

Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis

T. Matthew Eison · Bettina H. Ault · Deborah P. Jones ·
Russell W. Chesney · Robert J. Wyatt

Received: 10 March 2010 / Revised: 16 April 2010 / Accepted: 19 April 2010 / Published online: 23 July 2010
© IPNA 2010

Abstract Post-streptococcal acute glomerulonephritis (PSAGN) is one of the most important and intriguing conditions in the discipline of pediatric nephrology. Although the eventual outcome is excellent in most cases, PSAGN remains an important cause of acute renal failure and hospitalization for children in both developed and underdeveloped areas. The purpose of this review is to describe both the typical and less common clinical features of PSAGN, to outline the changes in the epidemiology of PSAGN over the past 50 years, and to explore studies on the pathogenesis of the condition with an emphasis on the search for the elusive nephritogenic antigen.

Keywords Acute glomerulonephritis · Group A beta-hemolytic streptococcus · Nephritogenic

Historical perspective

In 1812, Wells described the clinical features of acute nephritis that included a latent period between scarlatina and development of edema and urine that contained both a

red substance and a coagulable substance (protein) [1]. He also observed that the siblings of a child with nephritis were more likely to develop nephritis after scarlatina than the siblings of non-nephritic children. A decade later, Richard Bright combined the finding of the coagulable substance in the urine with the clinical features of dropsy and autopsy evidence of kidney “derangement” [2]. The term “Bright’s disease” became the acceptable name for both acute and chronic glomerulonephritis until the mid-20th century. The form of the disorder associated with scarlatina became known as acute hemorrhagic Bright’s disease [3]. During the last decades of the 19th and first decades of the 20th century, several descriptions of post-scarlatina glomerulonephritis appeared, and were termed “acute glomerulonephritis” [4–6].

The association between β -hemolytic streptococcal infection and acute glomerulonephritis was noted by Longcope et al., who stated that “no evidence could be obtained...that the streptococcus caused the glomerular nephritis by actual invasion of the kidney, for blood cultures and urine cultures were negative” [5]. The work of Dick and Dick [7] and Dochez and Sherman [8], demonstrating that a β -hemolytic streptococcus was the pathogenic species in scarlet fever, led to use of the term “post-streptococcal acute glomerulonephritis”.

By 1940 serologic findings of anti-streptococcal antibodies [9] and depression of complement [10] were noted in patients with post-streptococcal acute glomerulonephritis (PSAGN) and it became clear that glomerulonephritis followed both upper respiratory and cutaneous infections with β -hemolytic streptococci [11, 12]. In 1941, Seegal and Earle developed the concept of nephritogenic strains of streptococci that were different from those that caused rheumatic fever [13]. Thus, the concept that acute glomerulonephritis was a non-suppurative, immunologically mediated complication of group A β -hemolytic streptococcal infections became firmly established.

Dedication This review is dedicated to the memory of Shane Roy III (1936–2009). Dr. Roy was the first pediatric nephrologist in Tennessee. His scholarly interest in post-streptococcal acute glomerulonephritis spanned his 40-year career in Memphis, resulting in seminal clinical observations on the condition.

T. M. Eison · B. H. Ault · D. P. Jones · R. W. Chesney ·
R. J. Wyatt (✉)

Division of Pediatric Nephrology, Department of Pediatrics,
University of Tennessee Health Science Center,
and the Children’s Foundation Research Center at Le Bonheur
Children’s Medical Center,
Room 301 WPT, 50 North Dunlap,
Memphis, TN 38103, USA
e-mail: rwyatt@uthsc.edu

Epidemiology

Post-streptococcal acute glomerulonephritis remains an important non-suppurative complication of group A streptococcal infection worldwide. The estimated worldwide yearly burden of PSAGN is 472,000 cases; approximately 404,000 of those cases occur in children [14]. By far, most of the burden of PSAGN is borne by developing countries [14]. Pyoderma-associated PSAGN continues to prevail in tropical areas, where streptococcal skin infections may be endemic [15]. In contrast, in more temperate areas pharyngitis-associated PSAGN now predominates [16, 17].

The epidemiology of PSAGN has long been noted to differ from that of acute rheumatic fever [13, 18, 19] and led to the conclusion that certain strains of group A streptococci are either rheumatogenic or nephritogenic, while others are neither [13, 20]. Group A streptococci are most commonly typed by their surface M proteins [21], which are virulence factors. However, group A streptococci can also be divided into two groups based on the presence or absence of a lipoproteinase that causes serum to become opaque (serum opacity factor) [22, 23]. Each of these two groups contains a characteristic group of M proteins. The opacity factor-negative group contains the “rheumatogenic” strains, while the opacity factor-positive group contains the “nephritogenic” strains [24]. Thus, acute rheumatic fever and PSAGN should not result from the same streptococcal infection, making the reports of such associations difficult to explain [25, 26]. In addition, nephritogenic strains can be subdivided into those primarily associated with pyoderma and those that most often cause pharyngitis [27, 28]. This distinction is made more complicated by the fact that pyoderma-associated strains sometimes cause a simultaneous pharyngitis, presumably by transfer of bacteria from the skin to the oropharynx [20].

The serotype most frequently associated with pyoderma-associated pharyngitis is M49, “the Red Lake strain” [28, 29]. Other pyoderma-associated strains are M2, M42, M56, M57, and M60 [24]. The common pharyngitis-associated PSAGN M types are 1, 4, 25, and some but not all M12 strains [19, 30].

Two epidemics on the Red Lake Chippewa Indian Reservation in northern Minnesota provided important early insight into the epidemiology of PSAGN [31, 32]. In both epidemics, the nephritis followed cases of pyoderma due to the M49 serotype, which was discovered in the first epidemic in 1953 [28]. The second epidemic, in 1966, affected only children that were too young to have been alive during the first epidemic. This absence of nephritis in older children and young adults in the second epidemic was presumed to be due to immunity gained from exposure to the M49 serotype in the first epidemic [31].

Most of the well-studied PSAGN epidemics or clusters were pyoderma-associated [28, 29, 33–35]. However, a few

epidemics/clusters included a predominance of pharyngitis-associated strains [36, 37]. In geographical areas having distinct seasons, pyoderma-associated cases tend to occur in the late summer or early fall months [18, 33, 34, 38], while in regions with a constant tropical climate cases occur year round [31].

The incidence of PSAGN often varies over time in a population. In a health district in Santiago, Chile, the annual incidence of PSAGN doubled to 13.2 cases per 100,000 population in an “epidemic” period (1984–1989) compared to an earlier “endemic” period (1980–1983) [33]. Subsequently (1990–1999), the incidence decreased to a low of 1.7 cases per 100,000 population per year. Most cases during the epidemic period were pyoderma-associated and correlated significantly with family size and household overcrowding.

The apparent decline in the incidence of PSAGN in the United States over the past 40 years is assumed to be largely from the near eradication of streptococcal pyoderma due to better hygiene and/or a decreased prevalence of skin infection-associated nephritogenic M serotypes [39]. Most new cases now admitted to the Le Bonheur Children’s Medical Center in Memphis, TN, appear to be pharyngitis-associated [40]. This trend was documented in a 1990 study that found a marked overall decline in the number of children hospitalized for PSAGN from the period 1961–1970, when the average was 31 patients per year (70% pyoderma-associated), to the period of 1979–1988, when the average was 9.5 patients per year (38% pyoderma-associated) [17]. Thus, over these periods the prevalence of pharyngitis-associated PSAGN did not change significantly while that of pyoderma-associated PSAGN fell markedly. A similar decline in pyoderma-associated PSAGN was shown for northeast Florida for the period 1999–2006 as compared to 1959–1973 [16]. In the current era, since the near-disappearance of pyoderma-associated PSAGN in developed countries, virtually no epidemiologic data have been published on M types in PSAGN.

Pathogenesis

The concept of immune complex formation resulting in PSAGN dates to the early 20th century observations of Schick and Von Pirquet likening human PSAGN to acute serum sickness, with its similar latent interval [41, 42]. However, the exact mechanism by which PSAGN occurs remains a source of debate. Theories proposed have included glomerular trapping of circulating immune complexes as well as in situ immune complex formation resulting from antibodies reacting with either streptococcal components deposited in the glomerulus or with components of the glomerulus itself (“molecular mimicry”). Evidence has also been presented to support the anti-immunoglobulin activity

or glomerular plasmin binding activity of streptococcal components as causative of PSAGN.

In the 1960s and 1970s, work from the laboratories of Germuth, Dixon, and Michael [43–46] demonstrated similarities between PSAGN and an acute “one shot” serum sickness model in the rabbit: a latent interval, low levels of serum complement, glomerular deposition of antigen, antibody and complement, and the self-limited nature of both diseases. Such findings supported a circulating immune complex etiology for PSAGN [47, 48].

Serum levels of circulating immune complexes detected by a C1q binding assay were found in 67% of patients with PSAGN [49]. However, circulating immune complexes occurred with the same frequency in patients with uncomplicated group A streptococcal infections [50], and levels of circulating immune complexes were not correlated with clinical features of PSAGN [51]. Nordstrand et al. [52] noted that the time course of C3 deposition before that of IgG argues for complement activation by the alternative pathway, or by non-immune activation of the classical pathway that is now recognized as characteristic for the lectin pathway of complement activation [53]. Thus, the order of immune component deposition argued against glomerular deposition of the pre-formed immune complexes necessary for classical complement pathway activation [52].

The cross-reactivity of streptococci and mammalian tissue was demonstrated in the 1930s and 1940s [54, 55]. Experiments implicating molecular mimicry in acute rheumatic fever (ARF) [54, 56–59] led to evidence of a similar mechanism behind PSAGN [60]. Sera of patients with PSAGN contain antibodies to glomerular basement membrane (GBM) components laminin and type IV collagen [61]. Initially, cross-reactivity of streptococcal antigens with the GBM was demonstrated in the nephritogenic M12 strain [62]. However, later studies showed cross-reactivity with glomeruli of non-nephritogenic strains [63–65]. Kraus and Beachey [66] localized the antigenic determinant for cross-reactivity with human renal glomeruli of type 1 streptococcal M protein to a tetrapeptide (Ile-Arg-Leu-Arg) near the amino terminus. However, the similar cross-reactivity patterns of rheumatogenic and nephritogenic strains of streptococci argue against molecular mimicry involving M proteins [67].

Much of the early work on the pathogenesis of PSAGN focused on the group A-specific streptococcal M proteins, as nephritogenicity is restricted to certain M protein serotypes. M protein–fibrinogen complexes deposit in the glomeruli [68, 69]. However, not all strains of a nephritis-associated M protein serotype are nephritogenic [19], and while PSAGN only rarely recurs, many M protein serotypes do not confer lifetime immunity [48]. Additional evidence against an M protein etiology is the inability of convalescent serum to recognize free antigenic sites in early renal

biopsies in patients with PSAGN, even after incubation of the sera with M protein [70]. Recently, *Streptococcus zooepidemicus* (group C) has been associated with outbreaks of PSAGN [71, 72], providing further evidence against M protein as the nephritogenic antigen.

