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Management and Outcomes of Acute Post-Streptococcal Glomerulonephritis in Children

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Abstract

Acute post-streptococcal glomerulonephritis (APSGN) is the major cause of acute glomerulonephritis among children, especially in low- and middle-income countries. APSGN commonly occurs following pharyngitis due to the activation of antibodies and complements proteins against streptococcal antigens through the immune-complex-mediated mechanism. APSGN can be presented as acute nephritic syndrome, nephrotic syndrome, rapidly progressive glomerulonephritis, or it may be subclinical. The management of APSGN is mainly supportive in nature with fluid restriction, anti-hypertensives, diuretics, and renal replacement therapy with dialysis, when necessary, as the disease is self-limiting. Congestive heart failure, pulmonary edema, and severe hypertension-induced encephalopathy might occur during the acute phase of APSGN due to hypervolemia. APSGN generally has a favorable prognosis with only a small percentage of patients with persistent urinary abnormalities, persistent hypertension, and chronic kidney disease after the acute episode of APSGN. Decreased complement levels, increased CRP, and hypoalbuminemia are associated with disease severity. Crescent formations on renal biopsy and renal insufficiency on presentation may be the predictors of disease severity and poor outcomes in APSGN in children.

Key Words: Post-streptococcal glomerulonephritis; Pediatrics; Acute kidney injury; Nephrotic-range proteinuria; Nephritic syndrome

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Core Tip: Acute post-streptococcal glomerulonephritis (APSGN) is the major cause of acute glomerulonephritis among children, especially in the low- and middle-income countries. The clinical spectrum of APSGN can vary as acute nephritic syndrome, nephrotic syndrome, rapidly progressive glomerulonephritis (RPGN), or it may be subclinical. APSGN is generally self-limiting and has a good long-term prognosis. However, a small percentage of patients may have persistent urinary abnormalities, persistent hypertension, and chronic kidney disease after the acute episode of APSGN. This review discusses the management, prognosis, and outcomes of APSGN.

INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is the most common cause of acute glomerulonephritis among children which is mostly caused by group A b-hemolytic streptococci (GABHS)[1]. APSGN primarily affects children aged between 3 and 12 years and is uncommon among children below age 3[2, 3]. The most common presenting features of APSGN are hematuria, azotemia, hypertension, and peripheral edema[2]. The clinical spectrum of APSGN can vary as acute nephritic syndrome, nephrotic syndrome, rapidly progressive glomerulonephritis (RPGN), or it may be subclinical[1]. Therefore, the severity of APSGN can vary among patients where the patient can be presented with subclinical disease to RPGN requiring dialysis[4]. APSGN is generally self-limiting and has a good long-term prognosis[5].

The estimated global incidence of APSGN is 472, 000 cases per year with 77% of the cases from the low- and middle-income countries[6]. The rate of APSGN has decreased over the last few decades in high-income countries due to the use of antibiotics, improved socio-economic status, and improved hygiene[7]. However, APSGN remains

one of the important causes of acute kidney injury among the pediatric populations and the leading cause of hospital admission in developing countries[5]. The reported estimated annual incidence of APSGN is 9.3 cases per 100,000 persons in developing countries[8].

Most cases of APSGN occur the following pharyngitis with streptococci rather than skin infection[9]. However, the nature of the preceding infectious disease is not associated with the clinical course and severity of APSGN[2]. The two main antigens contributing to the pathogenesis of APSGN are nephritis-associated plasmin receptor (NAPlr) and streptococcal pyrogenic exotoxin B (SPeB)[7]. The infection activates the antibodies and complement proteins against NAPlr and SPEB, through immune complex-mediated mechanism causing aggregation of blood vessels in the glomeruli[2]. C3 is generally low in blood tests due to the activation of alternate complete pathway[10]. However, 15-30% of patients may have reduced C1 and C3 Levels and 10% of the patients have normal complement levels[11]. This review discusses the management, prognosis, and outcomes of APSGN.

