Arab Republic of Egypt

Egyptian Pediatric Clinical Practice Guidelines Committee (EPG)
Nephrotic syndrome Group

Evidence-Based Clinical Practice Guideline for steroid-resistant nephrotic syndrome (SRNS)

Adapted with permission from

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome (2020)

Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. Japanese Society of Nephrology and The Japanese Society for Pediatric Nephrology (2015)

KDIGO Clinical Practice Guideline on Glomerular Diseases (2012)

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Disease Work Group. KDIGO 2021.Clinical Practice Guideline for the management of Glomerular Diseases. KidneyInt. (2021).

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Clinical Practice Guidelines (CPGs) are "systematically developed statements to assist health care professionals and patients in medical decision-making for specific clinical conditions" or they are "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options". It is in no way a substitute for a medical professional's independent judgment. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

This CPG is a working document that reflects the state of the art in the field and is based upon the accessible best-updated published evidence. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made considering local resources and individual patient circumstances.

The members of the Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) Guideline Development/ Adaptation Groups (GDG/ GAG) and the external review groups receive no honoraria or expenses to attend the scientific review meetings, nor for the many hours spent reviewing the literature, appraising the guidelines, designing the implementation tools, and contributing to the writing of the report.

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- We acknowledge IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome (2020), Japanese Society of Nephrology and the Japanese Society for Pediatric Nephrology (2015), KDIGO Clinical Practice Guideline on Glomerular Diseases (2012), Kidney disease: Improving Global Outcomes (KDIGO) Glomerular Disease Work Group (2021) and KDIGO 2021 Clinical Practice Guideline for the management of Glomerular Diseases (2021) (the source original guidelines) for their cooperation in providing the permission for adapting our guidelines.
- Finally, we wish the best for all our patients and their families who inspired us. It is for them this work is being finalized.

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Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACR	American College of Rheumatology of SLE
Adolopment	Adoption-Adaptation-Development
AGREE II	Appraisal of Guidelines for Research and Evaluation Instrument
AGBM	Anti-glomerular basement membrane antibodies
AHUS	Atypical hemolytic uremic syndrome
AKI	Acute kidney injury
ANCA	Antineutrophil cytoplasmic antibodies
ANCAV	ANCA vasculitis
APS	Anti-phospholipid syndrome
ARBs.	Angiotensin receptor blockers
ASOT	Antistreptolysin O titer
AZA	Azathioprine
BMD	Bone mineral disease
C3/DDD	Complement 3/dense deposit disease
C3G	Complement 3 glomerulopathy
C3GN	Complement 3 glomerulonephritis
CR	Complete remission
CKD	Chronic kidney disease
CNI	Calcineurin
CPD	Chronic peritoneal dialysis
CPG	Clinical Practice Guideline
CRF	Chronic renal failure
CS	Corticosteroid
CSF	Cerebrospinal fluid
CYC	Cyclophosphamide
CYS R	Cyclosporin resistant

CVD	Cardiovascular disease
DDD	Dense deposit disease
DHS	Demographic and Health Survey
DMS	Diffuse mesangial sclerosis
EM	Electron microscopy
EMA	European Medicines Agency
EPG	Egyptian Pediatrics Clinical Practice Guidelines Committee
EPG CPG	EPG Clinical Practice Guideline
ERG	External Review Group
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
EULAR	European League Against Rheumatism/American College
FR	Frequent relapse
FSGS	focal and segmental glomerulosclerosis
GAG	Guideline Adaptation Group
GDG	Guideline Development Group
GFR	Glomerular filtration rate
GIT	Gastroenteritis
GPS	Good Practice Statement
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GT	Genetic tests
Glucocorticoids	Steroids
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IF	Immunofluorescopy
IFTA	Interstitial fibrosis tubular atrophy
IgAV	IgA vasculitis
IgAN	IgA nephropathy
INR	International formalized ratio
IPNA	International Pediatric Nephrology Association
ISKDC	International Study Kidney Disease in Children
ISN/RPS	International Society of Nephrology/Renal Pathology Society
I.V	Intravenous
IV CYC	Intravenous cyclophosphamide
IV MP	Intravenous methyl prednisone
KDIGO	Kidney Disease International Global outcome
LM	Light microscopy
LN	Lupus nephritis
MCD	Minimal change disease
MCNS	Minimal change nephrotic syndrome
MDR	Multidrug resistant
mg/kg	Milligram of medication per kilogram of body weight
MMF	Mycophenolate mofetil
MN	Membranous nephropathy

MP	Methylprednisolone
MP	Membranoproliferative
NCGL	National Clinical Guideline
NGS	Next-generation sequencing
NS	Nephrotic syndrome
NS-GAG	Nephrotic Syndrome Guideline Adaptation Group
PICO	population, intervention, comparison, and outcomes
PIPOH	Patient population, intervention, professionals, outcomes, and healthcare context
'DN	Prednisone
'E	Plasma exchange
'LA2R	Phospholipase A2 receptor antibodies
PNC	Pediatric nephrology center
PP	Practice point
PR	Partial remission
PSGN	Post streptococcal glomerulonephritis
RASI	Renin angiotensin system inhibitor
RIGHT	A Reporting Tool for Practice Guidelines in Health Care
RPGN	Rapidly progressive glomerulonephritis
SCr	Serum creatinine
SD	Steroid dependent
SLE	Systemic lupus erythematosus
SLEDAI	Diffuse activity index for lupus patients
SRNS	Steroid resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome
TMA	Thrombotic microangiopathy
TX	Transplantation
TTP	Thrombotic thrombocytopenic purpura
UPCR	Urine protein creatinine ratio
VZIG	Varicella-zoster immune globulin
WES	Whole exon sequencing
WGS	Whole genome sequencing

Glossary

Admission

Admission, for the purpose of this guideline, refers to a child being registered and entering inpatient care as a patient. This is distinguished from the term "enrolment", which is used for outpatient care.

Executive Summary

Nephrotic syndrome is one of the most common chronic kidney diseases in children. Steroid sensitive type (SSNS) constitutes about 85–90%, whereas steroid-resistant type (SRNS) only 15–20%. While MCD is the most common histopathology in SS type, children with SRNS have MCD, mesangial proliferative glomerulonephritis, or focal and segmental glomerulosclerosis (FSGS). SRNS is defined as those who do not show remission after 6 weeks and standard dose of oral steroids ± 3 IV MPD doses.

This guideline focuses on prevention and management of steroid-resistant nephrotic syndrome (SRNS).

Guideline development process and methods

After reviewing all the inclusion and exclusion criteria and quality appraisal results, the GDG/ GAG recommended using the following source original clinical practice guidelines (CPGs):

1- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome (2020).
2- Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. Japanese Society of Nephrology and The Japanese Society for Pediatric Nephrology (2015).
3- KDIGO Clinical Practice Guideline on Glomerular Diseases (2012).
4- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Disease Work Group. KDIGO 2021.Clinical Practice Guideline for the management of Glomerular Diseases. KidneyInt. (2021).

We conducted Adolopment for these guidelines: (Adoption, Adaptation, and Development)

- Adoption for most of the guideline recommendations.
- Development of Good Practice Statements

Recommendations and Good Practice Statements (GPS)

This version of the CPG includes recommendations and good practice statements on the following four sub-sections:

A. Diagnosis of steroid-resistant nephrotic syndrome.

The guideline covers infants 3 months till children and adolescents 18 years of age, presenting with nephrotic syndrome in secondary and tertiary healthcare setting like clinics, emergency rooms, dialysis, or transplant wards. Excluded population were infants with congenital NS presenting during the first 3 months of life.

B. Management of steroid-resistant nephrotic syndrome

This section includes recommendations and good practice statements on management of steroid-resistant nephrotic syndrome

We can summarize the guidelines' recommendations for steroid-resistant nephrotic syndrome in the following:

- We recommend clinical assessment to include family history for renal and extra-renal manifestations, consanguinity, patient age at onset of the disease, pattern of response to steroid therapy if already initiated (strong recommendation).
- We recommend careful physical examination of the patient including search for extra-renal manifestations, primary causes drugs, infections, autoimmune diseases. Identify high-Risk patients with severe edema, hypertension, low GFR (Strong recommendation).
- Extended laboratory investigations. We suggest performing Initial Basic Laboratory testing for blood, serum, and urine: Quantification of proteinuria, GFR. Screening for infections (hepatitis B, C, TB, syphilis, HIV and Covid-Sars to rule out secondary types of NS before immunosuppression, especially rituximab. Referral to secondary and tertiary PN centers with genetic facilities as indicated (conditional recommendation).
- We suggest Extended and follow-up investigations to include :
  Urine: Spot urine (first morning void) protein/creatinine or proteinuria 24 H. Urine analysis including hematuria.
  Blood-Complete blood count (CBC): C-reactive protein, creatinine, BUN, or urea, electrolytes, serum albumin, total protein. Estimated GFR
  Lipid profile: (LDL- and HDL-cholesterol, triglycerides)
  Glucose/fasting glucose: HbA1c. -C3, antinuclear antibodies, ds-DNA, ANA, ANCA, APLA2R.
  Infection screen: (bacterial, viral, parasitic). TB, Malaria Schistosomiasis in endemic areas. HBs-Ag, anti-HCV-IgG, syphilis, and HIV test, Immunoglobulin G
  Thyroid function: (T3, T4, TSH), Base line coagulation tests prothrombin time (INR), a PTT, fibrinogen, AT (111), ALP, PTH, 25(OH) vitamin D, Blood gas analysis (HCO3).
  Drug-specific monitoring: as appropriate.
  Imaging: Renal ultrasound, chest X ray, echocardiography, X-ray wrist for bone age for children < 5 y old should be evaluated for selected cases
  Assessment for extra-renal involvement:
  Depending on underlying disease and clinically evident extra-renal features:
  *Brain MRI * Ophthalmology *Cardiology *Endocrinology *Dermatology *Orthopedics *Immunology *Hematology (Good practice statement).
- We suggest genetic testing with high suspicious index for genetic types at any stage of disease presentation
  (1) Early if familial, syndromic, < less than 1 year age at disease onset.
  (2) After 4–6 weeks of steroid therapy for all steroid resistant if possible or those with target priority including (previously mentioned if not done), as well as all SR (FSGS, DMS) and CNI resistant,
  C3GN/DDD with suspected complement mutation, and pretransplant. We suggest Referral to the pediatric nephrology center with genetic experts and facilities being crucial for early diagnosis and proper management of these cases (Good practice statement).
  We strongly recommends the availability of genetic testing in all its university related pediatric nephrology centers and to be covered by medical insurance (Good practice statement).
- Familial, syndromic, congenital/infantile onset. All SRNS at confirmation period, if possible.
  All SRNS biopsy proven as FSGS/DMS to identify genetic types.

All SRNS/CNIs resistant after 6 m cyclosporine trial.
All C3GN/DDD with suspected complement mutation, resistant to plasma exchange and MMF. Such cases need treatment with complement blockade even after transplant to avoid recurrence.
All pretransplant donor and recipients as we follow live related donor transplant in a community with high rate of consanguinity (Good practice statement).

