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GUIDELINES

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Egyptian pediatric clinical practice adapted guidelines: evidence-based [2] steroid-resistant nephrotic syndrome (SRNS) 2022

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Abstract

Background 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% (Mickinney et al. Pediatr Nephrol 16:1040-1044, 2001). While MCD is the most common histopathology in SS type, children with SRNS have MCD, mesangial proliferative glomerulonephritis, or focal and segmental glomerulosclerosis (FSGS) (International Study Kidney Disease in children, Kidney Int 20;765-771, 1981). SRNS is defined as those who do not show remission after 6 weeks and standard dose of oral steroids ± 3 IV MPD doses (Trautmann et al. Pediatr Nephrol 35:1529-1561, 2020).

Objectives These national adapted guidelines aim to frame evidence-based recommendations adopted or adapted from the IPNA 2020, KDIGO 2021, and Japanese 2014 de novo guidelines for diagnosis and management of nephrotic children to be presented in two manuscripts: (1) steroid sensitive (SSNS) and (2) steroid-resistant nephrotic syndrome (SRNS).

Methodology Formulation of key questions was followed with a review of literature guided by our appraised guidelines using AGREE plus appraisal tool. Virtual monthly meetings all through the year 2021 were activated for reviewing and validation of final adaptation evidence-based draft, considering all comments of external reviewers including KDIGO assigned reviewer.

Discussion Rationale behind the selection of adopted statements and tailoring of others to suit our local facilities, expertise, and our local disease profile was discussed in the text with reasons.

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Conclusion The provided guidelines aim to optimize patient care and outcome and suggest research areas lacking validated research recommendations.

Keywords Steroid-resistant nephrotic syndrome, Diagnosis, Treatment, Follow up, Pediatric guidelines

1 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. Management recommendations for FSGS were mainly adopted/adapted from IPNA 2020. Other types (ANCA, IgA, LE, infection related, C3GN/DDD, and MN) were mainly adopted/adapted from KDIGO 2021 considering patient evaluation for genetic and secondary types. This CPG adaptation project for nephrotic syndrome is part of a national CPG program by the Egyptian Pediatric Clinical Practice Guidelines Committee (EPG), which was formulated in June 2018 by an initiative in collaboration with the faculty staff of 15 Egyptian Universities' Pediatrics Departments and a National Research Centre. EPG was later

affiliated with the Supreme Council of Egyptian University Hospitals, with the goal of defining the topics of pediatric evidence-based CPGs, assigning authors to them, and assisting in their adaption in accordance with a national strategic plan (http://epg.edu.eg) [18]. The EPG follows the "Adapted ADAPTE" as a formal CPG adaption method [19].

2 Methodology [20–28]

We followed the "Adapted ADAPTE" CPG formal adaptation methodology that consists of three phases and 24 steps and tools [20] (EPG methodology figures from 1 to 9 and Table A in Additional file 1).

3 Set-up phase

Nephrotic syndrome (NS) was highlighted as one of the prioritized health topics for the EPG CPG adaption initiatives during phase 1 (set-up). A preliminary search was carried out to see if any published NS CPGs existed. With 28 members, the Nephrotic Syndrome Guideline Adaptation Group (NS-GAG) was established. The NS-GAG included pediatrics and pediatric nephrology faculty academics and consultants from nine Egyptian universities covering Upper and Lower Egypt. Two members of the NS-GAG were involved in the development of the Adapted ADAPTE and had previous experience with CPG adaptation. The CPG methodologists provided capacity training for the NS-GAG pediatric and nephrology consultants on the Adapted ADAPTE from the start of the project. Continuous virtual meetings extending through 1 year starting at March 2020 were scheduled for inter active communications between working group members. Our scope was pediatric nephrotic syndrome including (1) SSNS and (2) SRNS/diagnosis and treatment recommendations. The target patient population for this CPG project include 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.

The target users include physicians (viz. pediatrics, primary healthcare, family medicine, pediatric nephrology), nurses, and clinical pharmacists. The work group was divided into two panels assigned to cover each type of SS and SR with continuous communication at monthly virtual meeting with attendance of all working groups members. This manuscript article will be devoted to (2) SRNS to be associated with another article (1) SSNS.

4 Adaptation phase (SRNS)

In phase 2, we identified 12 health questions, using the PIPOH model, including 6 questions for diagnosis and 6 for treatment. The PIPOH model included the target patient population (P), intervention(s) (I), professionals and clinical specialties (P), outcomes (O), and healthcare setting or context (H). The literature search was conducted using MEDLINE/PubMed and Google Scholar portals. Eligible source CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument. AGREE II is a valid and reliable instrument with 23 items organized into six domains and is considered the gold standard for quality assessment of CPGs [21–28] (refer to the Additional file 1 including appraisal for source CPGs [24–28], health questions, PIPOH model). The first draft of the adapted CPG marks the last step of this phase, where RIGHT-AD patient checklist reporting evidence-based SRNS guideline was used (see Additional file 1: Table A).

5 Finalization phase

Phase 3 involved finalizing the initial draft of the adapted CPG, as well as determining whether it was acceptable and suitable to the Egyptian healthcare system. After that, the document was sent out to a panel of four clinical (including one nominated by KDIGO) and one methodology external reviewers. Reviewers' comments were revised, and the updated draft was further reviewed within the Nephrotic Syndrome Guideline Adaptation Group (NS-GAG), considering the national context. The finalized version of the revised CPG contained useful tools and strategies for implementation.

