New Insights into Epidemiology and Outcome of Bacterial Infection–Related Glomerulonephritis

Nicholas R. Medjeral-Thomas and Charles D. Pusey

Infection-related GN encompasses a range of clinical entities and outcomes. Unlike acute poststreptococcal GN in children, the prognosis of bacterial infection–related GN in adults is often poor (1). Up to one half of patients will develop persistent kidney impairment, and one third will progress to kidney failure (2). Bacterial infection–related GN is more common in developing countries, where the consequences of CKD can be particularly difficult to manage (3). Multiple dynamic factors contribute to bacterial infection–related GN etiology and natural history. In addition to inherited characteristics that predispose to immune-mediated diseases, pathogen prevalence and virulence as well as access to adequate health care services contribute to bacterial infection–related GN incidence and severity. Furthermore, bacterial infection–related GN treatment is complicated by increasing frequency and a spectrum of antibiotic drug resistance (2). The epidemiology of bacterial infection–related GN is location and time specific, which limits the relevance of research from different eras or regions. The effectiveness of health care strategies and patient management protocols depends on understanding factors associated with disease severity and treatment response. Consequently, there is urgent unmet need for adult bacterial infection–related GN research, particularly in developing countries.

The observational retrospective cohort study by John et al. (4) in this issue of CJASN provides valuable insights into the epidemiology of adult bacterial infection–related GN in India and highlights a number of research areas that demand urgent attention. From retrospective review of 15,000 native kidney biopsies performed over 10 years, the authors identified and analyzed over 500 cases of adult bacterial infection–related GN (4). The study population is almost five times bigger than that in the next largest cohort study of infection-related GN in adults (1). Additional to the impressive study size, the use of novel subcohort definitions allowed the authors to identify characteristics that associated with kidney disease severity. The authors used the relative timing of GN presentation and infection to categorize cases. Latency was defined as parainfectious if the GN was diagnosed at the time of active infection, peri-infectious if the GN occurred within 1–7 days of infection, or postinfectious if there were at least 7 days between infection resolution and onset of GN (4). Parainfectious GN latency was independently associated with progression to kidney failure after multivariable analysis (4).

Interestingly, the parainfectious cohort was different from the peri- and postinfectious GN subgroups in a number of baseline criteria. The parainfectious GN cohort was characterized by more equal sex distribution, higher prevalence of diabetes, lower eGFR at biopsy, longer duration from clinical GN onset to kidney biopsy, and more frequent and severe interstitial fibrosis and tubular atrophy on biopsy (4). The parainfectious cohort also suffered different infections from the peri- and postinfection cohorts; urinary tract infection (UTI) was the most common infection site, nonstreptococcal organisms were more common, and almost all of the drug-resistant organisms were isolated from the parainfectious subcohort (4). These findings suggest that parainfectious GN is a distinct and severe clinical entity characterized by nonstreptococcal, drug-resistant organisms causing UTI, with rapid onset of GN and significantly reduced eGFR in patients with diabetes. Of course, like all retrospective cohort research, this study is unable to attribute causation, and conclusions should be made cautiously. The findings could be confounded by unaccounted practical factors. For example, UTI-associated GN might present diagnostic difficulties that contributed to diagnostic delay and poor outcomes in the parainfectious subgroup. Nevertheless, by raising awareness of the parainfectious GN phenotype, this study should affect and improve clinical care.

The article by John et al. (4) raises a number of other important issues. Electron microscopy was unavailable for the vast majority of patients and therefore was not used for bacterial infection–related GN diagnosis (4). This might be seen as a limitation of cohort uniformity and reliability. However, it also highlights the restricted accessibility of electron microscopy globally and the need to develop novel diagnostic techniques. The authors identified associations between renin-angiotensin blockade and survival...
from kidney failure that have not been identified in other studies. After multivariable analysis, the adjusted hazard ratio for progression to kidney failure was 0.2 (95% confidence interval, 0.09 to 0.5) for treatment with renin-angiotensin system blockers. Although these data could be confounded by the avoidance of renin-angiotensin blockers in patients with severe kidney impairment, they suggest that renin-angiotensin system blockers provide clinical benefit to patients with infection-related GN.

