined clinically and the diagnosis is one of exclusion [3].

In terms of treatment, in addition to traditional medical therapy, surgery has been judged to be an effective therapeutic option [4]. This meta-analysis aims to study the comparison and efficiency of surgical versus medical, as well as different medical therapies performed in children with PFAPA syndrome.

2. Methods

2.1. Study selection

A literature search was performed using Medline, Embase, Ovid and Cochrane databases for studies between 1987 and 2010 that compared PFAPA treatment in children. The following MeSH search headings were used: PFAPA, periodic fever, Marshall syndrome, outcome, and treatment. The following text searches and search headings and their combinations were used: PFAPA, FAPA, pharyngitis, periodic fever, aphthous stomatitis, cervical adenitis, treatment, tonsillectomy and conservative. The *related articles* function was used to broaden the search, and all abstracts, studies, and citations were reviewed. No language restrictions were imposed. The date of the most recent search was March 1st, 2010.

2.2. Data extraction

Two reviewers (SP and EK) independently performed the search before reviewing and extracting the following: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, number of subjects, length of follow-up and outcomes of interest. Areas of conflicts between the reviewers were subsequently discussed, and there was 100% agreement on the final interpretation of the data.

2.3. Inclusion criteria

In order to be included in the analysis, studies had to compare surgical and medical treatment of PFAPA syndrome in children and report at least one of the outcomes of interest.

2.4. Exclusion criteria

Studies were excluded from the analysis if the outcomes of interest were not clearly reported or it was impossible to extract or calculate the appropriate data from the published results. When the same institution reported two studies, either the one of better quality or the one most recent publication was included unless the study outcomes were mutually exclusive or measured at different intervals.

2.5. Outcomes of interest

We were interested in the following outcomes:

1. Comparison of surgical versus medical therapies.
2. Assess the effectiveness of tonsillectomy (+/− adenoidectomy).
3. Assess the effectiveness of different medical therapies.

2.6. Statistical analysis

This meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines [5,6]. As all variables were dichotomous, odds ratio (OR) was used as the summary statistic [7]. *P* value is considered to be statistically significant if it is equal or less than 0.05. The Mantel–Haenszel method was used to combine the OR for the outcomes of interest using a "random-effect" meta-analytical technique [7,8]. Yate correction was used for those studies that contained a zero in one cell for the number of events of interest in 1 of the 2 groups [9]. If there were no events for both groups the study was discarded from the meta-analysis of that outcome.

Both funnel plots and sensitivity analysis were performed to quantitatively assess heterogeneity (HG) [8]. Sensitivity analysis was undertaken using the following groups: (1) papers reporting more than 8 patients, (2) studies of higher quality with eight or more stars (as assessed by the Newcastle-Ottawa scale) and (3) those published in or after 2006. Analysis was conducted by using the statistical software Review Manager Version 5.0 (Review Manager (RevMan), Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

2.7. Quality of the study

The quality of the studies was assessed by using the Newcastle-Ottawa Scale with some modifications to match the needs of this meta-analysis. [10] A score of 0–12 was allocated to each retrospective study. The tool used three items to assess the quality of the studies: study selection, group comparability, and outcome assessment. One star was awarded for the provision of each of the following pieces of information: (1) total number of patients provided; (2) number of patients in the surgical intervention group; (3) number of patients in the medical intervention group; (4) comparability in terms of age, gender and duration of follow-up between the two groups was assessed, allocating more stars the more concordant they were; (5) comparability of surgery versus medical therapies, allocating more stars for better comparability; (6) comparability in terms of age of onset and recurrence of episodes, allocating more stars for better comparability; (7) if there were clearly defined outcomes of interest; and (8) if the follow-up period was longer than 12 months. Studies were considered high quality if they received eight or more stars.

3. Results

3.1. Studies selected

We identified 64 studies in the literature that investigated PFAPA syndrome. Of these, 32 studies were excluded after the abstracts were reviewed and further 18 studies were excluded after the full text was reviewed. A total of 50 were excluded because they did not meet the inclusion criteria. 14 studies published between 1999 and 2009 matched the selection criteria and therefore were included in the analysis [3,4,11–17,19,20,22–24]. All studies, except two [4,13] were retrospective in nature (Fig. 1).