M protein serotype 12 streptococci isolated from a patient with pharyngitis-associated PSAGN altered the carbohydrate composition of IgG in vitro, leading to the hypothesis that auto-immunogenic streptococcal-altered immunoglobulins underlie PSAGN [73]. Acute glomerulonephritis was induced in rabbits by administration of IgG altered by the same strain [74]. The autoimmunity-inducing IgG alteration in these studies was attributed to the actions of neuraminidase [75]. Anti-IgG antibodies were detected in the serum of 32% of patients with PSAGN [76], and in the glomeruli of 86% [77]. The arguments of Nordstrand et al. against the involvement of neuraminidase in the initiation of PSAGN are that (1) this would result in antibody deposition before C3, which is not observed in PSAGN [52], and (2) rheumatogenic and nephritogenic strains of streptococci both may produce neuraminidase [78].

Many studies have focused on the antigenic potential of certain components from nephritogenic strains of streptococci. As the glomerular basement membrane is negatively charged, cationic streptococcal components were investigated as the nephritogen, particularly histone-like proteins [79, 80]. In situ immune complex formation was proposed to result from anti-histone-like protein antibodies coupled with the ready adsorption of histone-like proteins to heparan sulfate-proteoglycans in the GBM [81]. However, anti-histone-like protein antibodies in the serum of patients with PSAGN or evidence of histone-like protein in their glomeruli have never been described [48].

Endostreptosin, a 40 to 50 kDa protein derived from streptococcal cell cytoplasm, has been detected in the glomeruli early in the clinical course of PSAGN, but not later in the disease [82, 83]. Antibodies directed against endostreptosin associate well with the course of the pathologic disease process [84]. These antibodies may represent a diagnostic marker for PSAGN, since they are elevated in patients with PSAGN as compared to healthy and disease (other types of glomerulonephritis and streptococcal infection) controls [85]. Perhaps endostreptosin was first studied in PSAGN by Treser [70], who showed that pre-incubating the serum with a fraction of streptococcus later determined to contain endostreptosin abolished staining of glomerular sections by serum IgG fractions from patients with PSAGN. Later, this was done with endostreptosin alone [86]. In a rat model, endostreptosin deposits along the GBM one day after injection but disappears in coincidence with the deposition of IgG and C3 at 8–12 days after injection [82]. This was explained by masking of the protein by bound antibody.

Yoshizawa et al. [87] isolated a 43 kDa protein called “pre-absorbing antigen” (PA-Ag) that others argue is identical to endostreptosin [48, 52]. PA-Ag was named for its ability to “pre-absorb” the antibody in convalescent PSAGN sera and prevent its glomerular deposition. PA-Ag activates the alternative complement pathway [87]. Antibody to PA-Ag was demonstrated in sera from 30 of 31 patients with PSAGN [87]. However, Rodriguez-Iturbe and Batsford [48] suggested that a subsequent study showed that sera of convalescent PSAGN patients had anti-IgG reactivity, which could result in the positive staining for endostreptosin in renal biopsies [76]. They also noted that injection of PA-Ag into rabbits resulted in findings that were inconsistent with PSAGN: mild proliferative (mesangial, endocapillary, or both) changes on biopsy and only mild hematuria and proteinuria [88]. In addition, Nordstrand et al. [89] found pre-absorbing antigen in non-nephritogenic strains of streptococci in their tissue cage mouse model of PSAGN.

Villareal et al. [90] isolated nephritis strain-associated protein (NSAP), a 46 to 47 kDa protein unique to the extracellular products of nephritogenic streptococci. NSAP was demonstrated in glomerular deposits for 14 of 21 patients with PSAGN, but none for control biopsies from five patients with acute renal failure (ARF) and 11 with nonstreptococcal glomerulonephritis. NSAP was also present in serum from 96% of PSAGN patients compared to 15–20% of patients with either ARF or impetigo [91]. NSAP has structural and biochemical properties identical to streptokinase. However, streptokinase cannot be demonstrated in glomerular deposits for patients with PSAGN [92], and serum levels of purified group A streptokinase were similar in patients with PSAGN and ARF. While NSAP and streptokinase may have similarities, they appear to be two distinct proteins [92]. Since a 43 kDa cleaved product of NSAP conserving NSAP’s epitope [93] shares the same isoelectric point and molecular weight as PA-Ag, it was suggested that PA-Ag and the cleaved product of NSAP were the same molecule [92].

Cunningham attributed the inability to detect glomerular deposition of streptokinase by immunofluorescence to the insensitivity of the method [24]. Streptokinase was demonstrated by immunogold-silver staining in the glomeruli of mice infected with the nephritogenic streptococcal strain NZ131, and rendered the strain non-nephritogenic through deletion of the *skal* gene responsible for production of streptokinase [94]. Reconstitution of the *skal* gene into the NZ131 strain via a plasmid vector restored its nephritogenic properties [95]. Earlier work in rabbits had shown that deletion of a streptokinase gene from a type 49 strain eliminated its nephritogenic properties [96].

Holm et al. [97–99] suggested that NSAP contributed to the pathogenesis of PSAGN via its ability to convert

plasminogen to plasmin, which cleaves C3, thus activating the alternative complement pathway and contributing to glomerular inflammation. Others suggested that active plasmin could induce PSAGN via degradation of extracellular matrix proteins and activation of matrix metalloproteinases [52, 100]. This has led to the investigation of other plasminogen-converting streptococcal components as possible nephritogenic antigens. Poon-King et al. [100] found a protein matching previous descriptions of NSAP that had plasmin binding properties and was identical to a precursor of streptococcal pyrogenic exotoxin B (speB). SpeB is a cationic extracellular cysteine proteinase with super antigenic properties produced by all group A streptococci strains [24]. Certain strains produce very high amounts of speB [101–103]. However, Poon-King et al. did not know if their protein was identical to the previously described NSAP, since antiserum prepared against NSAP was not available for direct comparison.

Further support for speB as the nephritogenic antigen is the finding that anti-speB antibodies are elevated in patients with PSAGN as compared to patients with ARF or scarlet fever or healthy individuals [104]. SpeB was found in the glomerular deposits in 67% of patients with PSAGN compared to 16% of patients with other glomerular diseases [104]. SpeB not only co-localized with C3 and IgG in the glomeruli of patients with PSAGN but was also demonstrated via immunogold-labeling of speB within the classic subepithelial hump [105]. A multicenter study showed that antibody to the zymogen of speB in South American patients with PSAGN was better than anti-streptolysin O and anti-DNAse B titers for demonstrating prior infection with nephritogenic streptococci [106].

Nordstrand et al. [52] felt that the role of speB in the pathogenesis of PSAGN was controversial, since sera from Ethiopian children showed no significant differences in reactivity against speB for patients with PSAGN and ARF. SpeB and its zymogen precursor were present during infection with both nephritic and non-nephritic streptococcal strains in a mouse tissue cage model of PSAGN [52]. In addition, sequencing of the genome of the group C *Streptococcus zooepidemicus* strain responsible for the PSAGN epidemic in Nova Serrana, Brazil revealed a lack of the gene encoding for speB, bringing into question its role as the sole nephritogenic antigen [71, 107].

Nephritis-associated plasmin receptor (NAPlr) was described by Yamakami et al. [108]. This 43 kDa glycolytic enzyme demonstrated plasmin binding and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity and was identical to a previously described plasmin receptor protein on group A streptococci [109]. Anti-NAPlr antibodies were detected in 92% of patients with PSAGN patients compared to 60% of patients with group A streptococcal pharyngitis patients without nephritis [110]. NAPlr was found in the

glomerular deposits of 100% of patients biopsied early in the course of PSAGN [110]. The glomerular distribution of NAPlr deposition and plasmin activity determined by in situ zymography was identical [111]. The fact that NAPlr did not co-localize with C3 in glomerular deposits was said to suggest that (1) complement was activated by NAPlr in the circulation rather than in situ, and (2) NAPlr induced PSAGN independently of complement activation by binding to the GBM and mesangial matrix via its adhesive character [110], and subsequently trapping and activating plasmin, causing in situ glomerular damage by degrading the GBM or activating latent matrix metalloproteases [111]. While speB was not expressed by the group C streptococcal strain responsible for the Nova Serrana, Brazil epidemic, NAPlr expression has been demonstrated in streptococcal groups A, C, and G [112]. However, Batsford et al. [105] failed to demonstrate either anti-NAPlr antibodies in serum from PSAGN patients or glomerular deposition of NAPlr. They suggested that the difference might have been due to the homogeneous Japanese population in the initial study [110] as compared to the diverse population from Venezuela in their study.

Since there is considerable evidence both for and against most putative nephritogenic antigens, collaborative efforts toward genomic sequencing of nephritogenic strains of streptococci have been initiated [107]. Discovery of new nephritogenic antigen candidates may be achieved by examination of conserved and differing regions of the genome. Such efforts will surely improve our understanding of the pathogenetic mechanism(s) underlying PSAGN.

Complement activation

Evidence from both serum complement profiles and immunofluorescence patterns for glomerular deposits indicates that C3 activation in PSAGN is predominately via the alternative pathway [113–115]. The immune deposits typically are made up of IgG, C3, properdin, and C5 [115]. These deposits virtually never contain the classical pathway components C1q and C4 [115]. C5b-9 (membrane attack complex) and its regulatory protein, the S protein, (vitronectin) localize in the same distribution as C3, indicating complete activation of the terminal complement pathway, which probably occurs in situ rather than in the circulation prior to deposition in the glomerulus [115, 116]. A recent study shows evidence for activation of the lectin-binding pathway from deposition of MBL in some patients with PSAGN [117].

Initially, some patients may have classical pathway activation, as evidenced by transient depression of serum C1q, C2, and/or C4 concentrations [118–120] and the presence of circulating C1-inhibitor-C1r-C1s complexes

[120] or C4d fragments [114] during the first two weeks after onset. These findings of classical complement pathway activation could reflect the presence of circulating immune complexes in the acute stage that are distinct from the glomerular immune deposits.

The depression of serum levels of properdin, C5, C6, and the MAC (C5b-9) corresponds temporally to the persistent depression of serum C3 [114, 121]. Serum levels of the alternative pathway regulatory proteins, H and I, remain normal throughout the clinical course of PSAGN [114].

PSAGN with typical renal pathologic findings on light microscopy, immunofluorescence, and electron microscopy may occur in patients with no evidence of complement activation, as manifested by depression of serum C3 concentration [122, 123]. A study from Cincinnati Children's Hospital showed that 10% of children with PSAGN had normal serum C3 concentration at clinical onset [122]. The diagnosis of PSAGN in these normocomplementemic patients was confirmed by demonstration of typical findings for PSAGN on renal biopsy. Hypocomplementemic patients differ from normocomplementemic patients by virtue of the presence of factor B in the glomerular deposits [115]. This finding, along with the absence of the alternative pathway regulatory protein factor H, may indicate that C3bBb convertase is present in the glomerular immune deposits and that the ongoing complement activation in PSAGN may be in situ rather than systemic.

Crescentic PSAGN may have an increased association with normocomplementemia. Five of the 10 crescentic PSAGN patients from Memphis [124] and four of 11 from New Zealand [125] had normal or near-normal serum C3 levels; however, none of the four reported by Lewy et al. [126] had normal or near-normal serum C3 levels. The reason for this possible association of normocomplementemia with crescent formation in PSAGN is not clear.

