10.2478/inmed-2022-0208

CLINICO-PATHOLOGICAL CORRELATIONS OF POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Marilena Stoian[1,2], Gabriel Scarlat[1], Bassil Dona[1], Bianca Procopiescu[1], Claudia Ciofu[1,2]
[1]Dr. I.Cantacuzino Hospital
[2]Carol Davila University of Medicine Bucharest, Romania

Abstract

Postinfectious glomerulonephritis is associated with bacterial, viral, fungal, and parasitic infectious agents and histologically appears most often as acute diffuse endocapillary or proliferative glomerulonephritis secondary infection with: group A streptococcus, streptococcus viridans, staphilococus aureus, diploccocus pneumoniae, Brucella melitensis, Salmonella typhi, Yershinia enterocolitica, Plasmodium falciparum, meningococcus, Mycoplasma, Klebsiella, varicella, variola, mumps.

Less commonly, it appears as diffuse crescentic glomerulonephritis and a lot of infectious causes are incriminated like: streptococcus, legionella, varicella, Treponema pallidum or as focal crescentic glomerulonephritis: streptococcus A. It rarely appears as mesangiocapillary glomerulonephritis secondary infection with: streptococcus viridans, hepatitis C virus; diffuse or focal mesangial proliferative glomerulonephritis: hepatitis B virus, salmonella, adenovirus, influenza virus, salmonella; focal segmental, necrotizing and sclerosing glomerulonephritis: bacterial endocarditis; membranous glomerulonephritis: hepatitis B virus, syphilis, filarial, Mycobacterium, plasmodium falciparum; focal proliferative: Mycoplasma; mesangiolytic glomerulonephritis :Echo virus.

Poststreptococcal glomerulonephritis (PSGN) is caused by prior infection with specific nephritogenic strains of group A beta-hemolytic streptococcus. The clinical presentation of PSGN varies from asymptomatic, microscopic hematuria to the full-blown acute nephritic syndrome, characterized by red to brown urine, proteinuria (which can reach the nephrotic range), edema, hypertension, and acute kidney injury. The prognosis is generally favorable, especially in children, but in some cases, the long-term prognosis is not benign. Managing a case of PSGN requires cooperation between internists, nephrologists, infectious disease consultants, pharmacists, and nursing staff, functioning as an interprofessional team, to provide excellent care for their patients.

Keywords: *poststreptococcal glomerulonephritis, haematuria, immunofluorescence, nephritic syndrome.*



Internal Medicine

General Reviews

Rezumat

Glomerulonefrita postinfecțioasă este asociată cu agenți infecțioși bacterieni, virali, fungici și parazitici și, histologic, apare cel mai adesea ca glomerulonefrită acută difuză endocapilară sau proliferativă secundară infecției cu: streptococ de grup A, streptococ viridans, staphilococus aureus, diploccocus pneumoniae, Brucella melitensis, Salmonella typhi, Yershinia enterocolitica, Plasmodium falciparum, meningococ, Mycoplasma, Klebsiella, varicelă, variolă, oreion.

Mai rar, apare ca glomerulonefrită crescentică difuză și sunt incriminate numeroase cauze infecțioase precum: streptococ, legionella, varicela, Treponema pallidum sau ca glomerulonefrită crescentică focală: streptococ A. Rareori apare sub formă de glomerulonefrită mezangiocapilară secundară infecției cu: streptococcus viridans, virusul hepatitei C; glomerulonefrită proliferativă mezangială difuză sau focală: virusul hepatitei B, salmonela, adenovirusul, virusul gripal, salmonella; glomerulonefrită necrozantă și sclerozantă focală segmentară: endocardită bacteriană; glomerulonefrită membranoasă: virusul hepatitei B, sifilisul, filaria, Mycobacterium, plasmodium falciparum; focal proliferativă: Mycoplasma; glomerulonefrita mesangiolitică: Echo virus.

Glomerulonefrita poststreptococică (PSGN) este cauzată de infecția anterioară cu tulpini nefritogenice specifice de streptococ beta-hemolitic de grup A. Prezentarea clinică a PSGN variază de la hematurie asimptomatică, microscopică până la sindromul nefritic acut în general, caracterizat prin urină roșie spre maro, proteinurie (care poate ajunge în intervalul nefrotic), edem, hipertensiune arterială și leziune renală acută. Prognosticul este în general favorabil, mai ales la copii, dar în unele cazuri, prognosticul pe termen lung nu este benign. Gestionarea unui caz de PSGN necesită cooperare între medici internişti, nefrologi, specialiști de boli infecțioase, farmaciști și personalul de asistență medicală, funcționând ca o echipă interprofesională, pentru a oferi îngrijiri adecvate pacienților.

