Infection-Related Glomerulonephritis: A Literature Review

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ABSTRACT

Glomerulonephritis (GN) is a term used to describe a set of immune-mediated kidney conditions that influence the glomeruli. This literature review aimed to presents the current literature on Infection-related GN epidemiology, pathophysiology, diagnosis, and treatment. Over the past decades, the epidemiology of IRGN has changed dramatically, including aspects such as incidence, geography, disease burden, age distribution, comorbidities, gender distribution, prognosis, and microbiology. Early diagnosis and timely treatment of IRGN are critical as they may prevent kidney damage. Therapeutic approach followed in many cases, including antibiotics, surgical intervention, immunosuppressive therapy, renin-angiotensin system blockade, sodium glucose co transporter 2 inhibitor, supportive therapy, and renal replacement therapy. Although the overall incidence of IRGN has declined due to improved living standards, access to antibiotics, and the health care system, it remains high in poor areas and increasingly affects adults, especially elderly patients with comorbidities. The pathophysiology of IRGN is predominantly based on the deposition of complement with or without bound immunoglobulins, followed by an immune and inflammatory reaction. Early diagnosis and timely treatment of IRGN can prevent kidney damage. Diagnosing IRGN by clinical features alone is insufficient because it is common in diverse GN classifications. Renal biopsy stays the gold standard for diagnosis, including the detection of subepithelial humps on electron microscopy. The IRGN treatment focuses on eradicating infection, managing complications, supportive care and immunosuppressive therapy in selected cases.

Keywords: Glomerulonephritis; Infection; Kidney; Literature

INTRODUCTION

Glomerulonephritis (GN) is a term used to describe a set of immune-mediated kidney conditions that influence the glomeruli [1]. The natural function of the glomeruli as high-flow filters results in various GN causalities because they are susceptible to different reasons for inflammatory damage [2]. Inappropriately treated GN can progress to irreversible kidney damage and could lead to chronic kidney disease (CKD) [3, 4], leading to the necessity for renal replacement therapy (RCT), including kidney transplantation or dialysis [5].

Since the mid-18th century, it has been known that infections are associated with kidney disease [6, 7]. A wide range of infections can cause GN [7, 8]. After non-renal infection, the classic type of immunologically mediated infection-associated GN is post-infectious GN (PIGN) [9]. Numerous microorganisms, such as parasites, fungi, viruses, bacteria, and microbes can result in PIGN [7, 10-12]. Symptoms of PIGN include hypertension, edema, mild to moderate proteinuria, and hematuria, with a latent duration after infection. PIGN may progress to CKD in some patients and in rare cases PIGN may also worsen rapidly [13].

The prototype for PIGN is acute post-Streptococcal GN (APSGN), which is linked with a prior infection of the throat or skin with group A Streptococcus or periodically Streptococcus groups G or C [14]. In recent years, the term PIGN has been replaced by infection-related GN (IRGN) [15]. IRGN includes not only PIGN, but also shunt nephritis, endocarditis-associated GN, and immunoglobulin Ig A-dominant PIGN [6, 16].

Over the past thirty years, there has been a change in the immunofluorescence (IF) spectrum, histopathology, clinical presentation, etiological factors, and epidemiology of IRGN, which has led to a change in its result [15]. Besides, studies have shown that typically represented PSGN can differ extensively from the IRGN biopsy findings and IRGN clinical characteristics. Physicians may face a challenge in treating and diagnosing IRGN cases due to their histologic variants, including emerging variants like C3 GN (C3GN) [17]. Thus, the variety of GN pathologies and the absence of a straightforward rational category to support these GN types result in challenges in teaching, learning, treating, and understanding GNs [2]. Considering the above challenges, this review aimed to study IRGN epidemiology, pathophysiology, diagnosis, and treatment.

EPIDEMIOLOGY

Over the past decades, the epidemiology of IRGN has changed dramatically, including aspects such as incidence, geography, disease burden, age distribution, comorbidities, gender distribution, prognosis, and microbiology (Table 1). Patients affected by these IRGN epidemiological changes are at increased risk of poor kidney consequences, so adequate knowledge of these changes is essential [21]. Therefore, enhancing understanding of acute GN in vulnerable groups is crucial in lessening the prospective burden of this condition [4].

