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 Review Article

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## Evidence-based treatment limitations prevent any therapeutic recommendation for acute poststreptococcal glomerulonephritis in children

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### Summary

The majority of children with the epidemic form of acute post-streptococcal glomerulonephritis (APSGN) have an excellent prognosis, which contrasts with the poor long-term outcome of sporadic cases. Therapy is largely supportive. Rarely, the disease shows long-term complications, worsening to chronic kidney disease requiring long-term interventional measures. To compare the effectiveness of different therapeutic strategies for the prevention and treatment of APSGN in childhood, the authors reviewed randomized controlled trials on the prevention and treatment of APSGN in children. Nine studies fit the inclusion criteria. Primary outcomes were the development of APSGN, the effectiveness of medication for controlling hypertension, and the development of chronic renal failure in patients with crescentic glomerulonephritis. No advantages of antimicrobials (cefuroxim, cefitibuten, and others) given for 5 days were found over penicillin V given for 10 days (4 trials). Nifedipine showed advantages in controlled acute hypertension (1 trial). ACE inhibitors (captopril and enalapril) had better control of blood pressure and echocardiographic changes than other antihypertensive drugs/diuretics (2 trials). The use of combined immunosuppressants for crescentic poststreptococcal glomerulonephritis showed no advantages over supportive therapy alone (1 study). The studies were of small number and with limitations that seriously weakened the results.

**key words:** post-streptococcal glomerulonephritis • prevention • treatment • randomized controlled trial • children

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## BACKGROUND

Acute poststreptococcal glomerulonephritis (APSGN) is a condition that occurs after pharyngitis or skin infections of group A streptococci. Typical APSGN usually presents with acute nephritic syndrome with variable severity and generally resolves without complications within a short period. Renal damage in APSGN is secondary to humoral immunity initiated by nephritogenic streptococcal antigens. The formation of antigen-antibody complexes and the glomerular deposits of circulating immune complexes lead to the activation of the classical and alternative complement pathways. In the acute stage of APSGN, serum levels of C3 are low and C4 levels are normal or only slightly depressed. However, a C3 nephritic factor and autoantibody against C3 convertase, which is detectable during the early stages of APSGN, may induce a continuous activation of the alternative complement pathway [1].

APSGN is defined by the following criteria: acute onset of glomerulonephritis with hematuria (with or without proteinuria), transient depression of serum C3, evidence of recent streptococcal infection by isolation of *Streptococcus pyogenes* in culture in the previous three months, and/or abnormal streptococcal serology. Kidney failure, measured as an elevation of serum creatinine or a reduced estimated glomerular filtration rate, hypertension, edema, and macroscopic hematuria, is not included in the diagnostic criteria for APSGN but indicates the severity of renal involvement and the effectiveness of the intervention measures [2].

The incidence of APSGN varies among populations, and microbiological factors seem to be involved [3,4]. In recent decades, the prevalence of postinfectious glomerulonephritis has tended to decline in most industrialized countries, but high rates persist in some developing communities [5]. Based on the Italian Biopsy Registry, the incidence of APSGN has been estimated at 0.3 cases per 100,000 persons/year. In particular, concerning children younger than 15 years, the incidence varied from 2.6% to 3.7% of all primary glomerulopathies [6]. The incidence of APSGN has dropped over the past decades. Between 1999 and 2006 the incidence of APSGN was 6.4 and between 1957 and 1973 it was 10.9/100,000 persons/year with a prevalence of 0.64 vs. 2.18/100,000 persons/year, respectively. Today, pharyngitis causes more APSGN than impetigo [7].

Despite the decrease in the incidence of poststreptococcal diseases in some populations, the problem remains important [8,9]. Although rare, APSGN can lead to complications such as crescentic glomerulonephritis, hypertension, and various degrees of renal failure [10]. Children followed for 15 to 18 years after an APSGN episode showed an incidence of 7.2% for non-nephrotic proteinuria, 5.4% for microhematuria, 3.0% for hypertension, and 0.9% for azotemia [11]. A delay in diagnosis can occur frequently in children with no visible signs of hematuria, hypertension, and/or congestive heart failure [12].