Serum immunoglobulin levels

Serum IgG levels were elevated in 44% of 75 children hospitalized with PSAGN [127]. Twenty of those with elevated serum IgG levels were biopsied and over half had no IgG in their glomerular deposits [127]. Also, patients with an elevated IgG level were more likely to have anti-streptolysin O titers ≥ 833 Todd units ($p < 0.001$). Elevated serum IgG concentration did not correlate with severity of disease, age of the patient, or the serum albumin or C3 level. There appears to be a subset of patients with elevated serum IgG levels who with high frequency have IgG absent from their glomerular deposits. Thus, failure to form antibody to a glomerular-bound protein produced by the nephritogenic streptococcus, widely assumed to be the origin of the IgG in the glomerular deposits, is in some way

significantly associated with elevated serum levels of IgG and antibody to streptolysin O.

Clinical manifestations—typical course, atypical features

The median age at presentation for PSAGN in childhood is between 6 and 8 years old [126, 128, 129]; the condition rarely occurs prior to age 2 [126, 130, 131]. The rarity of PSAGN in very young children was attributed to the low rate of streptococcal pharyngitis in this age group and an immature immune (or antibody) response [130]. Twice as many males are diagnosed with PSAGN as females [126, 130, 131]; the reason for this is unknown. There appears to be no difference in gender ratio whether PSAGN follows pharyngitis or pyoderma.

Children with PSAGN most often seek medical attention for edema or gross hematuria; occasionally symptoms or signs of hypertension will be the initial presenting feature leading to the diagnosis. The triad of edema, hematuria and hypertension is classic for PSAGN. Three phases of the disease can be identified: the latent phase, the acute phase, and the recovery phase. The general course is represented in Fig. 1. A preceding infection of the respiratory tract (usually pharyngitis) or of the skin is identified in the majority of cases. However, sub-clinical cases do occur, many of which are identified based upon the knowledge of an affected family member/contact. One report suggested that PSAGN occurs in about 20% of asymptomatic family members of patients with the condition [84]. The latency period between the streptococcal infection and the onset of the clinical syndrome ranges from 3–33 days [132] but on average is 7–14 days. The prevalence of clinical features

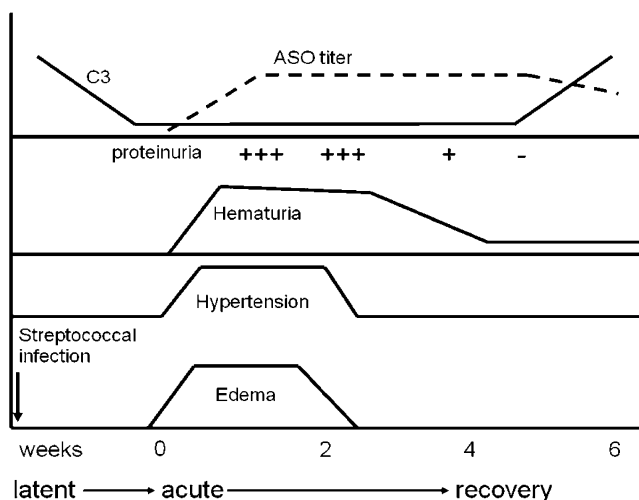


Fig. 1 Summary of the typical clinical course of post-streptococcal acute glomerulonephritis (PSAGN)

during the acute phase of PSAGN differs somewhat among the various case series depending upon the era of publication and the method of patient selection. In fact, some of the earliest descriptions of cases of acute GN may have included patients that actually had conditions other than PSAGN.

With the exception of rare cases with atypical presentation, hematuria is present in essentially all patients. The classic description of tea- or cola-colored urine occurs in approximately 25–60% of patients. Proteinuria is also typically present, but nephrotic syndrome is rare in most case series. While a single series [133] reported 10% with nephrotic syndrome, most have reported only 2–4% [126, 134]. Hypertension occurs in approximately 80–90% of cases [40, 135, 136]. Cerebral complications of hypertension including headaches, seizures, mental status changes, and visual changes occur in 30–35% of children [40, 135]. The mechanism for hypertension is most likely retention of sodium and water with resulting expansion of the extracellular space [134]. As with other causes of glomerulonephritis, fractional excretion of sodium is generally less than 1%, similar to pre-renal azotemia [137, 138]. Renin levels (plasma renin activity) are typically low at presentation [139, 140]. Fluid retention correlates with suppression of the plasma renin activity [140]. Diastolic blood pressure significantly correlates with the degree of fluid overload as assessed by weight change pre- and post-spontaneous diuresis [139]. Patients may sometimes present with clinical and radiologic signs of pulmonary edema. While dyspnea is a presenting complaint in only 5% of patients, evidence for congestive heart failure was found in half of the children in one early series [135].

Atypical presentations of PSAGN include those individuals with sub-clinical disease and those presenting with acute illness, usually related to hypertension or edema in the absence of overtly abnormal urine [141]. There are numerous case reports of children who present with extreme manifestations, usually from hypertensive crises, who do not display the typical urinary findings at presentation [141]. Serial examination of the urine after presentation may eventually confirm the suspicion of acute glomerulonephritis.

Another atypical feature at presentation is the presence of a typical Henoch-Schönlein purpura rash [142–144]. The diagnosis of PSAGN was confirmed by renal biopsy in those cases.

Examination of the urine sediment confirms acute glomerular involvement with the presence of dysmorphic red blood cells and leukocytes; red blood cell and white blood cell casts are usually identified. In the early part of the acute phase, urinary leukocytes may predominate over red blood cells.

The glomerular filtration rate (GFR) is often decreased during the acute phase of the disease. Increased blood urea nitrogen (BUN) was noted in 60–65% of patients [40, 135],

with decreased estimated creatinine clearance less than 90 ml/min/1.73 m² present in 20% [40]. Quantitation of urinary protein excretion in 78 cases of PSAGN between 1979–1988 revealed nephrotic range proteinuria (defined as >40 mg/m²/h) in 27 (34.6%) and normal urinary protein excretion (defined as <5 mg/m²/h) in 20 (25.6%) [17]. Hypoalbuminemia is quite common: in one large study of PSAGN serum albumin was lower than 3.0 g/dl in 46% and less than 2.5 g/dl in 15% [145].

Decreased blood hemoglobin is common in PSAGN. One large series showed that only 10% of 155 patients had a hemoglobin level of \pm 12 g/dl, and over 50% were below 10 g/dl [145]. In extreme cases, severe anemia may occur [145]. While traditionally the drop in hemoglobin has been attributed via clinical observation solely to volume overload [146], there could be other factors at work. In two instances, autoimmune hemolytic anemia was documented in the early stages of PSAGN [147, 148].

The serological markers most commonly used by the clinician are anti-streptolysin O (ASO) titer and depression of serum C3 level. Increased antibody levels to anti-streptococcal antigens [ASO, anti-hyaluronidase (A-H) and anti-DNAase] are documented less often than low levels of C3. ASO titers are higher in pharyngitis-associated PSAGN than pyoderma-associated PSAGN [9, 128, 149, 150]. In an early study, the sensitivity of an elevated ASO titer was extremely high (97%), but the specificity was only 80%, presumably due to the fact that up to 20% of unaffected controls show evidence of streptococcal exposure with a significantly elevated titer [151]. Early descriptions of the time course for increasing ASO and A-H titers show that in a group of patients with typical (previously known as type A) acute glomerulonephritis, ASO was increased above normal in 72% [135]. In Roy's series of biopsy-proven cases from Memphis, 60% had ASO titer elevation as defined by Todd units >333 [40]. Cases following pyoderma are more likely to demonstrate elevated anti-DNAase B titer than an elevated ASO titer [118, 128].

In children whose initial ASO titer is normal, subsequent measurements may be elevated, thus supporting the suspected diagnosis. This is demonstrated by Longcope [9] and Dodge et al. [128], who found that the ASO titer continued to increase over the four weeks after presentation in some cases [9] and the mean titer peaked at three weeks [128]. In addition, performance of more than one streptococcal antibody test increased the number of individuals with "positive" titers from 80 to 95% [151]. Travis et al. tested for ASO, AH, and anti-DNAase in 60 patients and often found ASO to be negative while anti-DNAase and/or AH were positive [136].

The acute reduction of serum C3 concentration in PSAGN with the typical return to normal levels within six weeks of onset is of foremost diagnostic importance

when renal biopsy is not performed [10, 114, 118, 152]. Depression of serum C3 level in PSAGN has been shown to precede the onset of hematuria [118, 120].

Hypertension usually resolves within 1–2 weeks, and rarely requires long-term treatment [135, 136]. Renal biopsy is indicated in cases in which the clinical diagnosis is not clear in order to confirm the diagnosis or in the presence of significant renal insufficiency to rule out crescentic glomerulonephritis.

The recovery phase occurs after resolution of fluid overload with diuresis—either spontaneous and/or pharmacologically induced—along with normalization of blood pressure and resolution of proteinuria and gross hematuria. Most case series note that the proteinuria disappears much earlier than the microscopic hematuria [40, 153] with the exception of Travis et al., who noted the opposite [136]. During this phase, the C3 level returns to normal in the majority of affected children. PSAGN has occurred in patients previously diagnosed (by biopsy) with IgA nephropathy [154–156]. Because IgA nephropathy is the most commonly occurring type of chronic glomerulonephritis and often goes undiagnosed, the association with PSAGN is most likely the chance occurrence of the two conditions in the same individual.

Second attacks of PSAGN have been reported but are rare [145, 157–160]. In the earlier reports, the PSAGN was pyoderma-associated for both attacks in most instances [145, 158, 159], while two case reports since 2000 were both pharyngitis-associated PSAGN [157, 160]. A recent case series reported two recurrences of PSAGN, but didn't specify the route of infection acquisition [161].

Renal biopsy findings

A renal biopsy is generally not indicated for diagnosis of PSAGN, but is usually performed when atypical clinical features occur. Such features that could lead to a biopsy are normocomplementemia [122], failure to document a recent streptococcal infection by a rise in ASO or streptozyme titer, and renal insufficiency, particularly when the GFR remains less than 30 ml/min/1.73 m² for more than one week [124].

In the past, some pediatric nephrologists recommended a renal biopsy for patients with presumed PSAGN whose C3 concentration remained depressed for more than eight weeks after clinical onset, mainly to exclude the diagnosis of membranoproliferative glomerulonephritis (MPGN). One study documented failure of C3 to become normal by eight weeks in five of 20 patients despite typical improvement in clinical features, including resolution of proteinuria and normal kidney function [162]. Renal biopsies that were performed in three of these patients showed typical findings of PSAGN. Thus, persistent hypocomplementemia with

resolving features of acute glomerulonephritis does not exclude the diagnosis of PSAGN, and the authors and others felt that the renal biopsy could be deferred. Subsequent studies have backed these findings [163, 164].

When a biopsy is performed, the typical light microscopy findings are diffuse hypercellularity of endothelial and mesangial cells and infiltration of the glomerular tuft with polymorphonuclear cells [165]. This endocapillary hypercellularity may lead to a reduction in the capillary lumen space that appears to associate with the initial severity of renal insufficiency [126]. Using a cell-proliferation marker, Ki-67, Chung and Kim [166] provided evidence that most of this hypercellularity is due to infiltrating inflammatory cells. In most cases of PSAGN there is little or no evidence of tubular, interstitial or vascular injury [47].