PATHOPHYSIOLOGY

The pathogenesis of IRGN highly relies on complement deposition with linked immunoglobulins or without it, followed by the immune and inflammatory reaction [16]. Firstly, the microbial antigen triggers an antibody response during infection, which leads to the formation of an immune complex within glomeruli, either in situ immune or circulating immune complex [7]. These immune complexes interact with glomerular cells, initiating an inflammatory response that activates complementary pathways [46]. The activation complements system causes damaging glomerular basement membrane (GBM) and glomerular endothelial cells resulting in subepithelial humps formations [7, 46, 47]. Besides

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Table 1. Epidemiology of IRGN

Epidemiological aspect	Description	References
Global incidence	The overall incidence of IRGN has declined due to improved living standards, access to antibiotics, the health care system, etc.	4, 12, 14, 18-24
Geographic differences	IRGN cases are still high in economically disadvantaged regions while they decrease in the developed areas.	4, 12, 14, 18, 20, 22, 25
Subclinical incidence	Clinically apparent IRGN cases are at least 4-fold less prevalent than subclinical IRGN cases, which implies that the correct incidence is higher than reported.	20, 23, 26
Global disease burden	IRGN accounts for approximately 5% of global glomerular disease cases, with a higher percentage in development areas.	27
Historical age distribution	It mainly affects children, especially after Streptococcal infection.	15, 28
Current age distribution	It increasingly impacts adults, particularly elderly patients with comorbidities.	9, 15, 21, 28
Comorbidities	Obesity, other immunocompromised conditions, malignancy, hypertension, liver disease, diabetes mellitus, rise prolonged utilization of central lines and indwelling catheters, etc.	21, 29-33
Gender distribution	Women are at a two times decreased risk of developing IRGN compared to men.	34, 35
Prognosis	Most adult cases progress to ESRD and CKD (poorer prognosis than children).	28, 36
Microbial shift	A shift from dominated by Streptococcus to dominated by Staphylococcus aureus, including MRSA.	15, 24, 29, 31, 33, 36-45
Microbial shift risk factors	Iatrogenic risk factors and lifestyle changes.	30, 32

IRGN, infection-related glomerulonephritis; ESRD, end-stage renal disease; CKD, chronic kidney disease; MRSA, methicillin-resistant Staphylococcus aureus.

Table 2. Treatment of IRGN

Therapeutic approach	Description	References
Antibiotics	The disease burden can be decreased by prescribing proper antibiotics guided by sensitivity and culture.	21
Surgical intervention	Surgical intervention may be necessary in some cases, and it even aids in decreasing the IRGN burden.	21
Immunosuppressive therapy	Immunosuppressants are generally not recommended for the treatment of IRGN as they may have adverse consequences due to their capability to deplete the body's defenses. However, immunosuppressants should be administered early to maintain kidney function in rapid progressive GN.	1, 27, 57
Supportive therapy	Supportive therapy is among the principal treatments in preponderance IRGNs. Targeted anti-viral and antibiotics are required for treating specific IRGNs.	56
RRT	RRT is used to treat complications such as uremic symptoms, pulmonary edema, and hyperkalemia in some cases when the patient has rapidly progressive kidney failure.	21
Renin-angiotensin system blockade/ sodium glucose co transporter 2 inhibitors	Renin-angiotensin system blockade/ sodium glucose co transporter 2 inhibitors is recommended to treat persistent heavy or moderate proteinuria as it declines disease progression. However, potassium levels and serum creatinine must be monitored.	21

IRGN, infection-related glomerulonephritis; RRT, renal replacement therapy.

subepithelial humps, interstitial changes or acute tubular necrosis may be formations depending on the severity and nature of the infection [7]. Besides the classical complement activations, the development of IRGN also encompasses coagulation cascade activations, recruitment of leukocytes to the injury site, and the production of proinflammatory factors and various cytokines [46].

AA amyloidosis can result from a persistent infection in infrequent cases [2]. The prior studies also highlight specific pathogens-related mechanisms:

Post-Streptococcal GN (PSGN): group A β-hemolytic Streptococci antigens result in complement activation by producing ani-factors B antibodies or directly [2].

Viruses (severe acute respiratory syndrome coronavirus 2, parvovirus B19, arbovirus, Epstein Barr virus, or human immunodeficiency virus (HIV)): these viruses result in podocytopathy by infecting podocytes [2].

Immunodeficiencies-related GN: IRGN results from circulating immune complexes deposition among patients with iatrogenic or acquired immunodeficiencies [2, 48].