Drugs currently in use to treat the clinical conditions associated with APSGN are antibiotics and antihypertensive drugs/diuretics. Of course, antibiotics are prescribed mainly to treat any child with streptococcal infections; antihypertensive drugs/diuretics are the choice for treating

hypertension, edema, hypertensive encephalopathy, and congestive heart failure during acute phases of the disease. Immunosuppressants were used in the past.

Normally, APSGN is a benign condition and renal changes rarely develop towards a chronic condition. The aim of this systematic review was to determine the effectiveness of different therapeutic strategies for the prevention and treatment of APSGN in childhood.

## MATERIAL AND METHODS

To review the antimicrobial, antihypertensive, diuretic, and immunosuppressant drugs in children with APSGN, we included randomized controlled trials (RCTs) and quasi-RCTs. Children aged from birth to 18 years with typical APSGN treated in a hospital or as outpatients were included in this study. For this review, the diagnosis of typical APSGN is defined as acute onset of glomerulonephritis with hematuria (with or without proteinuria), depression of serum complement (C3), and evidence of previous streptococcal infection [13]. The enrolled childhood population showed clinical conditions characterized by typical signs of APSGN accompanied by hypertension, nephrotic syndrome, and/or acute or chronic kidney failure. Children with infective acute glomerulonephritis for whom an infection by *Streptococcus pyogenes* had not been previously demonstrated in culture or serologically and children not treated with drugs or those treated but for whom therapy was not specified as to "how and when" were excluded from the cohort.

Trials involving any administration of antibiotics, classical anti-hypertensive drugs, diuretics, and ACE inhibitors, steroid and non-steroidal immunosuppressants, or a combination of drugs by a medical professional in community, hospital, or outpatient settings were included. We compared treatments of interest involving different therapy regimens and cases of no intervention. Primary outcomes were the development of APSGN, the effectiveness of medications in controlling hypertension, and the development of chronic renal failure in patients with crescentic glomerulonephritis. Secondary outcomes were hypertension, cardiac changes, and proteinuria.

Our search had no language restrictions. Terms used to find specific studies were "post streptococcal" or "poststreptococcal", "glomerulonephritis", "children (1–18 yrs)", "clinical trial", and "randomized controlled trial". Relevant studies were obtained from the following sources: the Cochrane Central Register of Controlled Trial (CENTRAL), the Cochrane Renal Group's Specialized Register, MEDLINE database (1966–2009), EMBASE database (1980–2009), and SCOPUS database (1966–2009). We looked at other resources such as the bibliographies of nephrology textbooks, review articles, and other relevant studies.

Data synthesis and analyses were done using the Mantel-Haenszel test. A weighted pooled treatment effect was calculated across the studies using a random effects model. We expressed the results as the risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes. We evaluated the risks of biases discussing the adequacy of sequence generation, allocation concealment, blinding, and presence of incomplete outcome data.