In more severe cases, epithelial crescents may form during the course of PSAGN. Rarely, patients with PSAGN will have crescentic involvement in over 50% of glomeruli, leading to the clinical picture of rapidly progressive glomerulonephritis [36, 124, 125].

The immunofluorescence pattern typically seen in biopsies performed during the acute phase of PSAGN shows discrete granular deposits of IgG and C3 in a capillary loop and mesangial distribution [32, 167]. However, about 30% of PSAGN biopsies show C3 and the absence of IgG even when the biopsies are performed early in the clinical course [32, 127, 168–170]. Sorger et al. [171] described the immunofluorescence patterns in PSAGN using the term “starry sky” to represent a typical pattern and the term “garland pattern” to indicate the presence of heavy and sometimes confluent capillary loop deposits with the total absence of mesangial deposits. This garland pattern was associated with more numerous and larger subepithelial “humps” and higher degrees of proteinuria. However, this association with heavy proteinuria has not been confirmed by any case series in the two decades following the initial report.

The hallmark pathologic finding on electron microscopy is the subepithelial hump, which was first noted by Kimmelstiel and associates in 1962 [172]. However, electron dense deposits may also occur in subendothelial and intramembranous locations [168] and the presence of such deposits should not lead one to dismiss the diagnosis of PSAGN, since they were found in PSAGN patients as early as 1966 [168].

Lewy et al. [126] observed an association between the degree of polymorphonucleocyte infiltration of the glomerular tuft and the number of subepithelial humps; they also noted that higher degrees of endocapillary proliferation were associated with lower complement levels. West and McAdams [173] demonstrated a significant association between absence of paramesangial (the portion of the capillary loop in continuity with the mesangium) deposits and low serum albumin levels in children with PSAGN. These patients

differed from those with paramesangial deposits in that they were more edematous, were less likely to have gross hematuria and tended to be normocomplementemic.

Treatment

Treatment remains largely supportive and usually addresses the most urgent problem of hypertension. No modern studies are available to guide the first choice of anti-hypertensive agent. However, salt restriction and loop diuretics are the first-line treatment for fluid overload and hypertension; thereafter, hypertensive therapy is often transitioned to vasodilators. Although successful treatment with ACE inhibition has been reported [106], ACE inhibitors are generally not used during the acute phase due to the potential for decrease in GFR and hyperkalemia. In those individuals with hypertensive emergencies, continuous infusion of anti-hypertensive medication is the preferred initial approach.

One difficult question that has yet to be definitively answered is whether prompt treatment of group A streptococcal pharyngitis or pyoderma will prevent or attenuate the subsequent development of PSAGN. In 1970, Dillon stated, “In spite of vigorous efforts to do so, we have not been able to prove unequivocally that we can prevent cases of AGN by prompt treatment of streptococcal skin infection” [34]. While more recent studies have not disputed this assertion, treating communities in which PSAGN is epidemic with benzathine penicillin G may reduce carriage of nephritogenic strains and thus lower the incidence of PSAGN [174].

Immunosuppression has not been proven to be effective, although it is often used in the clinical setting of rapidly progressive glomerulonephritis or when crescents are seen on biopsy. However, there is considerable debate as to whether immunosuppressive treatment is effective in this setting. Roy et al. [124], in a study of 10 patients, reported no difference in outcome between patients receiving quintuple therapy (prednisone, azathioprine, cyclophosphamide, dipyridamole, and anticoagulation) and those receiving supportive care. More recently, Wong et al. [125] reported the clinical course of 27 patients biopsied for difficult clinical course, 11 of whom had >50% crescents on biopsy, and found no benefit of immunosuppression.

Long-term outcome

A major problem with the attempts of older studies to make prognostic associations for PSAGN is that the statistical methodologies employed were non-existent or inadequate by today’s standards. Thus, many of the stated conclusions

reflect the bias of albeit excellent clinical observers. Since the current standard of clinical practice is to forego renal biopsy in typical cases of suspected PSAGN [134], it is important to note that 10–15% of clinical diagnoses of PSAGN were not supported after a renal biopsy was performed [128]. In a series of 47 patients, those erroneously diagnosed with PSAGN had a significantly worse prognosis than patients who had PSAGN. Clinical and histologic evidence of non-healing was observed in 50% of patients whose biopsies revealed exacerbation of other underlying renal disease, as opposed to only 5% of patients with PSAGN [128].

Published studies on the prognosis of PSAGN in children are comprised only of cases that are clinically apparent [134]. Sagel et al. [175] found that all biopsies of children with transient hypocomplementemia and microscopic hematuria following streptococcal infection demonstrated histologic evidence of glomerulonephritis. Published estimates of the ratio of subclinical to clinical cases of PSAGN are from 1.5:1 to 19:1 [31, 134, 175–177].

Reports on clinicopathologic correlations in PSAGN have sometimes described surprising disparities. A report published in 1969 found normalization of urinalysis in the presence of progressive post-streptococcal glomerular lesions, and, conversely, histopathologic healing with persistent urinary abnormalities [178]. In that study, the duration and degree of hypocomplementemia correlation did not associate with subsequent histologic healing.

Certain histologic findings may predict a poor prognosis. In a series of 23 patients with PSAGN, the single patient who died secondary to renal disease had more extensive subepithelial hump deposition than the other cases [136]. The garland pattern of immunofluorescence has been associated with heavy proteinuria and poor outcome [171]. While higher degrees of endocapillary hypercellularity appear to associate with the initial severity of renal insufficiency, this finding has not been shown to associate with progression to end stage renal disease (ESRD) [126].

Extracapillary crescent formation is the most ominous histologic finding in PSAGN. The patient who died in the case series of Travis et al. [136] had crescentic disease. In Lewy's case series of 46 patients with PSAGN published in 1971 [126], three of the four patients who died had crescents with glomerular sclerosis on biopsy, and well-developed epithelial crescents were present in three of four patients with a persistent course. In PSAGN patients studied between 1962 and 1970, two died from rapidly progressive glomerulonephritis during the acute phase of illness [179]. In a series of 36 children who were biopsied, the two who had many large crescents were uremic at onset and never remitted [133]. A recent study by Wong et al. [125] examined 27 renal biopsies diagnostic of PSAGN in

children over a 12-year period. They showed that progression to ESRD was more prevalent with crescentic PSAGN, occurring in two of 11 patients as opposed to none of the 16 children with PSAGN without crescents. Indications for biopsy in this study were anuric renal failure, acute severe glomerulonephritis, or unexpected delay in recovery from acute glomerulonephritis. These investigators estimated that only 2% of cases of PSAGN were severe enough to warrant biopsy, supporting earlier claims of good prognosis in children with PSAGN.

It is important to note that post-streptococcal crescentic glomerulonephritis may carry a better prognosis than crescent formation of other etiology. The Southwest Pediatric Nephrology Study Group found that of 50 children with crescent formation, five with PSAGN had normal GFR, compared to progression to ESRD for 23 of 42 patients with crescent formation of other etiology [180]. However, this concept was challenged by experience from northern India that suggested that the prognosis for post-streptococcal crescentic glomerulonephritis is equally as poor as that for other types of crescentic glomerulonephritis [181].

Studies on the outcome of sporadic PSAGN are summarized in Table 1. On the surface, with the notable exception of Baldwin's group in New York City [182], virtually all studies report good prognosis for the vast majority of children with PSAGN. The Baldwin group studies include a 1979 report that asserted that irreversible renal disease, as evidenced by hypertension, proteinuria, decreased renal function or glomerulosclerosis, occurred in at least 40% of children following sporadic PSAGN [133]. They even argued that their data were similar to those of earlier reports [126, 128, 136] and took issue with the criteria for favorable outcome in those reports [133]. Lewy et al. [126] reported normal creatinine clearance of >77 ml/min/1.73 m² in 25 of 26 patients with over three years follow-up, while the Baldwin group reported normal creatinine clearances of >105 ml/min/1.73 m² in 20 of 26 children and considered proteinuria of 200 to 500 mg per 24 h to represent irreversible glomerular damage [133]. They also chose to interpret the presence of sclerosis as chronicity rather than healing, as Travis et al. [136] had done.

The poor prognosis implied by the Baldwin group may also be due to insufficient length of time for follow-up, for although they followed some patients for up to 17 years, 46 out of 83 patients were followed for only two years. Selection bias related to the patients with recovery being lost to follow-up early surely applies to their work [182]. Roy et al. showed that recovery from PSAGN can be protracted. In their study, histologic healing occurred in 20% at two years, in 94% at 10 years, and in 97% at 12 years after disease onset [40].

Roy et al. [40] also argued that light microscopy more accurately determines healing than clinical indices of blood

Table 1 Outcome of sporadic cases of pediatric post-streptococcal acute glomerulonephritis

Study	No. of patients	Antecedent pyoderma	Antecedent URI/pharyngitis	Patient ages	Sex ratio M:F	Time of follow-up	Histologic healing	No. of renal-related deaths	Proteinuria at follow-up	Hypertension at follow-up	Decrease in GFR at follow-up	Hematuria at follow-up
Lewy et al. [126]	46	5/46	35/46 (6/46 with other)	≤7 (n=6) 8–14 (n=20) 15–21 (n=9) ≤22 (n=5) unknown (n=6)	29:17	6 months–9 years	34/46	4/46	3/21 (2–4 years) 2/13 (4–6 years) 2/5 (6–8 years) 1/1 (8–10 years) ^e	1/14 (2–4 years) 3/14 (4–6 years) 1/3 (6–8 years) 1/2 (8–10 years) ^b	2/19 (2–4 years) 3/14 (4–6 years) 2/6 (6–8 years) 0/1 (8–10 years) ^g	4/20 (2–4 years) 1/15 (4–6 years) 1/4 (6–8 years) 0/1 (8–10 years) ^f
Travis et al. [136]	60	25/60	26/60	2.5–24.5 years	39:21	3–10 years	49/54	1/60	31/54 (>1 year) 17/52 (≥2 years) ^{b,i}	2/40 (2–4 years) ^h 1/8 (4–6 years) ^{b,i}	6/22 (2–8 years) ^d	5/53 (6–12 months) None after 1 year
Roy et al. [40]	35	24/35	11/35	3.6–12.8 years	16:19	4–12 years	34/35	0/35	2/21 (2–4 years) 5/32 (4–6 years) 1/22 (6–12 years) ^e	0/22 (2–4 years) 0/34 (4–6 years) 1/25 (6–12 years) ^b	1/20 (2–4 years) 2/30 (4–6 years) 4/24 (6–12 years) ^g	6/21 (2–4 years) 9/21 (4–6 years) 9/22 (6–12 years) ^g
Sanjad et al. [192]	153	100/153	45/153	14 months–13 years	1.6:1	6 months–11 years		2/153	0/103	0/103	0/48	0/103
Schacht et al. [133]	83	6%	79% (4% both; 11% unknown)	2–16 years	43:40	≤17 years	10/12 at 2 years follow-up	0/54	24% (≥2 years) 16% (≥5 years) 18% (≥10 years) ^a	16% (≥2 years) 25% (≥5 years) 33% (≥10 years) ^b	16% (≥2 years) 26% (≥5 years) 35% (≥10 years) ^c	–
Clark et al. [179]	36	0/36	34/36 URI 4/36 tonsillitis 2/36 OM	1.9–14.3 years	21:15	5–12 years (n=32) 15–22 years (n=30)		2/36	3/30–34 (one biopsied type II MPGN)	1/30–34	0/33 (SCR <1.5 in males, <1.25 in females)	3/30–34 (≥10 RBC/μl)
Popovic-Rolovic et al. [193]	104	88.5%	11.5%	2–16 years	61.9:38.1	5–9 years (n=40) 10–17 years (n=88)		0/104	2/40 (5–9 years) 2/88 (10–17 years)	2/40 (5–9 years) 3/88 (10–17 years)	0/104	0/40 (5–9 years) 2/88 (10–17 years)
Herthelius and Berg [194]	33	?	?	2–16 years	25:8	2–11 months		0/22			2/22 (=92 ml/min/1.73 m ²)	
Kasahara et al. [195]	138	?none (either +ASO or +throat cx or latex agglut.)	?all	3–14 years	84:54	≤4 years		0/138	2.2% (1–2 years) 0.7% (2–3 years) 0% (3 years)	0/138		5.8% (2–3 years) 2.9% (3–4 years) 0% (4 years)