DIAGNOSIS

Early diagnosis and timely treatment of IRGN are critical as they may prevent kidney damage [27]. However, specific diagnostic biomarkers for IRGN have not been identified yet, making rapid diagnosis difficult [49]. Also, recognizing IRGN by clinical features alone, including hypertension, edema, abnormal kidney function, proteinuria, and/or hematuria [50], is insufficient as these features are prevalent in different types of GN [1]. GN is associated with abnormal cellular elements; urine microscopy can help identify these factors [51]. Still, a kidney biopsy remains essential for GN diagnosis and is the gold standard for diagnosis [1, 51]. In renal biopsy specimens, identification of subepithelial humps "ultrastructural hallmark of IRGN" on electron microscopic significantly improves diagnosis trust [16].

The following diagnostic criteria for IRGN were suggested by a prior minireview, with a positive diagnosis requiring at least three of the five items [34]: "(1) clinical or laboratory evidence of infection preceding or at the onset of glomerulonephritis, (2) depressed serum complement, (3) endocapillary proliferative and exudative glomerulonephritis, (4) C3-dominant or codominant glomerular IF staining, and (5) hump-shaped subepithelial deposits on electron microscopy."

An invasive diagnostic procedure known as kidney biopsy (KB) is designed to identify kidney diseases and determine the appropriate course of treatment to prevent the progression to chronic kidney disease and end-stage kidney disease. Currently, there is a general consensus that KB is not contraindicated for elderly individuals aged 60–65. The risk of complications, particularly bleeding, is the primary reason for the widespread reluctance to perform KB in very geriatric patients. However, these patients may also benefit from optimal therapeutic strategies. In elderly patients, the diagnosis of IRGN may be challenging because comorbidities may obscure the underlying infection; patients present with nonspecific manifestations related to pre-existing comorbidities rather than IRGN manifestations [30, 52, 53].

TREATMENT

The main therapeutic goal of IRGN treatment is the eradication of infection [51, 54, 55]. Treatment also includes managing complications [21, 27] and supportive therapy [56]. Immunosuppressive therapy may be indicated in specific cases. Previous studies have identified the therapeutic approach followed in many cases, including antibiotics, surgical intervention, immunosuppressive therapy, renin-angiotensin system blockade, sodium glucose co transporter 2 inhibitor, supportive therapy, and renal replacement therapy (Table 2).

CONCLUSION

Although the overall incidence of IRGN has declined due to improved living standards, access to antibiotics, and the health care system, it remains high in poor areas and increasingly affects adults, especially elderly patients with comorbidities. In addition, most cases of IRGN in adults progress to CKD and ESRD. The pathophysiology of IRGN is predominantly based on the deposition of complement with or without bound immunoglobulins, followed by an immune and inflammatory reaction. Early diagnosis and timely treatment of IRGN can prevent kidney damage. Diagnosing IRGN by clinical features alone is insufficient because it is common in diverse GN classifications. The IRGN treatment focuses on eradicating infection, managing complications, supportive care and immunosuppressive therapy in selected cases. Early detection and treatment, as well as regular monitoring of at-risk populations, can prevent many adverse events and prognoses associated with IRGN. Further research is recommended to improve diagnostic and treatment strategies and thus reduce the IRGN burden, especially among at-risk populations.