For clarity, we will report the adapted CPG recommendations of the EPG NS CPG in two separate papers: (1) steroid-sensitive and (2) steroid-resistant NS.

6 SRNS recommendations

R.1: Definitions we recommend.

All definitions are included in Table 1 IPNA related to pediatric NS including SR, CNI resistant, and MDR. **(A) IPNA.** Table 1 (refer to Additional file 1 in Supplementary File).

SRNS is defined as nephrotic children not responding to 4–6 weeks of standard oral steroids ± 3 IV methyl prednisone pulses.

R.2: Diagnosis we recommend.

R 2.1: Thorough clinical evaluation. **(A) IPNA**, EPG diagnosis workup (Fig. 1), and Table 2 IPNA 2020

Table 1 EPG diagnosis workup [Renal Biopsy, Serology antibodies] **[R 35-38]**

Renal Biopsy & Serology Findings in SRNS						
	Focal Segmental Glomerulo-sclerosis	Focal Segmental Necrotizing	Focal / Diffuse Proliferative	Membrano-proliferative/ C3GN/DDD	Membranous	Crescentic
Immuno-fluorescent microscopy	No Deposits No antibodies in Hereditary types .	Paucci D. Linear	Granular D. Immuno/comp C3,C4,C1q, IgG, IgA	Granular D . Immune/comp C3, C4, C1q, IgG C3 Predominant	Granular D . Immuno/comp . C3, C4, Cq1, IgG	• Paucci • Granular • Linear
Serology antibodies	No antibodies in Hereditary types .	. ANCA (PR3-MPO) . AGBM	. ASOT . ANA . Anti-ds DNA . APL.	. Nephritic F . Auto-ab. Anti FH, FB, FI, F5 antibodies . Mutations	APLA2Rab	According to primary pathology.
Electron microscopy	Podocyte foot process effacement	No Deposits	+ve Deposits	+ve Deposits . Subendothelial in Type 1 . Subepithelial in Type 2 . Intramembranous DDD . Mesangial, subepithelial in C3GN (comp.++)	+ve Deposits	+ve Deposits
Immuno-suppressive treatment	Figure 1	Figure 2	Figure 3 A & 3B Lupus / Figure 4 A & 4B IgA	Figure 5	Figure 6	

and KDIGO 2021 (refer to Additional file 1 in Supplementary File).
R 2.2: Extended laboratory investigations. **(B) IPNA 2020** (EPG Fig. 1) and Table 2 IPNA 2020 and KDIGO 2021 (refer to Additional file 1 in Supplementary File).
R 2.3: Genetic tests, when possible. **(A) IPNA 2020** with **tailoring to our target priorities.**
R 2.3 (a–d): **Referral** to secondary and tertiary PN centers with genetic facilities as indicated.
R 2.4: Renal biopsy. **(B) IPNA 2020.**

EPG (diagnosis Fig. 1, Table 1, and Fig. 8 management flowchart).

7 Genetic testing

R 2.3. a and b: When we recommend genetic testing. Our target groups.
R2.3. c: Which tests?
R 2.3. d: Why?

2.3. a: 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 **(A IPNA) (EPG-GPP)**.

- National guideline strongly recommends the availability of genetic testing in all its university-related pediatric nephrology centers and to be covered by medical insurance **(EPG-GPP)**.
- Dose, duration, efficacy, and complications for each drug have been summarized in

2.3. b: We define our **target population for referral** to include:

- Familial, syndromic, congenital/infantile onset. **(A) IPNA (EPG-GPP).**
- All SRNS at confirmation period **(B) [PNA)**, if possible **(EPG-GPP)**.
- All SRNS biopsy proven as FSGS/DMS to identify genetic types **(EPG-GPP).**