- We recommend Gene Panel SGS unless mutation is likely known where single gene analysis is recommended (Strong recommendation).
- We ssuggest referral to centers with genetic experts to:
  Avoid use of steroids and immunosuppressive, renal biopsy, pre- and posttransplant aggressive protocols of PE, and rituximab that are recommended for idiopathic nonhereditary FSGS (conditional recommendation).
  Allow genetic counseling, prenatal diagnosis. Transplant carries low recurrence rate (Good practice statement).
  In these centers, pre-transplant care is available and well presented (nutritional support, CPD, management of complications as infection and thrombosis), proper selection of donors especially when potential donors are family related and when disease inheritance is unidentified (Good practice statement).
- Special treatment is available for some types as Q. Early diagnosis and management control progress of extra renal manifestations as well (Good practice statement).
- We recommend Renal Biopsy (LM, IF, EM) for all SRNS excluding genetic types especially those known as CNIs resistant and also secondary NS related to drugs, infections, or malignancy (strong recommendation).
- In countries where genetic tests are not available or limited to few tertiary centers or expensive and not covered with medical insurance, renal biopsy and lab immunology may be the gold standard diagnostic workup for NS in children test to put therapeutic plan and predict disease outcome based on renal histopathology (strong resommendation).
- We recommend ACI or ARBS to start early at 4th week (strong recommendation).
- We suggest to avoided it in CKD, AKI, hyperkalemia, volume depletion, and female adolescent (Good practice statement).
- We recommend statin in MDR, high LDL cholesterol, control of BP if 95th (strong recommendation). calcium, vitamin D (conditional recommendation) levothyroxine T4 if hypothyroidism (strong recommendation), magnesium if hypomagnesaemia (conditional recommendation). Diuretics to treat edema if severe, considering the risk of hypovolemia and thrombosis in under filled patients (Good practice statement).
- We recommend oral or IV furosemide if severe edema. In refractory edema, metolazone, thiazides, and amiloride potassium sparing diuretic (conditional recommendation).
- Albumin infusion 1 mg/kg 20–25% albumin over 4 h with furosemides at the middle and the end (Good practice statement).
- We recommend identification of the cause of SRNS (1) secondary type need treatment of the cause (infections, drugs, auto immune disease). (2) Genetic types. Mostly need supportive care till transplantation is available, showing low recurrence rate. (3) Idiopathic types (MCD, FSGS, DMS) and (IMP, IMN) need immunosuppressive therapy (strong recommendation).
- We recommend for treatment plan to be based on cause, genetic testing, renal biopsy and lab immunology findings, and clinical severity of disease (GFR, presence of extrarenal manifestations) at its presentation (Good practice statement).

- We suggest to avoid excess salt intake 2 mEq/kg/day, with balanced fluid intake (conditional recommendation).
- We suggest statin in MDR, high LDL (conditional recommendation), control of BP if > 95th percentile (strong recommendation), calcium, vitamin D, (conditional recommendation), levothyroxine T4 if hypothyroidism (strong recommendation) magnesium if hypomagnesaemia (conditional recommendation).
- For prevention of infection, we suggest IVIG for children with recurrent infections or low IgG, (conditional recommendation).
- no routine antibiotics, cotrimoxazole in patients on rituximab 5–10 mg/kg/day three times weekly 3–6 m (conditional recommendation).
- Cotrimoxazole in patients on rituximab 5–10 mg/kg/day three times weekly 3–6 m (conditional recommendation).
- Receiving all vaccinations pneumococcal, meningococcal, influenza, and varicella (strong recommendation).
- Live vaccines should not be given to SR. on immunosuppressive. Family members can get live vaccines to limit risk of transfer to immunocompromised children but avoid exposure to their urine, stool, and respiratory excreta for 3–6 weeks after vaccination (Good practice statement).
- We recommend VZIG (Strong recommendation).
- on exposure to chickenpox, treatment with acyclovir 10 mg/kg 7 days within 7–10 days of exposure, varicella vaccine in remission (conditional recommendation).
- We suggest mobilization, avoid central lines (Good practice statement).
- We suggest low molecular weight heparin in previous history of thrombosis, central lines, hereditary thrombophilia predisposition, infection, or dehydration (conditional recommendation).
- We suggest thrombophilia screen in previous conditions for protein S, antithrombin, and factor V genes (conditional recommendation).
- While on dialysis and or waiting for kidney Transplant we recommend discussing with the family and dialysis team benefit risk of transplantation and post TX recurrence rate (Strong recommendation).
- We recommend daily monitoring of proteinuria for assessment of native residual function (Strong recommendation).
- We suggest nephrectomy if TX will be done before resolution of NS or if proteinuria is severe to minimize risk of thromboembolism (conditional recommendation).
- We recommend genetic tests to recipients as hereditary types show low recurrence as compared to non-genetic types (Strong recommendation).
- Discuss benefit risks for genetic and non- genetic. 43% of total kidney transplants in Egyptian children through 2009/2017 registry were identified as hereditary ESRD (Strong recommendation).
- We recommend TX ESRD/SRNS regardless of genetic or non-genetic (Strong recommendation).
- We recommend living related donor. Living related allograft donors should do GT as a part of evaluation in SRNS (Good practice statement).
- Donors candidate with a pathogenic or likely pathogenic variant in a dominant gene with or without symptoms to be excluded as a potential donor (Good practice statement).
- Carrier of recessive SRNS variant may be a potential donor after genetic counseling except in COL4A5, COL4A3, and COL4A4 (conditional recommendation).

- Asymptomatic carriers of a variant with unknown significance may be considered a TX donor following extensive evaluation and counseling where other organ donation options are not available (conditional recommendation).
- We recommend discussing risk of recurrence or graft failure with the donor (Strong recommendation).
- We ssuggest discouraging living related donation to recipients with previous recurrence in previous graft. Cadaveric graft always remains a better option than dialysis (conditional recommendation).
- We suggest for early diagnosis of recurrence, post TX monitoring of proteinuria daily for 4 months, weekly for 4 months, and monthly for 4 months for 1 year as a predictor of recurrence after exclusion of other causes; however, renal biopsy is conclusive (conditional recommendation).
- We suggest for prevention or of recurrence in high-risk types, pre and post-transplant plasma exchange (conditional recommendation).
- We suggest treating recurrence with pulse MPD, CNIs, rituximab, and plasma exchange (conditional recommendation).
- We recommend on recurrence to start RASI re-transplant as the deceased donor is ethically acceptable and considered more appropriate than dialysis (conditional recommendation).

Guideline Registration

PREPARE (Practice guideline REgistration for transPAREncy), WHO Collaborating Center for Guideline Implementation and Knowledge Translation, EBM Center, University of Lanzhou, Lanzhou, China. **Registration Number:** ((submitted and in process)). Link: http://www.guidelines-registry.org/

Introduction

Most nephrotic children have steroid-sensitive nephrotic syndrome (SSNS), with only 20% of them having steroid resistant nephrotic syndrome (SRNS), depending on the geographic area [1]. MCD is the most common histopathology in SSNS, while children with SRNS have MCD, mesangial proliferative glomerulonephritis, or focal and segmental glomerulosclerosis (FSGS) [2]. In children, SRNS is defined as those who do not show remission after 6 weeks and standard dose of oral steroids ± 3 IV MPD doses [3]. Most nephrotic children (85–92%) show idiopathic type that affects only the kidney without extrarenal involvement and without identifiable cause. MCD pathology constitutes (75–85%) and FSGS (7–10%), while other histological types are rare [KDIGO 2021] [4]. The secondary type where the immune complex renal injury is mediated by a primary cause is less common and is related to drugs, infections, and autoimmune diseases such as lupus, IgAV, ANCA vasculitis, Wegner granulomatosis, AGBM, sarcoidosis, malignancies, and sickle cell disease.
Congenital and hereditary podocytopathies constitute two thirds of SRNS presenting in the first year of life and result from mutation in podocytes regulating genes [KDIGO 2021] [4]. Identification of a podocyte gene defect is fundamental to determine treatment response to steroids and calcineurin inhibitors. It is far superior to histopathology classification in predicting response to immune suppression, clinical course and progress to ESRD, and risk of post-transplant recurrence, thereby subsequent management of SRNS. To date, over sixty

genes have been identified as causing monogenic forms of SRNS recessive or dominant with an onset before 25 years [5–8]. Family counseling, screening of at-risk family members, and prenatal diagnosis are major steps following genetic diagnosis.
Renal biopsy and antibody serology is also crucial. Light microscopy identifies histopathology as MCD, FSGS, DMS or MP, MN and grade tubular atrophy, interstitial fibrosis, and glomerulosclerosis as prognostic markers of chronicity [9]. Occasionally, SRNS is secondary to infectious disease, drugs, and autoimmune disease such as SLE, IgA vasculitis, and malignancy. Therefore, infection screen for viruses and bacteria as well as serology tests for antibodies (ASOT, ANA, ADNA, ANCA, PLA2R ab) are important. Renal biopsy with immunofluorescence reports immune complex/complement deposits with pauci or linear or granular pattern. This helps in the diagnosis of SLE, IgAV, ANCAV, C3 C4/DDD, and immune complement mediated with membranoproliferative changes [KDIGO 2021] [4]. Electron microscopy reports the ultrastructure of glomerular basement membrane
(GBM) and podocytes that are helpful in many hereditary and syndromic types. Light microscopy without IF and EM is not enough as it would report only histopathology without referring to pathogenesis if immune complex mediated or genetic in origin [10].
SRNS without genetic mutation is expected to respond to immunosuppressive drugs with complete remission in up to 60% of cases and with partial remission in up to 19%. Those with no genetic mutation have a substantial advantage in terms of kidney survival over 10 years, with ESRD occurring in 71% of those with a genetic disease versus 29% in those without [11, 12]. Genetic types need transplantation with less rate of disease recurrence. Early treatment of infections (bacterial, viral, parasitic) [13–15], and proper treatment of auto immune disease according to its therapy plan is mandatory to prevent progress of renal injury [16, 17]. Current EPG/SRNS is an adaptation GL using both de novo IPNA 2020 and KDIGO 2021 guidelines customized to our community with high rate of infections,
consanguinity, autoimmune diseases such as SLE, and with shortage of genetic testing as routine screening for all SRNS. Renal biopsy and lab immunology are more available and thereby were suggested for EPG based on immune suppressive drug therapy plans. However, exclusion of genetic and secondary types is mandatory, as this significantly determine therapy plan.

Purpose and Scope
These guidelines have been developed to standardize the delivery of services and to implement the guidance on the diagnosis and management of steroid-resistant nephrotic syndrome.
It provides guidance to physicians (viz. pediatrics, primary healthcare, family medicine, pediatric nephrology), nurses, and clinical pharmacists.
This version of the guideline includes recommendations and good practice statements for diagnosis and management of steroid-resistant nephrotic syndrome.

Methods

Methods of search:
A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. Keywords used for search are: Steroid-resistant nephrotic syndrome, Diagnosis, Treatment, Follow up, Pediatric guidelines.
Inclusion / exclusion criteria followed in the search and retrieval of guidelines to be adapted:

• Selecting only evidence-based guidelines (guideline must include a report on methodology of development including the systematic literature searches and explicit links between individual recommendations and their supporting evidence)
• Selecting national and/or international guidelines
• Specific range of dates for publication (using Guidelines published or updated 2013 and later or the last 5 years)
• Selecting peer-reviewed publications only
• Selecting guidelines written in English language
• Excluding guidelines written by a single author
The following three categories of databases and websites were searched:

1. *CPG databases and libraries (e.g., GIN, ECRI, SIGN, DynaMed, BIGG-REC PAHO)*
2. *Bibliographic databases (e.g., PubMed, Google Scholar)*
3. *Specialized professional societies (related to the pediatric subspecialty)*

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. The panel decided a cut-off point or rank the guidelines (any guideline scoring above 60% on the rigor dimension was retained)
After reviewing all the previous criteria the GDG/ GAG recommended using 5 guidelines:

1- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome (2020).
2- Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. Japanese Society of Nephrology and The Japanese Society for Pediatric Nephrology (2015).
3- KDIGO Clinical Practice Guideline on Glomerular Diseases (2012).
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We did Adolopment for these guidelines: (Adoption, Adaptation, and Development)

- Adoption for most of the guideline recommendations.
- Development of Good Practice Statement

Contributors to the guideline development process:
Guideline Development Group (GDG)/ Guideline Adaptation Group (GAG):
The GDG/ GAG included two subgroups; the clinicians/ healthcare providers subgroup and the guideline methodologists' subgroup.
Clinicians Subgroups
The clinicians' subgroup or clinical panel for this guideline included experts with a range of knowledge, technical skills and diverse perspectives in the field of pediatric nephrology.
The main functions of the clinical panel were adolopment of diagnosis and management of steroid-resistant nephrotic syndrome Guidelines, determining the scope of the guideline and guideline, reviewing the evidence, and formulating evidence-informed recommendations in case of changing strength of recommendations.
Guideline Methodologists Subgroup
There were 3 guideline methodologists with expertise in guidelines development, adaptation, GRADE and translation of evidence into recommendations. Methodologists provided orientation and overview of evidence-informed guideline development processes using the GRADE approach, guideline adaptation using the Adapted ADAPTE, provided AGREE II

assessment of the source guidelines in collaboration with the clinicians subgroup, generation of the EtD frameworks whenever applicable.

External Review Group:

The External Review Group for this guideline comprises 4 clinical experts who have interest and expertise in pediatric nephrology.

They were identified by Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) as people who can provide valuable insights during the guideline development process.