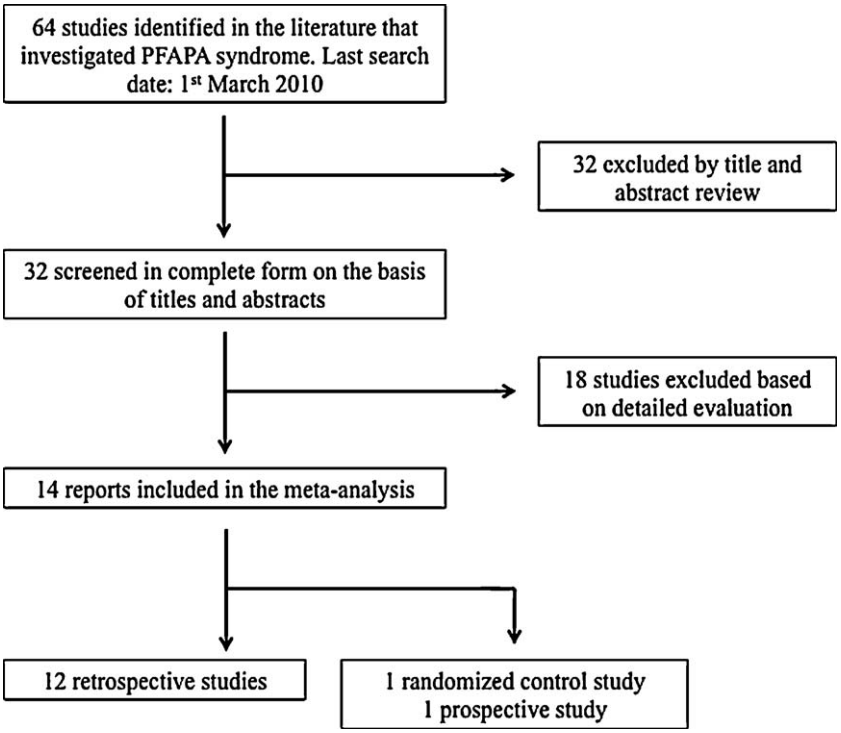

Fig. 1. Study selection flow chart.

The eligible studies reported outcomes on a total of 374 patients; 227 (60.69%) boys and 147 (39.31%) girls. The characteristics of the included studies are summarized in Table 1.

3.2. Meta-analysis of different medical therapies (antibiotics, cimetidine and steroids) for the resolution of PFAPA syndrome symptoms (Fig. 2a–c)

The use of antibiotics [3,12,17,19,20,22] in PFAPA syndrome is ineffective ($P < 0.00001$; OR, 0.01; 95% CI, 0.00–0.01). The use of cimetidine [4,14,16,17,19,22] is also ineffective ($P = 0.02$; OR, 0.15; 95% CI, 0.03–0.75). There is evidence that the use of steroids [4,11–13,15–17,19,20,23,24] is effective in the resolution of symptoms ($P < 0.00001$; OR, 43.82; 95% CI, 10.68–179.69).

3.3. Meta-analysis of surgical therapy for the resolution of PFAPA syndrome (Fig. 3)

Tonsillectomy (+/− adenoidectomy) as a treatment of PFAPA was reported in fourteen studies [3,4,11–17,19,20,22–24]. It was found to be an effective intervention for resolution of symptoms. ($P < 0.00001$; OR, 27.26; 95% CI, 6.70–110.91).

Table 1
Characteristics of included studies. R, retrospective; RCT, randomized control trial; P, prospective.