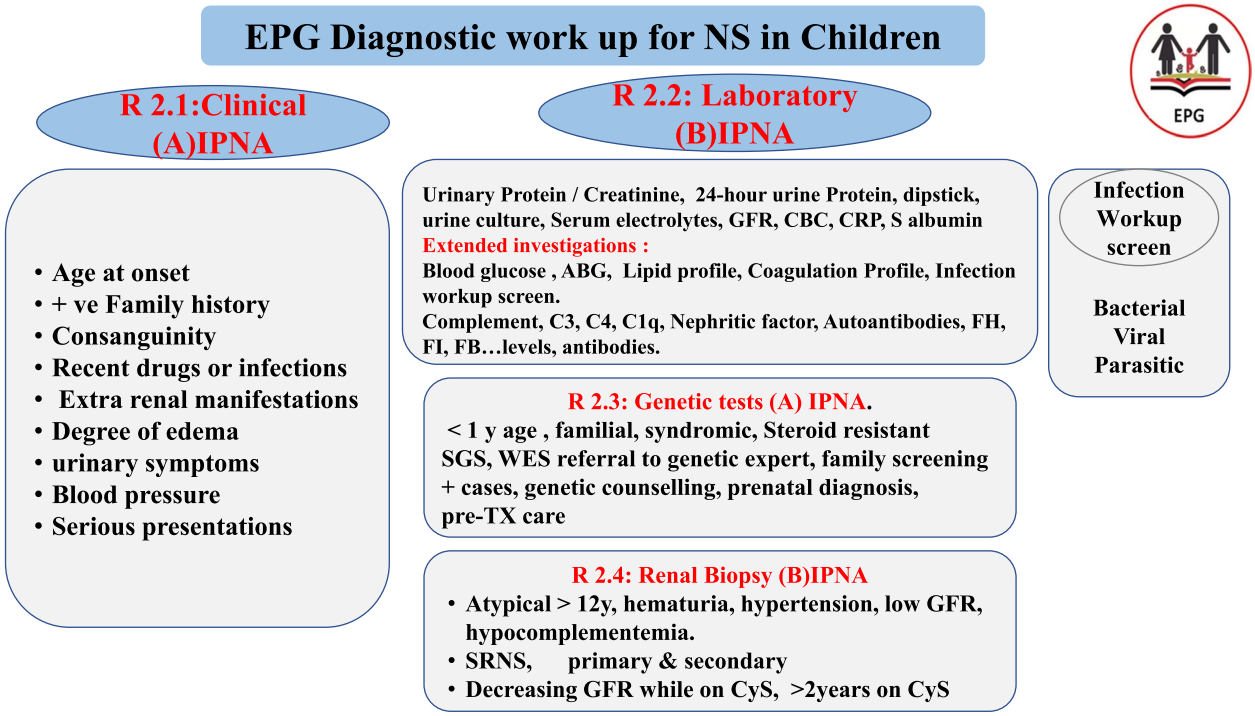

Fig. 1 EPG diagnostic workup for NS in children

- All SRNS/CNIs resistant after 6 m cyclosporine trial. **(A) IPNA (EPG-GPP).**
- 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. **EPG-(GPP).**
- All pretransplant donor and recipients as we follow live related donor transplant in a community with high rate of consanguinity **(EPG-GPP).**

8 Which tests and why recommended?

R 2.3.c: We recommend **Gene Panel SGS** unless mutation is likely known where single gene analysis is recommended **(B) IPNA.**
R 2.3.d: We recommend referral to centers with genetic experts to:

- Avoid use of steroids and immunosuppressive, renal biopsy **[R31] IPNA 2020**, pre- and post-transplant aggressive protocols of PE, and rituximab that are recommended for idiopathic nonhereditary FSGS. **(C) IPNA.**
- Allow genetic counseling, prenatal diagnosis **[R 23, 24] IPNA 2020.**
- Transplant carries low recurrence rate **(X) 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 **(X) IPNA.**
- Special treatment is available for some types as Q **[Ozaltin 2014].**
- Early diagnosis and management control progress of extra renal manifestations as well **[IPNA 2020]** [29, 30].

9 Renal biopsy: when to recommend for renal biopsy? Its value?

R 2.4: We recommend **Renal Biopsy** (LM, IF, EM) for **all SRNS (A) IPNA** excluding genetic types especially those known as CNIs resistant **(B) IPNA** and also secondary NS related to drugs, infections, or malignancy **(A IPNA)**. 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

test to put therapeutic plan and predict disease outcome based on renal histopathology. **(B) IPNA.**

R 3: Treatment recommendations

R 3.1.: Supportive treatment (IPNA 2020)

R 3.1 a: ACI or ARBS to start early at 4th week **(B)**, avoided in CKD, AKI, hyperkalemia, volume depletion, and female adolescent **(X).**

R 3.1.b: Statin. We suggest statin in MDR, high LDL cholesterol, control of BP if 95th **(A),** calcium C, vitamin D **(C),** levothyroxine T4 if hypothyroidism **(A),** magnesium if hypomagnesaemia **(D).**

R 3.1. C: Diuretics to treat edema if severe, considering the risk of hypovolemia and thrombosis in under filled patients **(X).** We recommend oral or IV furosemide if severe edema **(C).** In refractory edema **(C)**, metolazone, thiazides, and amiloride potassium sparing diuretic **(C).** Albumin infusion 1 mg/kg 20–25% albumin over 4 h with furosemides at the middle and the end **(X).**

R 3.1. D: We recommend identification of the cause of SRNS (1) secondary type need treatment of the cause (infections, drugs, auto immune disease) **IPNA.** (2) Genetic types. Mostly need supportive care till transplantation is available, showing low recurrence rate. **(B) IPNA.** (3) Idiopathic types (MCD, FSGS, DMS) and (IMP, IMN) need immunosuppressive therapy. **IPNA 2020, KDIGO 2021** (EPG Figs. 2, 3, 4, 5, 6, 7 and 8).

R 3.1. E: 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 **(EPG-GPP) (KDIGO 2021).** National guideline treatment recommendations are **based on histopathology and genetic tests** (when available) considering other mentioned factor. Recommendations are summarized in **EPG flow chart** (Fig. 8) **and** (Figs. 2, 3, 4, 5, 6 and 7) in detail for each type with graded evidence referring to its source guideline.

R 3.2: Immunosuppressive therapy

R 3.2.1: Patient evaluation before putting immunosuppression therapy plan aiming for

- Exclusion of drugs, infections, malignancy, hereditary types
- Assessment of severity of disease (proteinuria, GFR, extrarenal presentations)
- Histopathological classification

R 3.2.2: Immunosuppressive therapy plans (refer to Additional file 1 for detailed recommendations).

