Commentary on KDIGO glomerulonephritis guidelines

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Introduction

This report comments on the likely relevance and utility of the recently published global KDIGO Clinical Practice Guideline for the treatment of glomerulonephritis with respect to UK clinical practice (1). The KDIGO report is a comprehensive and systematic review of the available evidence in all major areas of management of the primary and systemic glomerular diseases, although in many areas in this field there is a lack of robust evidence to inform the recommendations. For steroid sensitive and resistant nephrotic syndrome and HSP there are specific guidelines for children. In addition mention is made of children in the lupus nephritis and membranoproliferative guidelines. For other diseases there is no specific reference to paediatric practice. The relative lack of evidence for many treatment decisions is reflected in the fact that there are only four recommendations that have evidence of grade A. For all other recommendations, the evidence is grade B or below, meaning that at best, there is a possibility that the true effect is substantially different from the estimate of the effect.

Chapter 3: Steroid-sensitive nephrotic syndrome in children

The recommendations are to initially commence therapy with a dose of prednisalone of 2mg/kg (max 60 mg) daily for 4 to 6 weeks followed by a further course of alternate day steroid of 1.5mg/kg alternative days to complete 12 weeks. It is then recommended that steroids be tapered over a 4-5 month period. Current UK practice is to start with a 4-week course of 60mg/m^2/d (max 80mg) and then 4 weeks alternate days at 40mg/m^2/d. To address this discrepancy we are currently engaging in a national multi-centre trial (PREDNOS) to compare an extended (sixteen-week) tapering prednisolone regimen with the standard eight-week regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC) (2) as there is some evidence this may reduce relapse rates (3). A recent Dutch study, published after the KDIGO guideline, compared 3 and 6 month of treatment courses with equal cumulative steroid doses and found no difference in relapse rates (4). This suggests that an extended treatment course may only be of benefit with an increased total steroid dose and the PREDNOS trial will examine this.

Relapses of NS are common and the recommendations are to give treatment doses of 2mg/kg daily until in remission for 3 days and then give an alternative day regimen of 1.5mg/kg for 4 weeks. This is low quality recommendation (grade 2C) and in the UK we limit steroids as much as possible due to their debilitating side effects. It is known that viral infections can precipitate relapse and it is recommended that steroids be intensified in this situation. Again the evidence for this is currently weak in the UK and there is a prospective placebo controlled trial being initiated to assess the benefit of this manoeuver here (PREDNOS2).

Steroid sparing agents are advocated in frequently relapsing NS (grade 1B), which is in line with UK practice. It is however unclear what is the optimal agent(s) of choice in this situation. The KDIGO guidelines do not give a recommendation here but discuss the advantages and disadvantages of the available choices. Commonly in the UK we start with Levamisole (12-month course) after steroids as it has less detrimental side effects compared to the other steroid sparing agents. It also has the highest degree of evidence supporting its use in the KDIGO guidelines (grade 1B). Thereafter there is a choice between alkylating agents including cyclophosphamide (2mg/kg/day) for 8-12 weeks (maximum 168mg/kg) or chlorambucil (0.1-0.2 mg/kg/day), calcineurin inhibitors and Mycophenolate mofetil. Rituximab is also suggested if frequent relapsing after these treatments have been tried or there are serious side effects with steroids (low level 2C). This is compatible with current UK practice.

It is currently not clear what is the most effective therapeutic approach with these agents. Going forward it is crucial we continue to run multicenter randomized controlled trials to ascertain the optimal treatment regimen with the least set of side effects in children with this condition.

Chapter 4: Steroid-resistant nephrotic syndrome in children

The guidelines suggest 8 weeks of non-response to steroid to be diagnostic. Generally in the UK we wait for 4 weeks and then consider a renal biopsy if no response to steroids. Some groups may also give an intravenous 3-day pulse of steroids at this time to ensure adequate steroid is present systemically. This has, however, not been investigated in a clinical trial. UK practice is to then give a calcineurin inhibitor as a second line therapy for at least 6 months, This is in keeping with KDIGO recommendations (grade 1B). If this is not successful Mycophenolate Mofetil may be considered with or without high dose steroids. Cyclophosphamide is not recommended in this setting but ACE inhibitors and/or ARBs are (grade 1B). This is compatible with our practice. We strongly advocate genetic testing in this condition as it is readily available in the UK and is important for deciding if toxic therapy is beneficial and also can help predict transplant recurrence risk as genetic mutations are less likely to relapse post surgery. There is now a clinically approved (UKGTN) Next Generation Sequencing test for SRNS in the UK, simultaneously testing all known genes for SRNS (www.nbt.nhs.uk/genetics)

Chapter 5: Minimal-change disease in adults

There are very few randomised controlled trials in this area and this is reflected by most recommendations being Grade 2C or 2D. However, they generally reflect what would be standard practice in the UK. Steroids are the recommended treatment for an initial episode, with the initial dose of prednisolone at 1mg/kg (maximum 80mg) maintained for a minimum of 4 weeks and tapered over 6 months. In the UK 60mg of prednisolone is generally used as the maximum dose. Oral cyclophosphamide (2-2.5mg/kg for 8 weeks) or a CNI (1-2 years) are alternatives for patients with relative contraindications. Cyclophosphamide, CNIs or MMF are recommended for frequently relapsing disease, based mainly on observational studies or case reports. Since the publication of these guidelines, there have been further observational studies published on the use of rituximab in this context, and this could be added to the list of therapies for consideration on an individual patient basis (5).