Similar to other published cohorts (5,6), there was no apparent association between corticosteroid treatment and protection from kidney failure (4). The absence of clinical benefit with corticosteroids was despite the majority of patients (376 of 501 or 75%) receiving 6 weeks of 2 mg/kg prednisolone alternate days followed by 6 weeks at tapering doses, with similar proportions of treated patients in the para-, peri-, and postinfectious GN cohorts (4). The result could be confounded by more severe disease in the subcohort treated with corticosteroids. At baseline, the steroid-treated group had more proteinuria, higher serum creatinine, lower eGFR, and more frequent histology features of severity, such as 50% glomerular crescents. However, the authors did not identify specific benefit of corticosteroids in patients with crescentic GN. Other published evidence supportive of immunosuppression for crescentic postinfectious GN is mostly anecdotal (7). Furthermore, 12% of the patients in the steroid subcohort and none of the patients in the no steroid subcohort developed dysglycemia. Therefore, the findings emphasize the caution with which immunosuppression should be used and the need to develop effective management strategies for bacterial infection–related GN.

The data by John et al. (4) reinforce the importance of understanding the role of autoimmunity in infection-related GN. Consistent with other cohorts, the authors identified evidence of overlap between bacterial infection–related GN, autoimmune disease, and complement system dysregulation (8). About 30% of patients had no evidence of infection or identifiable bacteria (4). Nineteen patients had IgA-dominant GN, but only one individual had staphylococcal infection. Almost 10% of the entire cohort had persistent hypocomplementemia. Therefore, a significant proportion of patients may have had autoimmune kidney disease, such as IgA nephropathy or C3 glomerulopathy, with clinical detection triggered by infection. The proportions of patients with no identifiable infection, hypocomplementemia, isolated C3 deposition, and each immunofluorescence pattern were similar between para-, peri-, and postinfectious cohorts (4). This indicates that bacterial infection–related GN subtypes share some immunopathologic pathways and that complement dysregulation may contribute to the pathogenesis of all types of infection-related GN.

A role for complement system activity in infection-related GN is well established and evidenced by universal glomerular C3 deposition and frequent hypocomplementemia (2). Recently, details of the role of complement were provided by the detection of anti–Factor B antibodies in pediatric acute postinfectious GN with typical transient hypocomplementemia (9). The antibodies, which bind a protein essential for complement pathway activation and amplification, were not detected in patients with C3 glomerulopathy and persistent hypocomplementemia (9). Therefore, transiently produced anti–Factor B antibodies could contribute to complement activation and inflammation caused by infection. Anti–Factor B antibodies could also differentiate infection-related GN from underlying C3 glomerulopathy. If similar complement variants were identified in adult bacterial infection–related GN, they could be developed as diagnostic biomarkers and novel therapeutic targets for transient, targeted complement inhibition.

Perhaps the most impactful aspect of the research by John et al. (4) is the unique study demographic among peer-reviewed publications. To our knowledge, this is the first publication in an international peer-reviewed journal of infection-related GN from the Indian subcontinent. India is the second most populous country in the world, and the biopsy incidence of infection-related GN is 3% (4). There is potential for a significant and unstudied infection-related GN disease burden in adults across the world. A meta-analysis of >12,000 native kidney biopsies from Africa found the frequency of mesangiocapillary GN to be 6.4%–20.7%, with marked differences between West, East and Central, Southern, and North Africa (10). However, the study did not attempt to identify infection-related GN specifically. As shown by John et al. (4), research can identify regional variations in disease epidemiology that demand simple, impactful differences in patient management and, subsequently, improve patient outcomes. For example, compared with other published studies, remission rates and renin-angiotensin system blocker use were higher in the population in the study by John et al. (4). These findings, indicating that simple treatment may improve kidney survival in bacterial infection–related GN, deserve further research with prospective studies of similar patient populations. Although science and technology investment has increased dramatically in many developing countries, research publication remains biased to developed countries with established academic and health care systems. The article by John et al. (4) demonstrates the urgent need to rebalance the deficit of clinical kidney research and academic publications from resource-limited settings.

Disclosures
C.D. Pusey reports ownership interest in Cell Medica; receiving honoraria from Med Update Europe; serving as an associate editor of CJASN, as a scientific advisor of the UK and Ireland Vasculitis Rare Disease Group, and as a medical advisor of Vasculitis UK; and serving on the editorial boards of JASN and Nephrology Dialysis Transplantation. The remaining author has nothing to disclose.

Funding
N.R. Medjeral-Thomas is funded by a Wellcome Trust and Imperial College London Research Fellowship grant (WIII_PS3459).

Acknowledgments
Because Dr. Charles D. Pusey is an associate editor of CJASN, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility for the information and views expressed herein lies entirely with the author(s).
References


Published online ahead of print. Publication date available at www.cjasn.org.