MANAGEMENT OF ACUTE GLOMERULONEPHRITIS

The management of APSGN is mainly supportive in nature as the disease is self-limiting[12]. Children who present with hypertension, generalized edema, or impaired renal function should be hospitalized to monitor the blood pressure and renal function[12]. APSGN should be managed with fluid restriction, anti-hypertensives, diuretics, and renal replacement therapy with dialysis when necessary[7].

ANTIBIOTICS PROPHYLAXIS

Two randomized controlled trials showed no significant difference in the risk of developing APSGN between cefuroxime for 5 days and penicillin V for 10 days as antibiotics prophylaxis[13, 14]. Furthermore, a Cochrane review of 27 trials showed that the efficacy of antibiotics treatment in preventing the development of APSGN after a

throat infection is statistically insignificant[15]. Antibiotic therapy during the initial Group A beta-hemolytic streptococcal (GAHBS) infection may help prevent the spread of infection and thereby prevent the development of APSGN[8]. However, antibiotics prophylaxis is generally not necessary in APSGN as the resolution of APSGN can occur without eradication of GAHBS, and recurrence of APSGN is uncommon[7].

ANTI-HYPERTENSIVE AGENTS

Thiazide diuretics are effective as a first-line medication in APSGN however loop diuretics may be considered in patients with renal impairment, especially with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 and significant edema[8]. Thiazide diuretics are associated with electrolyte abnormalities such as hypokalemia, hyperglycemia, and hypercalcemia[16]. Therefore, serum potassium and calcium levels should be monitored when the use of thiazides[16]. Hypertension in APSGN can be managed with diuretics alone or a combination of a diuretic and a vasodilator such as a calcium channel blocker to treat the hypervolemia from sodium and water retention[12]. Edematous or hypertensive patients should also be instructed on a reduced-sodium diet and may require fluid restriction[8]. Calcium channel blockers or beta-blockers may be considered in patients with the need for greater hypertension control[8]. Several studies showed that short-acting nifedipine is safe in children with severe hypertension or hypertensive emergencies and requires rapid reduction of blood pressure[17-19]. The minor adverse effects of short-acting nifedipine include flushing, tachycardia, edema, headache, dizziness, nausea and vomiting, pruritus, and gastrointestinal pain[18]. The occurrence of major adverse effects such as reduction in blood pressure by more than 40%, oxygen desaturation, and change in neurologic status is rare among pediatric populations [18, 19]. Furthermore, several studies have shown that angiotensin-converting enzyme (ACE) inhibitors have better control of blood pressure and edema in APSGN compared to diuretics[7]. However, ACE inhibitors or angiotensin receptor blockers are usually avoided in the acute phase because they may exacerbate any reduction in glomerular ultrafiltration and hyperkalemia[12].

SODIUM AND FLUID RESTRICTION AND PULMONARY EDEMA

Patients who present with generalized edema due to acute kidney injury or acute glomerulonephritis due to APSGN may benefit from sodium restriction[20]. A sodium-restricted diet between 1 and 2 mEq/kg/day is recommended for the reduction of edema and positive natriuresis[21]. Patients who are compliant with Na+ restriction will have self-limiting fluid restriction[21]. However, patients with severe edema may be treated with fluid restriction to two-thirds of maintenance or half or less of urine output once a brisk diuresis is achieved[21, 22]. Patients who are on fluid restriction should have close monitoring of fluid input and output, serum electrolytes, and vital signs [21].

Non-cardiogenic pulmonary edema can occur due to renal failure in patients with APSGN causing acute respiratory distress syndrome[22]. The management should focus on maintaining adequate oxygenation to the lung and treat the underlying cause[23]. Non-invasive positive pressure ventilation can be used in mild cases for respiratory support while conventional mechanical ventilation and high-frequency oscillatory ventilation can be used in more severe cases while the underlying cause is being treated[24]. The pharmacological management of non-cardiogenic pulmonary edema is limited[25]. Inhaled nitrate oxide (INO) can be used in patients with pulmonary hypertension and right ventricular dysfunction to reduce the ventilation/perfusion mismatch[24]. However, corticosteroids and surfactants are not recommended as routine therapy[26].

