STUDENTS' CORNER
INNOVATION ARTICLE

Grade-ADOLOPMENT of nephrology clinical practice guidelines and creation of referral algorithms for Pakistan

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Abstract

Objective: To develop evidence-based local clinical practice guidelines and primary care referral pathways for general physicians to help streamline the management of glomerular diseases and diabetes in chronic kidney disease patients in Pakistan.

Method: The study was conducted from October 2021 to February 2023 at the Centre for Clinical Best Practices, Aga Khan University Hospital, Karachi, in collaboration with the AKUH Section of Nephrology. Two source guidelines were selected by the local nephrologists after a thorough literature review on PubMed and Google Scholar. GRADE-ADOLOPMENT approach was used to adopt, adapt or exclude recommendations from the source guidelines in order to create the local clinical practice guidelines. Recommendations from the local clinical practice guidelines were used to create the primary care referral pathways.

Results: Management guidelines for glomerular diseases and diabetes in chronic kidney disease and two primary care referral pathways for the management and timely referral of the patients were created for general physicians to follow in Pakistan.

Conclusion: On the basis of two source guidelines, evidence-based local clinical practice guidelines and primary care referral pathways for general physicians were developed for general physicians in Pakistan for a smooth referral process.(JPMA 75: 156; 2025) **DOI: https://doi.org/10.47391/JPMA.10192**

Introduction

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide, with a global prevalence of 13.4%.[1] Low- and middle-income countries (LMICs) suffer a greater disease burden of CKD, having over 387.5 million cases compared to 109.9 million cases in high-income countries (HICs).[1] In Pakistan, a South Asian LMIC, the prevalence of CKD is as high as 21.2%, making CKD a major public health concern in the country.[2,3]

Evidence-based clinical practice guidelines (CPGs) are central to the management and improvement of outcomes for chronic kidney diseases.[4] Existing international CPGs for CKD were mostly developed in HICs, making it difficult to implement them in a low-resource setting where there is a lack of services, equipment, adequately-trained healthcare professionals, and a proper referral system.[5] It is difficult to create CPGs de novo in LMICs, owing to a lack of high-quality local data, resources and expertise. The next best step, however, is to modify existing CPGs for LMICs, like Pakistan, by contextualising them to local needs.

An efficient model has been devised by the United States Grading of Recommendations Assessment, Development and Evaluation (GRADE), Working Group, called the GRADE-ADOLOPMENT model, which is used to generate CPGs to enable evidence-based healthcare decisions.[6] 'Adolopment' is a newly devised term which proposes that CPGs can be created by a combination of adoption (using existing recommendations), adaptation (tailoring recommendations to region-specific needs) or created through de novo development.[6] For this purpose, GRADE-ADOLOPMENT makes use of evidence-to-decision (EtD) tables.[7] These tables provide general and context-specific evidence across set criteria standards, allowing professionals to make decisions about the relevance of current recommendations and advise modifications that are suitable to a specific country.[6,7]

The limited number of nephrologists in Pakistan means that the healthcare system relies heavily on general practitioners (GPs).[2,8] Currently, despite encountering a lot of CKD patients, GPs are inadequately aware of several

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aspects of nephrological care, including the need and indication for specialist referral.[8] There is a pressing need for thorough and transparent CPGs and primary care referral pathways for CKD to provide GPs with clear guidance regarding their role in patient care. While the Pakistan Society of Nephrology.[9] exists as a platform connecting those in the field across the country, it does not provide or disseminate any local CPGs to standardise clinical care in Pakistan. Thus, the current study was planned to develop local CPGs for the management of CKD by GPs in Pakistan, and to create primary care management and referral pathways.

Materials and Methods

The study was conducted from October 2021 to February 2023 at the Clinical and Translational Research Incubator (CITRIC), Centre for Clinical Best Practices (CCBP), Aga Khan University Hospital (AKUH), Karachi, in collaboration with the AKUH Section of Nephrology. The AKUH is a private-sector, not-for-profit institution in Pakistan, and is also the country's leading healthcare and biomedical research facility.[10]

The CCBP is concerned with the adaptation and development of evidence-based guidelines and care pathways to standardise healthcare in Pakistan and other LMICs. The study team comprised CCBP staff with extensive experience in the development of management guidelines, as well as senior faculty and attending nephrologists.

A source guideline is the single, original CPG that undergoes the GRADE-ADOLOPMENT process in the development of a local CPG. The Kidney Disease Improving Global Outcomes (KIDGO) 2020 Clinical Practice Guideline for Diabetes Management in CKD[11] and the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases[12] were selected as the source guidelines due to their comprehensive set of recommendations, integrated approach to management, and high-quality synthesis of available evidence.

First, a table of recommendations (ToR) was created by extracting and compiling all recommendations mentioned in the source guidelines.[11,12] Two senior attending nephrologists reviewed the source guidelines independently and categorised each recommendation as either 'Adopt', 'Adapt' or 'Exclude'. Discrepancies were settled in consultation and consensus with the Section Head of Nephrology. Recommendations marked 'Adopt' were incorporated into the development of the local guideline with no further changes or with minor additions, while those marked 'Exclude' were omitted from the local guideline. Exclusion was based on the recommendation pertaining to paediatric or inpatient management, or if the recommendation was deemed irrelevant to the Pakistani context.