Cuvinte cheie: *glomerulonefrită poststreptococică, hematurie, imunofluorescență, sindrom nefritic.*

Epidemiology of Poststreptococcal Glomerulonephritis

Although PSGN continues to be the most common cause of acute nephritis in children globally, it primarily occurs in developing countries. Of the estimated 470,000 new annual cases of PSGN worldwide, 97 percent occur in regions of the world with poor socioeconomic status, with an annual incidence that ranges from 9.5 to 28.5 per 100,000 individuals[1,2].

In more developed and industrialized countries, the incidence has continued to decrease from the 1970s to the 1990s[2-4]. Based upon data from the Italian Registry of Renal Biopsies, the estimated annual incidence was 0.3 per 100,000 individuals between 1992 and 1994[5].

The reasons may include the easier access to the treatment of streptococcal infections and the widespread presence of fluoride in water, which decreases virulence factors of Streptococcus pyogenes[6]. The risk of PSGN is increased in older patients (greater than 60 years of age) and in children between 5 and 12 years of age[5,7]. PSGN is uncommon in children less than three years of age. PSGN is twice as frequent in males as in females[8,9].

Poststreptococcal glomerulonephritis (PSGN) is the most common form of postinfectious glomerulonephritis. It affects mostly children after an infective episode or a skin infection with a latent period of 2-6 weeks. It`s incidence is lower in western (10- 40%) than eastern (40%) countries.

Poststreptococcal glomerulonephritis may be asymptomatic (subclinical) or may present with haematuria (100%), proteinuria (80-92%) ,edema (75-90%), hypertension (60-80%), oliguria (10-58%), and other symptoms (heat failure, nephritic syndrome, azotaemia) manifested more often in elderly patients. Low serum complement is found in over 90% of cases of poststreptococcal glomerulonephritis. Indications for renal biopsy are massive proteinuria, normal serum complement levels or persistent low levels and progressive increase in serum creatinine levels.

Pathogenesis of poststreptococcal glomerulonephritis

First step of the pathological mechanisms of post streptococcal glomerulonephritis is the incorporate in GBM of streptococcal antigens, which is gradually released during infection.[10].

A transient acute poststreptococcal glomerulonephritis has been induced in rabbits by infection with streptococci bearing the nephritis strain-associated protein (NSAP), which was then found in the glomerular deposits[11,12].

SAP is considered to have nephrotoxic properties and can covert plasminogen to plasmin.Streptoccocal M-protein shows cross-reactivity to GBM, binds to fibrinogen and localizes in the glomeruli.Endostreptosin may act as planted antigen and has been found in glomeruli during the early phase of the disease in association with high titers of circulating antibody.Nephritogenic streptococcal streptokinase can be found into renal tissue and facilitate further antigen planting via certain molecular domains. Streptococci trigger as autoimmune complex disease by releasing enzymes, such as neuraminidase[13,14,15].

Circulating or in situ-formed immune complexes containing streptococcal antigens are deposited within glomeruli. Plasmin, converted by NSAP, activates the alternate pathway of complement; low serum complement is a sign of ongoing antigen-antibody reactions. Streptococcal

neuraminidase causes depletion of sialic acid and renders normal IgG autoimmunogenic; this altered IgG stimulates the production of anti-IgG antibody and the formation of IgG-antiIgG complexes.

Cell-mediated mechanisms play an important role in maintaining the glomerular lesion. The patient s lymphocytes can activate normal human immunoglobulin while the monocytes exhibit increased secretion of IL1 and TNF alpha. There is also elevated concentration of monokine (e.g.IL8) in the patient s urine.Nephritogenic streptococcal proteins can alter the normal composition of GBM so that new GBM antigens are found.Antobodies of these antigens can sensitize T lymphocytes to develop specificity for these new GBM antigens (Figure 1).