The External Review Group was asked to comment on (peer review) the final guideline to identify any criticism on the content and to comment on clarity and applicability as well as issues relating to implementation, dissemination, ethics, regulations, or monitoring, but not to change the recommendations formulated by the GDG/ GAG. The members of the External Review Group were required to submit declarations of interest before the peer review process.

Guideline Development/ Adaptation Group meetings:

GDG/ GAG meetings were organized virtually (weekly/bimonthly). Due to the extensive scope of the guideline, EPG was responsible for overseeing the adolopment process. the timetable and objectives of each meeting. GDG/ GAG meetings were also attended by members of the methodologists. Working rules for each contributor type were outlined by the chair at the start of each meeting, covering aspects such as vocal rights, voting, and evidence to decision and recommendation formulating processes.

Declarations of interests:

Prospective members of the GDG/ GAG were asked to fill in and sign the standard WHO declaration of interest and confidentiality undertaking forms. All guideline members and methodologists were also asked to fill in and sign the standard WHO declaration-of-interests.

Members of the external review group will be asked to fill in and sign the standard WHO declaration-of-interests form before the peer review process.

Evidence for the guideline:

We used the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) for assigning the quality of evidence and strength of recommendations that includes the following definitions [18]. Informed by the evidence required for the GRADE Evidence to Decision (EtD) framework(s) was(were) done while considering changing strength of recommendations according to availability of some resources in the recommendations. Both ETD and changing strength of recommendation were not done in this guideline).

Description of the interpretation of the GRADE four levels of certainty of evidence:

Table 1. Classification of the Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

GRADE EtD's contextual factors, criteria and considerations that link to the strength of recommendations:

Criteria and Considerations:

1. Benefits and harms: When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks/harms), considering any previous recommendation or another alternative. The larger the gap or gradient in favor of the desirable effects over the undesirable effects, the more likely that a strong recommendation will be made.

2. Certainty of the evidence about the effects: The higher the certainty of the scientific evidence base, the more likely that a strong will be made.

3. Values and preferences: If there is no important uncertainty or variability in how much people value the main outcomes, it is likely that a strong recommendation will be made. Uncertainty or variability around these values that could likely lead to different decisions, is more likely to lead to a conditional recommendation.

4. Economic implications: Lower costs (monetary, infrastructure, equipment or human resources) or greater cost-effectiveness are more likely to support a strong recommendation.

5. Equity and human rights: If an intervention will reduce inequities, improve equity or contribute to the realization of human rights, the greater the likelihood of a strong recommendation.

6. Feasibility: The greater the feasibility of an intervention to all stakeholders, the greater the likelihood of a strong recommendation.

7. Acceptability: If a recommendation is widely supported by health workers and program managers and there is widespread acceptance for implementation within the health service, the likelihood of a strong recommendation is greater.

Table 2. Classification of the Strengths of Recommendations

Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (or vice versa), so most patients should receive the recommended course of action.

Conditional	There is uncertainty about the trade-offs. The clinician and patient need to discuss the patient's values and preferences, and the decision should be individualized.

Developing good practice statements:
The GDG/ GAG also developed good practice statements for this guideline, which are actionable messages relevant to the guideline questions. The justification for each good practice statement was carefully considered by the GDG/ GAG with an emphasis that they are clearly needed. Good practice statements were developed, guided by the following GRADE criteria:
1- Message is really necessary with regard to actual healthcare practice
2- Have large net positive consequence (relevant outcomes and downstream consequences) (GRADE EtD domains)
3- Collecting and summarizing the evidence is a poor use of time and resources
4- Include awell-documented, clear rationale connecting indirect evidence
5- Are clear and actionable statements.
The GDG/ GAG collectively drafted and finalized good practice statements with relevant justifications and remarks to help with their interpretation, with close support and input from the consultant and guideline methodologists.

We have used the Reporting Items for Practice Guidelines in Healthcare (RIGHT) extension for adapted guidelines (RIGHT-Ad@pt Tool) as a reporting checklist for this guideline adaptation process as recommended by the EQUATOR network.

Recommendations

Table 3. Recommendations					
A. **Definition**					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**

A1	What are the Definitions related to Nephrotic Syndrome?	IPNA 2020	defined as nephrotic children not responding to 4–6 weeks of standard oral steroids ± 3 IV methyl prednisone pulses We Recommend all definitions included in **Table (4)**	**high**	**Strong**

Table (4)

Term	Definitions
Nephrotic-range proteinuria	**UPCR ≥ 200 mg/mmol (2 mg/mg) in first morning void or 24 h urine sample ≥ 1000 mg/m^2/day corresponding to 3+ or 4+ by urine dipstick.**
Nephrotic syndrome	**Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/l) or edema when serum albumin level is not available.**
Complete remission	**UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on three or more consecutive occasions.**
Partial remission	**UPCR (based on first morning void or 24 h urine sample) > 20 but < 200 mg/mmol and, if available, serum albumin ≥ 30 g/l.**
Relapse	**Relapse Recurrence of nephrotic-range proteinuria.** **∗ In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥ 3+ on 3 consecutive days, or** **UPCR ≥ 200 mg/mmol (2 mg/mg) on a first morning urine sample, with or without reappearance of edema in a child who had previously achieved partial or complete remission.**
Confirmation Period	**Time period between 4 and 6 weeks from PDN initiation during which response to further oral PDN and/or pulses of iv MPDN and RAASi are ascertained in patients achieving only partial remission at 4 weeks.** **∗ A patient achieving complete remission at 6 weeks is defined as a late responder.** **∗ A patient not achieving complete remission at 6 weeks although he had achieved partial remission at 4 weeks is defined as SRNS.**
SSNS	**Complete remission within 4 weeks of prednisone or prednisolone (PDN) at standard dose (60 mg/m^2/day or 2 mg/kg/day, maximum 60 mg/day).**
Infrequent relapsing NS	**< 2 relapses per 6 months or < 4 relapses per 12 months.**
Frequent relapsing NS	**≤ 2 relapses per 6 months or ≤ 4 relapses per 12 months.**
Steroid dependent NS	**Relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation.**
SRNS	**Lack of complete remission within 4 weeks of treatment with PDN at standard dose.**
Late Responder NS	**Complete remission at 6 weeks.**
CNI-resistant SRNS	**Absence of at least partial remission after 6 months of treatment with a CNI at adequate doses and/or levels.**
Multi-drug-resistant SRNS	**Absence of complete remission after 12 months of treatment with 2 mechanistically distinct steroid-sparing agents at standard doses (see text).**

Secondary steroid resistance	**Children with initial steroid-sensitivity who in subsequent relapses develop SRNS.**
Recurrent nephrotic syndrome post-renal transplantation	**A child with SRNS presenting post-renal transplantation with a relapse of nephrotic-range proteinuria in the absence of other apparent causes and/or podocyte foot process effacement on kidney biopsy.** **This diagnosis should also be considered in case of persistent proteinuria (UPCR ≥ 100 mg/mmol (1 mg/mg) in a previously anuric patient, or** **An increase of UPCR ≥ 100 mg/mmol (1 mg/mg) in a patient with prevalent proteinuria at the time of transplant in the absence of other apparent causes.**
Table abbreviations	
UPCR urine protein/creatinine ratio, SSNS steroid sensitive nephrotic syndrome, SRNS steroid-resistant nephrotic syndrome, PDN prednisolone or prednisone, MPDN methylprednisolone, RAASi renin-angiotensin-aldosterone system, CNI calcineurin inhibitor	

Table 5. Recommendations					
B. Diagnosis					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
B1	What are the Initial Diagnosis workup of a child with SRNS?	IPNA 2020	We recommend clinical assessment to include family history for renal and extra-renal manifestations, consanguinity, patient age at onset of the disease, pattern of response to steroid therapy if already initiated	**High**	**Strong**
		IPNA 2020	We recommend careful physical examination of the patient including search for extra-renal manifestations, primary causes drugs, infections, autoimmune diseases. Identify high-Risk patients with severe edema, hypertension, low GFR.	**High**	**Strong**

		IPNA 2020	Extended laboratory investigations We suggest performing Initial Basic Laboratory testing for blood, serum, and urine: Quantification of proteinuria, GFR. Screening for infections (hepatitis B, C, TB, syphilis, HIV and Covid-Sars to rule out secondary types of NS before immunosuppression, especially rituximab. Referral to secondary and tertiary PN centers with genetic facilities as indicated.	**Low**	**conditional**
			We recommend Extended and follow-up investigations to include : **Urine**: Spot urine (first morning void) protein/creatinine or proteinuria 24 H. Urine analysis including hematuria. **Blood-Complete blood count (CBC):** C-reactive protein, creatinine, BUN, or urea, electrolytes, serum albumin, total protein. Estimated GFR **Lipid profile:** (LDL- and HDL-cholesterol, triglycerides)		**Good practice statement**

			Glucose/fasting glucose: HbA1c. -C3, antinuclear antibodies, ds-DNA, ANA, ANCA, APLA2R. **Infection screen:** (bacterial, viral, parasitic). TB, Malaria Schistosomiasis in endemic areas. HBs-Ag, anti-HCV-IgG, syphilis, and HIV test, Immunoglobulin G **Thyroid function:** (T3, T4, TSH), Base line coagulation tests prothrombin time (INR), a PTT, fibrinogen, AT (111), ALP, PTH, 25(OH) vitamin D, Blood gas analysis (HCO3). **Drug-specific monitoring:** as appropriate. **Imaging:** Renal ultrasound, chest X ray, echocardiography, X-ray wrist for bone age for children < 5 y old should be evaluated for selected cases **Assessment for extra-renal involvement:** Depending on underlying disease and clinically evident extra-renal features: *Brain MRI *Ophthalmology *Cardiology *Endocrinology *Dermatology *Orthopedics *Immunology *Hematology		

Table 6. Recommendations		

C. Genetic testing					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
C 1	When we recommend genetic testing?	IPNA 2020	We recommend genetic testing with high suspicious index for genetic types at any stage of disease presentation (1) Early if familial, syndromic, < less than 1 year age at disease onset. (2) After 4–6 weeks of steroid therapy for all steroid resistant if possible or those with target priority including (previously mentioned if not done), as well as all SR (FSGS, DMS) and CNI resistant, C3GN/DDD with suspected complement mutation, and pretransplant. We suggest Referral to the pediatric nephrology center with genetic experts and facilities being crucial for early diagnosis and proper management of these cases.		**Good practice statement**

		IPNA 2020	We strongly recommends the availability of genetic testing in all its university related pediatric nephrology centers and to be covered by medical insurance.		**Good practice statement**
C 2	What are the target population for referral?	IPNA 2020	• Familial, syndromic, congenital/infantile onset. All SRNS at confirmation period, if possible. • All SRNS biopsy proven as FSGS/DMS to identify genetic types. All SRNS/CNIs resistant after 6 m cyclosporine trial. All C3GN/DDD with suspected complement mutation, resistant to plasma exchange and MMF. Such cases need treatment with complement blockade even after transplant to avoid recurrence. All pretransplant donor and		**Good practice statement**

C 3	Which tests and why recommended ?		recipients as we follow live related donor transplant in a community with high rate of consanguinity.		
		IPNA 2020	We recommend Gene Panel SGS unless mutation is likely known where single gene analysis is recommended.	**Intermediate**	**Strong**
		IPNA 2020	We recommend referral to centers with genetic experts to: • Avoid use of steroids and immunosuppressive , renal biopsy, pre- and posttransplant aggressive protocols of PE, and rituximab that are recommended for idiopathic nonhereditary FSGS.	**Low**	**conditional**
		IPNA 2020	• Allow genetic counseling, prenatal diagnosis. Transplant carries low recurrence rate. .		**Good practice statement**

		Ozaltin 2014 IPNA 2020	• In these centers, pre-transplant care is available and well presented (nutritional support, CPD, management of complications as infection and thrombosis), proper selection of donors especially when potential donors are family related and when disease inheritance is unidentified. • Special treatment is available for some types as Q. Early diagnosis and management control progress of extra renal manifestations as well		**Good practice statement** **Good practice statement**

Table 7. Recommendations					
D. Renal biopsy					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
D1	What are the indications of renal biopsy in the initial presentation of NS?	IPNA 2020 IPNA 2020	We recommend Renal Biopsy (LM, IF, EM) for all SRNS excluding genetic types especially those known as CNIs resistant and also secondary	**High** **Intermediate** **High**	**Strong** **Strong** **Strong**