R 3.2.2. A: FSGS. Fig. (2) **R 3.2.2. B:** ANCAV Fig. 3

R 3.2.2. D: L. N Fig. 4a and b **R 3.2.4. E:** IgAV Fig. 5a and b

R 3.2.2. F: MP, C3/DDD Fig. 6 **R 3.2.2. G:** Membranous Fig. 7

R 3 .3: Follow-up and management of complications IPNA 2020

R 3.3.1: We suggest to avoid excess salt intake 2 mEq/kg/day **(C),** with balanced fluid intake **(C)**

R3.3.2: We suggest statin in MDR, high LDL **(C)**, control of BP if > 95th percentile **(A)**, calcium **(C)**, vitamin D **(C)**, levothyroxine T4 if hypothyroidism **(A)**, magnesium if hypomagnesaemia **(D)**

R 3.3.3: For prevention of infection, we suggest IVIG for children with recurrent infections or low IgG **(D)**, no routine antibiotics **(C)**, cotrimoxazole in patients on rituximab 5–10 mg/kg/day three times weekly 3–6 m **(C)**. Receiving all vaccinations pneumococcal, meningococcal, influenza, and varicella **(A)**. Live vaccines should not be given to SR on immunosuppressive **(X)**. 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 **(ungraded).**

We recommend VZIG **(A)** on exposure to chickenpox, treatment with acyclovir 10 mg/kg 7 days within 7–10 days of exposure, varicella vaccine in remission **(C)**

R 3.3.4: For prevention of thrombosis

- We recommend mobilization, avoid central lines **(X).**
- No sufficient evidence for routine anticoagulant with no previous history or risk of thrombosis **(ungraded)**
- We suggest low molecular weight heparin in previous history of thrombosis, central lines, hereditary thrombophilia predisposition, infection, or dehydration **(C).**
- We recommend thrombophilia screen in previous conditions for protein S **(C)**, antithrombin, and factor V genes **(C).**