Histopathology of Poststreptococcal Glomerulonephritis

Light Microscopy

All glomeruli are affected by infiltration initially of polymorphonuclear and in later stages of mononuclear leucocytes and CD4+ T lymphocytes. In addition, there is activation and proliferation of endothelial cells and, to a lesser degree, of mesangial and epithelial cells. All these transient and native cells occlude the capillary luminal and enlarge the glomerulus, producing expansion of its lobularity. The capillary walls are segmentally thickened. Under high power magnification, tiny subepithelial fuchinophilic dots can be identified on thin paraffin and plastic semi-thin sections. In some patients focal crescent formation may be found.

Tubular changes are not usually pronounced, unless there is florid glomerular involvement. Vacuolation of the proximal tubular epithelial cells, intraluminal erythrocytes, polymorphs and casts, focal tubulitis, dilation and atrophy can be observed. Interstitial involvement is variable, but usually not remarkable. Edema and focal inflammation may be found (Figure 1, Figure 2).

Immunofluorescence

Immunofluorescence reveals coarse granular deposits of C3 (predominantly) and IgG or IgM on the glomerular capillary wall and sometimes in the mesangium early in the course of the disease (“starry sky “pattern).These deposits may be densely packed or confluent or look linear in some areas of GBM (“garland” pattern).Latter, C3 deposits are confined to mesangial areas (mesangial pattern).In a few cases linear deposition of IgG and C3 on TBM has been described when severe tubular damage was accompanying PSGN (Figure 3).