Study (Reference)	Year	Study type	Number of patients	Inclusion criteria	Exclusion criteria	Matching criteria	Follow-up, (months) mean (range)	Study quality (Star Rating) (Max 12)
Andre S (11)	2009	R	1	1,3,4,10,11,12	–	1,2,3,4,5,8	5	*******
Galanakis E (3)	2002	R	15	1,2,4,7,9,11	1	1,2,3,4,6,8,9	(12–36)	*********
Berlucchi M (12)	2003	R	5	1,11,12	1,2	1,2,3,4,5,6,9	10 (7–14)	*********
Garavello W (13)	2009	RCT	19	2,3,4,9,10,11,12	1,2,3,4	1,2,3,4,8	18	–
Dahn KA (14)	2000	R	5	10,11	–	1,2,3,4,7,9	(12–32)	********
Licamelli G (15)	2008	R	27	1,2,7,11	1	1,2,3,4,5,6	(8–41)	*******
Feder HM (16)	2009	R	105	1,2,3,4,5,6,7,8	1	2,3,4,5,7,8,9	(1–120)	*********
Peridis S (17)	2009	R	9	1,2,3,4,7,11,12	1,4	1,2,3,4,5,6,7,8,9	12.1 (6–19)	**********
Pignataro L (4)	2009	P	9	4,7,9,10	1,2	2,3,4,5,7,8,	26 (12–53)	–
Thomas KT (19)	1999	R	94	1,3,7,10	3,4	2,3,4,5,6,7,8,9	1–112.8	**********
Tasher D (20)	2006	R	54	1,3,4,7,9,10,11	1,2	1,2,3,4,5,6,8,9	18 (12–48)	**********
Padeh S (23)	2009	R	28	1,11,13,14,15	5	1,2,3,4,5,8,9	(21.6–117.6)	**********
Parkish SR (22)	2003	R	2	1,11,15	–	1,2,3,4,6,7,8,9	(1–24)	*******
Schnopp C (24)	2003	R	1	1,3,4,5,11,12	–	1,2,3,4,5,8,9	3	*******

Inclusion criteria: 1, recurrent episodes of fever (38.9 °C); 2, febrile episodes lasting no more than 10 days; 3, recurrence of febrile episodes every 2–8 weeks; 4, symptom free intervals; 5, arthritis; 6, rash; 7, no cyclic neutropenia; 8, no other source of fever other than PFAPA; 9, normal growth and development; 10, onset of disease in early childhood (<5 years); 11, report at least one of the following: cervical adenitis, aphthous stomatitis, pharyngitis; 12, remission after corticosteroids admission; 13, exudative tonsillitis; 14, negative throat cultures; 15, failure of antibiotic treatment.
Exclusion criteria: 1, cyclic neutropenia; 2, respiratory tract infections; 3, other autoinflammatory syndromes; 4, Immunodeficiency, autoimmune disease, chronic infection; 5, symptoms respond to antibiotics.
Matching criteria: 1, age; 2, gender; 3, follow-up; 4, tonsillectomy (+/− adenoidectomy); 5, steroids; 6, antibiotics; 7, cimetidine; 8, age of onset; 9, recurrence of episodes.