		IPNA 2020	NS related to drugs, infections, or malignancy. In countries where genetic tests are not available or limited to few tertiary centers or expensive and not covered with medical insurance, renal biopsy and lab immunology may be the gold standard diagnostic workup for NS in children test to put therapeutic plan and predict disease outcome based on renal histopathology.	**Intermediate**	**Strong**

Table 8. Recommendations					
E. treatment					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
E 1	What is the first line treatment drug in first episode?	IPNA 2020	ACI or ARBS to start early at 4th week,	**Intermediate**	**Strong**
			avoided in CKD, AKI, hyperkalemia, volume depletion, and female adolescent.		**Good practice statement**
			Statin. We suggest statin in MDR, high LDL	**High**	**Strong**

E 2	Should vitamin D & Calcium supplements be routinely given to FR&SD?		cholesterol, control of BP if 95th,		
			calcium, vitamin D,	**Low**	**Conditional**
			levothyroxine T4 if hypothyroidism,	**High**	**Strong**
			magnesium if hypomagnesaemia.	**Very low**	**conditional**
			Diuretics to treat edema if severe, considering the risk of hypovolemia and thrombosis in under filled patients.		**Good practice statement**
			We recommend oral or IV furosemide if severe edema. In refractory edema, metolazone, thiazides, and amiloride potassium sparing diuretic.	**Low**	**conditional**
			Albumin infusion 1 mg/ kg 20–25% albumin over 4 h with furosemides at the middle and the end.		**Good practice statement**

	What are your	IPNA 2020 KDIGO 2021	We recommend identification of the cause of SRNS (1) secondary type need treatment of the cause (infections, drugs, auto immune disease). (2) Genetic types. Mostly need supportive care till transplantation is available, showing low recurrence rate. (3) Idiopathic types (MCD, FSGS, DMS) and (IMP, IMN) need immunosuppressive therapy.	**Intermediate**	**Strong**
		KDIGO 2021	We recommend for treatment plan to be based on cause, genetic testing, renal biopsy and lab immunology findings, and clinical severity of disease (GFR, presence of extrarenal manifestations) at its presentation.		**Good practice statement**

E 3	(Diet, Fluids, Activity) recommendations?	IPNA 2020	We suggest to avoid excess salt intake 2 mEq/kg/day, with balanced fluid intake.	**Low**	**Conditional**
			We suggest statin in MDR, high LDL,	**Low**	**Conditional**
			control of BP if > 95th percentile,	**High**	**Strong**
			calcium, vitamin D,	**Low**	**Conditional**
			levothyroxine T4 if hypothyroidism,	**High**	**Strong**
			magnesium if hypomagnesaemia	**Very low**	**Conditional**
			For prevention of infection, we suggest IVIG for children with recurrent infections or low IgG,	**Very low**	**Conditional**
			no routine antibiotics, cotrimoxazole in patients on rituximab 5–10 mg/kg/day three times weekly 3–6 m.	**Low**	**Conditional**

			cotrimoxazole in patients on rituximab 5–10 mg/kg/day three times weekly 3–6 m.	**Low**	**Conditional**
E 4	What are the recommended vaccinations?		Receiving all vaccinations pneumococcal, meningococcal, influenza, and varicella.	**High**	**Strong**
			Live vaccines should not be given to SR on immunosuppressive. Family members can get live vaccines to limit risk of transfer to immunocompromised children but avoid exposure to their urine, stool, and respiratory excreta for 3–6 weeks after vaccination.		**Good practice statement**
			We recommend VZIG.	**High**	**Strong**
			on exposure to chickenpox, treatment with acyclovir 10 mg/kg 7 days within 7–10 days of exposure,	**Low**	**Conditional**

			varicella vaccine in remission.		
E 5	What information & instructions you like to share with the family during follow-up? prevention of thrombosis		We recommend mobilization, avoid central lines.		**Good practice statement**
			• We suggest low molecular weight heparin in previous history of thrombosis, central lines, hereditary thrombophilia predisposition, infection, or dehydration.	**Low**	**Conditional**
			• We recommend thrombophilia screen in previous conditions for protein S, antithrombin, and factor V genes.	**Low**	**Conditional**

Table 9. Recommendations					
F. Management of SRNS/ESRD					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**

F 1	What information & instructions you like to share with the family considering transplantation ?	IPNA 2020	While on dialysis and or waiting for kidney Transplant we recommend discussing with the family and dialysis team benefit risk of transplantation and post TX recurrence rate.	**High**	**Strong**
			We recommend daily monitoring of proteinuria for assessment of native residual function.	**High**	**Strong**
			We recommend nephrectomy if TX will be done before resolution of NS or if proteinuria is severe to minimize risk of thromboembolism.	**Very low**	**conditional**
			We recommend genetic tests to recipients as hereditary types show low recurrence as compared to non-genetic types.	**Intermediate**	**Strong**
			Discuss benefit risks for genetic		

			and non- genetic. 43% of total kidney transplants in Egyptian children through 2009/2017 registry were identified as hereditary ESRD.	**High**	**Strong**

Table 10. Recommendations					
G. Proper donor selection					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
G 1	What information & instructions you like to share with the family considering transplantation & donor?		We recommend TX ESRD/SRNS regardless of genetic or non-genetic. We recommend living related donor. Living related allograft donors should do GT as a part of evaluation in SRNS. Donors candidate with a pathogenic or likely pathogenic variant in a dominant gene with or without symptoms to be excluded as a potential donor.	**Intermediate**	**Strong** **Good practice statement** **Good practice statement**

			Carrier of recessive SRNS variant may be a potential donor after genetic counseling except in COL4A5, COL4A3, and COL4A4.	**Low**	**conditional**
			Asymptomatic carriers of a variant with unknown significance may be considered a TX donor following extensive evaluation and counseling where other organ donation options are not available.	**Low**	**conditional**

Table 11. Recommendations					
H. Recurrence risk					
N	**Health questions**	**Source Guideline**	**Recommendations**	**Quality of evidence**	**Strength of Recommendation**
H1	What information & instructions you like to share with the family considering recurrence?		We recommend discussing risk of recurrence or graft failure with the donor. We recommend discouraging living related	**High**	**Strong**

			donation to recipients with previous recurrence in previous graft. Cadaveric graft always remains a better option than dialysis.	**Low**	**conditional**
			We recommend for early diagnosis of recurrence, post TX monitoring of proteinuria daily for 4 months, weekly for 4 months, and monthly for 4 months for 1 year as a predictor of recurrence after exclusion of other causes; however, renal biopsy is conclusive	**Low**	**conditional**
			We suggest for prevention or of recurrence in high-risk types, pre and post-transplant plasma exchange.	**Low**	**conditional**
			We recommend treating recurrence with pulse MPD, CNIs, rituximab, and plasma exchange.	**Low**	**conditional**

			We recommend on recurrence to start RASI re-transplant as the deceased donor is ethically acceptable and considered more appropriate than dialysis.	**Low**	**conditional**

Evidence to recommendations: Considerations

The GDG/ GAG was guided by the results of the AGREE II appraisals of the eligible CPGs and thoroughly reviewed the recommendations of the original source WHO CPGs in consideration of local contextual factors related to the national Egyptian health system like burden of the disease, equity, acceptability, feasibility, and other relevant factors. The GDG decided through an informal consensus process to adopt most recommendation. Both ETD and changing strength of recommendation were not done in this guideline).
Also, GDG/ GAG develops group of good practice statements to improve acceptability and feasibility.

Implementation Tools and Considerations

To improve healthcare provision, quality, safety, and patient outcome, evidence-based recommendations must not only be developed, but also disseminated and implemented at national and local levels and integrated into clinical practice.
Dissemination involves educating related healthcare providers to improve their awareness, knowledge and understanding of the guideline's recommendations. It is one part of implementation, which involved translation of evidence-based guidelines into real life practice with improvement of health outcomes for the patients.
Implementation requires an evidence-based strategy involving professional groups and stakeholders and should consider the local cultural and socioeconomic conditions. Cost-effectiveness of implementation programs should be assessed.
Specific steps need to be followed before clinical practice recommendations can be integrated into local clinical practice, particularly in low resource settings.
Steps of implementing steroid-resistant nephrotic syndrome diagnosis, treatment, and prevention strategies into the Egyptian health system:

1. Develop a multidisciplinary working group.
2. Assess the status of nutritional care delivery, care gaps and current needs.
3. Select the material to be implemented, agree on the main goals, identify the key recommendations for diagnosis, treatment and prevention and adapt them to the local context or environment.
4. Identify barriers to, and facilitators of implementation.
5. Select an implementation framework and its component strategies.

6. Develop a step-by-step implementation plan:
    - Select the target populations and evaluate the outcome.
    - Identify the local resources to support the implementation.
    - Set timelines.
    - Distribute the tasks to the members.
    - Evaluate the outcomes.
7. Continuously review the progress and results to determine if the strategy requires modification.

Guideline implementation strategies will focus on the following: -

1. **For Practitioners**
    - Educational meetings: conferences, lectures, workshops, grand rounds, seminars, and symposia.
    - Educational materials: printed or electronic information (software).
    - Web-based education: computer-based educational activities.
    - A trained person meets with providers in their practice setting to provide information with the intention of changing the provider's practice. The information may include feedback on the performance of the provider(s).
    - Reminders: the provision of information verbally, on papers or on a computer screen to prompt a health professional to recall information or to perform or avoid a particular action related to patient care.
    - Optimize professional-patient interactions, through mass media campaigns, reminders, and education materials.
    - Practice tools: tools designed to facilitate behavioral/practice changes, e.g., flow charts.
2. **For Patients and care givers**
    - Patient education materials (Arabic booklet): Printed/electronic information aimed at the patient/consumer, family, caregivers, etc.
    - Reminders: the provision of information verbally, on papers or electronically to remind a patient/consumer to perform a particular health-related behaviors.
    - Mass media campaigns.
3. **For Nurses**
    - Educational meetings: lectures, workshops or traineeships, seminars, and symposia.
    - Educational materials: printed.
    - A trained person meets with nurses in their practice setting to provide information with the intention of changing the provider's practice.
    - Reminders: the provision of information verbally, on paper or on a computer screen to prompt them to recall information or to perform or avoid a particular action related to patient care.
    - Practice tools: tools designed to facilitate behavioral/practice changes.
4. **For Stakeholders**

    Plans have been made to contact with all the health sectors in Egypt including all sectors of the Ministry of Health and Population, National Nutrition Institute, University Hospitals, Ministry of Interior, Ministry of Defense, Non-Governmental Organizations, Private sector, and all Health Care Facilities.

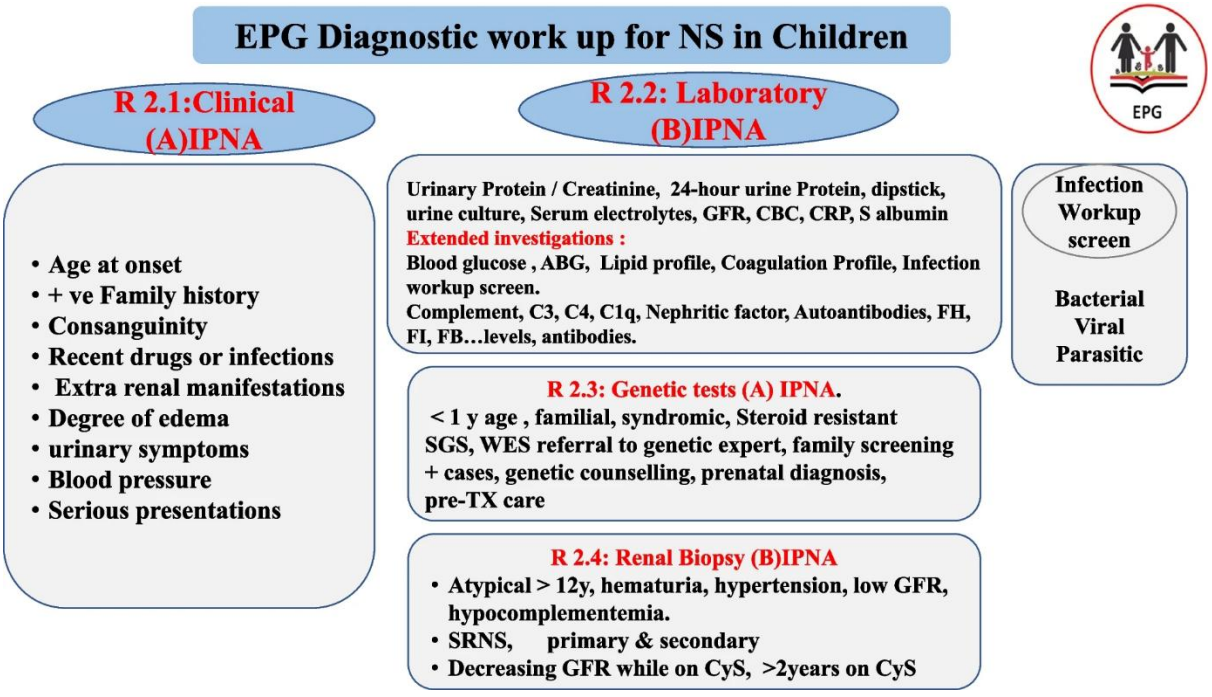
- Information and communication technology: Electronic decision support, order sets, care maps, electronic health records, office-based personal digital assistants, etc.
- Any summary of clinical provision of health care over a specified period may include recommendations for clinical action. The information is obtained from medical records, databases, or observations by patients. Summary may be targeted at the individual practitioner or the organization.
- Administrative policies and procedures.
- Formularies: Drug safety programs, electronic medication administration records.

