Central Asian Journal of Nephrology
(eISSN 3105-4145)

Short Communication

Integrating Novel Complement Inhibitors into Clinical Practice: A National Call to Action for C3 Glomerulopathy and IgA Nephropathy in Kazakhstan

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Abstract:

Received: August 27, 2025
Accepted: September 7, 2025
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The advent of targeted complement inhibitors represents a paradigm shift in managing complement-mediated nephropathies. Integrating these therapies into healthcare systems, particularly in resource-variable settings, requires strategic planning.

A national council of experts was convened in October 2024 with the purpose of obtaining a clinical expert opinion to develop practical recommendations for improving the organization and optimization of medical care for patients with C3 glomerulopathy (C3G) and IgA nephropathy (IgAN) in Kazakhstan.

The council identified critical systemic gaps, including inconsistent use of renal biopsy, lack of specialized nephropathology, absence of treatment algorithms, and fragmented patient care. A consensus was reached on key recommendations for a new national clinical protocol. These include mandating pathological confirmation, creating detailed treatment and monitoring algorithms, establishing a national registry and coordination center, and investing in specialized training for healthcare professionals.

The systematic framework proposed by the council provides an actionable roadmap to overcome barriers to care. This model ensures equitable patient access to novel therapies

and may serve as a blueprint for other nations navigating the integration of advanced treatments into clinical practice.

Keywords: C3 Glomerulopathy; IgA Nephropathy; Complement System; Targeted Therapy; Iptacopan; Clinical Protocol; Kazakhstan; Healthcare Policy

Introduction

C3 glomerulopathy (C3G) and IgA nephropathy (IgAN) are complex immune-mediated glomerular diseases where dysregulation of the alternative complement pathway is a key driver of inflammation and progression to end-stage renal disease (1, 2). For decades, management has relied on non-specific immunosuppression with variable efficacy and significant side-effect profiles. The recent development of targeted complement inhibitors, such as the oral factor B inhibitor iptacopan, has revolutionized the therapeutic landscape. Iptacopan has demonstrated significant efficacy in reducing proteinuria in patients with IgAN in the phase III APPLAUSE-IgAN trial (3) and has shown promising results in C3G (4,5), leading to recent regulatory approvals.

However, the integration of such highly specific, costly therapies into clinical practice presents significant challenges. In Kazakhstan, the absence of a unified national approach creates disparities in care and limits patient access. This short communication presents the consensus resolutions and strategic recommendations of a national expert council convened with the specific mandate to develop practical recommendations on:

- Improving the organization and optimization of medical care for C3G and IgAN;
- Assessing and improving the state of diagnostics and provision of effective treatment within the current therapeutic landscape;
- Creating and implementing effective patient routing algorithms involving interdisciplinary interaction.

THE COUNCIL'S DELIBERATIONS: IDENTIFYING SYSTEMIC BARRIERS

Guided by its core mandate, the expert council, comprising leading nephrologists, pathomorphologists, and healthcare administrators, highlighted several interconnected barriers that currently impede optimal care for patients with C3G and IgAN in Kazakhstan:

1. **Diagnostic Inconsistency and Quality:** The practice of renal biopsy is not uniformly mandated or accessible across the country. A definitive diagnosis of C3G requires immunohistochemical staining and often electron microscopy, expertise for which is concentrated in major urban centers, creating a significant bottleneck. This directly impacts the assessment of diagnostics and limits opportunities for effective treatment.
2. **Fragmented Care Pathways and Routing:** The absence of a standardized national algorithm for referral, diagnosis, treatment initiation, and long-term monitoring leads to delays and inconsistencies in management. There is no central entity to coordinate care for these complex patients, hindering interdisciplinary interaction and effective routing.
3. **Knowledge Gaps:** There is a recognized need for continuous medical education focused on the pathophysiology of complement-mediated diseases, the interpretation of pathological findings, and the practical management of novel therapies, including their safety profiles. This gap affects the overall organization and quality of care provided.
4. **Lack of Epidemiological Data:** Without a national registry, the prevalence, natural history, and outcomes of C3G and IgAN in

Kazakhstan remain unknown, hindering public health planning, resource allocation, and the optimization of care systems.

5. **Therapeutic Access Barriers:** Even with drugs becoming available, the lack of a clear protocol for prerequisite vaccinations (e.g., against meningococci), monitoring for adverse events, and criteria for therapy initiation and continuation poses a significant risk of inequitable access and limits the provision of high-quality, effective treatment.

KEY RECOMMENDATIONS FOR A NATIONAL PROTOCOL

To systematically address these challenges and fulfill its mandate, the council formulated the following core recommendations to be enshrined in the new national clinical protocol:

1. **Mandatory Pathological Diagnosis:** Institute **mandatory renal biopsy** with a specialist nephropathology review as a non-negotiable standard for confirming the diagnosis of C3G and for risk stratification in IgAN before considering targeted therapy. This is the critical first step in improving diagnostic standards.
2. **Structured Treatment and Routing Algorithms:** Develop a detailed, step-by-step national algorithm that covers:
    - **Patient Workup and Routing:** Standardized pre-therapy screening and clear referral pathways to ensure interdisciplinary interaction.
    - **Therapy Initiation:** Clear criteria based on proteinuria and eGFR thresholds for starting targeted therapy.
    - **Monitoring and Dispensary Observation:** Protocols for assessing efficacy (reduction in proteinuria), safety (monitoring for infection), and long-term follow-up.
3. **Establish a National Registry and Coordination Center:** Create a **national registry** for C3G and IgAN, integrated with the existing DAMU MED electronic healthcare portal. This should be managed by a designated **Coordination Center** (e.g., based at the National Kidney Fund) to track patients, oversee care quality, facilitate research, and improve the overall organization of care.
4. **Investment in Specialist Capacity Building:** Launch a dedicated national educational program featuring:
    - **Pathologist Training:** Scholarships and partnerships for the training of pathomorphologists in specialized nephropathology techniques.
    - **Nephrologist Education:** Regular workshops and teleconferences on the practical management of complement-mediated diseases and novel therapeutics to optimize treatment provision.
5. **Consideration for Orphan Disease Status:** Advocate for the official recognition of C3G as an orphan disease within Kazakhstan to streamline access to dedicated resources and funded therapies, addressing the challenge of limited therapeutic options.

Conclusion

The arrival of targeted complement therapy necessitates an evolution from fragmented care to a coordinated, system-wide approach. The recommendations put forth by this expert council provide a comprehensive and actionable framework to modernize the management of C3G and IgAN in Kazakhstan. By focusing on accurate diagnosis, centralized coordination, continuous education, and systematic monitoring, this framework directly addresses the initial mandate of improving care organization, optimizing diagnostics and treatment, and implementing effective patient routing. This initiative ensures that breakthroughs in medical science translate equitably into improved patient outcomes and

may serve as a valuable model for other healthcare systems embarking on a similar journey.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: The authors would like to thank all participants of the expert council for their valuable contributions. This communication reflects the consensus view of the council.

Funding: None.

Ethics approval: Not applicable.

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