Recommendations marked 'Adapt' underwent review and revision via the GRADEPro tool before incorporation into the local CPGs. An important differentiation between the current process and that described originally[13] was the absence of de novo recommendations. However, if additional recommendations were deemed necessary for any of the referral pathways, these recommendations were identified via the best evidence review process.

Following that, the CCBP staff in collaboration with the Section Head of Nephrology used the recommendations present in the two CPGs to create a management algorithm for primary care practitioners. The focus was on early identification and diagnosis, primary care management, and timely referral to specialists.

The final synthesis of CPG and referral pathway was concluded by a meeting of the CCBP staff with the panel of expert nephrologists where the final versions of the CPGs and the referral care pathways were presented to the Section Head of Nephrology.

The guidelines were finalised in November 2022, while the referral pathways were completed by February 2023.

Given the lack of involvement of patients or other human participants, a waiver was obtained from the institutional ethics review committee. All processes were conducted and completed in accordance with the highest ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments.[14]

Results

The CPGs included recommendations regarding diagnostic tests, glycaemic monitoring and targets, lifestyle interventions, anti-hyperglycaemic therapies and self-management educational programmes (Table).

Primary care management and referral pathways for the two renal disorders were created using recommendations in the locally created CPGs (Figures 1-2). The clinical referral algorithms focussed on basic evaluation, diagnosis, primary care level management and referral, when necessary, to tertiary care centres.

Discussion

The detailed CPGs and referral care pathways can help educate and guide GPs to deliver better quality primary care to CKD patients, while also serving as a triage gateway to specialist care.

In a country where there are limited specialist resources

Table: Management of glomerular disease and diabetes in Pakistani patients of chronic kidney disease (CKD).

General principles for the management of Glomerular Disease
The kidney biopsy is the "gold standard" for the diagnostic evaluation of glomerular diseases. However, under some circumstances, treatment may proceed without a kidney biopsy confirmation of diagnosis. [PP]
The evaluation of kidney tissue should meet standards of biopsy adequacy (at least 8-10 glomeruli in the sample) [PP]
Repeat kidney biopsy should be performed if the information will potentially alter the therapeutic plan or contribute to the estimation of prognosis. [PP]
Obtain 24-hour urine collection to determine total protein excretion in patients with glomerular disease for whom initiation or intensification of immunosuppression is necessary, or who have a change in clinical status. [PP]
Random "spot" urine collections for PCR are not ideal as there is variation over time in both protein and creatinine excretion. [PP]
First morning urine collections may underestimate 24-hour protein excretion in orthostatic proteinuria. [PP]
When feasible, a reasonable compromise is to collect an "intended" 24-hour urine sample and measure PCR in an aliquot of the collection. [PP]
There is no need to simultaneously and routinely quantify sodium excretion on each timed urinary collection, unless there is reason to suspect a failure to adhere to suggestions regarding dietary sodium restriction. [PP]
Quantify proteinuria in glomerular disease, as it has disease-specific relevance for prognosis and treatment decision-making. Qualitative assessment of proteinuria may be useful in selected instances. [PP]
Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of glomerular disease. [PP]
Monitoring of haematuria (magnitude and persistence) may have prognostic value in many forms of glomerular disease. This is particularly applicable to immunoglobulin A nephropathy (IgAN) and vasculitis. [PP]
Management of complications of glomerular disease. [PP]
Management of hypertension and proteinuria reduction in glomerular disease. [PP]
Management of hyperlipidaemia in glomerular disease. [PP]
Full anticoagulation is indicated for patients with thromboembolic events occurring in the context of nephrotic syndrome. Prophylactic anticoagulation should be employed in patients with nephrotic syndrome when the risk of thromboembolism exceeds the estimated patient-specific risks of an anticoagulation-induced serious bleeding event. [PP]
Anticoagulant dosing considerations in patients with nephrotic syndrome. [PP]
Use pneumococcal vaccine in patients with glomerular disease and nephrotic syndrome, as well as patients with chronic kidney disease (CKD). Patients and household contacts should receive the influenza vaccine. Patients should receive herpes zoster vaccination (Shingrix). [PP]
Screen for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis in clinically appropriate patients. [PP]
Strongyloides superinfection should be considered in patients receiving immunosuppression who once resided in endemic tropical environments and who have eosinophilia and elevated serum immunoglobulin E (IgE) levels. [PP]
Prophylactic trimethoprim–sulfamethoxazole (TMP-SMX) should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide). [PP]
Goals for proteinuria reduction with treatment vary among the various specific causes of glomerular disease. [PP]
A >40% decline in eGFR from baseline over a 2–3-year period has been suggested as a surrogate outcome measure for kidney failure. [PP]
Pharmacologic aspects of immunosuppression. [PP]
Dietary management in glomerular disease [PP]

Care for the pregnant patient with glomerular disease needs coordination between nephrology and obstetrics, and ideally, such planning should be considered before pregnancy.
[PP]

Patients with glomerular disease should be offered participation in a disease registry and clinical trials, whenever available.
[PP]

Immunoglobulin A nephropathy

Considerations for the diagnosis of immunoglobulin A nephropathy (IgAN):

- IgAN can only be diagnosed with a kidney biopsy.
- Determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.
- There are no validated diagnostic serum or urine biomarkers for IgAN.
- Assess all patients with IgAN for secondary causes.