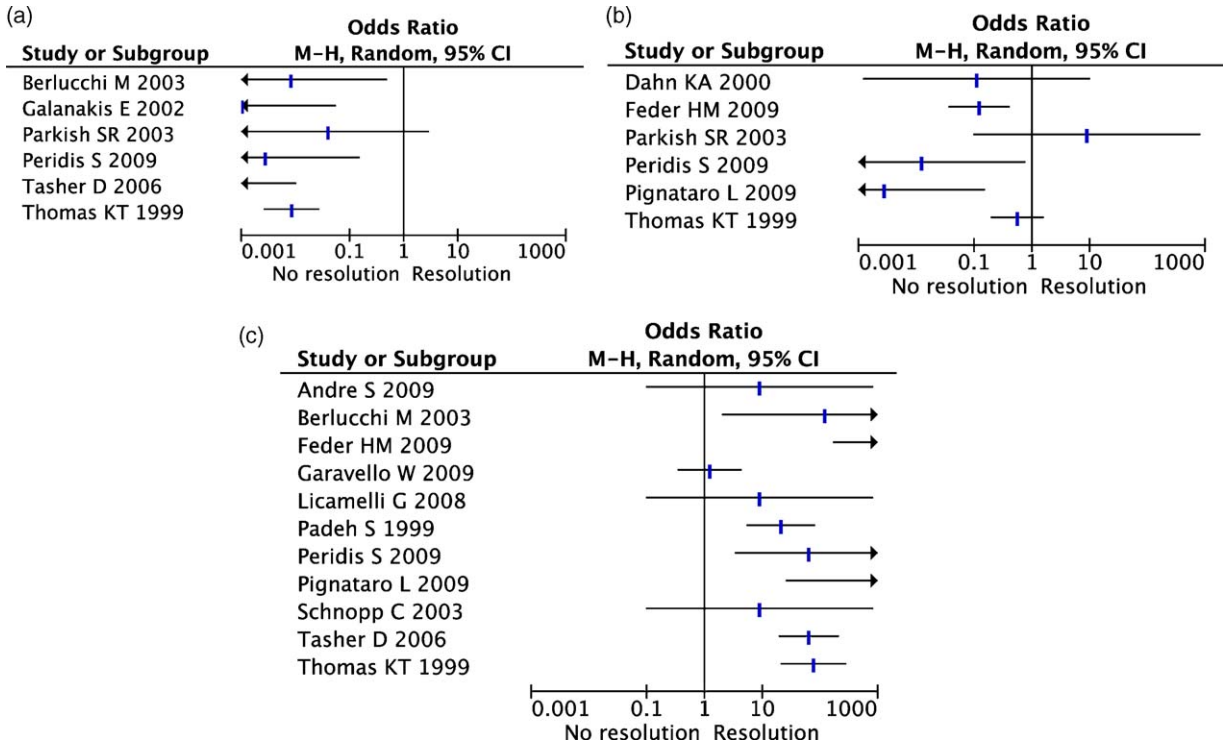

Fig. 2. Forest plots of comparison. Medical therapies: (a) antibiotics, (b) cimetidine, and (c) steroids.

3.4. Meta-analysis of surgical (tonsillectomy, +/− adenoidectomy) versus medical therapies (Fig. 4a–c)

Meta-analysis of surgery versus cimetidine [4,14,16,17,19,22], and surgery versus antibiotics [3,12,17,19,20,22], demonstrated that surgery is a significantly more effective treatment for PFAPA syndrome ($P = 0.0003$; OR, 11.89; 95% CI, 2.36–60.02) and ($P < 0.00001$; OR, 106.49; 95% CI, 30.28–374.44), respectively. A comparison of treatment with steroids or surgery [4,11–13,15–17,19,20,23,24] did not show any statistically significant difference, confirming the effectiveness of both therapies for the resolution of PFAPA syndrome ($P = 0.83$; OR, 0.90; 95% CI, 0.36–2.26). All analyses are summarized in Table 2.

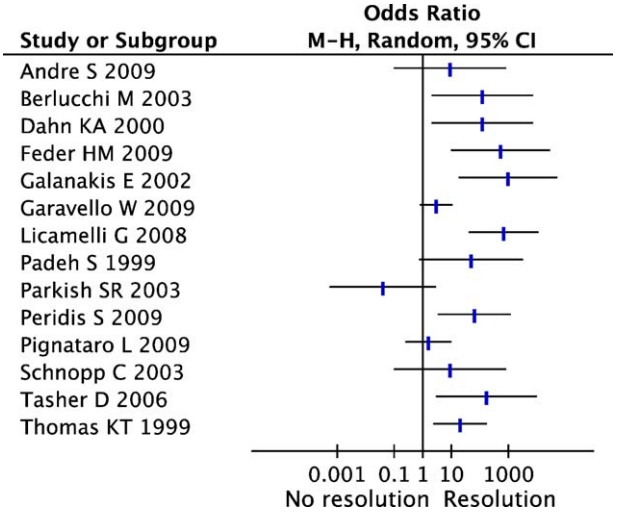

Fig. 3. Forest plot of comparison. Surgical therapy: adenotonsillectomy.

3.5. Sensitivity analysis (Table 3)

Similar results to the original analysis were obtained in the meta-analysis on papers reporting ≥8 patients [3,4,13–17,19,20], meta-analysis of studies in or after 2006 [4,11,13,15–17,20], and meta-analysis of high quality studies [4,12,14,16,17,19,20].

