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Editorial

Commentary on the KDIGO Clinical Practice Guideline for Glomerulonephritis

Not so long ago, a paper published in *Kidney International* explored the reasons for the paucity of high-quality clinical trials in glomerulonephritis (GN).[1] The authors identified several factors, including the low prevalence of disease, variability in clinical presentation, variability in treatment responses, lack of consensus about definitions, difficulty in recruiting patients, the high cost of randomized controlled trials, and the lack of collaborative research efforts. To this list, I would also add our poor understanding of the pathogenesis of most if not all of the glomerulonephritides commonly encountered in clinical practice. This point is relevant because it limits the variety of new therapies that we can put up for clinical trials, and ultimately our ability to punch through the therapeutic envelope, so to speak. This is not to say that progress has not been made, but simply that we do not have enough hard data to provide precise advice on all aspects of therapy.

Hence, there is a need for clinical practice guidelines. Guidelines serve many purposes, the most important of which is to set down boundaries to define what is reasonable to do, and in so doing, either directly or indirectly, also set down what is not reasonable to do.

The KDIGO Clinical Practice Guideline for Glomerulonephritis published in 2012 aims to do this and much more.[2] It attempts to present a series of treatment recommendations and suggestions based on the available evidence for a number of glomerulonephritides. It also grades the quality of evidence behind these recommendations. Notably, several conditions are not covered, such as the management of diabetic nephropathy, dysproteinaemias, fibrillary GN and haemolytic-uraemic syndrome. Arguably, these latter conditions are not strictly inflammatory glomerulonephritides, but nonetheless, they can affect the glomerulus predominantly. In a series of chapters, each dedicated to a specific GN, a set format is used to tackle various aspects of clinical management such as induction therapy, maintenance therapy, management of relapse, and management of resistant disease. At the start of these subsections, recommendations and suggestions are made (annotated Level 1 and 2, respectively), followed by grading of the quality of evidence behind these recommendations (annotated A, B, C and D for high, moderate, low and very low quality of evidence). A brief background is provided, the rationale for these recommendations/suggestions is discussed, including a summary of the most relevant clinical trials, and a number of recommendations are made for future research. The references to publications are listed together in one location at the end of the document.

To achieve this mammoth task, an Evidence Review Team of physician-methodologists worked closely with a Work Group of clinicians to develop the relevant clinical questions, search the literature up to November 2011, grade the quality of evidence for each topic, and finally arrive at a series of recommendations and suggestions. There seems to be an operational assumption that every minute aspect of our clinical decision-making process has to be based on a randomized controlled trial. This position may be scientifically sound, but it is not achievable in reality or even desirable. Incidentally, the panel of clinicians which made up the Work Group is international in representation, and I note with interest the inclusion of an Australian nephrologist in the group.

In total, 47 Level 1 recommendations and 120 Level 2 suggestions were made. The major problem, however, lies with the fact that the vast majority (77%) of these recommendations and suggestions were made based on what was judged to be either low (class C) or very low (class D) quality evidence. It is important to note that the available quality of evidence varies widely between the different conditions. For example, the quality of evidence for some aspects of management in lupus nephritis and idiopathic membranous nephritis was moderate, but very low for others such as focal and segmental glomerulosclerosis. Only four of 47 Level 1 recommendations were based on high quality (class A) evidence, and 24 of 47 Level 1 recommendations were based on moderate quality (class B) evidence. That left 19 Level 1 recommendations based on class C or D evidence. On the other hand, 110 of the 120 Level 2 suggestions were based on class C or D evidence.

One would think that Level 1 recommendations should only be made in the context of class A and B evidence, and that no recommendations or suggestions should be made based on class C or D evidence. But this is apparently not the case. In the 'Methods for guideline development' section, we are told that besides the quality of evidence, the Work Group took into account other factors such as the balance of benefits and harm, cost, perception of what the majority of nephrologists would do in a particular situation, and on top of these, I suspect perhaps a dose of 'expert opinion'. In relation to cost, there is regular mention at the start of each chapter that 'the cost implications for global application of this guideline' have been addressed in an earlier chapter. However, cost-benefit analysis is nowhere to be found in this document. For relatively cheap medicines such as prednisolone, this is probably not a significant issue. But this is a relevant issue for expensive items such as mycophenolate mofetil or rituximab, and it is

relevant not only in developing countries, but also in developed countries such as Australia where there are competing demands for a finite health dollar.