Chapter 6: Idiopathic Focal Segmental Glomerulosclerosis in Adults

Genetic testing is not recommended for all patients and would not be standard practice in the UK. The evidence for all these guidelines is weak (grade 2C/D or ungraded). However they provide a sensible stepwise approach to the treatment of FSGS which would be standard practice for most UK units. Corticosteroids and immunosuppression are recommended only for patients with features of the nephrotic syndrome. Corticosteroids are first line therapy with a regimen similar to minimal change disease. Cyclosporin is recommended for steroid resistant FSGS. Tacrolimus is often used in UK units, and is an appropriate alternative.

Chapter 7: Idiopathic membranous nephropathy

The guidelines emphasise the need to distinguish Idiopathic Membranous Nephropathy (IMN) from secondary disease as this is important in directing therapy. Some UK units may have access to assays for antibodies against the M-type antiphospholipase A2 receptor which are now commercially available. However the role of this test in clinical practice not been clearly defined as discussed in the guideline.

KDIGO recommends a restrictive policy in the selection of patients for immunosuppression which is supported by a study from the Netherlands published after the guideline (6). Alternating therapy of monthly cycles of steroids and alkylating agents (the Ponticelli regimen) is recommended as 1st line in patients selected for immunosuppression. The authors draw attention to the high toxicity of this regime, which some patients may find unacceptable, and suggest use of a CNI as an alternative. The guidelines recommend that patients with IMN resistant to alkylating agents/steroid-based therapy be treated with a CNI, and vice versa. A UK Trial has been published after the guideline, suggesting that use of a CNI is less effective than chlorambucil and prednisalone for patients with declining renal function (7). In choosing between alkylating agents and CNIs for initial therapy the stronger evidence for alkylating agents will be considered alongside their greater toxicity. Impaired or declining renal function will also limit the use of CNIs as is common practice in the UK and supported by the abovementioned UK trial.

Rituximab may be an effective alternative in these patients (7), and is often considered in the UK, especially for those with a reduced GFR, but the evidence remains sparse.

Chapter 8: Idiopathic membranoproliferative glomerulonephritis
The guideline refers to adults and children. It is recommended to evalulate all patients with an MPGN pattern on biopsy for underlying causes. The guideline discusses the recent concept of classifying MPGN into those with predominant C3 deposition (C3 glomerulopathy) and those with immunoglobulin deposition. After a thorough search for underlying causes it is noted that true idiopathic MPGN is rare. For idiopathic MPGN, treatment with cyclophosphamide or MMF and low-dose prednisolone is suggested for nephrotic syndrome and a progressive decline in renal function. In the presence of deteriorating renal function there may be an argument for a higher initial steroid dose. It is acknowledged that the evidence for this is weak and it is difficult to be sure how many cases in published series are truly idiopathic.

Chapter 9: Infection-related glomerulonephritis
For glomerulonephritis associated with streptococcal, endocardial, shunt, or HIV infection, treatment with antibiotics or antiretrovirals is the basis of therapy and this reflects usual practice in the UK with shared care between the specialist treating the particular infection, and nephrologists. The guidelines relating to antiviral treatment of hepatitis B/C in patients are highly specific. In the UK nephrologists would usually refer decisions regarding antiviral treatment to the hepatologist/infectious diseases specialists.

There is only weak evidence for the recommendation (Grade 2D) for the use of plasmapheresis, rituximab or cyclophosphamide with methyl prednisolone, for patients with hepatitis C related GN in conjunction with antiviral therapy, but most UK units would consider these agents on an individual patient basis.

Decisions regarding treatment of schistosomal, filarial and malarial nephropathies would not be made in isolation by most UK nephrologists but would be taken in conjunction with the Infectious Diseases Specialist involved in the case.

Chapter 10: Immunoglobulin A nephropathy
There is evidence that prognosis in IgA nephropathy is strongly linked with proteinuria, and there are specific recommendations that are not made for other glomerular diseases in the guideline. ACE inhibitors or ARBs are recommended with proteinuria of more than 1g/day (grade 1B) and this would be widespread practice in the UK. They are also less strongly recommended with proteinuria of 0.5-1g/day (grade 2D). This would be common but not universal practice, in keeping with the lower strength of recommendation.