3.6. Other outcomes of interest

Signs and symptoms in children with PFAPA syndrome were reported in the eligible studies as follows: pharyngitis (84.18%); cervical adenitis (72.88%); fever (100%), with a mean duration of 4.05 days and a range of 2–8 days; aphthous stomatitis (51.99%); cutaneous exanthem (10.74%); nasal obstruction (33.89%); mean erythrocyte sedimentation rate (ESR) 33.58 mm/h (range 25.3–41 mm/h); headache (46.13%); vomiting (36.44%); abdominal pain (45%); arthralgia (23.64%); and diarrhoea (22.50%).

4. Discussion

The results of this meta-analysis showed better resolution of symptoms of PFAPA syndrome in children after tonsillectomy (+/− adenoidectomy), than those treated with cimetidine and antibiotics. The comparison of surgery versus steroids showed that both therapies are effective for the resolution of PFAPA syndrome; 1 dose of prednisolone (1–2 mg/kg) causes cessation a fever cycle within 12–24 h. However, administration of corticosteroids does not prevent future fever cycles and can shorten the interval between episodes [15,17,24]; therefore, tonsillectomy (+/− adenoidectomy) is the most effective intervention for long-term resolution of PFAPA syndrome symptoms.

In the literature, it has been described that cessation of PFAPA episodes has been observed after tonsillectomy (with or without adenoidectomy) [3,15,19,25]. There is one randomized study reporting the spontaneous resolution of 50% within 1 year in PFAPA patients randomized to no surgery [18]. Adenoidectomy by

Table 2
Outcomes of interest of included studies (OR, odds ratio; CI, confidence interval; HG, heterogeneity). Statistically significant values are marked in bold.

Outcome of interest	No. of studies	No. of patients	OR	95% CI	*P* value	HG *P* value
Medical therapy						
Antibiotics	6	143	0.01	0.00–0.01	**P < 0.00001**	*P* = 0.48
Cimetidine	6	70	0.15	0.03–0.75	**P = 0.02**	**P = 0.02**
Steroids	11	257	43.82	10.68–179.69	**P < 0.00001**	**P < 0.00001**
Surgical treatment						
Tonsillectomy (+/− adenoidectomy)	14	124	27.26	6.70–110.91	**P < 0.00001**	**P = 0.0003**
Surgical versus medical therapy						
Surgical versus antibiotics	6	191	106.49	30.28–374.44	**P < 0.00001**	*P* = 0.65
Surgical versus cimetidine	6	117	11.89	2.36–60.02	**P = 0.003**	*P* = 0.10
Surgical versus steroids	11	358	0.90	0.36–2.26	*P* = 0.83	*P* = 0.33

itself does not result in resolution of symptoms, and it seems of no difference in patient outcome whether or not an adenoidectomy is performed alongside of the tonsillectomy [17].

The exact role that tonsillectomy plays in symptom resolution is unclear, but the syndrome may be caused by an immune response generated at the tonsillar parenchyma [12].

The use of non-steroidal anti-inflammatory agents has shown poor results in resolving symptoms of PFAPA syndrome. Acetaminophen and ibuprofen provide symptomatic relief. Other medications including aciclovir, and colchicine, have provided minimal if any relief of symptoms. [24] Administration of antibiotics has no effect [3].

The use of meta-analytical techniques allowed the inclusion of 374 patients, of which 124 (33.15%) underwent surgery, 143 (38.24%) were treated with antibiotics, 70 (18.72%) with cimetidine, and 257 (68.72%) with steroids. A sample of this size is substantial, given the small sample sizes previously reported in the literature.

Despite the strength of our study, some limitations should be discussed. Firstly, 12 out of 14 studies included are retrospective [3,11,12,14–17,19,20,22–24]. In this case, there is a practical consideration that limits the number of cases that can be collected and analyzed. Another limitation of the present study was the small number of studies available in the literature that compared both surgical and medical therapies (most of the studies were published in or after 2006). Despite these limitations, our study provides significant information concerning the impact of tonsillectomy as a definite therapy to children with PFAPA syndrome, which may be used in the future for designing prospective studies.

The effectiveness of tonsillectomy in patients with PFAPA syndrome is still a matter of debate, and only a few articles have been published; most of these support the efficacy of tonsillectomy, with complete recovery in 64% to 100% of cases [3,12,15,17–20,25], but the possibility of an incomplete recovery or a stationary clinical picture is well known [14,15,19,22,25]. Leong et al. [21] have expressed some hesitancy about the effectiveness of tonsillectomy in children with PFAPA syndrome, based on the heterogeneity of the surgical success rate, the tendency for spontaneous resolution of the syndrome, the limited series of patients reported, and the scarcity of prospective studies [4].