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REFERENCES

1. Kaartinen K, Safa A, Kotha S, et al. Complement dysregulation in glomerulonephritis. Semin Immunol 2019; 45(1): 1-10
2. Romagnani P, Kitching AR, Leung N, et al. The five types of glomerulonephritis classified by pathogenesis, activity and chronicity (GN-AC). Nephrol Dial Transplant 2023; 38(1): 3-10.
3. Global regional and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395(1): 709-33.
4. Guo Q, Wu S, Xu C, et al. Global Disease Burden From Acute Glomerulonephritis 1990-2019. Kidney Int Rep 2021; 6(1): 2212-7.
5. Anders HJ, Kitching AR, Leung N, et al. Glomerulonephritis: immunopathogenesis and immunotherapy. Nat Rev Immunol 2023; 23(1): 453-71.
6. Gupta P, Gupta RK. Infection Related Glomerulonephritis (IRGN). Atlas Clin Case St 2022; 1(1): 67-75.
7. Malaga-Dieguez L. Infection-Associated Glomerulonephritis. Cham 2018; 1(1): 1-14.
8. Rodríguez-Iturbe B, Burdmann EA, Barsoum RS. Glomerular diseases associated with infection. Comp clin nephro 2010; 662(1): 1-17.
9. Nast CC. Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis 2012; 19(1): 68-75.
10. Duong MD, Reidy KJ. Acute Postinfectious Glomerulonephritis. Pediatr Clin North Am 2022; 69(1): 1051-78.
11. Roy S, Wall HP, Etteldorf JN. Second attacks of acute glomerulonephritis. J Pediatr 1969; 75(1): 758-67.
12. Carapetis JR, Steer AC, Mulholland EK, et al. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005; 5(1): 685-94.
13. Sethi S, De Vriese AS, Fervenza FC. Acute glomerulonephritis. Lancet 2022; 399(1): 1646-63.
14. Rodriguez-Iturbe B, Haas M. Post-streptococcal glomerulonephritis. Health Sci 2016; 1(1): 1-16.
15. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. Kidney Int 2013; 83(1): 792-803.
16. Khalighi MA, Chang A. Infection-Related Glomerulonephritis. Glomerular Dis 2021; 1(1): 82-91.
17. Chamarthi G, Clapp WL, Bejjanki H, et al. Infection-related Glomerulonephritis and C3 Glomerulonephritis - Similar Yet Dissimilar: A Case Report and Brief Review of Current Literature. Cureus 2020; 12(1): 1-17.
18. World Health Organization. A review of the technical basis for the control of conditions associated with group A streptococcal infections [Internet]. 2005 [accessed October 07, 2024]. Avaliable from: https://iris.who.int/handle/10665/69064
19. Swaminathan S, Leung N, Lager DJ, et al. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. Clin J Am Soc Nephrol 2006; 1(1): 483-7.
20. Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol 2009; 5(1): 259-69.
21. Thomas E, VP AR, Issac R, et al. Clinicopathological profile of patients with infection related glomerulonephritis in a tertiary care centre. Int J Acad Med Pharm 2023; 5(1): 103-7.
22. World Health Orgnization. The current evidence for the burden of group A streptococcal diseases [Internet]. 2005 [accessed October 07, 2024]. Available from: https://iris.who.int/bitstream/handle/10665/69063/WHO_FCH_CAH_05.07.pdf.