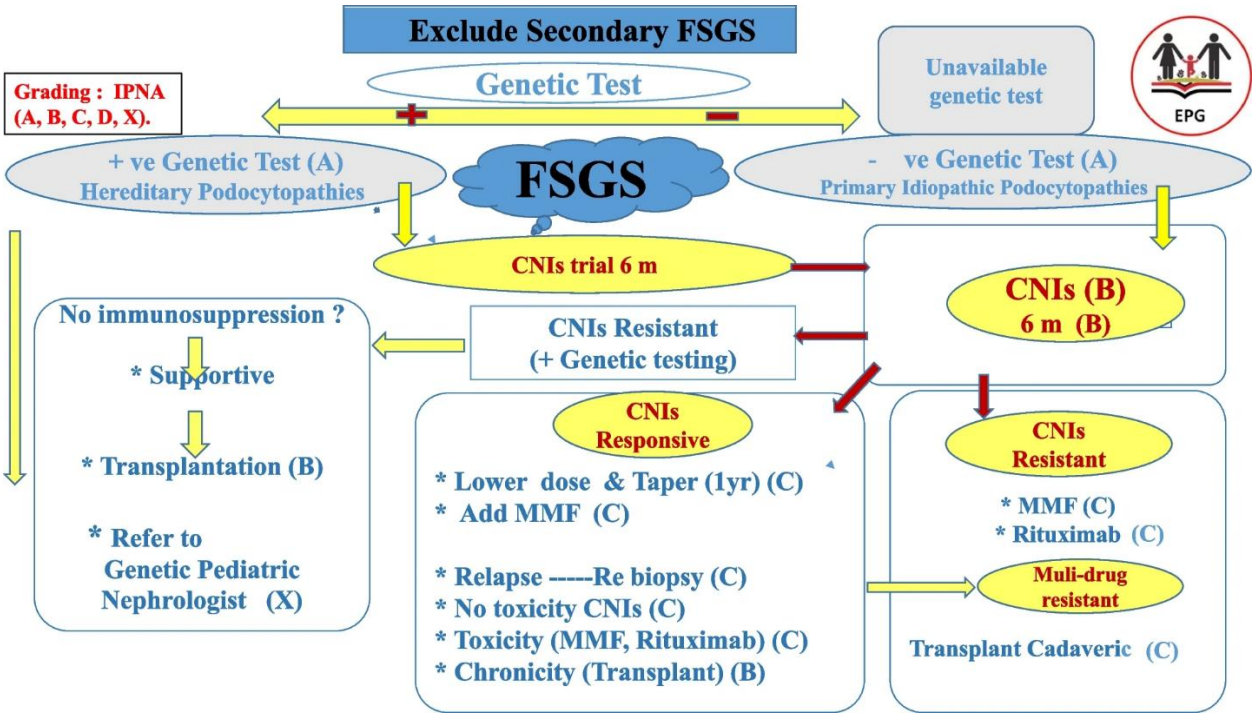
5. **Other activities to assist the implementation of the adapted guideline's recommendations include:**
   - **International initiative:** Dissemination of the presented adapted CPG internationally via sending the final adapted CPG to the Guidelines International Network (GIN) Adaptation Working Group and contacting the CPG developers.
   - **Gantt chart** has been designed to manage the dissemination and implementation stages for the adapted CPG over an accurate time frame (Appendix).

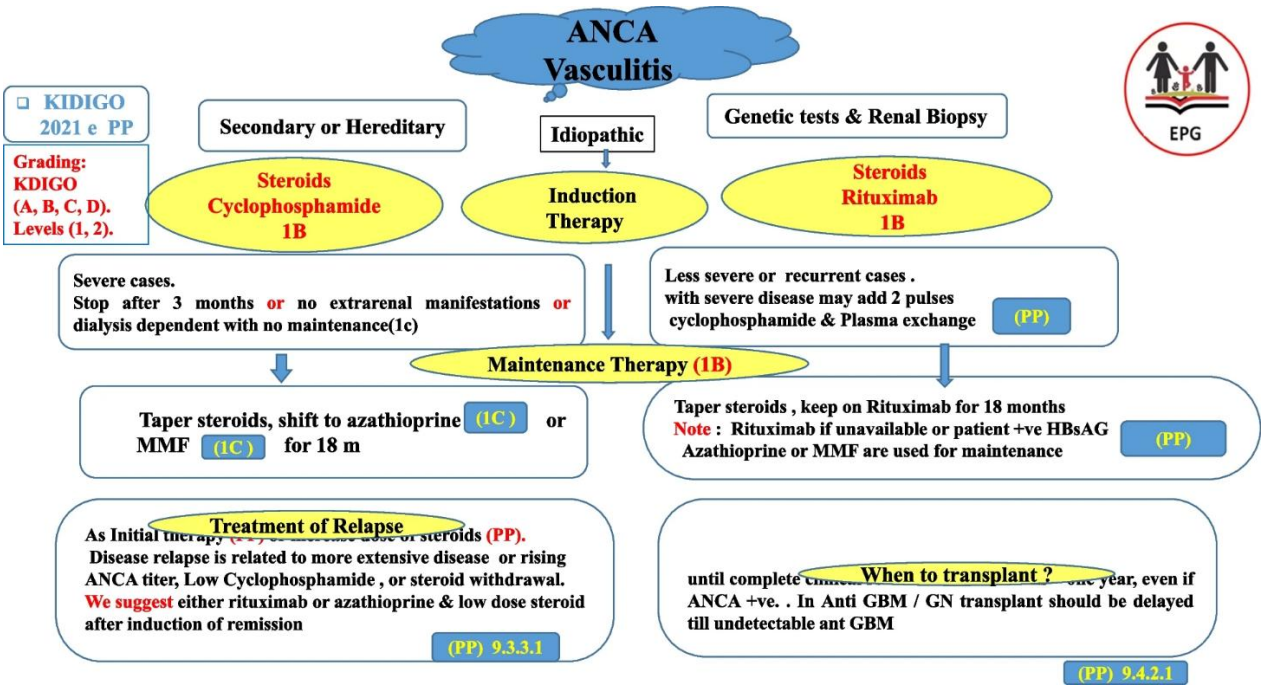
Guideline Implementation Tools

Educational materials based on this Adapted CPG for steroid-resistant nephrotic syndrome have been made available in form of:

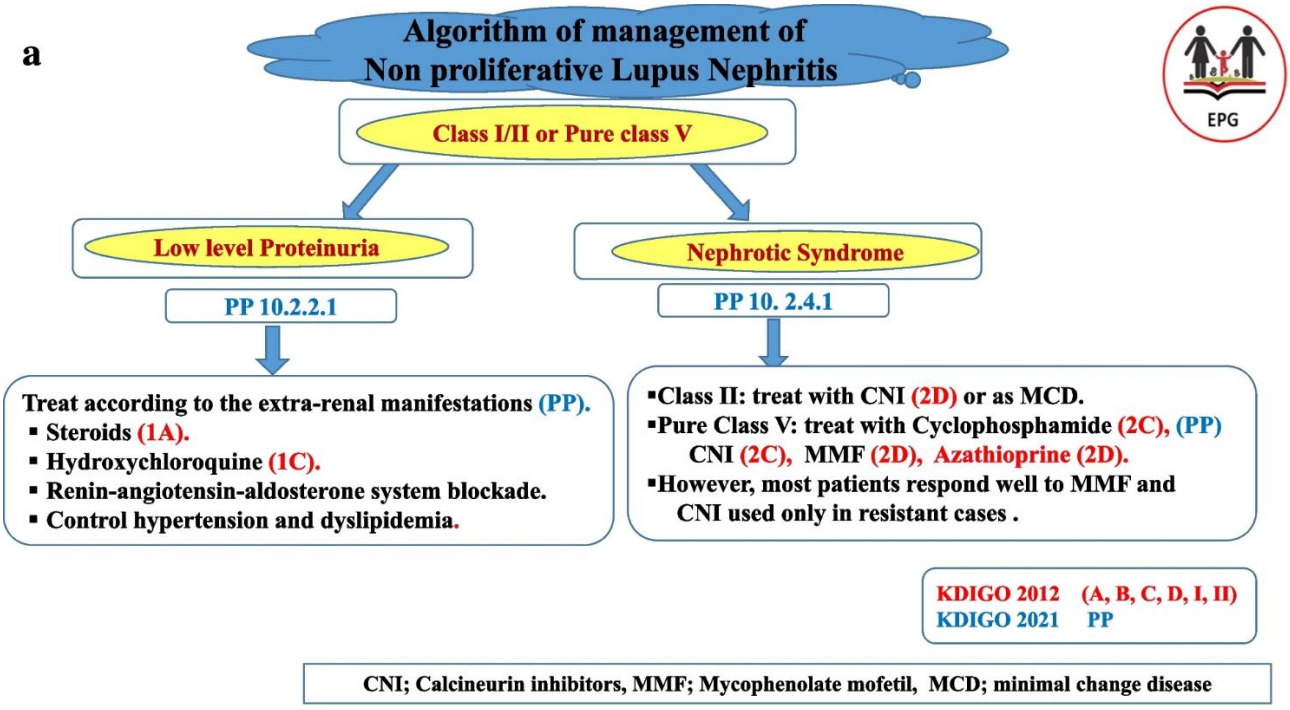
1. Manual for physician for diagnosis and algorithm for diagnosis and management of steroid-resistant nephrotic syndrome