[PP]

Considerations for the prognostication of primary IgAN:

- Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
- The International IgAN Prediction Tool incorporates clinical information at the time of biopsy and cannot be used to determine the likely impact of any treatment regimen.
- There are no validated prognostic serum or urine biomarkers for IgAN other than eGFR and proteinuria.

[PP]

Considerations for treatment of all patients with IgAN who do not have a variant form of primary IgAN:

- The primary focus of management should be optimized supportive care.
- Assess cardiovascular risk and commence appropriate interventions as necessary.
- Give lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate.

- Other than dietary sodium restriction, no specific dietary intervention has been shown to alter outcomes in IgAN.
- Variant forms of IgAN: IgA deposition with minimal change disease (MCD), IgAN with acute kidney injury (AKI), and IgAN with rapidly progressive glomerulonephritis (RPGN) may require specific immediate treatment.

[PP]

Algorithm for the initial assessment and management of the patient with IgAN.
[PP]

We recommend that all patients have their blood pressure managed. If the patient has proteinuria >0.5 g/d, we recommend that initial therapy be with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).
[1B]

We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB.
[1B]

Considerations for treatment of patients with IgAN who are at high risk of progressive CKD despite maximal supportive care.

- High risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite >90 days of optimized supportive care.
- Immunosuppressive drugs should be considered only in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care (The patients enrolled in the only large randomized controlled trial [RCT] suggesting benefit of immunosuppression had an average of 2.4 g/d of proteinuria).
- In view of the current uncertainty over the safety and efficacy of existing immunosuppressive treatment choices, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial.
- In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognizing that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m^2.
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in IgAN.
- There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy.
- The International IgAN Prediction Tool cannot be used to determine the likely impact of any particular treatment regimen.
- Dynamic assessment of patient risk over time should be performed, as decisions regarding immunosuppression may change.

[PP]

Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable treatment target.
[PP]

We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m^2
[2B]

Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely in situations listed below:

- eGFR <30 ml/min per 1.73 m^2
- Diabetes
- Obesity (BMI > 30kg/m^2)
- Latent infection (e.g viral hepatitis, TB)
- Secondary disease (e.g., cirrhosis)
- Active peptic ulceration
- Uncontrolled psychiatric illness
- Severe osteoporosis

There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when any glucocorticoid therapy should be commenced.
[PP]

There is no data to support efficacy or reduced toxicity of alternate-day glucocorticoid regimens, or dose-reduced protocols.
[PP]

Where appropriate, treatment with glucocorticoid (prednisone equivalent ‡0.5 mg/kg/d) should incorporate prophylaxis against Pneumocystis pneumonia along with gastroprotection and bone protection, according to local guidelines.
[PP]

Management of patients with IgAN who remain at high risk for progression after maximal supportive care.
[PP]

Other pharmacologic therapies evaluated in IgAN
[PP]

Tonsillectomy in IgAN:

- Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.
- Tonsillectomy is suggested in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.
- Multiple studies from Japan have reported improved kidney survival and partial or complete remission of haematuria and proteinuria following tonsillectomy alone or with pulsed glucocorticoids

[PP]

IgAN with nephrotic syndrome:

- Rarely, patients with IgAN present with nephrotic syndrome (including oedema and both hypoalbuminaemia and nephrotic-range proteinuria >3.5 g/d).
- In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling MCD.
- It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.
- Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD
- Patients with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients at high risk of progressive CKD despite maximal supportive care.
- Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (FSGS) (e.g., obesity, uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.

[PP]

IgAN with AKI:

- AKI can occur in patients with IgAN in the context of severe visible haematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks following cessation of the haematuria. Immediate management of AKI with visible haematuria should focus on supportive care for AKI.
- IgAN may also present with AKI either de novo or during its natural history due to an RPGN with extensive crescent formation, commonly in the absence of visible haematuria. In the absence of visible haematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.

[PP]

IgAN with RPGN:

- Rapidly progressive IgANis defined as a >50%decline in eGFR over <3months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.
- A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.
- The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any GFR decline. If this occurs, a second kidney biopsy may be considered.
- Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids in accordance with the guidelines for AAV.
- Prophylactic measures that should accompany immunosuppression.
- There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN

[PP]

IgAN and pregnancy planning:

IgAN is a disease predominantly of young adults, and all women of

childbearing potential should be offered preconception counseling when appropriate.