23. Ilyas M, Tolaymat A. Changing epidemiology of acute post-streptococcal glomerulonephritis in Northeast Florida: a comparative study. Pediatr Nephrol 2008; 23(1): 1101-6.
24. Oda T, Yoshizawa N. Factors Affecting the Progression of Infection-Related Glomerulonephritis to Chronic Kidney Disease. Int J Mol Sci 2021; 22(1): 1-18.
25. Dagan R, Cleper R, Davidovits M, et al. Post-Infectious Glomerulonephritis in Pediatric Patients over Two Decades: Severity-Associated Features. Isr Med Assoc J 2016; 18(1): 336-40.
26. Rodríguez-Iturbe B, Rubio L, García R. Attack rate of poststreptococcal nephritis in families. A prospective study. Lancet 1981; 1(1): 401-3.
27. Prasad N, Patel MR. Infection-Induced Kidney Diseases. Front Med (Lausanne) 2018; 5(1): 327-30.
28. Jain R, Sezhiyan B, Balasubramaniyan T. Clinical profile, histopathology and outcomes of infection related glomerulonephritis in a tertiary care centre from south india-a prospective follow up study. Kid Inter Rep 2024; 9(1): 149-60.
29. Worawichawong S, Girard L, Trpkov K, et al. Immunoglobulin A-dominant postinfectious glomerulonephritis: frequent occurrence in nondiabetic patients with Staphylococcus aureus infection. Hum Pathol 2011; 42(1): 279-84.
30. Satoskar AA, Suleiman S, Ayoub I, et al. Staphylococcus Infection-Associated GN - Spectrum of IgA Staining and Prevalence of ANCA in a Single-Center Cohort. Clin J Am Soc Nephrol 2017; 12(1): 39-49.
31. Haas M, Racusen LC, Bagnasco SM. IgA-dominant postinfectious glomerulonephritis: a report of 13 cases with common ultrastructural features. Hum Pathol 2008; 39(1): 1309-16.
32. Boils CL. Endocarditis-Associated Glomerulonephritis. Cham 2017; 1(1): 87-116.
33. Nasr SH, Markowitz GS, Whelan JD, et al. IgA-dominant acute poststaphylococcal glomerulonephritis complicating diabetic nephropathy. Hum Pathol 2003; 34(1): 1235-41.
34. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. Nephron Clin Pract 2011; 119(1): 18-25.
35. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol 2008; 19(1): 1855-64.
36. Nadasdy T, Hebert LA. Infection-related glomerulonephritis: understanding mechanisms. Semin Nephrol 2011; 31(1): 369-75.
37. Chatterjee SS, Otto M. Improved understanding of factors driving methicillin-resistant Staphylococcus aureus epidemic waves. Clin Epidemiol 2013; 5(1): 205-17.
38. Tattevin P, Diep BA, Jula M, et al. Long-term follow-up of methicillin-resistant Staphylococcus aureus molecular epidemiology after emergence of clone USA300 in San Francisco jail populations. J Clin Microbiol 2008; 46(1): 4056-7.
39. Satoskar AA, Nadasdy G, Plaza JA, et al. Staphylococcus infection-associated glomerulonephritis mimicking IgA nephropathy. Clin J Am Soc Nephrol 2006; 1(1): 1179-86.
40. King MD, Humphrey BJ, Wang YF, et al. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med 2006; 144(1): 309-17.
41. DeLeo FR, Otto M, Kreiswirth BN, et al. Community-associated meticillin-resistant Staphylococcus aureus. Lancet 2010; 375(1): 1557-68.
42. Pola E, Logroscino G, De Santis V, et al. Onset of Berger disease after Staphylococcus aureus infection: septic arthritis after anterior cruciate ligament reconstruction. Arthroscopy 2003; 19(1): 29-36.
43. Pan ES, Diep BA, Carleton HA, et al. Increasing prevalence of methicillin-resistant Staphylococcus aureus infection in California jails. Clin Infect Dis 2003; 37(1): 1384-8.
44. Nimmo GR. USA300 abroad: global spread of a virulent strain of community-associated methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect 2012; 18(1): 725-34.
45. Tattevin P, Diep BA, Jula M, et al. Methicillin-resistant Staphylococcus aureus USA300 clone in long-term care facility. Emerg Infect Dis 2009; 15(1): 953-5.
46. Hunt EAK and Somers MJG. Infection-Related Glomerulonephritis. Pediatr Clin North Am 2019; 66(1): 59-72.
47. Schwartz M, Jennette J, Olson J, et al. Pathology of the kidney. Wilkins 2007; 1(1): 1-15.
48. Tavakol M, Jamee M, Azizi G, et al. Diagnostic Approach to the Patients with Suspected Primary Immunodeficiency. Endocr Metab Immune Disord Drug Targets 2020; 20(1): 157-71.
49. Uchida T, Oda T. Glomerular Deposition of Nephritis-Associated Plasmin Receptor (NAPlr) and Related Plasmin Activity: Key Diagnostic Biomarkers of Bacterial Infection-related Glomerulonephritis. Int J Mol Sci 2020; 21(1): 1-20.
50. Floege J, Amann K. Primary glomerulonephritides. Lancet 2016; 387(1): 2036-48.
51. Bonner RW, Moreno V, Jain K. Infection-Associated Glomerulonephritis. Adv Kidney Dis Health 2024; 31(1): 246-54.
52. Jennette JC, D'Agati VD. Heptinstall's Pathology of the Kidney. Wilkins 2023; 1(1): 1-13.
53. Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. Nat Rev Nephrol 2020; 16(1): 32-50.
54. McGuire BM, Julian BA, Bynon JS, et al. Brief communication: Glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Intern Med 2006; 144(1): 735-41.
55. Razzak Chaudhary S, Workeneh BT, Montez-Rath ME, et al. Trends in the outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. Nephrol Dial Transplant 2015; 30(1): 1734-40.
56. Iyengar A, Kamath N, Radhakrishnan J, et al. Infection-Related Glomerulonephritis in Children and Adults. Semin Nephrol 2023; 43(1): 1-15.
57. Arivazhagan S, Lamech TM, Myvizhiselvi M, et al. Efficacy of Corticosteroids in Infection-Related Glomerulonephritis-A Randomized Controlled Trial. Kidney Int Rep 2022; 7(1): 2160-5.