The PFAPA syndrome may resemble other periodic fevers, such as cyclic neutropenia, familial Mediterranean fever, hyperglobu-

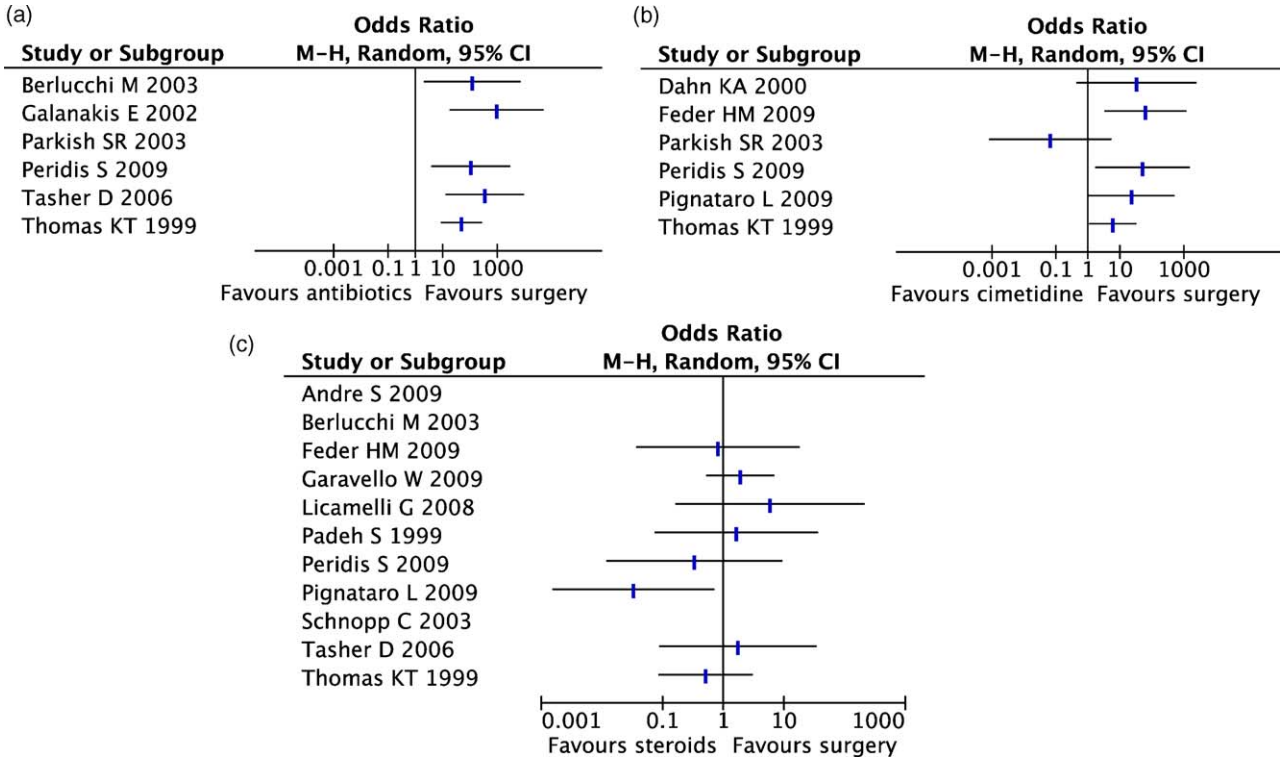

Fig. 4. Forest plots of comparison. Surgical versus medical therapies: (a) surgery versus antibiotics, (b) surgery versus cimetidine, and (c) surgery versus steroids.

Table 3
Sensitive analysis of outcomes of interest (OR, odds ratio; CI, confidence interval; HG, heterogeneity). Statistically significant values are marked in bold.