Electron Microscopy

Electron microscopic examination reveals

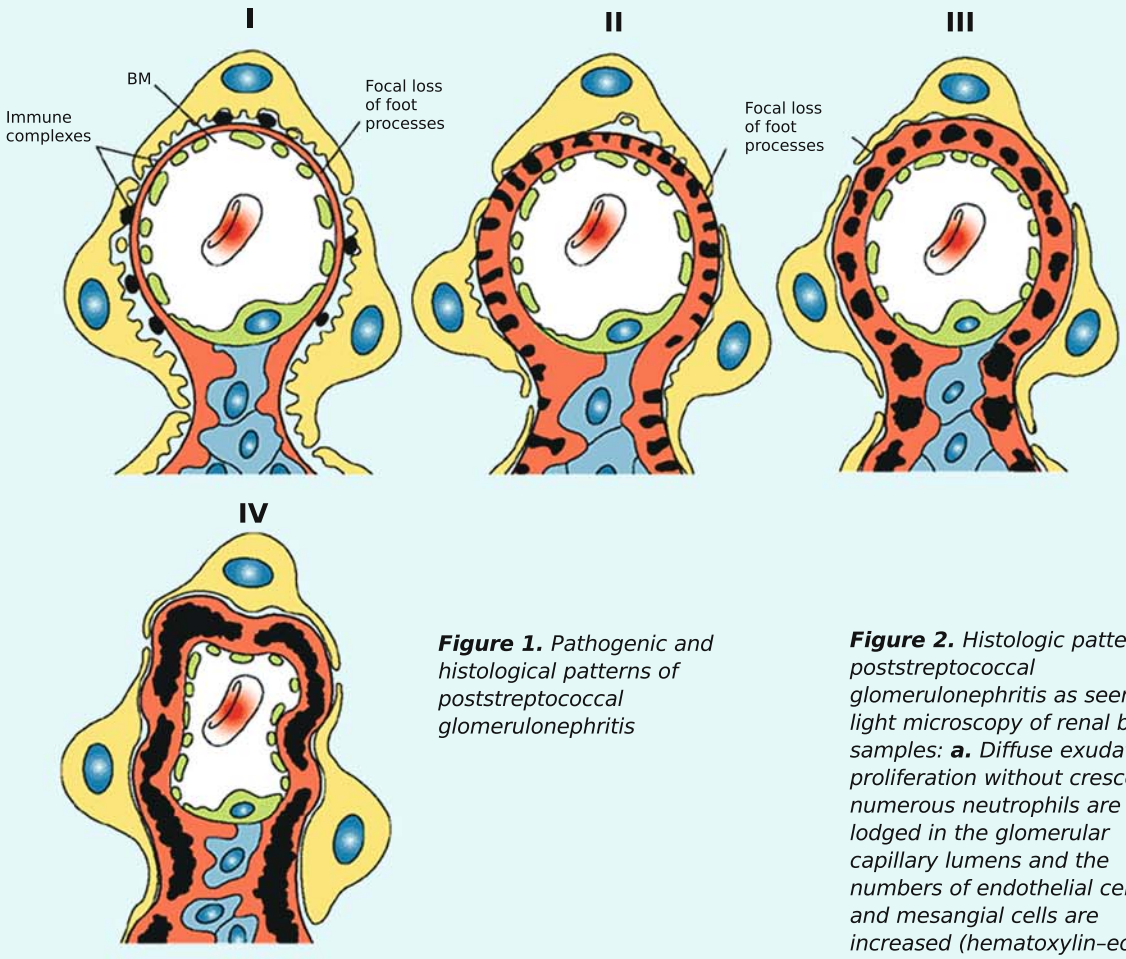


Figure 1. *Pathogenic and histological patterns of poststreptococcal glomerulonephritis*

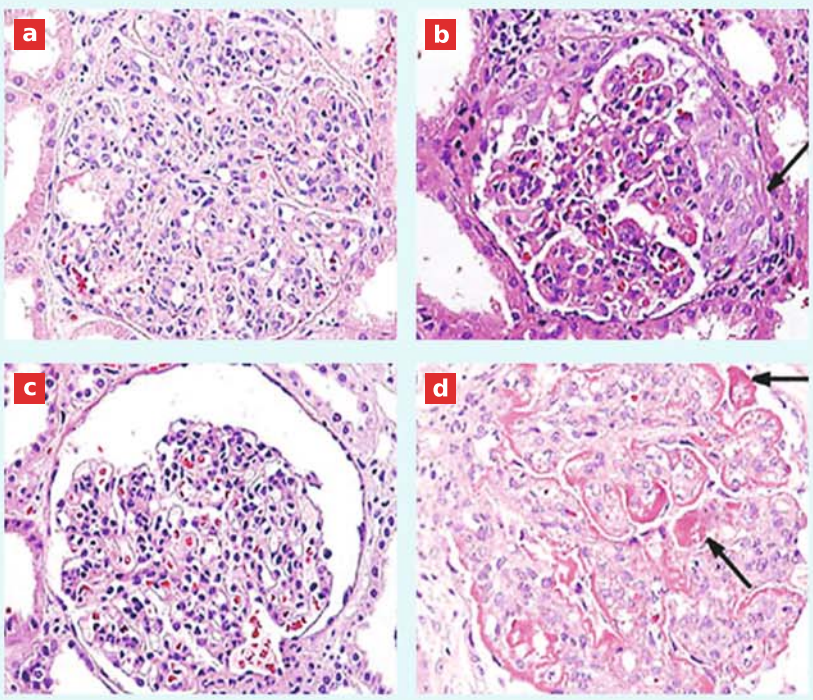
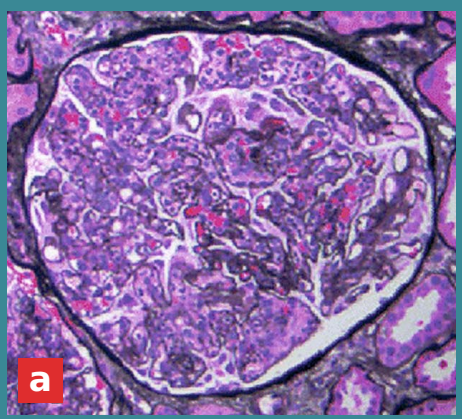
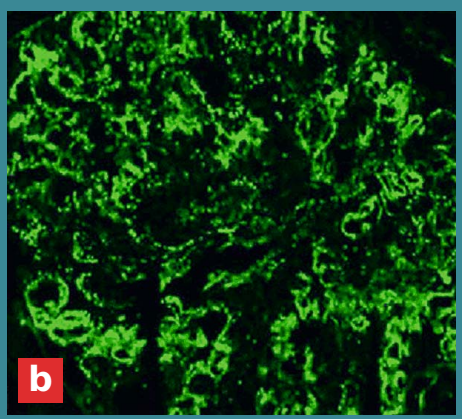