- Preconception counseling should include a discussion on cessation of renin–angiotensin system (RAS) blockade.
- Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.
- In those women at high risk of progressive CKD despite maximal supportive care, a trial of immunosuppression to optimize immunologic activity and reduce proteinuria prior to conception may be preferable to emergent initiation of immunosuppression during pregnancy.
- Evidence for the use of non-glucocorticoid immunosuppressants in addition to glucocorticoids is scarce, but this approach may be considered in more severe cases.
- As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome.
- Aim for proteinuria <200 mg/d (<400 mg/1.73 m2/d) or PCR <200 mg/g (<0.2 g/g [<20 mg/mmol]).
- Aim for blood pressure at SBP <90th percentile for age, sex, and height.
- Continue to follow patients even after complete remission, as they can relapse even after many years.

[PP]

Immunoglobulin A vasculitis

Unlike children, there are no internationally agreed upon criteria for the diagnosis of IgAV in adults, although a clinical diagnosis of IgAV is often made based on the criteria described for children.
[PP]

In adults with a vasculitic rash typical of IgAV, a kidney biopsy should be performed in the setting of features consistent with a persistent and/or significant nephritis, RPGN, proteinuria >1g/d, and/or impaired kidney function.
[PP]

Assess all adult patients with IgAV for secondary causes.
[PP]

Assess all adult patients with IgAV for malignancy, with age- and sex-appropriate screening tests.
[PP]

Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation, and hypertension and mean proteinuria during follow-up, as predictors of a poor kidney outcome in adults with IgAV. [PP]

The Oxford Classification has not been validated for IgAV.
[PP]

The International IgAN Prediction Tool is not designed for prognostication in IgAV.
[PP]

We recommend not using glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV.
[1B]

Considerations for the treatment of all patients with IgAV-associated nephritis (IgAVN) who do not have an RPGN:

- Assess cardiovascular risk and commence appropriate interventions as necessary.
- Give lifestyle advice, including information on smoking cessation, weight control, and exercise, as appropriate.
- No specific dietary intervention has been shown to alter outcomes in IgAVN.
- Treat to nationally agreed-upon blood pressure targets. KDIGO suggests treating to an SBP target of <120 mm Hg measured using standardized office blood pressure measurement.
- Treat with maximally tolerated dose of ACEi or ARB if proteinuria >0.5 g/d.
- Offer participation in a clinical trial if one is available.

[PP]

Considerations for the treatment of patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care:

- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in patients with IgAVN.
- The presence of crescents in the kidney biopsy is not in itself an automatic indication for commencement of immunosuppression.
- In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient with a recognition that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m2.
- In those patients who wish to try immunosuppressive therapy, treatment with glucocorticoids is as described above for IgAN.

[PP]

IgAV with RPGN:

- The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.
- Patients agreeing to treatment should be treated in accordance with the guidelines for AAV.
- IgAV with RPGN as well as other IgAVN may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.
- There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role for the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV. Clinicians are referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.

[PP]

Membranous nephropathy

A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome

and a positive anti-PLA2R antibody test.
[PP]

Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies antibodies are present or absent.

- Full history (systemic disease, thyroid disease etc) and physical exam (skin, joints)
- Screening for malignancies population- and age-appropriately
- Ultrasound kidneys
- Chest Xray (sarcoidosis)
- HBV, HCV, HIV, treponemal infection (as indicated)
- Drug History (NSAID, gold, penicillamine)
- Anti-nuclear antibodies

[PP]

In patients with MN, use clinical and laboratory criteria to assess the risk of progressive loss of kidney function.
[PP]

All patients with primary MN and proteinuria should receive optimal supportive care.
[PP]

Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury.
[PP]

Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, serum albumin >30 g/l by bromocresol purple (BCP) or immunometric assay, and eGFR >60 ml/min per 1.73 m^2.
[PP]

Immunosuppressive therapy is not required in patients with MN, nephrotic syndrome, and normal eGFR, unless at least one risk factor for disease progression is present or serious complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred.
[PP]

For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI-based therapy for >6 months, with the choice of treatment depending on the risk estimate.
[1B]

Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN and can be used to guide adjustments to therapy.
[PP]

Algorithm for the treatment of patients with MN and initial relapse after therapy.
[PP]

Algorithm for management of patients with treatment-resistant MN
[PP]

Evaluation of a kidney transplant recipient with MN.
[PP]

Prophylactic anticoagulant therapy in patients with MN and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications.
[PP]

Minimal change disease (MCD) in adults

MCD in adults can be diagnosed only with a kidney biopsy.
[PP]

Long-term kidney survival is excellent in patients with MCD who respond to glucocorticoids, but less certain for patients who do not respond.
[PP]

We recommend high-dose oral glucocorticoids for initial treatment of MCD.
[1C]

Algorithm for the initial treatment of MCD in adults.
[PP]

High-dose glucocorticoid treatment for MCD should be given for no longer than 16 weeks. [PP]

Begin tapering of glucocorticoids 2 weeks after complete remission.
[PP]