**Table 1.** Intervention in acute poststreptococcal glomerulonephritis: studies included in the systematic review.

Study ID	Participants (n)	Inclusion criteria	Experimental intervention	Definition of renal outcome	Follow-up
<i>Antimicrobials (PV=penicillin V, CA= cefuroxime axetil) for prevention of APSGN</i>					
Adam 2000 [14]	2264	Culture-proven tonsillo-pharyngitis	A) CA 20 mg/kg/d × 5 d B) PV 50,000 IU/kg × 10 d	Glomerulonephritis	6–12 m
Adam 2000 [16]	4171	Age 1–18 y, clinical and laboratory diagnosis of tonsillo-pharyngitis	A) (Amoxicillin/ clavulanate 37.5 mg/kg/d or ceftibuten 9 mg/kg/d or CA 20 mg/kg/d or loracarbef 15 mg/kg/d or clarithromycin 15 mg/kg/d or erythromycin 40 mg/kg/d) × 5 d B) Oral PV 50,000 IU/kg/d × 10 d	Glomerulonephritis	12 m
Adam 2001 [15]	2099	Age 1–18 y, culture-proven streptococcal tonsillo-pharyngitis	A) Ceftibuten 9 mg/kg × 5 d B) PV 50,000 IU/kg × 10 d	Glomerulonephritis	7–8 w
Scholz 2004 [17]	1952	Age 1–17 y, tonsillo-pharyngitis	A) CA 20 mg/kg/d × 5 d B) PV 50,000 IU/kg × 10 d	Glomerulonephritis	1 y
<i>Treatment of hypertension in APSGN</i>					
Ribeiro 1992 [18]	30	Age 3–11 y, clinical and laboratory diagnosis	A) Nifedipine 0.25–0.50 mg/kg every 8 h B) Placebo	Blood pressure	8 h
Tanphaichitr 1977 [22]	20	Age 4–14 y	A) Furosemide 1–8.5 mg/kg/d, fractioned from 1 to 3 doses per os B) reserpine 0.07 mg/kg, 2–3 times	1. Blood pressure 2. Diuresis	1–4 d
Morsi 1992 [19]	20	Age 4–10 y, hypertension	A) Captopril 0.2 mg/kg, maintenance 1.5 mg/kg/d B) Reserpine 0.02 mg/kg plus furosemide 2 mg/kg/d	Blood pressure	3 d
Jankauskiene 2005 [20]	51	Age 3–16 y, acute tonsillo-pharyngitis, impetigo, acute nephritic syndrome, urine changes of APSGN	A) Enalapril 5–10 mg (6 weeks) B) β-blockers, vasodilators, diuretics and central acting agents (given if needed)	1. Blood pressure 2. Echocardiographic changes	6–8 w
<i>Treatment of crescentic glomerulonephritis from APSGN</i>					
Roy 1981 (21)	10	Age 5–16 y, comparable crescentic glomerulonephritis at renal biopsy	A) Prednisone (1 mg/kg/d), azathioprine (1 mg/kg/d), cyclophosphamide (1 mg/kg/d), dipyridamole (10 mg/kg/d) for 3 m, heparin for 2 w, followed by warfarin B) Supportive care	Crescentic glomerulonephritis at renal biopsy	8–60 m

d – day; h – hour; m – month; w – week; y – year.

## RESULTS

### Trial selection and characteristics

The Cochrane Central Register of Controlled Trials contained eleven records [14–24]. Of these, nine were enrolled in our study because they fit well with the inclusion criteria [14–22], while the trial by Faye et al. was excluded from the analysis because it did not specifically refer to poststreptococcal sequelae [25] and that by Lord was excluded [26] because it referred to another trial [16]. Eight

records were found in the PUBMED database. The Faye et al. [25] and Lord [26] trials were excluded for the reasons mentioned above. In the end, six trials in PUBMED were included in the analysis. Of these, only one [22], which had not been previously cited, was included in the list of trials. Four records were found in the EMBASE database. Of these, only one [16] was included in our analysis, but it had already been identified. Furthermore, eight records were found in the SCOPUS database. The studies by Lord [26] and Faye et al. [25] were excluded. Finally, three previously identified trials were included in the analysis [15–17].

**Table 2.** Intervention in acute poststreptococcal glomerulonephritis: studies excluded from the analysis.

Study ID	Participants (n)	Inclusion criteria	Experimental intervention	Definition of renal outcome	Follow-up	Results
Sólomon-Santibañez 1971 [23]	20	Age 4–15 y, laboratory confirmed post-streptococcal infection	A) Furosemide 20 mg every 6 h B) PV 4,000,000 IU, guanethidine (10 mg every 6 h)	1. Blood pressure 2. Diuresis	24 hours	Blood pressure reduction (DBP 82.4 vs. 85.5) and diuresis more pronounced with furosemide
Powell 1980 [24]	16	Age 4–12 y	A) furosemide (2 mg/kg) B) methyldopa or reserpine or diazoxide	1. Hypertension 2. Oliguria 3. Edema	Weeks (unspecified)	I. Shorter hypertension (mean: 4.7 range: 2–9 d) vs. controls (mean: 11.0 range: 7–20 d) II. Faster edema-free (6.8, range: 4–12 d) vs. controls (13.9, range: 6–23 d)

d – day; m – month; y – year.