URI upper respiratory infection, OM otitis media, cx culture, latex agglut latex agglutination

^a Proteinuria defined as ≥200–500 mg/24 h

^b Hypertension defined as >140/90 mmHg

^c GFR of 105 ml/min/1.73 m² defined as lower limit of normal

^d GFR of <60 ml/min/m² (<104 ml/min/1.73 m²) defined as lower limit of normal

^e Proteinuria defined as >50 mg/12 h

^f Hematuria defined as Addis count of >1×10⁶ red blood cell (RBC)

^g Creatinine clearance of 90 ml/min/1.73 m² defined as lower limit of normal

^h Familial hypertension, 2nd attack PSAGN

ⁱ Familial hypertension

pressure elevation, proteinuria, and hematuria. Although six of 35 patients in their study were labeled “non-healed” by these clinical criteria at 49 to 135 months from onset of PSAGN, all had healed histologically, as indicated by light microscopy.

It is generally accepted that epidemic cases of PSAGN carry a better prognosis than sporadic cases, with some asserting that healing occurs in all cases [136]. This may be secondary to sporadic cases often presenting in a hospital setting, while the increased index of suspicion inherent in epidemics leads to the presentation of a greater number of mild cases [133]. Other factors may be the portal of entry and the strain of streptococci. Drachman et al. [183], citing studies originating from Trinidad [184, 185], Maracaibo [37], and New York (Baldwin group) [182, 186, 187], as well as their own [188, 189], noted that the prognosis was more favorable in pyoderma-associated than pharyngitis-associated PSAGN, and that glomerulonephritis following infection with the M55 strain had a favorable prognosis. However, Roy et al. [40] showed that initial histologic changes were more severe in the pyoderma-associated than pharyngitis-associated PSAGN, but that there was no difference in subsequent healing rates.

The future of PSAGN

The availability of a vaccine for group A streptococci is highly desirable and anticipated, both in terms of preventing invasive disease and nonsuppurative complications [190]. Presumably, a vaccine that eradicated all group A streptococci would eliminate PSAGN. There are two approaches for the development of a vaccine against group A streptococci. The most difficult and costly approach target a protein common to all group A streptococci. Alternatively, since antibodies to M proteins are generally protective against the strain from which the M protein comes, a multivalent vaccine could be designed. The current thrust of group A streptococcal vaccine research has been to target M proteins [191]. Because invasive disease and acute rheumatic fever are the most important preventable complications of group A streptococcal infection in the industrialized world, the vaccine currently in development is a 26-valent vaccine that targets the variable region of the M proteins of the most common rheumatogenic streptococci [191]. This vaccine appears to be well tolerated in adults and immune sera have been successful in preventing invasive disease in rabbits. Unfortunately, no M proteins from nephritogenic streptococci were included in the vaccine. In addition, because the most common M protein types differ geographically, this vaccine may be of limited efficacy in the developing world, which would presumably continue to bear the majority of the world burden of PSAGN and ARF.

Thus, prevention of PSAGN in the developing world continues to be based upon public health measures such as improved hygiene and better housing conditions. The elimination of epidemic pyoderma, as occurred in the southern United States over the past 25 years, offers the best hope for control.

References

1. Wells CD (1812) Observations on the dropsy which succeeds scarlet fever. *Trans Soc Imp Med Chir Knowledge* 3:167–186
2. Bright R (1836) Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. *Guy Hosp Rep* 1:338–341
3. Peitzman SJ (2007) Dropsy, dialysis, transplant. A short history of failing kidneys. Johns Hopkins University Press, Baltimore
4. Klebs MR: Cited by Charcot JM (1878) Lectures on Bright's disease of the kidneys, translated by Millard HB. New York, William Wood & Co
5. Longcope WT, O'Brien DP, McGuire J, Hansen OC, Denny ER (1927) Relationship of acute infections to glomerular nephritis. *J Clin Invest* 5:7–30
6. Reichel H (1905) Uber Nephritis bei Scharlach. *Z Heil* 6:72–78
7. Dick GF, Dick GH (1924) Experimental scarlet fever. *J Am Med Assoc* 81:1166–1167
8. Dochez AR, Sherman L (1924) The significance of *Streptococcus hemolyticus* in scarlet fever and the preparation of a specific antiscarlatinal serum by immunization of the horse to *Streptococcus hemolyticus* scarlatinae. *J Am Med Assoc* 82:542–544
9. Longcope WT (1936) Studies of the variations in the antistreptolysin titer of the blood serum from patients with hemorrhagic nephritis. II. Observations on patients suffering from streptococcal infections, rheumatic fever and acute and chronic hemorrhagic nephritis. *J Clin Invest* 15:277–294
10. Kohler PF, Ten Bessel R (1969) Serial complement component alterations in acute glomerulonephritis and systemic lupus erythematosus. *Clin Exp Immunol* 4:191–202
11. Fitcher PH (1940) Glomerular nephritis following skin infections. *Arch Intern Med* 65:1192–1210
12. Lyttle JD, Seegal D, Loeb EN, Jost EL (1938) The serum antistreptolysin titer in acute glomerulonephritis. *J Clin Invest* 17:631–639
13. Seegal D, Earle DP (1941) A consideration of certain biological differences between glomerulonephritis and rheumatic fever. *Am J Med Sci* 201:528–539
14. Carapetis JR, Steer AC, Mulholland EK, Weber M (2005) The global burden of group A streptococcal diseases. *Lancet Infect Dis* 5:685–694
15. Sulyok E (2004) Acute proliferative glomerulonephritis. In: Avner ED, Harmon WE, Niaudet P (eds) *Pediatric nephrology*, 5th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 601–613
16. Ilyas M, Tolaymat A (2008) Changing epidemiology of acute post-streptococcal glomerulonephritis in Northeast Florida: a comparative study. *Pediatr Nephrol* 23:1101–1106
17. Roy S 3rd, Stapleton FB (1990) Changing perspectives in children hospitalized with poststreptococcal acute glomerulonephritis. *Pediatr Nephrol* 4:585–588
18. Bisno AL, Pearce IA, Wall HP, Moody MD, Stollerman GH (1970) Contrasting epidemiology of acute rheumatic fever and acute glomerulonephritis. *N Engl J Med* 283:561–565
19. Rammelkamp CH Jr, Weaver RS (1953) Acute glomerulonephritis, the significance of the variations in the incidence of the disease. *J Clin Invest* 32:345–358