Although daily oral glucocorticoids are used most often to treat MCD, the route and frequency of administration can be individualized to patient needs.
[PP]

For patients in whom glucocorticoids may be relatively contraindicated, consider initial therapy with cyclophosphamide, a CNI, or MMF.
[PP]

Algorithm for treatment of frequently relapsing (FR)/steroid-dependent (SD) MCD in adults.
[PP]

Treat infrequent relapses with glucocorticoids.
[PP]

We recommend cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) for the treatment of frequently relapsing/steroid dependent MCD, rather than prednisone alone or no treatment.
[1C]

Focal segmental glomerulosclerosis (FSGS) in adults

Adults with FSGS who do not have nephrotic syndrome should be

evaluated for a secondary cause.
[PP]

Immunosuppression should not be used in adults with FSGS of undetermined cause (FSGS-UC), or in those with secondary FSGS.
[PP]

We recommend that high-dose oral glucocorticoids be used as the first-line immunosuppressive treatment for primary FSGS
[1D]

Suggested dosing schedule for glucocorticoids in the initial treatment of primary FSGS.
[PP]

Initial high-dose glucocorticoids should be continued until complete remission is achieved, or as tolerated by patients up to a maximum of 16 weeks, whichever is earlier.
[PP]

Adults with primary FSGS who respond to glucocorticoid treatment should receive glucocorticoids for >6 months.
[PP]

In adults with relative contraindications or intolerance to glucocorticoids, alternative immunosuppression with CNIs should be considered as the initial therapy in patients with primary FSGS.
[PP]

For adults with steroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for >6 months rather than continuing with glucocorticoid monotherapy or not treating.
[1C]

Treatment of steroid-resistant primary FSGS: Suggested dosing schedule for cyclosporine and tacrolimus.
[PP]

Adults with steroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses.
[PP]

Adults who have steroid-resistant primary FSGS with resistance to or intolerance of CNIs should be referred to specialized centers for consideration of re-biopsy, alternative treatment, or enrollment in a clinical trial.
[PP]

Adults with previous steroid-sensitive primary FSGS who experience a relapse can be treated using the same approach as that for adults with relapsing MCD.
[PP]

Infection-related glomerulonephritis

Bacterial infection-related GN

Kidney biopsy can be useful in suspected bacterial infection-related glomerulonephritis (GN), particularly when culture evidence of infection is elusive or the diagnosis is in doubt, to assess prognosis, and/or for potential therapeutic reasons. In some cases, biopsy may be critical for arriving at the correct diagnosis, as comorbidities may contribute to confounding effects.
[PP]

Prognosis and suggested therapy of bacterial infection–related GN.
[PP]

Hepatitis B virus (HBV) infection–related GN

Patients with proteinuric glomerular disease should undergo testing for HBV infection. [PP]

Adult patients with chronic HBV infection should be considered at risk for the development of kidney failure.
[PP]

We recommend that patients with replicative HBV infection (as denoted by HBV DNA levels >2000 IU/ml) and GN receive treatment with nucleos(t)ide analogues as recommended for the general population by standard clinical practice guidelines for HBV infection.
[1C]

Pegylated interferon regimens should not be used to treat patients with replicative HBV infection and GN.
[PP]

Immunosuppressive agents, such as cyclophosphamide or rituximab, may accelerate HBV replication and should be avoided in patients with untreated replicative HBV infection and GN.
[PP]

Rituximab and cyclophosphamide should be avoided in patients with simultaneous HBV infection and anti-PLA2R antibody–mediated MN until a sustained virologic remission has been obtained by nucleos(t)ide analogue therapy.
[PP]

Plasma exchange may be tried in patients with accompanying cryoglobulinemic vasculitis.
[PP]

Hepatitis C virus (HCV) infection–related GN

We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease.

[Not Graded]

We recommend that patients with HCV-associated glomerular disease be treated for HCV.
[1A]

- We recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA.

[1C]

- We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange.

[1C]

- We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease

[1B].

- We recommend rituximab as the first-line immunosuppressive treatment.

[1C]

Human immunodeficiency virus (HIV)–related GN

A kidney biopsy should be performed, when feasible, to evaluate the morphology of HIV-related kidney disease. A pathology-based description of HIV-related kidney disease should be used to help define and guide therapy.
[PP]

The factors contributing to the long-term outcome of HIV infection associated with GN are numerous and include persistence of viral replication, response to antiviral treatment, genetic predisposition to glomerular injury (e.g., APOL1 risk alleles), coinfection with other viruses, and development of immune complex disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.
[PP]

We recommend that antiretroviral therapy be initiated in all patients with HIV and CKD, especially biopsy-proven HIV-associated nephropathy (HIVAN), regardless of CD4 count, adjusted to the degree of kidney function.
[1C]

A decision for the use of glucocorticoids as an adjunct therapy for HIVAN must be made on a case by-case basis, as the risks and benefits long-term are uncertain.
[PP]