These comments aside, what is my assessment of the guideline's recommendations and suggestions? Based on my reading of the literature, my clinical experience, observation of what my departmental colleagues would do in particular clinical situations, and also my perception of what Australian nephrologists would do, it is my impression that this KDIGO document has made resoundingly good calls in general, and it reaffirms what I think is the solid middle ground of clinical recommendations. I think that the chapters on idiopathic membranous nephropathy and lupus nephritis are particularly well written and informative. I also feel that the Work Group for lupus nephritis should be commended for not insisting on the use of mycophenolate mofetil in preference to cyclophosphamide for induction treatment in lupus nephritis. This would have limited its global applicability. It comes back to the question of whether to recommend a very expensive drug if it might only be marginally better than a cheaper drug.

Several areas, however, are more contentious. I think that the most controversial is the suggestion to give 6 months of corticosteroid therapy to IgA GN patients with persistent proteinuria $\geq$1 g/d, based on what is judged low quality evidence (2C). One of the two suggested regimens uses a total of 9 gm of IV methylprednisolone spread over 6 months.[3] It is hard to imagine that this quantity of corticosteroid will not lead to some side effect in the long term. I wonder how the authors of this suggestion weighed potential harm *versus* benefit in the face of low quality short-term evidence.

I also want to take issue with use of the words 'We suggest'. The words 'to suggest' carry with it the notion of 'to prompt' or 'to propose'. I would have preferred to use a more neutral word such as 'to consider' followed by the qualification 'note low quality evidence' clearly in brackets. The problem is compounded further by the definition given for a Level 2 grade 'we suggest' of 'The majority of patients in your situation would want the recommended course of action, but many would not'.[2] I simply do not see this scenario playing out for IgA GN patients in relation to the use of corticosteroid for this condition at the moment in Australian nephrology practice, but I appreciate that these are points of opinion.

The chapter on idiopathic membranoproliferative GN (or more commonly known as mesangiocapillary GN in Australia) must have been particularly challenging to write. The quality of evidence of therapies in membranoproliferative GN is generally very low, and our understanding of this field is still evolving.[4] I look forward to reading future editions of this chapter. Lastly, there are a few miscellaneous points to mention. In relation to the use of cyclophosphamide, there is mention in several places in the guideline of the need to reduce dosage of cyclophosphamide in elderly patients and in those with poor renal function. I would have liked to see this very important advice in a table, similar to what recent ANCA-vasculitis clinical trials have done.[5] In relation to the prevention of opportunistic pneumocystis infection because of immunosuppression, especially when it involves cyclophosphamide, I would have liked to see more reminders throughout the document to use prophylactic antibiotic.

Overall, I thought that the guideline was excellent, compact, easy to read, well-referenced, not overly prescriptive, and furthermore, readily applicable to local nephrology practice. In tune with the format of the guidelines, I highly recommend to the ANZSN Specialist Advisory Committee to make this guideline document compulsory reading for all trainees, and I would also strongly suggest that all practising nephrologists read it.

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REFERENCES

1. Leaf DE, Appel GB, Radhakrishnan J. Glomerular disease: Why is there a dearth of high quality clinical trials? *Kidney Int.* 2010; **78**: 337–42.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int. Suppl.* 2012; **2**: 139–274.
3. Pozzi C, Bolasco PG, Fogazzi GB *et al*. Corticosteroids in IgA nephropathy: A randomised controlled trial. *Lancet* 1999; **353**: 883–7.
4. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. *Nat. Rev. Nephrol.* 2012; **8**: 634–42.
5. PEXIVAS. Protocol version 1.1. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis: An international randomized controlled trial. 2010. [Cited 5 May 2013.] Available from URL: http://www.vasculitis.org/images/pexivas%201.1%20protocol.pdf