20. Stollerman GH (1971) Rheumatogenic and nephritogenic streptococci. *Circulation* 43:915–921
21. Lancefield RC (1928) The antigenic complex of *Streptococcus haemolyticus*. I. Demonstration of a type-specific substance in extracts of *Streptococcus haemolyticus*. *J Exp Med* 47:91–96
22. Widdowson JP, Maxted WR, Grant DL (1970) The production of opacity in serum by group A streptococci and its relationship with the presence of M antigen. *J Gen Microbiol* 61:343–353
23. Widdowson JP, Maxted WR, Grant DL, Pinney AM (1971) The relationship between M-antigen and opacity factor in group A streptococci. *J Gen Microbiol* 65:69–80
24. Cunningham MW (2000) Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* 13:470–511
25. Kwong YL, Chan KW, Chan MK (1987) Acute post-streptococcal glomerulonephritis followed shortly by acute rheumatic fever. *Postgrad Med J* 63:209–210
26. Matsell DG, Baldree LA, DiSessa TG, Gaber LS, Stapleton FB (1990) Acute poststreptococcal glomerulonephritis and acute rheumatic fever: occurrence in the same patient. *Child Nephrol Urol* 10:112–114
27. Dillon HC Jr (1967) Pyoderma and nephritis. *Annu Rev Med* 18:207–218
28. Updyke EL, Moore MS, Conroy E (1955) Provisional new type of group A streptococci associated with nephritis. *Science* 121:171–172
29. Parker MT, Bassett DC, Maxted WR, Arneaud JD (1968) Acute glomerulonephritis in Trinidad: serological typing of group A streptococci. *J Hyg (Lond)* 66:657–675
30. Stetson CA, Rammelkamp CH Jr, Krause RM, Kohen RJ, Perry WD (1955) Epidemic acute nephritis: studies on etiology, natural history and prevention. *Medicine (Baltimore)* 34:431–450
31. Anthony BF, Kaplan EL, Wannamaker LW, Briese FW, Chapman SS (1969) Attack rates of acute nephritis after type 49 streptococcal infection of the skin and of the respiratory tract. *J Clin Invest* 48:1697–1704
32. Fish AJ, Herdman RC, Michael AF, Pickering RJ, Good RA (1970) Epidemic acute glomerulonephritis associated with type 49 streptococcal pyoderma. II. Correlative study of light, immunofluorescent and electron microscopic findings. *Am J Med* 48:28–39
33. Berrios X, Lagomarsino E, Solar E, Sandoval G, Guzman B, Riedel I (2004) Post-streptococcal acute glomerulonephritis in Chile—20 years of experience. *Pediatr Nephrol* 19:306–312
34. Dillon HC Jr (1970) Streptococcal skin infection and acute glomerulonephritis. *Postgrad Med J* 46:641–652
35. Dillon HC Jr, Moody MD, Maxted WR, Parker MT (1967) The epidemiology of impetigo and acute glomerulonephritis. Results of serological typing of group A streptococci. *Am J Epidemiol* 86:710–723
36. Anand SK, Trygstad CW, Sharma HM, Northway JD (1975) Extracapillary proliferative glomerulonephritis in children. *Pediatrics* 56:434–442
37. Rodriguez-Iturbe B, Garcia R, Rubio L, Cuenca L, Treser G, Lange K (1976) Epidemic glomerulonephritis in Maracaibo. Evidence for progression to chronicity. *Clin Nephrol* 5:197–206
38. Reinstein CR (1955) Epidemic nephritis at Red Lake, Minnesota. *J Pediatr* 47:25–34
39. Schwartz B, Facklam RR, Breiman RF (1990) Changing epidemiology of group A streptococcal infection in the USA. *Lancet* 336:1167–1171
40. Roy S 3rd, Pitcock JA, Etteldorf JN (1976) Prognosis of acute poststreptococcal glomerulonephritis in childhood: prospective study and review of the literature. *Adv Pediatr* 23:35–69
41. Schick B (1912) Die Nachkrankheiten des Scharlach: pathogenese der Nachkrankheiten. In: Escherich T, Schick B (eds) *Scharlach*. Holder, Leipzig, p 151
42. von Pirquet C (1911) Allergy. *Arch Int Med* 7:259–288
43. Dixon FJ, Feldman JD, Vazquez JJ (1961) Experimental glomerulonephritis. The pathogenesis of a laboratory model resembling the spectrum of human glomerulonephritis. *J Exp Med* 113:899–920
44. Fish AJ, Michael AF, Vernier RL, Good RA (1966) Acute serum sickness nephritis in the rabbit. An immune deposit disease. *Am J Pathol* 49:997–1022
45. Germuth FG Jr (1953) A comparative histologic and immunologic study in rabbits of induced hypersensitivity of the serum sickness type. *J Exp Med* 97:257–282
46. Germuth FG Jr, Senterfit LB, Dreesman GR (1972) Immune complex disease. V. The nature of the circulating complexes associated with glomerular alterations in the chronic BSA-rabbit system. *Johns Hopkins Med J* 130:344–357
47. Nadasdy T, Silva FG (2007) Acute postinfectious glomerulonephritis and glomerulonephritis caused by persistent bacterial infection. In: Jennette JC, Olson JL, Schwartz MM, Silva FG (eds) *Heptinstall's pathology of the kidney*, 6th edn. Lippincott Williams and Wilkins, Philadelphia, pp 322–396
48. Rodriguez-Iturbe B, Batsford S (2007) Pathogenesis of post-streptococcal glomerulonephritis a century after Clemens von Pirquet. *Kidney Int* 71:1094–1104
49. Rodriguez-Iturbe B, Carr RI, Garcia R, Rabideau D, Rubio L, McIntosh RM (1980) Circulating immune complexes and serum immunoglobulins in acute poststreptococcal glomerulonephritis. *Clin Nephrol* 13:1–4
50. Yoshizawa N, Treser G, McClung JA, Sagel I, Takahashi K (1983) Circulating immune complexes in patients with uncomplicated group A streptococcal pharyngitis and patients with acute poststreptococcal glomerulonephritis. *Am J Nephrol* 3:23–29
51. Mezzano S, Olavarria F, Ardiles L, Lopez MI (1986) Incidence of circulating immune complexes in patients with acute poststreptococcal glomerulonephritis and in patients with streptococcal impetigo. *Clin Nephrol* 26:61–65
52. Nordstrand A, Norgren M, Holm SE (1999) Pathogenic mechanism of acute post-streptococcal glomerulonephritis. *Scand J Infect Dis* 31:523–537
53. Walport MJ (2001) Complement. First of two parts. *N Engl J Med* 344:1058–1066
54. Jaffe R, Holz E (1948) Experimental allergic myocarditis. *Exp Med Surg* 6:189–202
55. Kendall FE, Heidelberger M, Dawson MH (1937) A serologically inactive polysaccharide elaborated by mucoid strains of group A hemolytic streptococci. *J Biol Chem* 118:61
56. Cavelti PA (1947) Studies on pathogenesis of rheumatic fever, experimental production of autoantibodies to heart, skeletal muscle and connective tissue. *Arch Pathol* 44:1–7
57. Frick E (1951) Animal experiments on an allergotuberculous myocarditis. *Z Gesamte Exp Med* 117:393–404
58. Kaplan MH (1958) Immunologic studies of heart tissue. I. Production in rabbits of antibodies reactive with an autologous myocardial antigen following immunization with heterologous heart tissue. *J Immunol* 80:254–267
59. Kaplan MH, Meyeresian M (1962) An immunological cross-reaction between group-A streptococcal cells and human heart tissue. *Lancet* 1:706–710
60. Christensen P, Schalen C, Holm SE (1979) Reevaluation of experiments intended to demonstrate immunological cross-reactions between mammalian tissues and streptococci. *Prog Allergy* 26:1–41
61. Kefalides NA, Ohno N, Wilson CB, Fillit H, Zabriski J, Rosenbloom J (1993) Identification of antigenic epitopes in type IV collagen by use of synthetic peptides. *Kidney Int* 43:94–100
62. Markowitz AS, Lange CF Jr (1964) Streptococcal related glomerulonephritis. I. Isolation, immunochemistry and compar-

- ative chemistry of soluble fractions from type 12 nephritogenic streptococci and human glomeruli. *J Immunol* 92:565–575
63. Holm SE (1967) Precipitinogens in beta-hemolytic streptococci and some related human kidney antigens. *Acta Pathol Microbiol Scand* 70:79–94
 64. Holm SE, Braun D, Jonsson J (1968) Antigenic factors common to human kidney and nephritogenic and non-nephritogenic streptococcal strains. *Int Arch Allergy Appl Immunol* 33:127–130
 65. Kingston D, Glynn LE (1971) A cross-reaction between *Str. pyogenes* and human fibroblasts, endothelial cells and astrocytes. *Immunology* 21:1003–1016
 66. Kraus W, Beachey EH (1988) Renal autoimmune epitope of group A streptococci specified by M protein tetrapeptide Ile-Arg-Leu-Arg. *Proc Natl Acad Sci USA* 85:4516–4520
 67. Robinson JH, Kehoe MA (1992) Group A streptococcal M proteins: virulence factors and protective antigens. *Immunol Today* 13:362–367
 68. Kantor FS (1965) Fibrinogen precipitation by streptococcal M protein. I. Identity of the reactants, and stoichiometry of the reaction. *J Exp Med* 121:849–859
 69. Kaplan MH (1958) Localization of streptococcal antigens in tissues. I. Histologic distribution and persistence of M protein, types 1, 5, 12, and 19 in the tissues of the mouse. *J Exp Med* 107:341–352
 70. Treser G, Semar M, McVicar M, Franklin M, Ty A, Sagel I, Lange K (1969) Antigenic streptococcal components in acute glomerulonephritis. *Science* 163:676–677
 71. Balter S, Benin A, Pinto SW, Teixeira LM, Alvim GG, Luna E, Jackson D, LaClaire L, Elliott J, Facklam R, Schuchat A (2000) Epidemic nephritis in Nova Serrana, Brazil. *Lancet* 355:1776–1780
 72. Francis AJ, Nimmo GR, Efstratiou A, Galanis V, Nuttall N (1993) Investigation of milk-borne *Streptococcus zooepidemicus* infection associated with glomerulonephritis in Australia. *J Infect* 27:317–323
 73. McIntosh RM, Kulvinskask C, Kaufman DB (1971) Alteration of the chemical composition of human immunoglobulin G by *Streptococcus pyogenes*. *J Med Microbiol* 4:535–538
 74. McIntosh RM, Kaufman DB, McIntosh JR, Griswold W (1972) Glomerular lesions produced by autologous serum and autologous IgG modified by treatment with a culture of a-haemolytic streptococcus. *J Med Microbiol* 5:1–7
 75. Mosquera J, Rodriguez-Iturbe B (1984) Extracellular neuraminidase production of streptococci associated with acute nephritis. *Clin Nephrol* 21:21–28
 76. Sesso RC, Ramos OL, Pereira AB (1986) Detection of IgG-rheumatoid factor in sera of patients with acute poststreptococcal glomerulonephritis and its relationship with circulating immune-complexes. *Clin Nephrol* 26:55–60
 77. McIntosh RM, Garcia R, Rubio L, Rabideau D, Allen JE, Carr RL, Rodriguez-Iturbe B (1978) Evidence of an autologous immune complex pathogenic mechanism in acute poststreptococcal glomerulonephritis. *Kidney Int* 14:501–510
 78. Potter EV, Shaughnessy MA, Poon-King T, Earle DP (1982) Streptococcal neuraminidase and acute glomerulonephritis. *Infect Immun* 38:1196–1202
 79. Vogt A, Batsford S, Rodriguez-Iturbe B, Garcia R (1983) Cationic antigens in poststreptococcal glomerulonephritis. *Clin Nephrol* 20:271–279
 80. Vogt A, Schmiedecke T, Stockl F, Sugisaki Y, Mertz A, Batsford S (1990) The role of cationic proteins in the pathogenesis of immune complex glomerulonephritis. *Nephrol Dial Transplant* 5 (Suppl 1):6–9
 81. Stinson MW, McLaughlin R, Choi SH, Juarez ZE, Barnard J (1998) Streptococcal histone-like protein: primary structure of hlpA and protein binding to lipoteichoic acid and epithelial cells. *Infect Immun* 66:259–265
 82. Cronin WJ, Lange K (1990) Immunologic evidence for the in situ deposition of a cytoplasmic streptococcal antigen (endostreptosin) on the glomerular basement membrane in rats. *Clin Nephrol* 34:143–146
 83. Lange K, Seligson G, Cronin W (1983) Evidence for the in situ origin of poststreptococcal glomerulonephritis: glomerular localization of endostreptosin and the clinical significance of the subsequent antibody response. *Clin Nephrol* 19:3–10
 84. Lange K, Azadegan AA, Seligson G, Bovie RC, Majeed H (1988) Asymptomatic poststreptococcal glomerulonephritis in relatives of patients with symptomatic glomerulonephritis. Diagnostic value of endostreptosin antibodies. *Child Nephrol Urol* 9:11–15
 85. Seligson G, Lange K, Majeed HA, Deol H, Cronin W, Bovie R (1985) Significance of endostreptosin antibody titers in poststreptococcal glomerulonephritis. *Clin Nephrol* 24:69–75
 86. Cronin W, Deol H, Azadegan A, Lange K (1989) Endostreptosin: isolation of the probable immunogen of acute poststreptococcal glomerulonephritis (PSGN). *Clin Exp Immunol* 76:198–203
 87. Yoshizawa N, Oshima S, Sagel I, Shimizu J, Treser G (1992) Role of a streptococcal antigen in the pathogenesis of acute poststreptococcal glomerulonephritis. Characterization of the antigen and a proposed mechanism for the disease. *J Immunol* 148:3110–3116
 88. Yoshizawa N, Oshima S, Takeuchi A, Kondo S, Oda T, Shimizu J, Nishiyama J, Ishida A, Nakabayashi I, Tazawa K, Sakurai Y (1997) Experimental acute glomerulonephritis induced in the rabbit with a specific streptococcal antigen. *Clin Exp Immunol* 107:61–67
 89. Nordstrand A, Norgren M, Holm SE (1996) An experimental model for acute poststreptococcal glomerulonephritis in mice. *APMIS* 104:805–816
 90. Villarreal H Jr, Fischetti VA, van de Rijn I, Zabriskie JB (1979) The occurrence of a protein in the extracellular products of streptococci isolated from patients with acute glomerulonephritis. *J Exp Med* 149:459–472
 91. Ohkuni H, Friedman J, van de Rijn I, Fischetti VA, Poon-King T, Zabriskie JB (1983) Immunological studies of post-streptococcal sequelae: serological studies with an extracellular protein associated with nephritogenic streptococci. *Clin Exp Immunol* 54:185–193
 92. Mezzano S, Burgos E, Mahabir R, Kemeny E, Zabriskie JB (1992) Failure to detect unique reactivity to streptococcal streptokinase in either the sera or renal biopsy specimens of patients with acute poststreptococcal glomerulonephritis. *Clin Nephrol* 38:305–310
 93. Johnston KH, Zabriskie JB (1986) Purification and partial characterization of the nephritis strain-associated protein from *Streptococcus pyogenes*, group A. *J Exp Med* 163:697–712
 94. Nordstrand A, Norgren M, Ferretti JJ, Holm SE (1998) Streptokinase as a mediator of acute post-streptococcal glomerulonephritis in an experimental mouse model. *Infect Immun* 66:315–321
 95. Nordstrand A, McShan WM, Ferretti JJ, Holm SE, Norgren M (2000) Allele substitution of the streptokinase gene reduces the nephritogenic capacity of group A streptococcal strain NZ131. *Infect Immun* 68:1019–1025
 96. Holm SE, Ferretti JJ, Simon D, Johnston K (1992) Deletion of a streptokinase gene eliminates the nephritogenic capacity of a type 49 strain. In: Orefici G (ed) *New perspectives on streptococci and streptococcal infections*. Proceedings of the XI Lancefield International Symposium. Gustav-Fischer-Verlag, New York, pp 261–263
 97. Holm SE (1990) Hypothesis on the pathogenesis of post-streptococcal glomerulonephritis based on recent clinical and experimental research. *Zentralbl Bakteriell* 274:325–332