IMMUNOSUPPRESSANTS AND DIALYSIS

Patients may require kidney biopsy if they present with undifferentiated and rapidly progressive severe acute kidney injury to exclude other causes of kidney disease which may have specific managements[27]. High-dose intravenous corticosteroids may be used in patients whose has severe clinical presentations requiring renal biopsy, however, the use of corticosteroid is based on anecdotal evidence only[28]. Immunosuppression with

corticosteroids with or without an alkylating agent can be used in patients with severe crescentic glomerulonephritis (>75% crescents) to reduce the extra-capillary inflammation[4]. However, several studies also show that immune suppressive therapy does not have a clear benefit on the long-term outcome[4]. Finally, dialysis is recommended in children with severe renal impairment causing volume excess and electrolyte abnormalities such as hyperkalemia or acidosis[12, 29]. Renal replacement therapy (RRT) should be initiated in patients with overt fluid overload with cumulative fluid overload of more than 20% or more than 10% of the body weight and not responsive to diuretics[30, 31]. The available modalities for RRT are intermittent hemodialysis (IH), continuous renal replacement therapy (CRRT), and peritoneal dialysis (PD) in patients with acute kidney injury due to APSGN[32]. IHD is suitable for patients who are hemodynamically stable while patients who are hemodynamically less stable are more suitable for CRRT, especially in the ICU settings[29]. PD is less suitable in patients in critically ill patients because the dialysis depends on peritoneal circulation and there are increased risks of catheter-related infections and peritoneal fluid leakage[29].

COMPLICATIONS

The complications that might occur during the acute phase of APSGN include congestive heart failure, pulmonary edema, and severe hypertension-induced encephalopathy due to hypervolemia[10]. Serious complications such as hypertensive emergency, congestive heart failure, encephalopathy, and retinopathy were reported in 21.5%, 12.3%, 4.6%, and 1.5% of all cases of APSGN respectively[33]. A study in French Polynesia demonstrated that 22%of the patients had severe presentations which include cardiac failure and severe hypertension with or without encephalopathy[34]. A study by Kasahara *et al* showed that hypertension is the most common initial complication of APSGN with 64% of the children presenting with hypertension[35]. 30 – 35% of children with APSGN have been reported to have cerebral complications of hypertension[9, 33]. Children with severe hypertension may present with abnormal neurological symptoms

such as generalized seizures[27]. A study by Gunasekaran *et al* reported that 21.5 % of children required the treatment of intravenous infusion of sodium nitroprusside in an intensive care setting due to hypertensive emergency[33]. Anemia is the most common laboratory abnormality in patients with APSGN due to intravascular fluid overload and/or suppressed erythropoietin secretion and is significantly associated with the degree of azotemia[2].

PROGNOSIS AND OUTCOMES

Studies showed that around 34–44% of proteinuria cases in APSGN are in the nephrotic range at APSGN onset however it is not associated with disease severity or renal failure[27, 34]. A study done in Turkey by Demircioglu Kılıc *et al* showed that hypoalbuminemia, high CRP, neutrophil count, and neutrophil/Lymphocyte ratio (NLR) were associated with decreased eGFR in APSGN[1]. Besides that, the study also showed that 75% of the 16 children with low C4 with nephrotic range proteinuria at APSGN showed decreased eGFR[1]. However, another study from New Zealand showed that none of the patients had reduced C4 among 27 patients with APSGN with severe kidney involvement[4]. On the other hand, a study by Becquet showed that patients with severe-onset APSGN had decreased C3 Levels[34]. Furthermore, another study by Dagan *et al* also showed that decreased C3 Levels were associated with the presence of azotemia and/or full-blow nephritic syndrome[2]. In addition to that, the study by Han *et al* showed that a decrease in serum C3 Level was associated with the increased rate of acute nephritic features such as edema. Decreased serum in C3 Levels are found in 90% of children with APSGN and is associated with the increase in severity due to deposition of C3 glomerular sub-epithelial through complement activation *via* alternative pathway[4, 36]. Therefore, increased CRP, hypoalbuminemia, and hypocomplementemia are associated with disease severity and more severe clinical presentations[2].