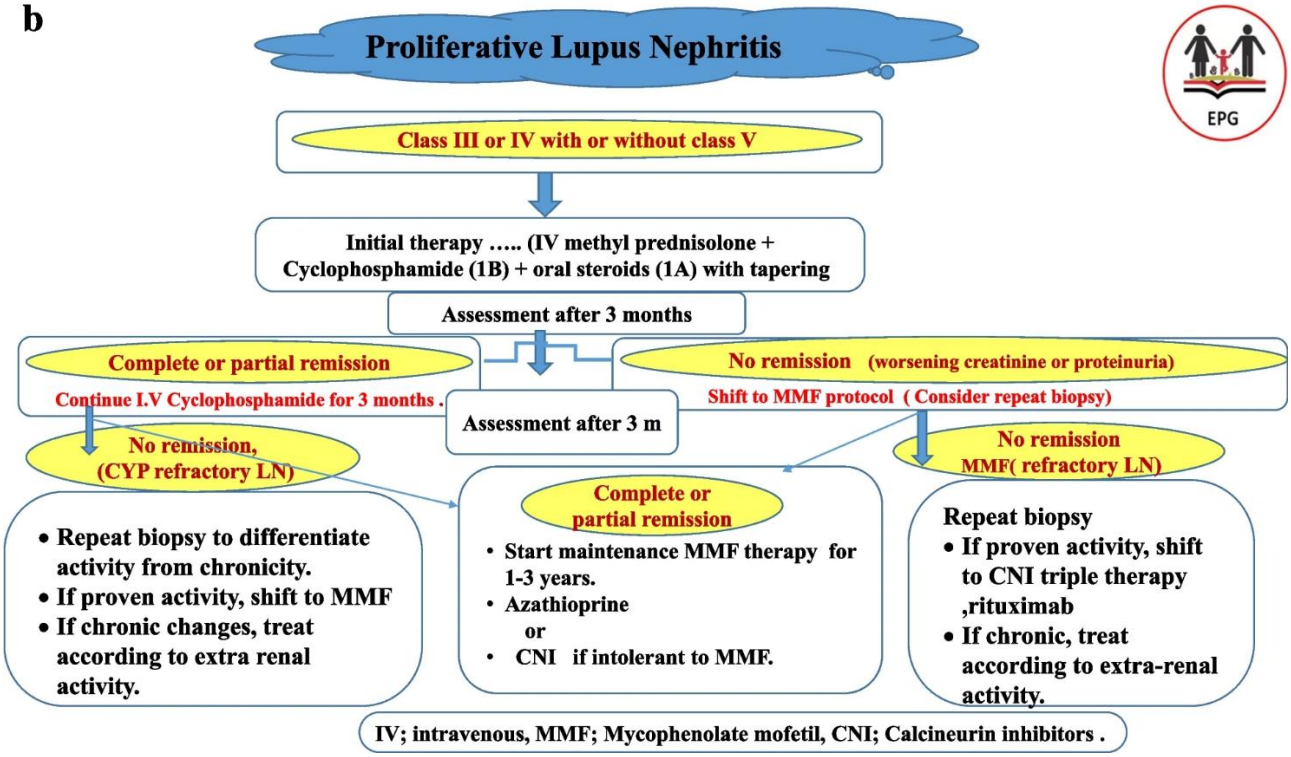

Exclude Secondary FSGS
Genetic Test
Unavailable genetic test
EPG
Grading : IPNA (A, B, C, D, X).
+ ve Genetic Test (A)
Hereditary Podocytopathies
FSGS
- ve Genetic Test (A)
Primary Idiopathic Podocytopathies
CNIs trial 6 m
CNIs (B) 6 m (B)
No immunosuppression ?
* Supportive
* Transplantation (B)
* Refer to Genetic Pediatric Nephrologist (X)
CNIs Resistant (+ Genetic testing)
CNIs Responsive
* Lower dose & Taper (1yr) (C)
* Add MMF (C)
* Relapse -----Re biopsy (C)
* No toxicity CNIs (C)
* Toxicity (MMF, Rituximab) (C)
* Chronicity (Transplant) (B)
CNIs Resistant
* MMF (C)
* Rituximab (C)
Muli-drug resistant
Transplant Cadaveric (C)


ANCA Vasculitis
EPG
KIDIGO 2021 e PP
Grading: KDIGO (A, B, C, D). Levels (1, 2).
Secondary or Hereditary
Idiopathic
Genetic tests & Renal Biopsy
Steroids Cyclophosphamide 1B
Induction Therapy
Steroids Rituximab 1B
Severe cases.
Stop after 3 months or no extrarenal manifestations or dialysis dependent with no maintenance(1c)
Less severe or recurrent cases .
with severe disease may add 2 pulses cyclophosphamide & Plasma exchange (PP)
Maintenance Therapy (1B)
Taper steroids, shift to azathioprine (1C) or MMF (1C) for 18 m
Taper steroids , keep on Rituximab for 18 months
Note : Rituximab if unavailable or patient +ve HBsAG
Azathioprine or MMF are used for maintenance (PP)
Treatment of Relapse
Disease relapse is related to more extensive disease or rising ANCA titer, Low Cyclophosphamide , or steroid withdrawal.
We suggest either rituximab or azathioprine & low dose steroid after induction of remission
(PP) 9.3.3.1
When to transplant ?
ANCA +ve. . In Anti GBM / GN transplant should be delayed till undetectable ant GBM
(PP) 9.4.2.1

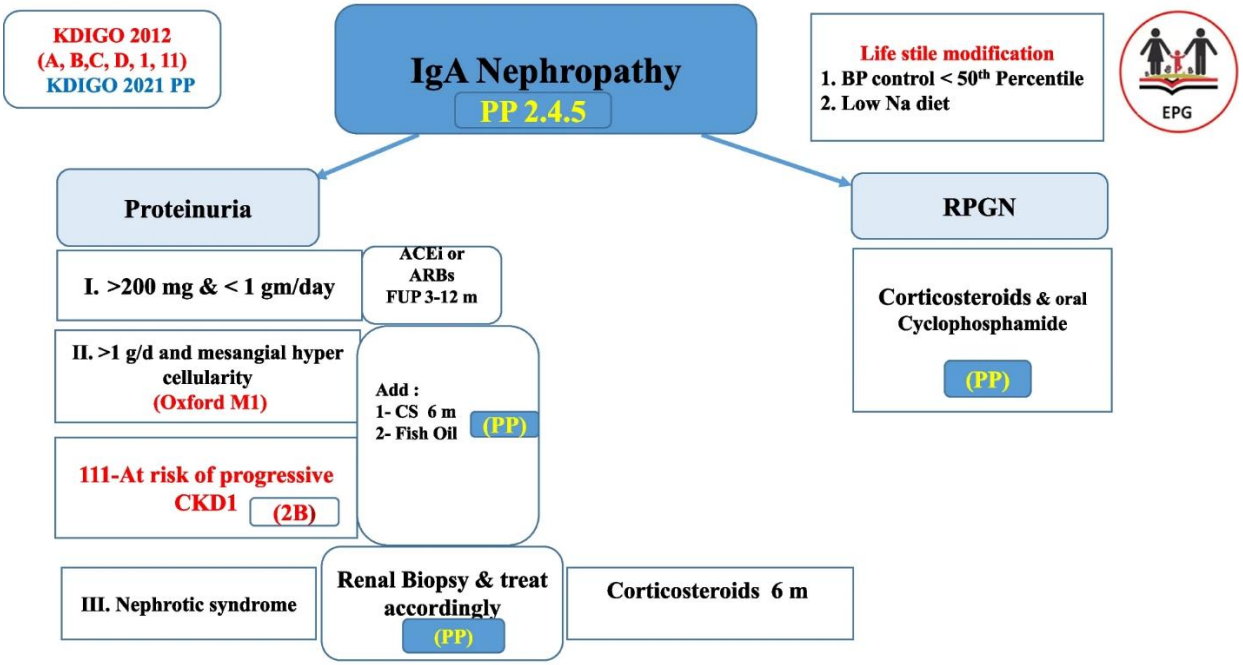
a


Algorithm of management of
Non proliferative Lupus Nephritis
EPG
Class I/II or Pure class V
Low level Proteinuria
Nephrotic Syndrome
PP 10.2.2.1
PP 10. 2.4.1
Treat according to the extra-renal manifestations (PP).
▪ Steroids (1A).
▪ Hydroxychloroquine (1C).
▪ Renin-angiotensin-aldosterone system blockade.
▪ Control hypertension and dyslipidemia.
▪Class II: treat with CNI (2D) or as MCD.
▪Pure Class V: treat with Cyclophosphamide (2C), (PP)
CNI (2C), MMF (2D), Azathioprine (2D).
▪However, most patients respond well to MMF and
CNI used only in resistant cases .
KDIGO 2012 (A, B, C, D, I, II)
KDIGO 2021 PP
CNI; Calcineurin inhibitors, MMF; Mycophenolate mofetil, MCD; minimal change disease