98. Holm SE (1988) The pathogenesis of acute post-streptococcal glomerulonephritis in new lights. Review article. *APMIS* 96:189–193
99. Holm SE, Bergholm AM, Johnston KH (1988) A streptococcal plasminogen activator in the focus of infection and in the kidneys during the initial phase of experimental streptococcal glomerulonephritis. *APMIS* 96:1097–1108
100. Poon-King R, Bannan J, Viteri A, Cu G, Zabriskie JB (1993) Identification of an extracellular plasmin binding protein from nephritogenic streptococci. *J Exp Med* 178:759–763
101. Gerlach D, Knoll H, Kohler W, Ozegowski JH, Hribalova V (1983) Isolation and characterization of erythrogenic toxins. V. Communication: identity of erythrogenic toxin type B and streptococcal proteinase precursor. *Zentralbl Bakteriell Mikrobiol Hyg A* 255:221–233
102. Kapur V, Topouzis S, Majesky MW, Li LL, Hamrick MR, Hamill RJ, Patti JM, Musser JM (1993) A conserved *Streptococcus pyogenes* extracellular cysteine protease cleaves human fibronectin and degrades vitronectin. *Microb Pathog* 15:327–346
103. Musser JM, Stockbauer K, Kapur V, Rudgers GW (1996) Substitution of cysteine 192 in a highly conserved *Streptococcus pyogenes* extracellular cysteine protease (interleukin 1beta convertase) alters proteolytic activity and ablates zymogen processing. *Infect Immun* 64:1913–1917
104. Cu GA, Mezzano S, Bannan JD, Zabriskie JB (1998) Immunohistochemical and serological evidence for the role of streptococcal proteinase in acute post-streptococcal glomerulonephritis. *Kidney Int* 54:819–826
105. Batsford SR, Mezzano S, Mihatsch M, Schiltz E, Rodriguez-Iturbe B (2005) Is the nephritogenic antigen in post-streptococcal glomerulonephritis pyrogenic exotoxin B (SPE B) or GAPDH? *Kidney Int* 68:1120–1129
106. Parra G, Rodriguez-Iturbe B, Batsford S, Vogt A, Mezzano S, Olavarria F, Exeni R, Laso M, Orta N (1998) Antibody to streptococcal zymogen in the serum of patients with acute glomerulonephritis: a multicentric study. *Kidney Int* 54:509–517
107. Rodriguez-Iturbe B, Musser JM (2008) The current state of poststreptococcal glomerulonephritis. *J Am Soc Nephrol* 19:1855–1864
108. Yamakami K, Yoshizawa N, Wakabayashi K, Takeuchi A, Tadakuma T, Boyle MD (2000) The potential role for nephritis-associated plasmin receptor in acute poststreptococcal glomerulonephritis. *Methods* 21:185–197
109. Broeseker TA, Boyle MD, Lottenberg R (1988) Characterization of the interaction of human plasmin with its specific receptor on a group A streptococcus. *Microb Pathog* 5:19–27
110. Yoshizawa N, Yamakami K, Fujino M, Oda T, Tamura K, Matsumoto K, Sugisaki T, Boyle MD (2004) Nephritis-associated plasmin receptor and acute poststreptococcal glomerulonephritis: characterization of the antigen and associated immune response. *J Am Soc Nephrol* 15:1785–1793
111. Oda T, Yamakami K, Omasu F, Suzuki S, Miura S, Sugisaki T, Yoshizawa N (2005) Glomerular plasmin-like activity in relation to nephritis-associated plasmin receptor in acute poststreptococcal glomerulonephritis. *J Am Soc Nephrol* 16:247–254
112. Fujino M, Yamakami K, Oda T, Omasu F, Murai T, Yoshizawa N (2007) Sequence and expression of NAP1r is conserved among group A streptococci isolated from patients with acute post-streptococcal glomerulonephritis (APSGN) and non-APSGN. *J Nephrol* 20:364–369
113. Gewurz H, Pickering RJ, Naff G, Snyderman R, Mergenhagen SE, Good RA (1969) Decreased properdin activity in acute glomerulonephritis. *Int Arch Allergy Appl Immunol* 36:592–598
114. Wyatt RJ, Forristal J, West CD, Sugimoto S, Curd JG (1988) Complement profiles in acute post-streptococcal glomerulonephritis. *Pediatr Nephrol* 2:219–223
115. Wyatt RJ, McAdams AJ, Forristal J, Snyder J, West CD (1979) Glomerular deposition of complement-control proteins in acute and chronic glomerulonephritis. *Kidney Int* 16:505–512
116. Matsell DG, Wyatt RJ, Gaber LW (1994) Terminal complement complexes in acute poststreptococcal glomerulonephritis. *Pediatr Nephrol* 8:671–676
117. Hisano S, Matsushita M, Fujita T, Takeshita M, Iwasaki H (2007) Activation of the lectin complement pathway in post-streptococcal acute glomerulonephritis. *Pathol Int* 57:351–357
118. Derrick CW, Reeves MS, Dillon HC Jr (1970) Complement in overt and asymptomatic nephritis after skin infection. *J Clin Invest* 49:1178–1187
119. Levy M, Sich M, Pirotzky E, Habib R (1985) Complement activation in acute glomerulonephritis in children. *Int J Pediatr Nephrol* 6:17–24
120. Sjöholm AG (1979) Complement components and complement activation in acute poststreptococcal glomerulonephritis. *Int Arch Allergy Appl Immunol* 58:274–284
121. Matsell DG, Roy S 3rd, Tamerius JD, Morrow PR, Kolb WP, Wyatt RJ (1991) Plasma terminal complement complexes in acute poststreptococcal glomerulonephritis. *Am J Kidney Dis* 17:311–316
122. Strife CF, McAdams AJ, McEnery PT, Bove KE, West CD (1974) Hypocomplementemic and normocomplementemic acute nephritis in children: a comparison with respect to etiology, clinical manifestations, and glomerular morphology. *J Pediatr* 84:29–38
123. Tina LU, D'Albora JB, Antonovych TT, Bellanti JA, Calcagno PL (1968) Acute glomerulonephritis associated with normal serum B1C-globulin. *Am J Dis Child* 115:29–36
124. Roy S 3rd, Murphy WM, Arant BS Jr (1981) Poststreptococcal crescentic glomerulonephritis in children: comparison of quintuple therapy versus supportive care. *J Pediatr* 98:403–410
125. Wong W, Morris MC, Zwi J (2009) Outcome of severe acute post-streptococcal glomerulonephritis in New Zealand children. *Pediatr Nephrol* 24:1021–1026
126. Lewy JE, Salinas-Madrigal L, Herdson PB, Pirani CL, Metcalf J (1971) Clinico-pathologic correlations in acute poststreptococcal glomerulonephritis. A correlation between renal functions, morphologic damage and clinical course of 46 children with acute poststreptococcal glomerulonephritis. *Medicine (Baltimore)* 50:453–501
127. West CD, McAdams AJ (1998) Serum and glomerular IgG in poststreptococcal glomerulonephritis are correlated. *Pediatr Nephrol* 12:392–396
128. Dodge WF, Spargo BH, Travis LB, Srivastava RN, Carvajal HF, DeBeukelaer MM, Longley MP, Menchaca JA (1972) Post-streptococcal glomerulonephritis. A prospective study in children. *N Engl J Med* 286:273–278
129. Sarkissian A, Papazian M, Azatian G, Arikians N, Babloyan A, Leumann E (1997) An epidemic of acute postinfectious glomerulonephritis in Armenia. *Arch Dis Child* 77:342–344
130. Bingler MA, Ellis D, Moritz ML (2007) Acute post-streptococcal glomerulonephritis in a 14-month-old boy: why is this uncommon? *Pediatr Nephrol* 22:448–450
131. Li Volti S, Furnari ML, Garozzo R, Santangelo G, Mollica F (1993) Acute post-streptococcal glomerulonephritis in an 8-month-old girl. *Pediatr Nephrol* 7:737–738
132. Addis T (1950) Glomerular nephritis: diagnosis and treatment. The Macmillan Company, New York
133. Schacht RG, Gallo GR, Gluck MC, Iqbal MS, Baldwin DS (1979) Irreversible disease following acute poststreptococcal glomerulonephritis in children. *J Chronic Dis* 32:515–524
134. Rodriguez-Iturbe B (1984) Epidemic poststreptococcal glomerulonephritis. *Kidney Int* 25:129–136
135. Burke EC, Titus JL (1966) Poststreptococcal acute glomerulonephritis in children. *Med Clin North Am* 50:1141–1158