Figure 2. *Histologic patterns of poststreptococcal glomerulonephritis as seen on light microscopy of renal biopsy samples:* ***a.*** *Diffuse exudative proliferation without crescents: numerous neutrophils are lodged in the glomerular capillary lumens and the numbers of endothelial cells and mesangial cells are increased (hematoxylin–eosin stain; magnification 400).* ***b.*** *Diffuse endocapillary proliferation with segmental crescents: a segmental cellular crescent (arrow) has compressed the glomerular tuft; the tuft is filled with leukocytes and proliferating endothelial cells (hematoxylin–eosin stain; magnification 400).* ***c.*** *Mesangial proliferation: the mesangium is prominent, with increased cellularity. A few neutrophils can be seen in some capillary lumens (hematoxylin–eosin stain; magnification 400).* ***d.*** *Membranoproliferative glomerulonephritis: prominent lobulation is observed, with confluent deposition of eosinophilic material (arrows) along the capillary wall. Infiltrating neutrophils are present (hematoxylin–eosin stain; magnification 400).*





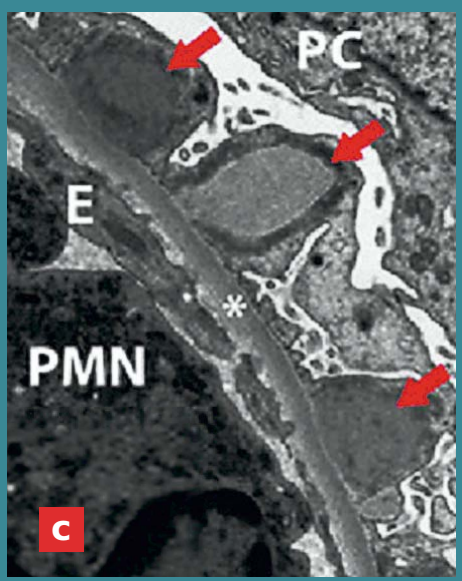


Figure 3. *Poststreptococcal glomerulonephritis*

a. Light microscopy: *global endocapillary hypercellularity/proliferation with prominent influx of inflammatory cells, including many neutrophils in capillary lumina and swollen endothelial cells (Jones methenamine silver stain, 40Â objective).*
b. Immunofluorescence: *Coarse granular pattern of C3 deposition in peripheral capillary walls and mesangial regions of a glomerulus, showing in some areas a "starry sky" pattern.*
c. Electron microscopy: *Characteristic subepithelial hump-like deposits (arrows) over the subepithelial aspect of the glomerular basement membranes (asterisk). Abbreviations: PMN polymorphonuclear, PC podocyte, E endothelial cell (11,000Â)*

glomerular subepithelial bulging, electron dense deposits (humps) numerous in the first few weeks and gradually resolving and disappearing within 6 weeks.

Some intramembranous (lamina densa), subendothelial, mesangial and along Bowman s capsule dense deposits may also be seen. Endothelial cells are disrupted and polymorphs are adjacent to the denuded GBM, which may show rare gaps (Figure 3)[16].

Clinicopathological correlations and clinical outcome

Increased glomerular hypercellularity is correlated with low glomerular filtration rate, very low levels of serum complement, an increase in number of humps, and a more protracted clinical picture. Subendothelial deposits are not associated with any particular findings in the urine. Garland deposits are most often observed in patients with severe proteinuria or nephritic syndrome.

Starry sky deposits are seen in early cases in association with increased cellularity: some of them correspond to subendothelial electron dense deposits). Mesangial deposits are related to the resolving stage of poststreptococcal glomerulonephritis and to the subsequent mesangial proliferation.

Acute poststreptococcal glomerulonephritis may change to a membranoproliferative pattern or may be transformed to membranous glomerulonephritis, especially when associated with severe infections. The last form of poststreptococcal glomerulonephritis is the most significant lesion correlated with poor outcome when crescents are large and affect more than 40% of the glomeruli and there is global glomerulosclerosis and interstitial fibrosis. The severity of the tubulointerstitial damage is correlated with increasing of serum creatinine levels. Arterial and arteriolar sclerosis contributes to an unfavorable prognosis (as it happens in other diseases).

Complete clinical and morphological recovery has been observed in children (92%) and adult in 60%.

There are patients that continue to have proteinuria, haematuria, hypertension, and renal failure for several months or years; in those cases the histology usually shows mesangial hypercellularity or a chronic form of glomerulonephritis. End stage renal disease is the aftermath of a crescentic or complicated chronic glomerulonephritis. However, death from renal or cardiac failure, hypertensive encephalopathy, or infection itself can occur. The mortality rate is higher in adult (5-9%) than in children (1%)[17,18,19].