R 4: Management of SRNS/ESRD. IPNA 2020 adopted, Pretransplant workup

R 4.1.a: While on dialysis and or waiting for kidney transplant

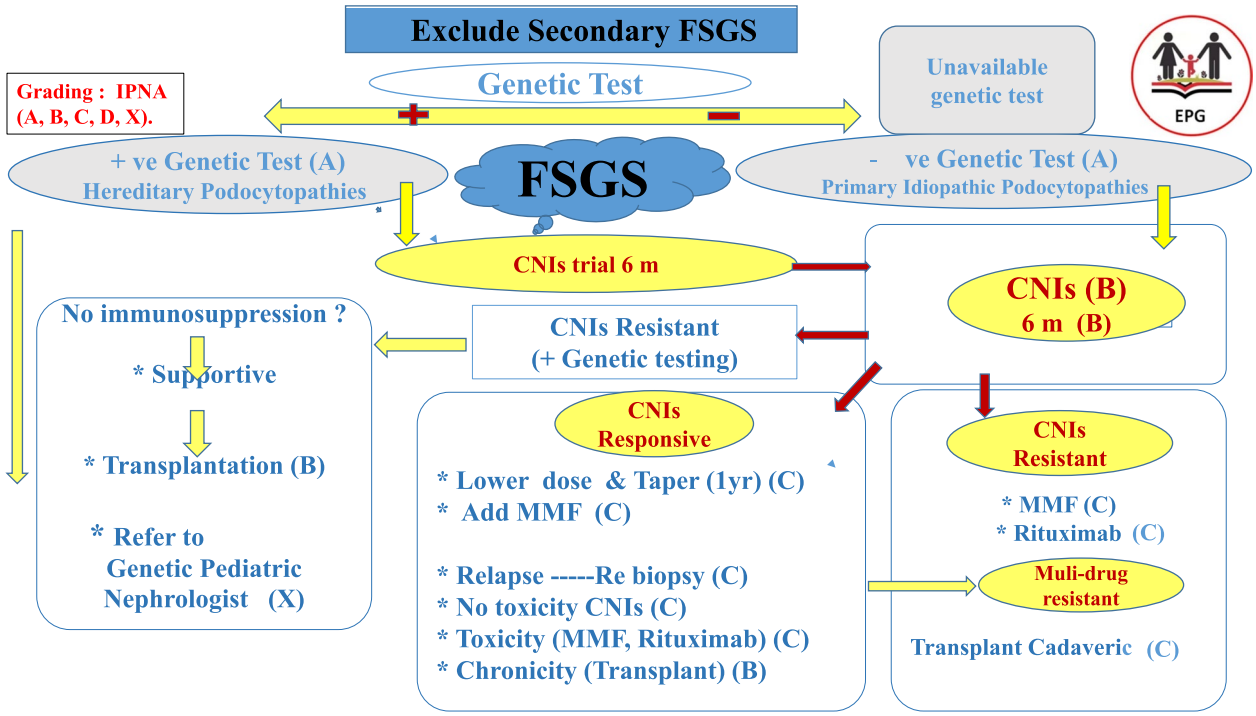

Fig. 2 EPG management plan for idiopathic and hereditary FSGS. R 3.2.2. A: FSGS

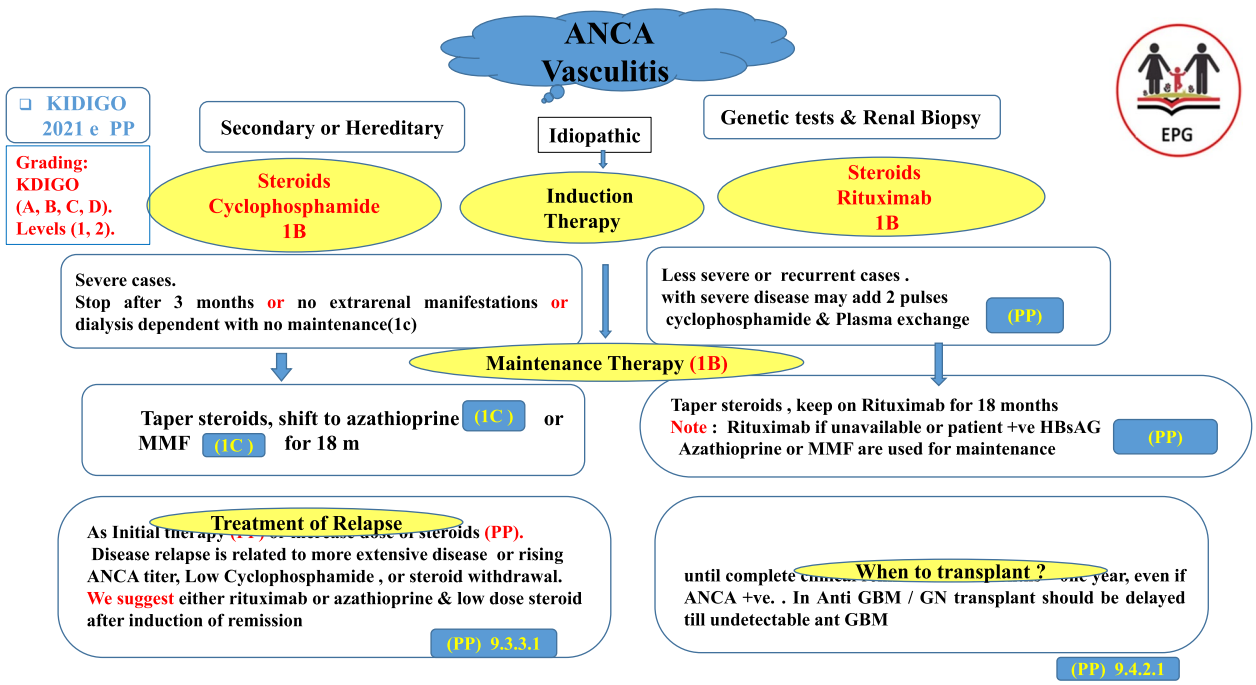

Fig. 3 EPG management of idiopathic ANCAV after excluding secondary and genetic types. R 3.2.2B