Outcome of interest	No. of studies	No. of patients	OR	95% CI	*P* value	HG *P* value
Studies reporting ≥8 patients						
Antibiotics	4	136	0.00	0.00–0.01	**P < 0.00001**	*P* = 0.31
Cimetidine	4	68	0.09	0.01–0.58	**P = 0.01**	**P = 0.01**
Steroids	7	249	59.09	10.45–468.62	**P < 0.00001**	**P < 0.00001**
Tonsillectomy (+/− adenoidectomy)	7	101	38.18	5.48–265.80	**P = 0.0002**	**P = 0.0002**
Surgical versus antibiotics	3	130	83.55	19.77–353.14	**P < 0.00001**	*P* = 0.39
Surgical versus cimetidine	4	108	15.01	4.34–51.95	**P < 0.0001**	*P* = 0.45
Surgical versus steroids	5	247	0.42	0.13–1.36	*P* = 0.15	*P* = 0.43
High quality studies (≥8 stars)						
Antibiotics	5	141	0.01	0.00–0.01	**P < 0.00001**	*P* = 0.46
Cimetidine	4	68	0.09	0.01–0.58	**P = 0.01**	**P = 0.01**
Steroids	5	189	126.15	41.14–386.84	**P < 0.00001**	*P* = 0.14
Tonsillectomy (+/− adenoidectomy)	8	69	49.97	9.10–269.01	**P < 0.00001**	**P = 0.03**
Surgical versus antibiotics	5	187	106.49	30.28–374.44	**P < 0.00001**	*P* = 0.65
Surgical versus cimetidine	4	108	15.01	4.34–51.95	**P < 0.0001**	*P* = 0.45
Surgical versus steroids	6	257	0.42	0.13–1.36	*P* = 015	*P* = 0.43
Studies published in or after 2006						
Antibiotics	2	50	0.00	0.00–0.01	**P < 0.00001**	*P* = 0.55
Cimetidine	3	40	0.03	0.00–0.35	**P = 0.005**	*P* = 0.14
Steroids	4	136	119.89	18.64–771.13	**P < 0.00001**	**P = 0.05**
Tonsillectomy (+/− adenoidectomy)	7	82	29.85	4.03–220.86	**P = 0.0009**	**P = 0.0007**
Surgical versus antibiotics	2	65	195.29	18.69–2041.04	**P < 0.0001**	*P* = 0.62
Surgical versus cimetidine	3	69	42.22	6.91–258.14	**P < 0.0001**	*P* = 0.89
Surgical versus steroids	5	189	0.36	0.06–2.03	*P* = 0.25	*P* = 0.30

linemia D syndrome, Behçet disease, juvenile rheumatoid arthritis, and the autosomal dominant familial fevers [3,19]. Because PFAPA syndrome is a diagnosis of exclusion, cardinal signs and symptoms must be carefully observed for a differential diagnosis, such as onset in early childhood, before the age of 5 years (male predominance has been described) [20]; periodic abrupt onset of febrile episodes that last 4–5 days and occur every 4–6 weeks on average; and episodes that are often accompanied by intraoral ulcers, pharyngitis, and cervical lymph node enlargement [15]. Although the fever, ulcers, and pharyngitis of cyclic neutropenia are very similar to PFAPA syndrome, it is distinguished by a cyclic drop in neutrophils and (not always) by abdominal pain and diarrhoea [15,17].

Conflict of interest statement

None reported.