APSGN generally has a favorable prognosis with less than 1% of children progressing to end-stage renal failure[37]. A 7-year follow-up of children with acute glomerulonephritis in Iran reported that none of the patients had hypertension or renal impairments, 3.1% had proteinuria and 6.3% had microscopic hematuria[38]. Furthermore, a 10-year follow-up of the children that developed APSGN in Brazil demonstrated that an increase in the frequency of hypertension in APSGN groups compared to control groups but no significant difference in renal function evaluation which includes serum creatinine, cystatin C, eGFR, albuminuria, and hematuria[39]. The study also showed improvement in the stabilization of median eGFR and a decrease in albuminuria in the follow-up of the same patients in 2, 5, and 10 years after the acute episode of APSGN[39]. Nevertheless, as few as 5% up to 20% of children may have persistent abnormalities in the urinary findings, either hematuria or proteinuria[2]. A 9-year follow-up study by Kasahara *et al* demonstrated that serum complement levels were normalized by 12 wk of diagnosis of APSGN and no patients had residual proteinuria by 3 years of diagnosis and hematuria disappeared by 4 years[35]. However, children with APSGN in low and middle-income countries may have a poorer prognosis due to severe presentation with 30% requiring dialysis due to acute kidney injury and <30% of the patients recovering fully[7, 40].

3 to 6% of patients with resolved APSGN may have persistent hypertension[37]. A study Vivante *et al* showed that childhood glomerular disease which includes APSGB, and steroid-responsive nephrotic syndrome is a risk factor for developing hypertension in adulthood[41]. The predictors of poor long-term prognosis of APSGN include the presence of nephrotic syndrome, renal insufficiency at the onset, and crescent formation on biopsy findings[8]. A retrospective study by Wong *et al* reviewed 27 patients with APSGN requiring renal biopsies due to anuric renal failure, acute severe glomerulonephritis, mixed nephrotic nephritic syndrome, and delayed recovery from glomerulonephritis[4]. The study reported that 12 patients required acute dialysis and 11 patients showed more than 50% of crescents on renal biopsies[4]. Patients with crescentic

glomerulonephritis had a higher frequency of needing acute dialysis and tended to have persistent proteinuria up to 8 years of follow-up[4]. Furthermore, 8 of the 12 patients who required acute dialysis had developed either ESRD, chronic renal failure, or persistent proteinuria of 2 to 4+ on urinalysis[4]. Kidney damage may persist or be superimposed years after APSGN due to persisting or secondary inflammation after infection and hyper-perfusion or hypertrophy of the nephron[42].

CONCLUSION

In conclusion, APSGN has a good prognosis and outcome in children. Severe systemic complications can occur due to severe renal inflammation and hypervolemia but are rare. Increased CRP, hypoalbuminemia, and hypocomplementemia are associated with disease severity. The predictors of severity of disease and poor outcome in APSGN in children may include the presence of nephrotic syndrome, crescent formations on renal biopsy, and renal insufficiency on presentation. A small percentage of patients may have persistent hypertension, persistent hematuria or proteinuria, or progression to chronic kidney disease following the acute episode of APSGN. Therefore, yearly follow-up is recommended to screen for any urinary abnormalities, hypertension, or renal impairment. Further prospective, multicenter, long-term studies should be conducted to evaluate the long-term outcomes of children with APSGN.

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