A 6 month course of corticosteroids are recommended for all patients with proteinuria more than 1g/day and preserved renal function (graded 2C). This would not be common practice in the UK. Fish oil is also recommended for patients with proteinuria more than 1g/day (graded 2D) and this is also not common practice in the UK. Immunosuppressive agents other than corticosteroids are not recommended except in patients with crescentic IgA and rapidly deteriorating renal function with corticosteroids and cyclophosphamide being used in these patients (grade 2D). The use of cytotoxic therapy in crescentic IgA often presents a dilemma. Many UK nephrologists would initiate corticosteroids and cyclophosphamide with acutely deteriorating function and active crescents on histology but may stop the treatment early (less than 3 months) if there is no sign of a response.

Chapter 11: Henoch-Schonlein purpura nephritis

(a) Children
It is suggested that patients with persistent proteinuria be treated with ACE inhibitors or ARBs if proteinuric (>0.5g/day/1.73m^2) as renal protection against proteinuria. If there is more significant proteinuria (>1g/day/1.73m^2) and a GFR of greater than 50ml/min then a prolonged course of prednisolone is recommended for 6 months. Both of these suggestions are of the lowest level

evidence (2D). In view of the lack of evidence UK practice is to try and reduce steroid exposure as much as possible due to its debilitating side effects. Many units will perform a renal biopsy in children with a nephrotic/ nephritic picture or nephrotic range proteinuria to guide management although the evidence for treatment options is lacking. To this end there is some encouraging pilot data that the use of MMF may be beneficial in the treatment of active HSP nephritis (8) but more high quality studies are required to prove this.

HSP nephritis can be associated with a rapidly progressive GN and in this situation KDIGO recommends that the same protocol for rapidly progressive crescentic IgA GN be used. This is compatible with UK practice, however again there is low quality of evidence that this is the optimal therapy (2D). KDIGO recommends that prophylactic corticosteroids not to be used in the prevention of HSP nephritis. There is moderate evidence (1B) to support this recommendation from KDIGO which we agree with. This advice is also supported by a UK based large randomized prospective trial that has recently been published (9).

It is clear that adequately powered prospective studies are required to define the best treatment regimen in HSP nephritis in children.

(b) Adults

The recommendation is to treat adults as suggested for children, which is the same as IgA nephropathy. A 6 month course of steroids is recommended for patients with preserved renal function and proteinuria > 1g/day. Although few UK nephrologists would do this in IgA nephropathy, some may be more likely to prescribe corticosteroids for HSP.

Chapter 12: Lupus nephritis

(a) Adults

The recommended initial therapy for class III or IV proliferative nephritis is corticosteroids with cyclophosphamide or MMF. There can be few nephrologists or rheumatologists in the UK who would disagree with this statement. The dilemma in clinical practice is usually around the choice between MMF and cyclophosphamide and if cyclophosphamide, then what dosing regimen to use. These options are discussed, though guidance is not given as a listed recommendation but embedded in the text of the document. The options for cyclophosphamide are iv pulses at 0.5-1g monthly/m^2 for 6 months (NIH regimen), iv pulses at 500mg every 2 weeks for 3 months (Eurolupus regimen) or oral cyclophosphamide at 1-1.5mg/kg for 2-4 months. The message within the text of the guideline is that NIH regimen cyclophosphamide may be preferred for severe LN, and MMF (or Eurolupus cyclophosphamide) may be preferred for mild proliferative LN. This is in part because of the preserved mean GFR in trials of MMF and Eurolupus cyclophosphamide. However mild clinical disease (as assessed by GFR) does not necessarily mean mild histological disease. Therefore it seems likely that conclusions from trials of treatment for patients with mild clinical disease and proliferative nephritis will be relevant to patients with lower GFRs. In keeping with this, many UK many units would use MMF as initial therapy in all patients even with severe LN and would use Eurolupus cyclophosphamide in patients who failed MMF, or in patients with severe LN. Few would use NIH regimen cyclophosphamide in any patients.

Rituximab is mentioned as an option for refractory lupus nephritis. Although there is no clear evidence from clinical trials, it appears effective in some patients. UK practice would be to consider Rituximab after MMF and cyclophosphamide. Guidance on the use of Rituximab in SLE is given in the recent Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus in adults, NHS England, September 2013.

It is recommended that nephrotic patients with class V LN be treated the same as class III/IV, with immunosuppression withheld from patients who are not nephrotic. This is certainly in line with UK practice. Although not listed as a recommendation, the text of the guideline suggests that testosterone be given to men (in addition to sperm banking) and GnRH agonsits be given to women to protect fertility. The evidence for this is not strong and there are significant side effects. Infertility is also rare after a single course of Eurolupus cyclophosphamide (total dose 3g). The use of testosterone and GnRH agonists is not widespread practice in the UK.