Nine studies were included in the meta-analysis (Table 1), among which RCTs, quasi-RCTs, and clinical trials involving 10,617 children of whom 10,486 were subjects in antimicrobial trials, 121 in antihypertensive/diuretics trials, and 10 in immunosuppressant trials. Six trials were published in English [14,16,17,19–22], one trial in German [15], and two in Spanish [18,23].

Two studies [23,24] did not have suitable statistical data to perform a meta-analysis (Table 2). These two trials explored therapy for hypertension and oliguria with furosemide in 36 children with APSGN. Both studies agreed that blood pressure and diuresis were better controlled by furosemide than by no treatment at all or by conventional antihypertensive drugs.

Overall, the studies showed plausible bias that seriously weakens confidence in the results. In particular, eight trials of the nine had randomly selected patients [14–21]. One study [22] did not clarify how the patients were allocated in each group. Therefore, none reported adequate allocation concealments. One study [16] partially clarified the method of allocation. No trial reported an intention to treat analysis. Blinding of participants and investigators occurred in only one trial [18]. Loss at follow-up was reported in four trials, ranging between 0 to 37.3% [14–16,20].

### Antimicrobials

The effects of different antimicrobials (such as cephalosporin) administered for 5 days vs. penicillin V for 10 days during streptococcal infections as a preventive measure against onset of APSGN were evaluated by four trials. Two RCTs assessed cefuroxim treatment for 5 days vs. penicillin V for 10 days and found no significant difference in the risk of developing APSGN after 6–7 weeks of follow-up (3864 children,  $RR=2.98$ ,  $CI: 0.31–28.64$ ) [14,17]. However, the same conclusion was reached in trials with cefitibuten treatment vs. penicillin (one trial, 1803 children,  $RR=1.06$ ,  $CI: 0.04–25.88$ ) [15] or other different antimicrobials (one trial, 4171 children,  $RR=6.38$ ,  $CI: 0.26–156.45$ ) administered for 5 days vs. penicillin V for 10 days [16].

### Antihypertensives

The efficacy of antihypertensive treatment is available in one trial [18], which assessed the treatment of hypertension with nifedipine vs. placebo; it showed good control of blood pressure (after 8 hours, 30 children,  $MD=-9.8$ ,  $CI: -11.14$  to  $-8.46$ ). However, one trial [22] that assessed hypertension and edema during APSGN treated with furosemide showed better results than with reserpine (20 children,  $RR=0.06$ ,  $CI: 0.00–0.90$ ). Moreover, another trial [19] that assessed captopril therapy vs. reserpine-furosemide therapy for hypertension during APSGN showed significantly better control of supine and standing blood pressure with ACE inhibitors (20 children,  $MD=-8$ ,  $CI: -15.46$  to  $-0.54$ ). Another trial [20] that assessed echocardiographic changes in patients treated with enalapril or with  $\beta$ -blockers, vasodilators, diuretics, and central acting agents (given if needed) to manage hypertension during APSGN showed better results after 6–8 weeks of treatment with ACE inhibitors (left ventricular mass, 32 children,  $MD=-7.33$ ,  $CI: -12.32$  to  $-2.34$ ).

### Immunosuppressants

The effectiveness of immunosuppressant drugs was investigated by only one trial [21], which compared quintuple therapy including immunosuppression with prednisone, azathioprine, and cyclophosphamide for biopsy-documented crescentic PSGN and supportive treatment alone; the results showed no clinical advantages of the former over the latter in outcome (10 children,  $RR=2.0$ ,  $CI: 0.26–15.62$ ). Moreover, one patient in the treatment group died following a massive pulmonary hemorrhage.