Schistosomal nephropathy

Test for appropriate endemic coinfections (Salmonella, HBV, HCV, HIV), as targeted treatment may alter the aggressiveness of an underlying GN or the sequela of schistosomiasis.
[PP]

Obtain a kidney biopsy in patients suspected of having schistosomal GN in the presence of a viral coinfection (HCV, HBV, HIV).
[PP]

Treat patients with schistosomal infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. There are no indications for use of immunosuppressive agents in schistosomal nephropathy.
[PP]

Monitor patients with hepatic fibrosis from schistosomiasis for the development of kidney disease.
[PP]

Evaluate patients with a history of schistosomiasis and an elevated SCr and/or hematuria for bladder cancer and/or urinary obstruction.
[PP]

Filariasis and glomerular disease

Treat patients with filarial infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism.
[PP]

Malarial nephropathy

Treat patients with malarial infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism from blood and hepatosplenic sites. There are no indications for use of immunosuppressive agents in malarial nephropathy.
[PP]

Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury

Evaluate patients with immune complex–mediated GN (ICGN) for underlying disease.
[PP]

Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy.
[PP]

If no underlying etiology is found for ICGN after extensive workup, evaluate for both complement dysregulation and drivers of complement dysregulation.
[PP]

Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at ‡50 years of age.
[PP]

When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process.
[PP]

Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.
[PP]

For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone. [PP]

For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.
[PP]

For patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.
[PP]

For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.
[PP]

For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m2, treat with supportive care alone.
[PP]

Patients who fail to respond to the treatment approaches should be considered for a clinical trial where available.
[PP]

In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.
[PP]

a. Patients who fail to respond to the treatment approaches should be considered for a clinical trial where available.
[PP]

Adoloped from:

1. KDIGO 2021 Clinical Practice Guideline for The Management of Glomerular Diseases. VOL 100 | ISSUE 4S | OCTOBER 2021[12]
2. KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, Official Journal of the International Society of Nephrology, VOLUME 98 | ISSUE 4S | OCTOBER 2020, www. Kidney-international.org[11]

Abbreviations

[PP]: Practice Point
[1C]: Strong Recommendation, Low quality of Evidence
[2 B]: Weak Level Recommendation, Moderate Quality of Evidence
PCR: polymerase chain reaction
IgAN: Ig A Nephropathy
eGFR: Estimated glomerular filtration rate
RAS: renin angiotensin system
AKI: Acute Kidney Injury
CNIs: calcineurin inhibtors
MCD: Minimal Change Disease
MMF: Mycophenolate mofetil
RPGN: Rapidly progressive glomerulonephritis
ACEi: Angiotensin converting Enzyme inhibitor
ARB: Agiotensin II Receptor Blocker
CKD: Chronic kidney disease
RCT: Randomized control trial
MPGN: membranoproliferative glomerulonephritis
MN: membranous nephropathy
FSGS: focal segmental glomerulosclerosis
DAA: direct acting antivirals
AAV: Anca associated glomerulonephritis