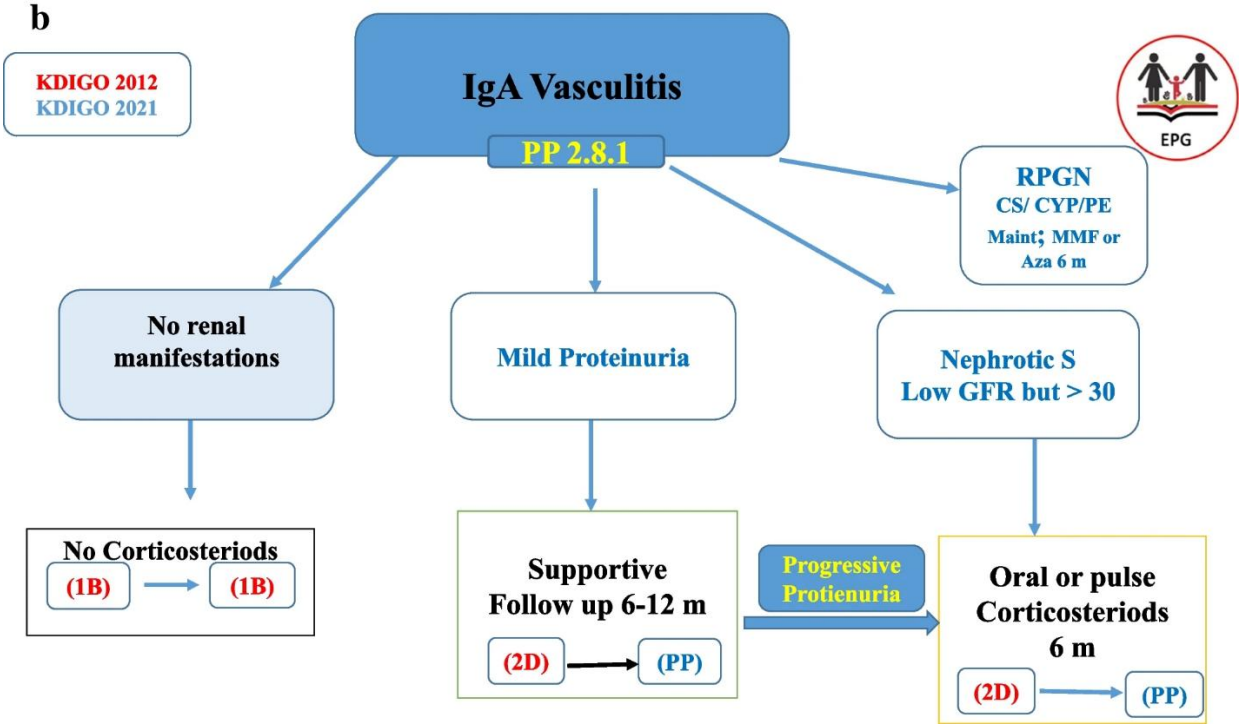
b

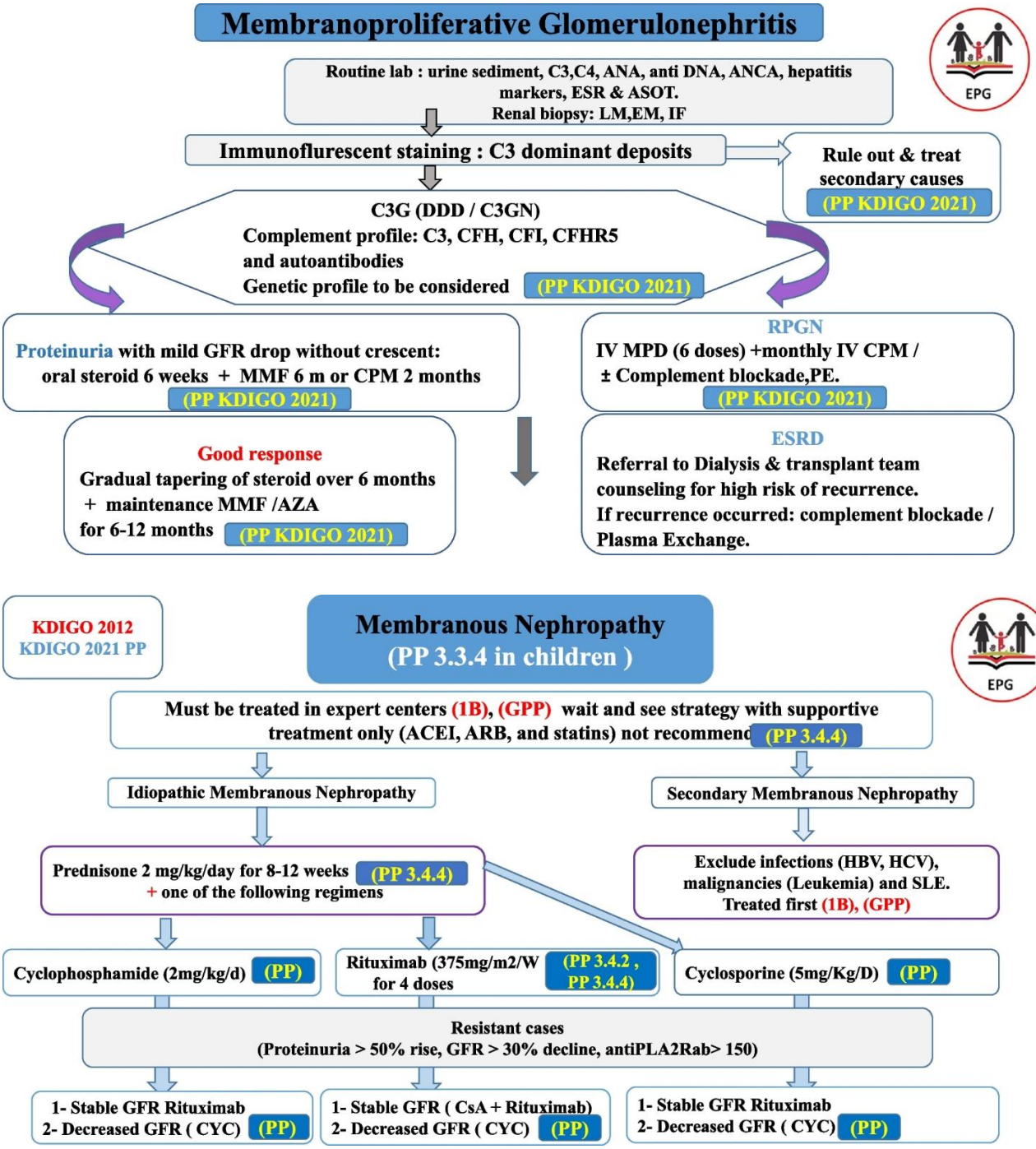

Proliferative Lupus Nephritis
EPG
Class III or IV with or without class V
Initial therapy ….. (IV methyl prednisolone +
Cyclophosphamide (1B) + oral steroids (1A) with tapering
Assessment after 3 months
Complete or partial remission
Continue I.V Cyclophosphamide for 3 months .
No remission (worsening creatinine or proteinuria)
Shift to MMF protocol (Consider repeat biopsy)
Assessment after 3 m
No remission,
(CYP refractory LN)
No remission
MMF(refractory LN)
Complete or
partial remission
• Repeat biopsy to differentiate activity from chronicity.
• If proven activity, shift to MMF
• If chronic changes, treat according to extra renal activity.
• Start maintenance MMF therapy for 1-3 years.
• Azathioprine
or
• CNI if intolerant to MMF.
Repeat biopsy
• If proven activity, shift to CNI triple therapy ,rituximab
• If chronic, treat according to extra-renal activity.
IV; intravenous, MMF; Mycophenolate mofetil, CNI; Calcineurin inhibitors .

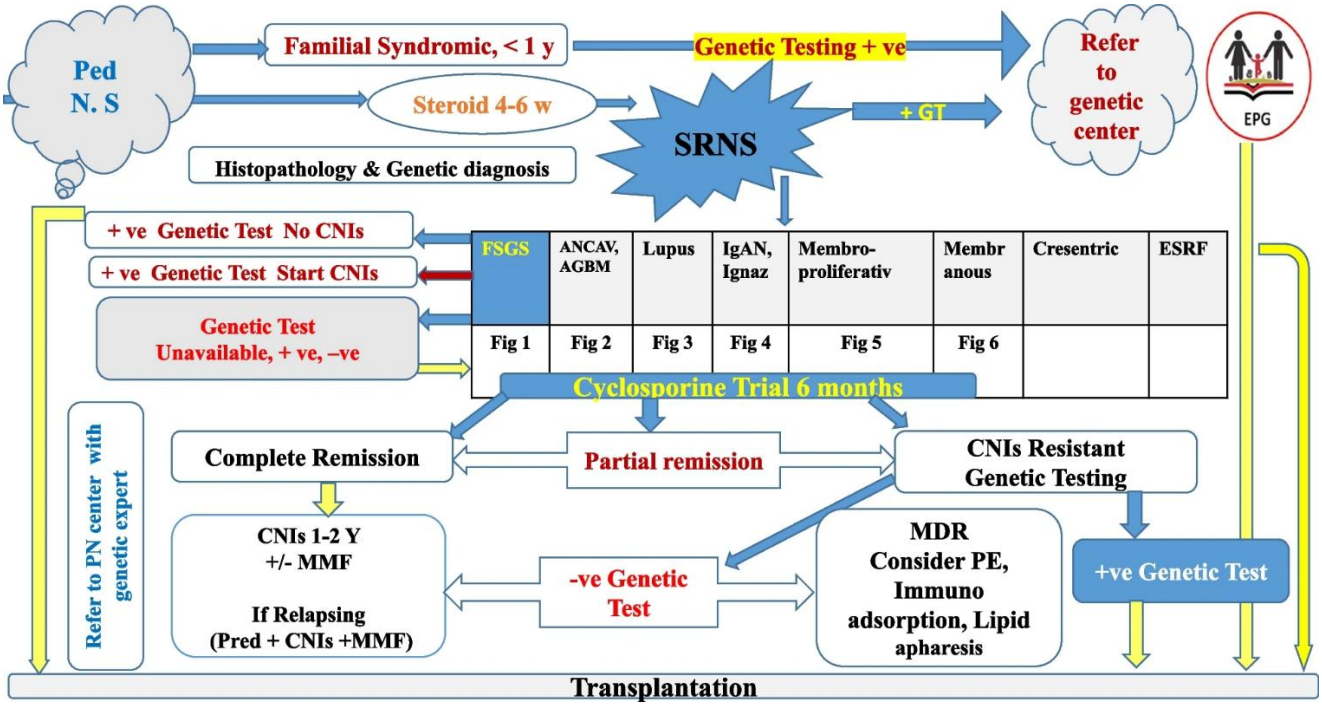
a


KDIGO 2012
(A, B,C, D, 1, 11)
KDIGO 2021 PP
IgA Nephropathy
PP 2.4.5
Life stile modification
1. BP control < 50th Percentile
2. Low Na diet
EPG
Proteinuria
RPGN
I. >200 mg & < 1 gm/day
ACEi or ARBs FUP 3-12 m
Corticosteroids & oral Cyclophosphamide
(PP)
II. >1 g/d and mesangial hyper cellularity
(Oxford M1)
Add :
1- CS 6 m
2- Fish Oil
(PP)
111-At risk of progressive CKD1
(2B)
III. Nephrotic syndrome
Renal Biopsy & treat accordingly
(PP)
Corticosteroids 6 m

b


KDIGO 2012
KDIGO 2021
IgA Vasculitis
PP 2.8.1
EPG
RPGN
CS/ CYP/PE
Maint; MMF or Aza 6 m
No renal manifestations
Mild Proteinuria
Nephrotic S
Low GFR but > 30
No Corticosteriods
(1B)
(1B)
Supportive
Follow up 6-12 m
(2D)
(PP)
Progressive Protienuria
Oral or pulse Corticosteriods 6 m
(2D)
(PP)


Membranoproliferative Glomerulonephritis
EPG
Routine lab : urine sediment, C3,C4, ANA, anti DNA, ANCA, hepatitis markers, ESR & ASOT.
Renal biopsy: LM,EM, IF
Immunoflurescent staining : C3 dominant deposits
Rule out & treat secondary causes
(PP KDIGO 2021)
C3G (DDD / C3GN)
Complement profile: C3, CFH, CFI, CFHR5 and autoantibodies
Genetic profile to be considered (PP KDIGO 2021)
Proteinuria with mild GFR drop without crescent:
oral steroid 6 weeks + MMF 6 m or CPM 2 months
(PP KDIGO 2021)
RPGN
IV MPD (6 doses) +monthly IV CPM /
± Complement blockade,PE.
(PP KDIGO 2021)
Good response
Gradual tapering of steroid over 6 months
+ maintenance MMF /AZA
for 6-12 months (PP KDIGO 2021)
ESRD
Referral to Dialysis & transplant team
counseling for high risk of recurrence.
If recurrence occurred: complement blockade / Plasma Exchange.
KDIGO 2012
KDIGO 2021 PP
Membranous Nephropathy
(PP 3.3.4 in children)
EPG
Must be treated in expert centers (1B), (GPP) wait and see strategy with supportive treatment only (ACEI, ARB, and statins) not recommend (PP 3.4.4)
Idiopathic Membranous Nephropathy
Secondary Membranous Nephropathy
Prednisone 2 mg/kg/day for 8-12 weeks (PP 3.4.4)
+ one of the following regimens
Exclude infections (HBV, HCV), malignancies (Leukemia) and SLE.
Treated first (1B), (GPP)
Cyclophosphamide (2mg/kg/d) (PP)
Rituximab (375mg/m2/W for 4 doses (PP 3.4.2 , PP 3.4.4)
Cyclosporine (5mg/Kg/D) (PP)
Resistant cases
(Proteinuria > 50% rise, GFR > 30% decline, antiPLA2Rab> 150)
1- Stable GFR Rituximab
2- Decreased GFR (CYC) (PP)
1- Stable GFR (CsA + Rituximab)
2- Decreased GFR (CYC) (PP)
1- Stable GFR Rituximab
2- Decreased GFR (CYC) (PP)



Limitations and suggestions for further research needs

Future research recommendations for the management of steroid-resistant nephrotic syndrome in children in the Egyptian context could include:

- National Genetic Profile Registries: Conducting nationwide epidemiological and genetic mapping studies to identify common monogenic mutations unique to Egyptian pediatric SRNS cases, particularly in regions with high rates of consanguinity.
- Efficacy and Safety of Novel Biologics: Carrying out multicenter prospective clinical trials to assess the long-term safety, optimal dosing, and efficacy of steroid-sparing agents (e.g., Rituximab, Mycophenolate Mofetil) and complement inhibitors within the local healthcare setting.
- Post-Transplant Recurrence Outcomes: Establishing long-term registry tracking to better quantify recurrence rates of non-genetic SRNS post-kidney transplantation in living-related donor cohorts.
- Secondary Cause Screen Optimization: Developing standardized, cost-effective screening protocols for endemic infections (such as schistosomiasis or hepatitis) that contribute to secondary nephrotic syndrome.

These recommendations aim to address specific challenges and characteristics of the Egyptian context, potentially leading to more effective prevention and management strategies for steroid-resistant nephrotic syndrome in children.

Challenges

- High Cost & Limited Access to Genetic Testing: Genetic testing remains expensive, limited to a few tertiary centers, and is not fully covered by national medical insurance, necessitating reliance on renal biopsy and laboratory immunology.

- High Rates of Consanguinity: Consanguinity presents unique diagnostic challenges for living-related organ donation, requiring extensive genetic counseling and pre-transplant donor screening.

Strengthen the evidence base of the next update of this guideline by generating GRADE summary of finding tables, evidence profiles, and EtD frameworks.

Monitoring and evaluating the impact of the guideline.

The following are three performance measures or indicators for implementing this adapted CPG for steroid-resistant nephrotic syndrome in children:

1. **Adherence to steroid-resistant nephrotic syndrome Guidelines**
   - *Numerator:* Number of children with steroid-resistant nephrotic syndrome who received treatment as per guideline recommendations.
   - *Denominator:* Total number of children diagnosed with steroid-resistant nephrotic syndrome
   - *Data Source:* Hospital or clinic patient records.
2. **Duration of Hospital Stay**
   - *Numerator:* Total number of hospital stay days for children with steroid-resistant nephrotic syndrome
   - *Denominator:* Total number of children admitted with steroid-resistant nephrotic syndrome *Data Source:* Hospital admission and discharge records.
3. **Rate of Readmission**
   - *Numerator:* Number of children readmitted with symptoms of steroid-resistant nephrotic syndrome within a certain period (e.g., 30 days) after discharge.
   - *Denominator:* Total number of children initially admitted with steroid-resistant nephrotic syndrome
   - *Data Source:* Hospital readmission records.

These key performance indicators are designed to measure the effectiveness and adherence to the guidelines, the efficiency of the treatment in terms of resource utilization (hospital stay), and the success of the treatment in preventing further complications (readmissions).