136. Travis LB, Dodge WF, Beathard GA, Spargo BH, Lorentz WB, Carvajal HF, Berger M (1973) Acute glomerulonephritis in children. A review of the natural history with emphasis on prognosis. *Clin Nephrol* 1:169–181
137. Espinel CH, Gregory AW (1980) Differential diagnosis of acute renal failure. *Clin Nephrol* 13:73–77
138. Miller TR, Anderson RJ, Linas SL, Henrich WL, Berns AS, Gabow PA, Schrier RW (1978) Urinary diagnostic indices in acute renal failure: a prospective study. *Ann Intern Med* 89:47–50
139. Powell HR, Rotenberg E, Williams AL, McCredie DA (1974) Plasma renin activity in acute poststreptococcal glomerulonephritis and the haemolytic-uraemic syndrome. *Arch Dis Child* 49:802–807
140. Rodriguez-Iturbe B, Baggio B, Colina-Chourio J, Favaro S, Garcia R, Sussana F, Castillo L, Borsatti A (1981) Studies on the renin-aldosterone system in the acute nephritic syndrome. *Kidney Int* 19:445–453
141. Brouhard BH, Travis LB (1992) Acute postinfectious glomerulonephritis. In: Edelman CM (ed) *Pediatric kidney disease*, 2nd edn. Little, Brown and Company, Boston, pp 1199–1221
142. Goodyer PR, de Chadarevian JP, Kaplan BS (1978) Acute poststreptococcal glomerulonephritis mimicking Henoch-Schönlein purpura. *J Pediatr* 93:412–415
143. Lau KK, Wyatt RJ, Gaber LW (2005) Purpura followed by proteinuria in a 7-year-old girl. *Am J Kidney Dis* 46:1140–1144
144. Matsukura H, Ohtsuki A, Fuchizawa T, Miyawaki T (2003) Acute poststreptococcal glomerulonephritis mimicking Henoch-Schönlein purpura. *Clin Nephrol* 59:64–65
145. Sanjad S, Tolaymat A, Whitworth J, Levin S (1977) Acute glomerulonephritis in children: a review of 153 cases. *South Med J* 70:1202–1206
146. James JA (1976) Acute glomerulonephritis. In: James JA (ed) *Renal disease in childhood*, 3rd edn. The C. V. Mosby Company, St. Louis, pp 191–213
147. Greenbaum LA, Kerlin BA, Van Why S, Punzalan RC, Trost BA, Pan CG, Scott JP (2003) Concurrent poststreptococcal glomerulonephritis and autoimmune hemolytic anemia. *Pediatr Nephrol* 18:1301–1303
148. Lau KK, Hastings MC, Delos Santos NM, Gaber LW, Ault BH (2007) A child with post-streptococcal acute glomerulonephritis complicated by Coombs positive autoimmune hemolytic anemia. *Internet J Nephrol* 4
149. Alpert JJ, Pickering MR, Warren RJ (1966) Failure to isolate streptococci from children under the age of 3 years with exudative tonsillitis. *Pediatrics* 38:663–666
150. Markowitz M, Bruton HD, Kuttner AG, Cluff LE (1965) The bacteriologic findings, streptococcal immune response, and renal complications in children and impetigo. *Pediatrics* 35:393–404
151. Ayoub EM, Wannamaker LW (1962) Evaluation of the streptococcal deoxyribonuclease B and diphosphopyridine nucleotidase antibody tests in acute rheumatic fever and acute glomerulonephritis. *Pediatrics* 29:527–538
152. West CD, Northway JD, Davis NC (1964) Serum levels of beta-1C globulin, a complement component, in the nephritides, lipid nephrosis, and other conditions. *J Clin Invest* 43:1507–1517
153. Perlman LV, Herdman RC, Kleinman H, Vernier RL (1965) Poststreptococcal glomerulonephritis. A ten-year follow-up of an epidemic. *JAMA* 194:63–70
154. Fujinaga S, Ohtomo Y, Mochizuki H, Murakami H, Shimizu T, Yamashiro Y, Kaneko K (2009) Rapidly progressive acute post-streptococcal glomerulonephritis in a child with IgA nephropathy. *Pediatr Int* 51:425–428
155. Hiki Y, Tamura K, Shigematsu H, Kobayashi Y (1991) Superimposition of poststreptococcal acute glomerulonephritis on the course of IgA nephropathy. *Nephron* 57:358–364
156. Lau KK, Delos Santos NM (2005) Post-infectious acute glomerulonephritis with predominant mesangial deposition of IgA. *Clin Exp Nephrol* 9:262–263
157. Derakhshan A (2002) Another case of acute poststreptococcal glomerulonephritis with recurrence. *Pediatr Nephrol* 17:462
158. Dodge WF, Spargo BH, Bass JA, Travis LB (1968) The relationship between the clinical and pathologic features of poststreptococcal glomerulonephritis. A study of the early natural history. *Medicine (Baltimore)* 47:227–267
159. Roy S 3rd, Wall HP, Etteldorf JN (1969) Second attacks of acute glomerulonephritis. *J Pediatr* 75:758–767
160. Watanabe T, Yoshizawa N (2001) Recurrence of acute post-streptococcal glomerulonephritis. *Pediatr Nephrol* 16:598–600
161. Becquet O, Pasche J, Gatti H, Chenel C, Abely M, Morville P, Pietremont C (2010) Acute post-streptococcal glomerulonephritis in children of French Polynesia: a 3-year retrospective study. *Pediatr Nephrol* 25:275–280
162. Dedeoglu IO, Springate JE, Waz WR, Stapleton FB, Feld LG (1996) Prolonged hypocomplementemia in poststreptococcal acute glomerulonephritis. *Clin Nephrol* 46:302–305
163. Butani L (2001) Prolonged hypocomplementemia after post-streptococcal glomerulonephritis. *Nephrol Dial Transplant* 16:869
164. Payne D, Houtman P, Browning M (2008) Acute post-streptococcal glomerulonephritis associated with prolonged hypocomplementaemia. *J Clin Pathol* 61:1133–1135
165. Jennings RB, Earle DP (1961) Post-streptococcal glomerulonephritis: histopathologic and clinical studies of the acute, subsiding acute and early chronic latent phases. *J Clin Invest* 40:1525–1595
166. Chung WY, Kim YJ (2000) Expression of Ki-67 antigen using monoclonal antibody MIB-1 in children with post-streptococcal glomerulonephritis. *Pediatr Nephrol* 14:389–392
167. McCluskey RT, Vassalli P, Gallo G, Baldwin DS (1966) An immunofluorescent study of pathogenic mechanisms in glomerular diseases. *N Engl J Med* 274:695–701
168. Michael AF Jr, Drummond KN, Good RA, Vernier RL (1966) Acute poststreptococcal glomerulonephritis: immune deposit disease. *J Clin Invest* 45:237–248
169. Morel-Maroger L, Leatham A, Richet G (1972) Glomerular abnormalities in nonsystemic diseases. Relationship between findings by light microscopy and immunofluorescence in 433 renal biopsy specimens. *Am J Med* 53:170–184
170. Yoshizawa N, Suzuki Y, Oshima S, Takeuchi A, Kondo S, Ishida A, Nakabayashi I, Nishiyama J, Tazawa K, Sagel I (1996) Asymptomatic acute poststreptococcal glomerulonephritis following upper respiratory tract infections caused by Group A streptococci. *Clin Nephrol* 46:296–301
171. Sorger K, Gessler U, Hubner FK, Kohler H, Schulz W, Stuhlinger W, Thoenes GH, Thoenes W (1982) Subtypes of acute postinfectious glomerulonephritis. Synopsis of clinical and pathological features. *Clin Nephrol* 17:114–128
172. Kimmelstiel P, Kim OJ, Beres J (1962) Studies on renal biopsy specimens, with the aid of the electron microscope. II. Glomerulonephritis and glomerulonephrosis. *Am J Clin Pathol* 38:280–296
173. West CD, McAdams AJ (1998) Glomerular deposits and hypoalbuminemia in acute post-streptococcal glomerulonephritis. *Pediatr Nephrol* 12:471–474
174. Johnston F, Carapetis J, Patel MS, Wallace T, Spillane P (1999) Evaluating the use of penicillin to control outbreaks of acute poststreptococcal glomerulonephritis. *Pediatr Infect Dis J* 18:327–332
175. Sagel I, Treser G, Ty A, Yoshizawa N, Kleinberger H, Yuzeoglu AM, Wasserman E, Lange K (1973) Occurrence and nature of glomerular lesions after group A streptococci infections in children. *Ann Intern Med* 79:492–499

176. Dodge WF, Spargo BH, Travis LB (1967) Occurrence of acute glomerulonephritis in sibling contacts of children with sporadic acute glomerulonephritis. *Pediatrics* 40:1028–1030
177. Rodriguez-Iturbe B, Rubio L, Garcia R (1981) Attack rate of poststreptococcal nephritis in families. A prospective study. *Lancet* 1:401–403
178. Treser G, Ehrenreich T, Ores R, Sagel I, Wasserman E, Lange K (1969) Natural history of “apparently healed” acute poststreptococcal glomerulonephritis in children. *Pediatrics* 43:1005–1017
179. Clark G, White RH, Glasgow EF, Chantler C, Cameron JS, Gill D, Comley LA (1988) Poststreptococcal glomerulonephritis in children: clinicopathological correlations and long-term prognosis. *Pediatr Nephrol* 2:381–388
180. A report of the Southwest Pediatric Nephrology Study Group (1985) A clinico-pathologic study of crescentic glomerulonephritis in 50 children. *Kidney Int* 27:450–458
181. Srivastava RN, Moudgil A, Bagga A, Vasudev AS, Bhuyan UN, Sundraem KR (1992) Crescentic glomerulonephritis in children: a review of 43 cases. *Am J Nephrol* 12:155–161
182. Baldwin DS, Gluck MC, Schacht RG, Gallo G (1974) The long-term course of poststreptococcal glomerulonephritis. *Ann Intern Med* 80:342–358
183. Drachman R, Aladjem M, Vardy PA (1982) Natural history of an acute glomerulonephritis epidemic in children. An 11- to 12-year follow-up. *Isr J Med Sci* 18:603–607
184. Nissenson AR, Mayon-White R, Potter EV, Mayon-White V, Abidh S, Poon-King T, Earle DP (1979) Continued absence of clinical renal disease seven to 12 years after poststreptococcal acute glomerulonephritis in Trinidad. *Am J Med* 67:255–262
185. Potter EV, Abidh S, Sharrett AR, Burt EG, Svartman M, Finklea JF, Poon-King T, Earle DP (1978) Clinical healing two to six years after poststreptococcal glomerulonephritis in Trinidad. *N Engl J Med* 298:767–772
186. Baldwin DS (1977) Poststreptococcal glomerulonephritis. A progressive disease? *Am J Med* 62:1–11
187. Schacht RG, Gluck MC, Gallo GR, Baldwin DS (1976) Progression to uremia after remission of acute poststreptococcal glomerulonephritis. *N Engl J Med* 295:977–981
188. Bergner-Rabinowitz S, Ferne M (1978) Type distribution of beta-hemolytic streptococci in Israel: a 10-year study. *J Infect Dis* 138:152–159
189. Lasch EE, Frankel V, Vardy PA, Bergner-Rabinowitz S, Ofek I, Rabinowitz K (1971) Epidemic glomerulonephritis in Israel. *J Infect Dis* 124:141–147
190. Dale JB (2008) Current status of group A streptococcal vaccine development. *Adv Exp Med Biol* 609:53–63
191. Dale JB, Penfound T, Chiang EY, Long V, Shulman ST, Beall B (2005) Multivalent group A streptococcal vaccine elicits bactericidal antibodies against variant M subtypes. *Clin Diagn Lab Immunol* 12:833–836
192. Sanjad S, Tolaymat A, Whitworth J, Levin S (1977) Acute glomerulonephritis in children: a review of 153 cases. *South Med J* 70:1202–1206
193. Popović-Rolović M, Kostić M, Antić-Peco A, Jovanović O, Popović D (1991) Medium- and long-term prognosis of patients with acute poststreptococcal glomerulonephritis. *Nephron* 58:393–399
194. Herthelius M, Berg U (1999) Renal function during and after childhood acute poststreptococcal glomerulonephritis. *Pediatr Nephrol* 13:907–911
195. Kasahara T, Hayakawa H, Okubo S, Okugawa T, Kabuki N, Tomizawa S, Uchiyama M (2001) Prognosis of acute poststreptococcal glomerulonephritis (APSGN) is excellent in children, when adequately diagnosed. *Pediatr Int* 43:364–367

Copyright of Pediatric Nephrology is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.