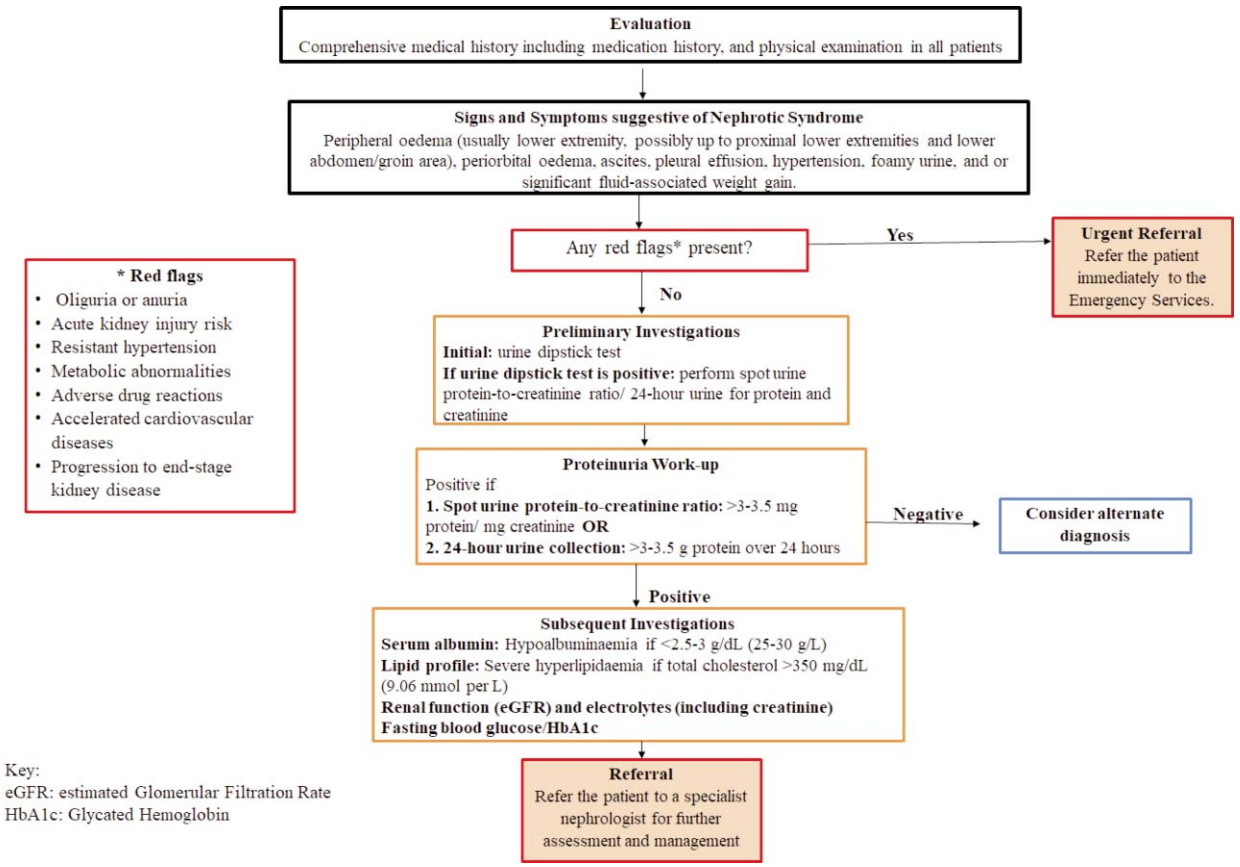

Figure-1: Primary care referral pathway for the management of glomerular diseases.

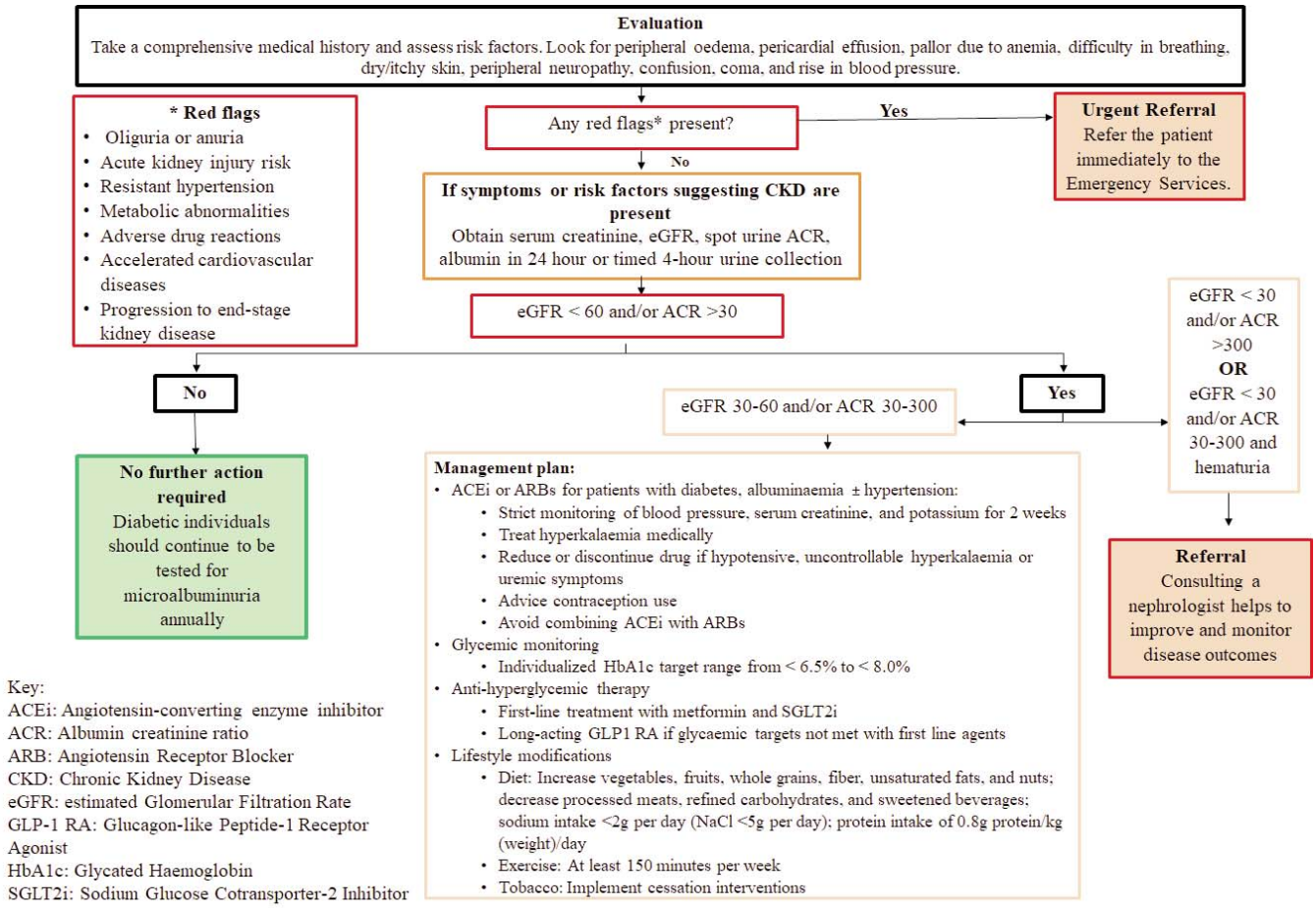

Figure-2: Primary care referral pathway for chronic kidney disease (CKD) in Pakistan patients.