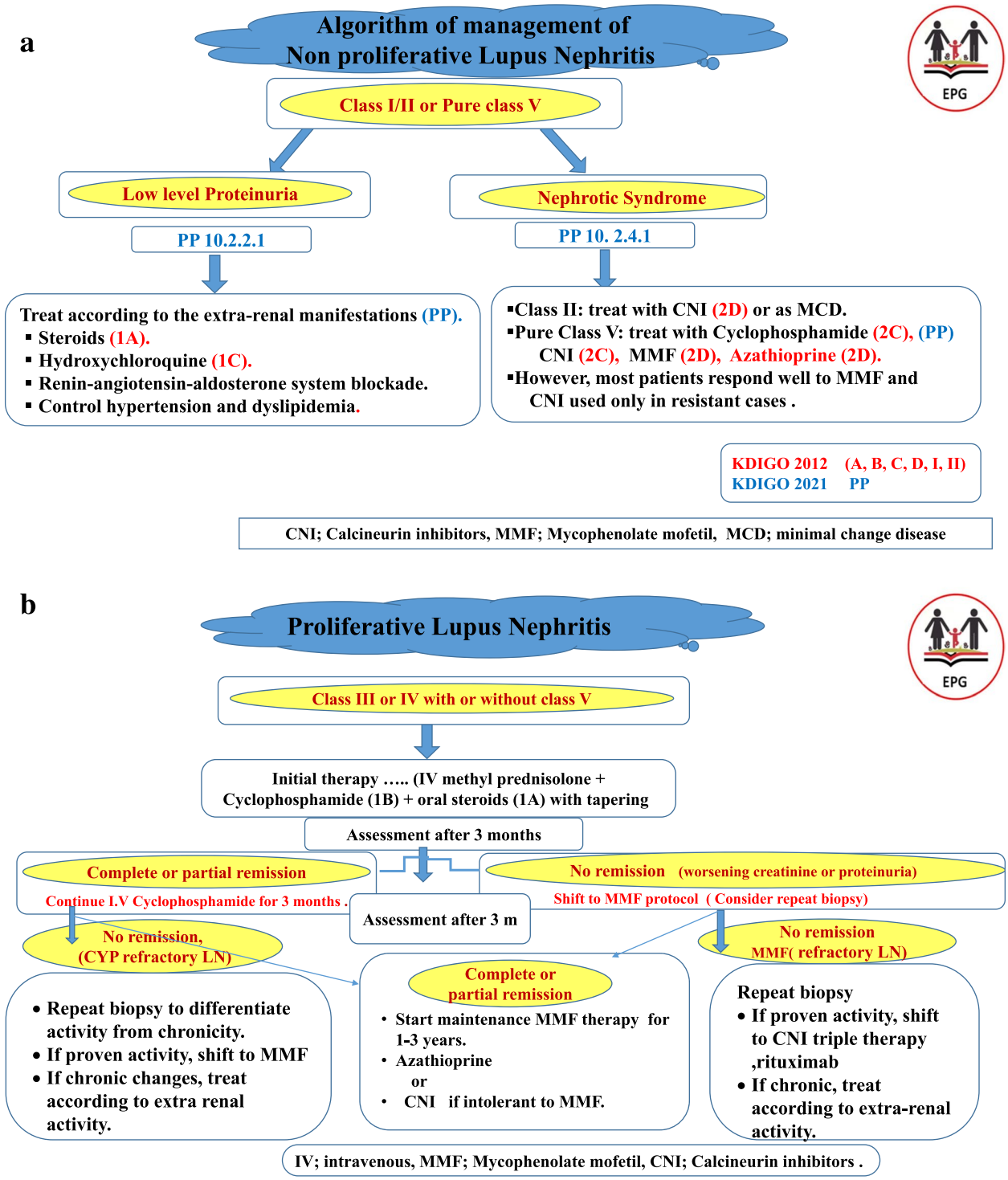

Fig. 4 **a** EPG management of lupus nephropathy classes I, II, and V (pure MN) R 3.2.2D. **b** EPG management of lupus nephropathy classes III and IV. R 3.2.2 D

We recommend **discussing with the family** and dialysis team benefit risk of transplantation and post TX recurrence rate **(A).**

R 4.1. b: We recommend daily **monitoring of proteinuria** for assessment of native residual function **(A).**

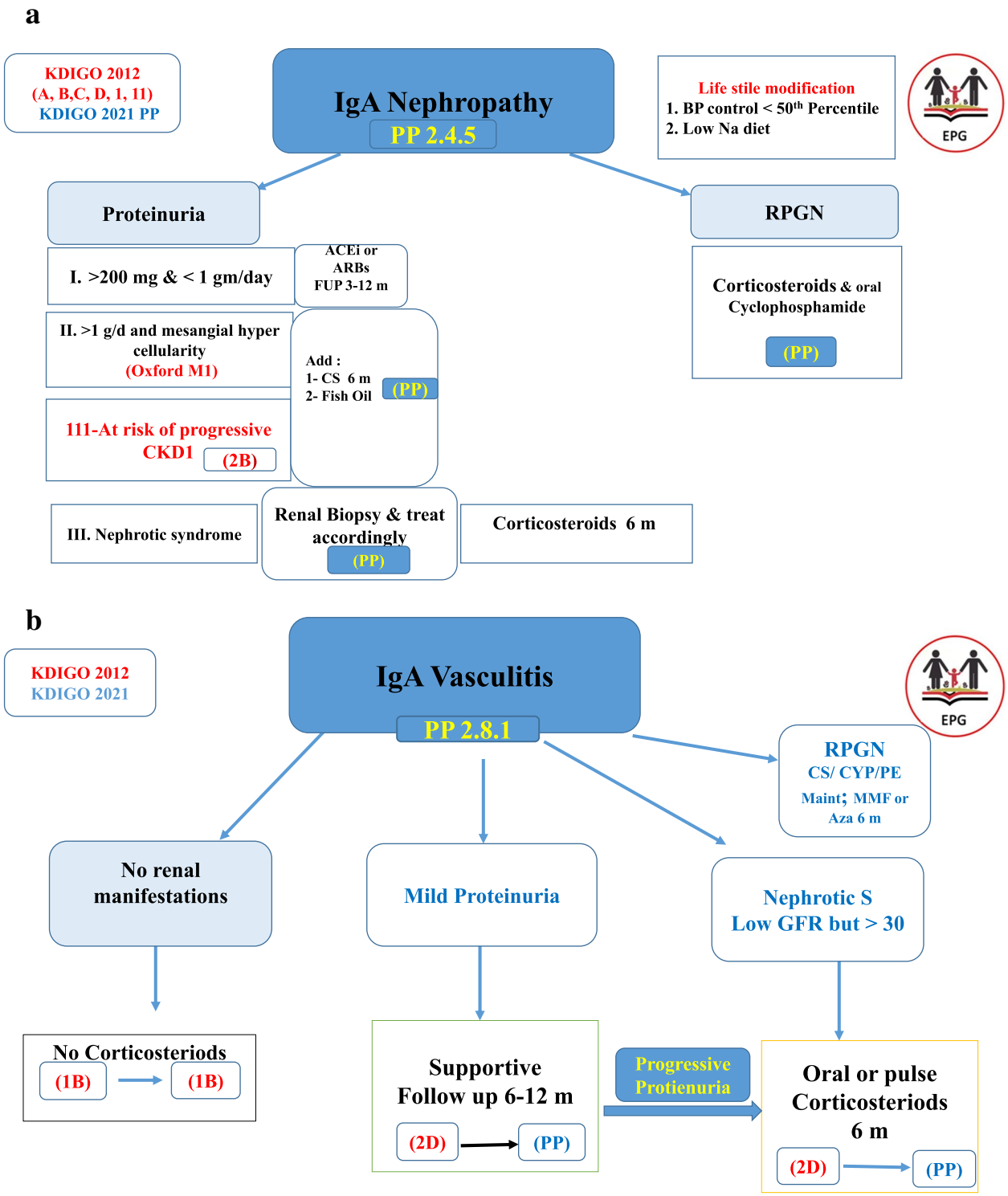

Fig. 5 **a** EPG management of IgA nephropathy. R 3.2.2 E. **b** EPG management of IgA vasculitis. R 3.2.2 E