Guidance on maintenance therapy is given as a listed recommendation for azathioprine or MMF with low dose corticosteroids. No firm recommendation for MMF over azathioprine is given. It is acknowledged that in the ALMs trial extension phase superiority for MMF was shown (10). Therefore it is surprising that this is not incorporated into the formal recommendation, with the caveat of switching to azathioprine in pregnancy. This may be due to the MAINTAIN trial data suggesting equivalence for MMF and azathioprine (11), although the design of this trial meant that patients were not necessarily in remission at the time of entry. Certainly most clinicians in the UK would favour MMF over azathioprine for maintenance, especially in view of the widespread use of MMF for initial therapy.

Anticoagulation is recommended for patients with renal thrombotic microangiopathy (TMA) associated with antiphospholipid syndrome. It is noted that 15% of patients with histological renal APS may not have a lupus anticoagulant (LAC) or anticardiolipin antibodies (ACA), and it is recommended to treat this group with anticoagulation. Despite the lack of direct evidence for anticoagulation his is common practice in patients with LAC or ACA. The use of anticoagulants in patients who are ACA or LAC negative is reasonable but more controversial. Although it is not something that the guideline could address, we note a common clinical dilemma of deciding on the significance of mild changes suggesting TMA in patients who have an active LN. This may particularly be an issue in LAC or ACA negative patients.

Regarding pregnancy, it is recommended that cyclophosphamide MMF, ACE inhibitors and angiotensin receptor blockers are not used and this is one of the four grade 1A recommendations. It is also recommended that patients who become pregnant while on MMF switch to azathioprine and that relapses during pregnancy are treated with corticosteroids and azathioprine. Whilst few would argue with the avoidance of cyclophosphamide, ACE inhibitors and angiotensin receptor blockers, the maternal benefits of MMF have to be weighed against fetal risk since azathioprine is not as effective for active proliferative LN. The harmful effects of MMF occur in the first trimester and we are aware of several patients with LN who have been successfully treated with MMF during later pregnancy. Therefore, providing the gestational stage is confirmed on a scan, the use of MMF should be considered in some cases.

Children
In paediatrics in view of the lack of randomised controlled studies in children these adult guidelines are broadly followed with adjustments to doses according to weight/ surface area.

Chapter 13: Pauci-immune focal and segmental necrotizing glomerulonephritis
It is recommended that cyclophosphamide and corticosteroids be used as initial treatment and this is one the four grade 1A recommendations. Rituximab is recommended as an alternative in patients without severe disease or in whom cyclophosphamide is contraindicated. Plasma exchange is recommended for patients needing dialysis or with a rapidly rising creatinine or for patients with pulmonary haemorrhage.

The options for cyclophosphamide dosing are tabulated and include pulsed iv 0.75g/m^2 every 3-4 weeks or oral 1.5-2mg/kg per day. There is no listed recommendation on the cyclophosphamide dosing regimens in ANCA vasculitis though the options are discussed. This is a common clinical dilemma and a source of variation in practice. Oral cyclophosphamide is commonly used in UK renal units. Although pulsed therapy entails a lower total dose and is as effective at inducing remission, it is associated with a higher relapse risk. This was shown in a metanalysis in 2010 (12), which included only short term data from the CYCLOPs trial with three other smaller trials, and confirmed in long term data from CYCLOPs (13) which was published, after the KDIGO guideline.

The use of Rituximab as an alternative in selected patients is in line with a recent Clinical Commissioning Policy: Rituximab for Anti-Neutrophil Cytoplasmic Antibody- Associated Vasculitis, NHS England, April 2013. It is not recommended as first line in view of cost and lack of data on long-term outcome. Although the RAVE trial did not include patients with severe disease (14), clinical experience has shown that it is often effective and also an option in these patients. The

statement on plasma exchange is in line with UK practice and further evidence here will be provided by the PEXIVAS trial which is in progress.

For maintenance therapy, azathioprine is preferred over MMF and the duration is suggested to be at least 18 months. Methotrexate is a third option for maintenance therapy. Cotrimoxazole is recommended for maintenance in patients with upper respiratory tract disease. Avoidance of Etanercept is recommended and this is the third grade 1A recommendation. The above points (this paragraph) are all standard practice in UK nephrology.

Chapter 14: Treatment of anti-glomerular basement membrane antibody glomerulonephritis
Recommended initial treatment is with cyclophosphamide, corticosteroids and plasma exchange for all patients except those that are dialysis dependant at presentation and have 100% crescents. No maintenance therapy is recommended and the advice is to delay kidney transplantation until anti-GBM antibodies have been undetectable for 6 months. These recommendations are all in line with usual UK practice.

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