for nephrology care, it is important that a watertight and efficient triage system be developed. An effective triage system helps alleviate the burden on specialist nephrologists, increases and accelerates access to healthcare, improves the quality of referrals, and reduces unneeded specialist visits. Similar action at the national and local levels in the United Kingdom has helped increase the understanding and clinical capacity of GPs, with regards to the management of CKD.[15] In the US, improved partnership between primary care practitioners and specialist nephrologists has led to improved medication management and a reduced exposure to potential nephrotoxins.[16] Thus, it is believed that the referral pathways created currently have the potential to bring about similarly positive changes. In addition, given the resource-constrained setting of Pakistan, timely referral of patients with CKD can also have significant economic benefits.[17]

The current study has a few limitations. Firstly, institutional biases may have affected the decision-making behind the GRADE-ADOLOPMENT process. In addition, the study did not include external stakeholders, such as nephrologists from other institutions, primary care practitioners, and patients themselves. However, the transparency of the GRADE-ADOLOPMENT process will aid GPs to make more informed decisions, while the thorough step-by-step referral pathways will help streamline the referral process. The clear methodology will also aid researchers from other LMICs in the process of developing a similar CPG and referral pathways to suit their own contexts.

Conclusion

Using the GRADE-ADOLPOMENT methodology, evidence-based local CPGs and primary care referral pathways for GPs were developed. These are likely to bring the healthcare system a step closer to achieving optimal health outcomes for CKD patients in Pakistan.

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References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0158765. doi: 10.1371/journal.pone.0158765
2. Jafar TH. The growing burden of chronic kidney disease in Pakistan. N Engl J Med 2006;354:995-7. doi: 10.1056/NEJMp058319
3. Hasan M, Sutradhar I, Gupta RD, Sarker M. Prevalence of chronic kidney disease in South Asia: a systematic review. BMC Nephrol 2018;19:291. doi: 10.1186/s12882-018-1072-5
4. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014;63:713-35. doi: 10.1053/j.ajkd.2014.01.416
5. Jha V, Arici M, Collins AJ, Garcia-Garcia G, Hemmelgarn BR, Jafar TH, et al. Understanding kidney care needs and implementation strategies in low- and middle-income countries: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2016;90:1164-7. doi: 10.1016/j.kint.2016.09.009
6. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017;81:101-10. doi: 10.1016/j.jclinepi.2016.09.009
7. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016;353:i2089. doi: 10.1136/bmj.i2089.
8. Yaqub S, Kashif W, Raza MQ, Aaqil H, Shahab A, Chaudhary MA, et al. General practitioners' knowledge and approach to chronic kidney disease in Karachi, Pakistan. Indian J Nephrol 2013;23:184-90. doi: 10.4103/0971-4065.111842
9. Cabra-Bautista G, Florez ID, Calvache JA. Clinical practice guidelines in low and middle income countries: experiences from colombia. J Clin Epidemiol 2021;138:232-3. doi: 10.1016/j.jclinepi.2021.05.024
10. Haq IU, Rehman ZU. Medical Research in Pakistan; A Bibliometric Evaluation from 2001 to 2020. Libr Philos Pract (e-journal) 2021;2021:e5294.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2020;98(Suppl 4):s1-15. doi: 10.1016/j.kint.2020.06.019.
12. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021;100(Suppl 4):s1-276. doi: 10.1016/j.kint.2021.05.021.
13. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017;81:101-10. doi: 10.1016/j.jclinepi.2016.09.009
14. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4. doi: 10.1001/jama.2013.281053
15. Stevens PE, de Lusignan S, Farmer CK, Tomson CR. Engaging primary care in CKD initiatives: the UK experience. Nephrol Dial Transplant 2012;27(Suppl 3):iii5-11. doi: 10.1093/ndt/gfs103
16. Baldwin MD. The primary care physician/nephrologist partnership in treating chronic kidney disease. Prim Care 2014;41:837-56. doi: 10.1016/j.pop.2014.08.004
17. Lee J, Lee JP, Park JI, Hwang JH, Jang HM, Choi JY, et al. Early nephrology referral reduces the economic costs among patients who start renal replacement therapy: a prospective cohort study in Korea. PLoS One 2014;9:e99460. doi: 10.1371/journal.pone.0099460.

Authors: Contribution:

All Authors were involved in:

i- conceptualization and creation of the guideline via the RADE-ADOLOPMENT process.

ii- Critical revision and final approval.

iii All authors agree to be accountable for all aspects of the work.