Conclusion

Poststreptococcal glomerulonephritis is an immune-complex mediated renal disease with significant participation of cellular immunity with a favorable prognosis for the majority of patients: the prognosis in children is excellent but adults tend to have a protracted course with at least 30 to 50% developing renal dysfunction and hypertension.[20]

Managing a case of PSGN requires cooperation between internists, nephrologists, infectious disease consultants, pharmacists, and nursing staff, functioning as an interprofessional team, to provide excellent care for their patients.

References

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005; 5:685.

2. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol 2008; 19:1855.



Internal Medicine

General Reviews

3. Zhang Y, Shen Y, Feld LG, Stapleton FB. Changing pattern of glomerular disease at Beijing Children's Hospital. Clin Pediatr (Phila) 1994; 33:542.

4. Roy S 3rd, Stapleton FB. Changing perspectives in children hospitalized with poststreptococcal acute glomerulonephritis. Pediatr Nephrol 1990; 4:585.

5. Coppo R, Gianoglio B, Porcellini MG, Maringhini S. Frequency of renal diseases and clinical indications for renal biopsy in children (report of the Italian National Registry of Renal Biopsies in Children). Group of Renal Immunopathology of the Italian Society of Pediatric Nephrology and Group of Renal Immunopathology of the Italian Society of Nephrology. Nephrol Dial Transplant 1998; 13:293.

6. Thongboonkerd V, Luengpailin J, Cao J, et al. Fluoride exposure attenuates expression of Streptococcus pyogenes virulence factors. J Biol Chem 2002; 277:16599.

7. Blyth CC, Robertson PW, Rosenberg AR. Post-streptococcal glomerulonephritis in Sydney: a 16-year retrospective review. J Paediatr Child Health 2007; 43:446.

8. Lewy JE, Salinas-Madrigal L, Herdson PB, et al. 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) 1971; 50:453.

9. Rodriguez-Iturbe B. Postinfectious glomerulo-nephritis. Am J Kidney Dis 2000; 35: XLVI.

10. Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int 2007; 71:1094.

11. Oda T, Yoshizawa N, Yamakami K, et al. Localization of nephritis-associated plasmin receptor in acute poststreptococcal glomerulonephritis. Hum Pathol 2010; 41:1276.

12. Oda T, Tamura K, Yoshizawa N, et al. Elevated urinary plasmin activity resistant to alpha2-antiplasmin in acute poststreptococcal glomerulonephritis. Nephrol Dial Transplant 2008; 23:2254.

13. Cu GA, Mezzano S, Bannan JD, Zabriskie JB. Immunohistochemical and serological evidence for the role of streptococcal proteinase in acute post-streptococcal glomerulonephritis. Kidney Int 1998; 54:819.

14. Poon-King R, Bannan J, Viteri A, et al. Identification of an extracellular plasmin binding protein from nephritogenic streptococci. J Exp Med 1993; 178:759.

15. Batsford SR, Mezzano S, Mihatsch M, et al. Is the nephritogenic antigen in post-streptococcal glomerulonephritis pyrogenic exotoxin B (SPE B) or GAPDH? Kidney Int 2005; 68:1120.

16. McCluskey RT, Vassalli P, Gallo G, Baldwin DS. An immunofluorescent study of pathogenic mechanisms in glomerular diseases. N Engl J Med. 1966 Mar 31. 274(13):695-701

17. Hoy WE, White AV, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. Kidney Int 2012; 81:1026.

18. Pinto SW, Sesso R, Vasconcelos E, et al. Follow-up of patients with epidemic poststreptococcal glomerulo-nephritis. Am J Kidney Dis 2001; 38:249.

19. Wong W, Lennon DR, Crone S, Neutze JM, Reed PW. Prospective population-based study on the burden of disease from post-streptococcal glomerulonephritis of hospitalised children in New Zealand: epidemiology, clinical features and complications. J Paediatr Child Health. 2013 Oct. 49(10):850-5

20. Zaffanello M,Cataldi L,Franchini M,Fanos V, Evidence-based treatment limitations prevent any therapeutic recommendation for acute poststreptococcal glomerulo-nephritis in children. Medical science monitor: international medical journal of experimental and clinical research. 2010 Apr