References

[1] G.S. Marshall, K.M. Edwards, J. Butler, A.R. Lawton, Syndrome of periodic fever, pharyngitis and aphthous stomatitis, J. Pediatr. 110 (1987) 43–46.
[2] J.A. Førsvoll, K. Oymar, C-reactive protein in the periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, Acta Paediatr. 96 (2007) 1670–1673.
[3] E. Galanakis, C.E. Papadakis, E. Giannoussi, A.D. Karatzanis, M. Bitsori, E.S. Helidonis, FAPA syndrome in children evaluated for tonsillectomy, Arch. Dis. Child 86 (2002) 434–435.
[4] L. Pignataro, S. Torretta, M.C. Pietrogrande, R.M. Dellepiane, P. Pavesi, A. Bossi, et al., Outcome of tonsillectomy in selected patients with PFAPA syndrome, Arch. Otolaryngol. Head Neck Surg. 135 (2009) 548–553.
[5] M. Clarke, R. Horton, Bringing it all together: lancet-cochrane collaborate on systematic reviews, Lancet 357 (2001) 1728.
[6] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group, JAMA 283 (2000) 2008–2012.
[7] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control Clin. Trials 7 (1986) 177–188.
[8] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (1997) 629–634.
[9] N. Mantel, W. Haenszel, Statistical aspects of the analysis of data from retrospective studies of disease, J. Natl. Cancer Inst. 22 (1959) 719–748.
[10] T. Athanasiou, S. Al-Ruzzeh, P. Kumar, M.C. Crossman, M. Amrani, J.R. Pepper, et al., Off-pump myocardial revascularization is associated with less incidence of stroke in elderly patients, Ann. Thorac. Surg. 77 (2004) 745–753.
[11] S.C. André, F. Vales, E. Cardoso, M. Santos, PFAPA syndrome, Acta Otorrinolaringol. Esp. 60 (2009) 208–209.
[12] M. Berlucchi, A. Meini, A. Plebani, M.G. Bonvini, D. Lombardi, P. Nicolai, Update on treatment of Marshall's syndrome (PFAPA syndrome): report of five cases with review of the literature, Ann. Otol. Rhinol. Laryngol. 112 (2003) 365–369.
[13] W. Garavello, M. Romagnoli, R.M. Gaini, Effectiveness of adenotonsillectomy in PFAPA syndrome: a randomized study, J. Pediatr. 155 (2009) 250–253.
[14] K.A. Dahn, M.P. Glode, K.H. Chan, Periodic fever and pharyngitis in young children: a new disease for the otolaryngologist? Arch. Otolaryngol. Head Neck Surg. 126 (2000) 1146–1149.
[15] G. Licameli, J. Jeffrey, J. Luz, D. Jones, M. Kenna, Effect of adenotonsillectomy in PFAPA syndrome, Arch. Otolaryngol. Head Neck Surg. 134 (2008) 136–140.
[16] H.M. Feder, J.C. Salazar, A clinical review of 105 patients with PFAPA (a periodic fever syndrome), Acta Paediatr. 99 (2010) 178–184.
[17] S. Peridis, E. Koudoumnakis, A. Theodoridis, K. Stefanaki, G. Helmis, M. Houlakis, Surgical outcomes and histology findings after tonsillectomy in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome, Am. J. Otolaryngol. (2009), doi:10.1016/j.amjoto.2009.06.005.
[18] M. Renko, E. Salo, A. Putto-Laurila, H. Saxen, P.S. Mattila, J. Luotonen, et al., A randomized, controlled trial of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome, J. Pediatr. 151 (2007) 289–292.
[19] K.T. Thomas, H.M. Feder Jr., A.R. Lawton, K.M. Edwards, Periodic fever syndrome in children, J. Pediatr. 135 (1999) 15–21.
[20] D. Tasher, E. Somekh, I. Dalal, PFAPA syndrome: new clinical aspects disclosed, Arch. Dis. Child 91 (2006) 981–984.
[21] S.C. Leong, P.D. Karkos, M.T. Apostolidou, Is there a role for the otolaryngologist in PFAPA syndrome? A systematic review, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 1841–1845.
[22] S.R. Parikh, E.R. Reiter, M.A. Kenna, D. Roberson, Utility of tonsillectomy in 2 patients with the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis, Arch. Otolaryngol. Head Neck Surg. 129 (2003) 670–673.
[23] S. Padeh, N. Brezniak, D. Zemer, E. Pras, A. Livneh, P. Langevitz, et al., Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome, J. Pediatr. 135 (1999) 98–101.
[24] C. Schnopp, M. Mempel, K. Brockow, J. Ring, D. Abeck, Recurrent episodes of fever with oral aphthae, lymph node swelling and joint symptoms in a 9-year-old boy. Diagnosis: PFAPA syndrome (Marshall syndrome), Hautartz 54 (2003) 1208–1210.
[25] K.K. Wong, J.C. Finlay, J.P. Moxham, Role of tonsillectomy in PFAPA Syndrome, Arch. Otolaryngol. Head Neck Surg. 134 (2008) 16–19.