### DISCUSSION

The majority of children with the epidemic form of PSGN have an excellent prognosis, which contrasts with the poor long-term outcome of sporadic cases [5]. Moreover, the incidence and prevalence of APSGN have decreased over the past few years [7], with an increased risk of delayed diagnosis [12]. The reduced incidence of APSGN may agree with the widespread use of antibiotics, an amelioration of

behavior, hygiene, and both. Therapy is largely supportive; in most cases the abnormal immune response observed is self-limiting [5]. Rarely, the disease shows long-term complications and worsens to chronic kidney disease requiring long-term intervention measures [11], even after eradication of the causative organism [5].

The treatment-based literature for children with APSGN is inconclusive since very few studies, of poor quality, and no evidence-based guidelines are available as to which drugs, if any, can be used (and how) to prevent and treat the complications that arise during an acute episode or any long-term complications. There are few reports in the literature of prospective and retrospective studies concerning APSGN with severe clinical patterns treated with immunosuppressants, mostly with steroids alone [2,10,27–29], or in combination with cyclophosphamide, in more severe cases [10]. Therefore, no structured trials are available that demonstrate substantial effectiveness and usefulness of treating severe forms of disease with steroids. However, the literature reports few structured trials concerning antimicrobials, antihypertension drugs/diuretics and combined immunosuppressants.

This systematic review of RCTs identified nine trials, four of which compared two types of antimicrobial regimens to prevent APSGN in children with laboratory-proven streptococcal group A infection. Meta-analyses showed no advantages of cefuroxime axetil, cefitibuten, or other antimicrobials given for 5 days over penicillin V given for 10 days [14–17]. These antibiotic trials seem misleading since they were not powered to look at APSGN. However, the number of cases of APSGN in all of these trials was extremely low.

Antihypertensive treatment with nifedipine given during APSGN clearly showed better control of blood pressure than placebo [18]. However, furosemide showed better control of both blood pressure and edema than reserpine, an antihypertensive drug no longer in clinical use for many years in most countries [22]. This result was reached in the two RCTs excluded from the meta-analysis [23,24]. Thus, the limited relevance of these studies needs to be emphasized. Moreover, ACE inhibitors such as captopril [19] and enalapril [20] had better control of blood pressure and echocardiographic changes than other antihypertensive drugs/diuretics. In agreement, the superiority of ACE inhibitors in managing renal protection over conventional antihypertensive regimens is suggested for several kidney diseases [30]. Finally, the use of combined immunosuppressants for crescentic poststreptococcal glomerulonephritis showed no advantages, and perhaps more disadvantages, than supportive therapy alone [21].

The available RCTs regarding the prevention of APSGN and treatment of its complications were of poor quality concerning both evidence and thoroughness. The applicability of the clinical evidence is deficient when we consider the choice of antimicrobial treatment in preventing APSGN following a streptococcal infection. Clinicians are likely to be reluctant to enroll children with laboratory-proven streptococcal infection into RCTs due to placebo harm. Moreover, the available RCTs that investigated the treatment of hypertension and related adverse heart conditions following APSGN are limited and of poor quality. Finally, one poor-quality RCT

discourages immunosuppression for crescentic poststreptococcal biopsy-proven glomerulonephritis.

The mortality from APSGN is said to be approximately 1%. Less than 2% of patients progress to end-stage renal disease, and most of the sporadic deaths and cases of chronic disease occur in adults, whereas most epidemic cases occur in children, overall in less developed countries [9]. Although uncommon, severe APSGN in Maori and Pacific Island children resulted in a high rate of long-term renal morbidity and the immunosuppressive drugs administered to those patients with crescentic disease showed doubtful efficacy [31].

## CONCLUSIONS

Concerning the treatment approach, we showed that very few and inconclusive remarks are available from the published controlled clinical trials. In particular, the role of antimicrobials in preventing the development of APSGN remains unproven. Poor data suggest the efficacy of ACE inhibitors and calcium antagonists in managing hypertension in children with APSGN. Treatment with immunosuppressive drugs during the acute phase of disease may be unnecessary, of doubtful efficacy, and sometime dangerous. Finally, the evidence-based literature for the prevention and management of APSGN in children is quite limited and of low overall quality, preventing any therapeutic recommendations.

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