Updating of the guideline

The EPG Nephrotic syndrome Group has decided to conduct the next review of this adapted CPG for updates after five years. This should be carried out in 2029 after checking for updates in the source CPGs, consultation of expert opinion on the changes needed for updating according to the newest evidence and recommendations published in this area and the clinical audit and feedback from implementation efforts in the aforementioned local healthcare settings except if any breakthrough evidence- based recommendations are published before that date. The process will be guided by the Checklist for the Reporting of Updated Guidelines (CheckUp) Tool that is freely provided by the AGREE Enterprise and by the Reporting Items for Practice Guidelines in Healthcare (RIGHT) extension for adapted guidelines RIGHT-Ad@pt Checklist.

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Annexes

Annex Table 1.
Declaration of Conflict of Interests

The members of the guideline development/ adaptation group and the external review group have no academic, financial, or competing interests to declare and none of them were involved in the development of the original source guideline(s).
Any identified potential COI has been reported below.

Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) *Guideline Adaptation Group (Clinical subgroup)*			
Name	**Affiliation, Area of expertise / Role, Country / Primary location [work]**	**Declaration of interests**	
		Interest identified	**Management plan & decision**
Bahia Moustafa	Professor of Pediatrics & Pediatric Nephrology, Cairo University, Egypt	None	Not Applicable
Sawsan Moselhy	Department of Pediatric, Pediatric Nephrology Division, Faculty of	None	Not Applicable

	Medicine, Ain Shams University, Cairo, Egypt.		
Moftah Rabie	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Azhar University, Cairo, Egypt.	None	Not Applicable
Ayman Hammad	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Mansoura University, Mansoura, Egypt.	None	Not Applicable
Doaa Youssef	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Zagazig University, Zagazig, Egypt.	None	Not Applicable
Mohamed Shouman	Department of Pediatric, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt.	None	Not Applicable
Samuel Makar	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Cairo University, Cairo, Egypt	None	Not Applicable
Ahmed Badr	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Cairo University, Cairo, Egypt	None	Not Applicable
Sameh Mansour	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Azhar University, Cairo, Egypt.	None	Not Applicable
Dina Ebrahim	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Ain Shams University, Cairo, Egypt.	None	Not Applicable
Marwa Nabhan	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Cairo University, Cairo, Egypt	None	Not Applicable

Fatma Ateia	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Cairo University, Cairo, Egypt	None	Not Applicable
Hend Abdel-Nabi	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Tanta University, Tanta, Egypt.	None	Not Applicable
Ahmed Hussein	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Ain Shams University, Cairo, Egypt.	None	Not Applicable
Manal Salman	Department of Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.	None	Not Applicable
Mai S. Korkor	Department of Pediatric, Pediatric Nephrology Division, Faculty of Medicine, Mansoura University, Mansoura, Egypt.	None	Not Applicable
Esraa A. Elbahkiry	Clinical Pharmacist, Faculty of Medicine, Mansoura University, Mansoura, Egypt.	None	Not Applicable
Marwa Dagher	Clinical Pharmacist, Faculty of Medicine, Mansoura University, Mansoura, Egypt.	None	Not Applicable
Abeer Selim	Department of Pediatric, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt.	None	Not Applicable
Guideline Adaptation Group (Methodology Subgroup)			
Prof. Ashraf Abdel Baky	Professor of Pediatrics Ain Shams University, Egypt Founder and Chair of EPG	None	Not Applicable
Dr. Yasser Sami Amer	1. Pediatrics Department and Clinical Practice Guidelines and Quality Research Unit, Quality Management Department, King Saud University Medical City, Riyadh, Saudi Arabia;	None	Not Applicable

	2. Research Chair for Evidence-Based Health Care and Knowledge Translation, King Saud University, Riyadh, Saudi Arabia; 3. Chair, Adaptation Working Group, Guidelines International Network (GIN), Perth, Scotland 4. Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo (FMRP-USP), Ribeirão Preto, São Paulo, Brazil.		
Tarek El-Sayed Ismail Omar	Professor of Pediatrics and Pediati Neurology Alexandria Center for Evidence-Based Clinical Practice Guidelines Faculty of Medicine Alexandria University, Egypt.	None	Not Applicable
Dr. Lamis Mohsen Elsholkamy	Lecturer of Pediatrics, Faculty of Medicine, Modern University for Technology and Information (MTI), Egypt	None	Not Applicable
External Review Group			
Amr Sarhan	Pediatric Nephrology Mansoura University	None	Not Applicable
Neveen A Soliman	Pediatric Nephrology Cairo University	None	Not Applicable
Ihab El Hakim	Pediatric Nephrology Ain Shams University	None	Not Applicable
External Reviewer for methodology			
Prof. Iván D. Flórez	Department of Pediatrics, University of Antioquia, Medellín, Colombia, Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada, Leader, AGREE Collaboration (Appraisal of Guidelines for Research & Evaluation) Director, Cochrane Colombia	None	Not Applicable
International Peer Reviewers			
Federica Zotta	Division of Nephrology, Department of Pediatric subspecialities. Bambino Gesu	None	Not Applicable

	Children Hospital (IRCCS), Rome, Italy.		

Web annexes

The following annexes can be added as a package of standalone supplementary documents.

Keywords: The MeSH terms for "Guideline for the steroid-resistant nephrotic syndrome " on PubMed are: : Steroid-resistant nephrotic syndrome, Diagnosis, Treatment, Follow up, Pediatric guidelines.

Annex Table 2. Results of the AGREE II assessment of

A- IPNA clinical practice recommendations for the diagnosis and management of children

with steroid-resistant nephrotic syndrome

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
84%	82%	80%	79%	77%	80%	80%	Yes - 3, Yes with modifications - 6, No - 0

Overall Assessment

	Appraiser 6	Appraiser 19	Appraiser 9	Appraiser 11	Appraiser 14	Appraiser 18	Appraiser 10	Appraiser 3	Appraiser 12	Appraiser 5	Appraiser 15
OA1	6	6	6	5	6	5	6	6	6	6	6

b- Evidence-Based Clinical Practice Guidelines for Nephrotic Syndrome JSPN 2014,

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
82%	79%	81%	83%	84%	85%	83%	Yes - 0, Yes with modifications - 5, No - 0

Overall Assessment

	Appraiser 7	Appraiser 3	Appraiser 4	Appraiser 8	Appraiser 5
OA1	6	6	6	6	6

c- KDIGO Clinical Practice Guideline on Glomerular Diseases, using the AGREE II Instrument.

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
77%	75%	77%	75%	74%	73%	76%	Yes - 6, Yes with modifications - 6, No - 1

Appendix Table 4. The RIGHT-Ad@pt checklist

7 sections, 27 topics, and 34 items		Assessment	Page(s)*	Note(s)
BASIC INFORMATION				
Title/subtitle				
1	Identify the report as an adaptation of practice guideline(s), that is include "guideline adaptation", "adapting", "adapted guideline/recommendation(s)", or similar terminology in the title/subtitle.	☒ Yes ☐ No ☐ Unclear		
2	Describe the topic/focus/scope of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Cover/first page				
3	Report the respective dates of publication and the literature search of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
4	Describe the developer and country/region of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Executive summary/abstract				
5	Provide a summary of the recommendations contained in the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Abbreviations and acronyms				
6	Define key terms and provide a list of abbreviations and acronyms (if applicable).	☒ Yes ☐ No ☐ Unclear		
Contact information of the guideline adaptation group				
7	Report the contact information of the developer of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
SCOPE				
Source guideline(s)				
8	Report the name and year of publication of the source guideline(s), provide the citation(s), and whether source authors were contacted.	☒ Yes ☐ No ☐ Unclear		
Brief description of the health problem(s)				
9	Provide the basic epidemiological information about the problem (including the associated burden), health systems relevant issues, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
Aim(s) and specific objectives				
10	Describe the aim(s) of the adapted guideline and specific objectives, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
Target population(s)				
11	Describe the target population(s) and subgroup(s) (if applicable) to which the recommendation(s) is addressed in the adapted guideline, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
End-users and settings				
12	Describe the intended target users of the adapted guideline, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
13	Describe the setting(s) for which the adapted guideline is intended, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
RIGOR OF DEVELOPMENT				
Guideline adaptation group				

Appendix Table 4. The RIGHT-Ad@pt checklist

7 sections, 27 topics, and 34 items		Assessment	Page(s)*	Note(s)
14	List all contributors to the guideline adaptation process and describe their selection process and responsibilities.	☒ Yes ☐ No ☐ Unclear		
Adaptation framework/methodology				
15	Report which framework or methodology was used in the guideline adaptation process.	☒ Yes ☐ No ☐ Unclear		
Source guideline(s)				
16	Describe how the specific source guideline(s) was(were) selected.	☒ Yes ☐ No ☐ Unclear		
Key questions				
17	State the key questions of the adapted guideline using a structured format, such as PICO (population, intervention, comparator, and outcome), or another format as appropriate.	☒ Yes ☐ No ☐ Unclear		
18	Describe how the key questions were developed/modified, and/or prioritized.	☐ Yes ☒ No ☐ Unclear		
Source recommendation(s)				
19	Describe how the recommendation(s) from the source guideline(s) was(were) assessed with respect to the evidence considered for the different criteria, the judgements and considerations made by the original panel.	☐ Yes ☒ No ☐ Unclear		
Evidence synthesis				
20	Indicate whether the adapted recommendation(s) is/are based on existing evidence from the source guideline(s), and/or additional evidence.	☐ Yes ☒ No ☐ Unclear		
21	If new research evidence was used, describe how it was identified and assessed.	☐ Yes ☒ No ☐ Unclear	NA	
Assessment of the certainty of the body of evidence and strength of recommendation				
22	Describe the approach used to assess the certainty/quality of the body/ies of evidence and the strength of recommendations in the adapted guideline and note any differences (if applicable) compared to the source guideline(s).	☐ Yes ☒ No ☐ Unclear	NA	
Decision-making processes				
23	Describe the processes used by the guideline adaptation group to make decisions, particularly the formulation of recommendations.	☒ Yes ☐ No ☐ Unclear		
RECOMMENDATIONS				
Recommendations				
24	Report recommendations and indicate whether they were adapted, adopted, or *de novo*.	☒ Yes ☐ No ☐ Unclear		
25	Indicate the direction and strength of the recommendations and the certainty/quality of the supporting evidence and note any differences compared to the source recommendations(s) (if applicable).	☒ Yes ☐ No ☐ Unclear		
26	Present separate recommendations for important subgroups if the evidence suggests important differences in factors influencing recommendations and note any differences compared to the source recommendations(s) (If applicable).	☒ Yes ☐ No ☐ Unclear		
Rationale/explanation for recommendations				
27	Describe the criteria/factors that were considered to formulate the recommendations or note any relevant differences compared to the source guideline(s) (if applicable).	☒ Yes ☐ No ☐ Unclear		
EXTERNAL REVIEW AND QUALITY ASSURANCE				

Appendix Table 4. The RIGHT-Ad@pt checklist

7 sections, 27 topics, and 34 items		Assessment	Page(s)*	Note(s)
External review				
28	Indicate whether the adapted guideline underwent an independent external review. If yes, describe the process.	☒ Yes ☐ No ☐ Unclear		
Organizational approval				
29	Indicate whether the adapted guideline obtained organizational approval. If yes, describe the process.	☒ Yes ☐ No ☐ Unclear	SNS & NEBMC	
FUNDING, DECLARATION, AND MANAGEMENT OF INTEREST				
Funding source(s) and funder role(s)				
30	Report all sources of funding for the adapted guideline and source guideline(s), and the role of the funders.	☒ Yes ☐ No ☐ Unclear		
Declaration and management of interests				
31	Report all conflicts of interest of the adapted and the source guideline(s) panels, and how they were evaluated and managed.	☒ Yes ☐ No ☐ Unclear		
OTHER INFORMATION				
Implementation				
32	Describe the potential barriers and strategies for implementing the recommendations (if applicable).	☒ Yes ☐ No ☐ Unclear		
Update				
33	Briefly describe the strategy for updating the adapted guideline (if applicable).	☒ Yes ☐ No ☐ Unclear		
Limitations and suggestions for further research				
34	Describe the challenges of the adaptation process, the limitations of the evidence, and provide suggestions for future research.	☐ Yes ☒ No ☐ Unclear	--	