R 4.1.c: We recommend **nephrectomy** if TX will be done before resolution of NS or if proteinuria is severe to minimize risk of thromboembolism **(D).**

R 4.1.d: We recommend **genetic tests** to recipients as hereditary types show low recurrence as compared to non-genetic types. (B) Discuss benefit

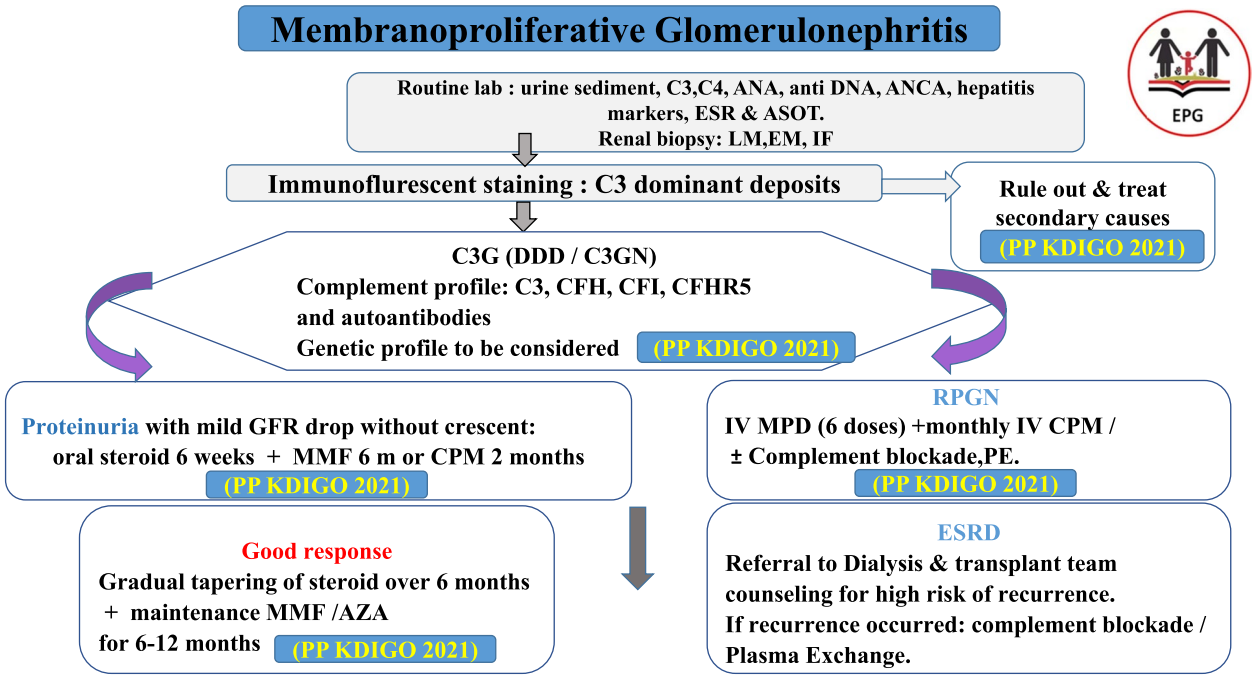

Fig. 6 EPG management of C3G/DDD with membranoproliferative changes. R 3.2.2 F

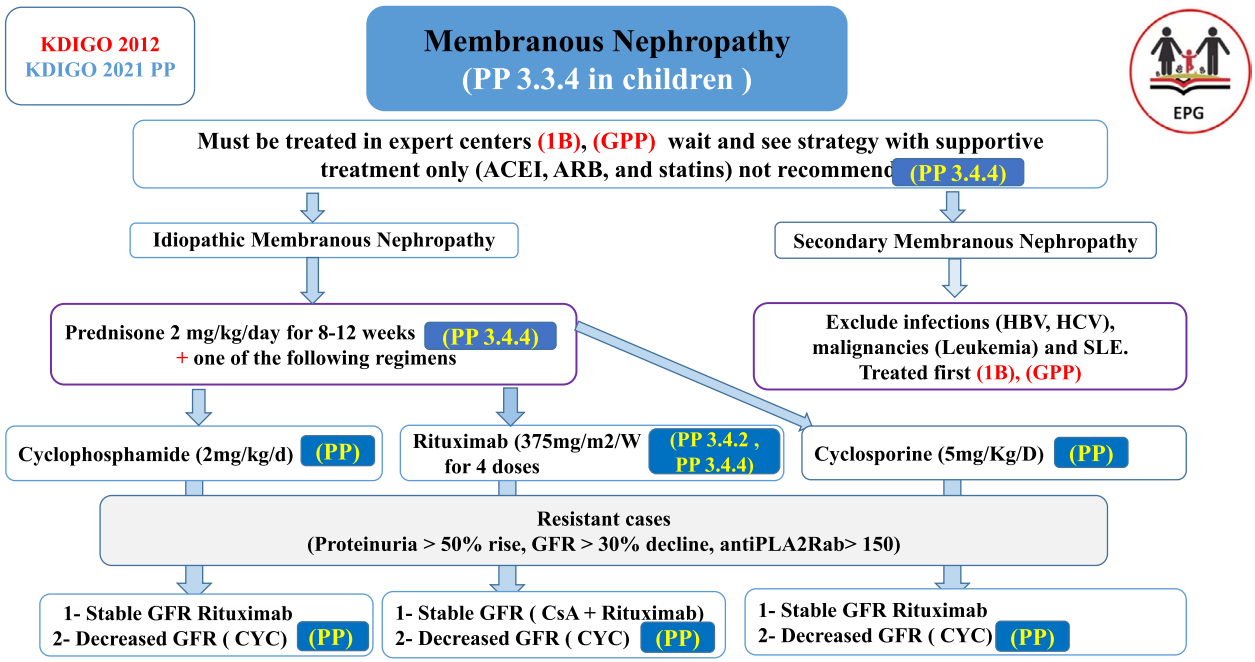

Fig. 7 EPG management of MN. R 3.2.2 G

risks for genetic and non- genetic. **(A)** 43% of total kidney transplants in Egyptian children through 2009/2017 registry were identified as hereditary ESRD [51]

10 Proper donor selection

R 4.2 a: We recommend TX ESRD/SRNS regardless of genetic or non-genetic **(B)**

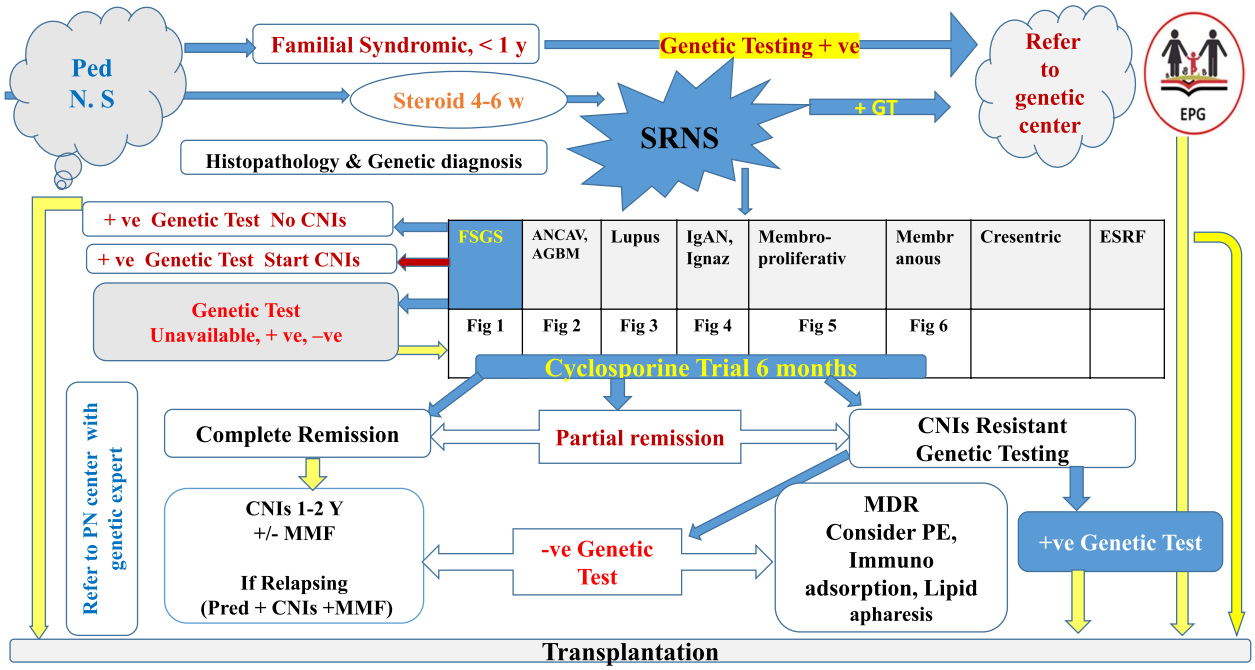

Fig. 8 EPG/SRNS management flow chart. R 3.2.2

We recommend living related donor **(X).**

R 4.2.b: Living related allograft donors should do GT as a part of evaluation in SRNS **(X)**

R 4.2.C: Donors candidate with a pathogenic or likely pathogenic variant in a dominant gene with or without symptoms to be excluded as a potential donor **(X)**

- Carrier of recessive SRNS variant may be a potential donor after genetic counseling except in COL4A5, COL4A3, and COL4A4 **(C).**
- 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 **(C).**

11 Recurrence risk

R 4.3.a: We recommend discussing risk of recurrence or graft failure with the donor **(A)**

R 4.3.b: We recommend discouraging living related donation to recipients with previous recurrence in previous graft. Cadaveric graft always remains a better option than dialysis **(C)**

R 4.3.c: 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 **(C)** after exclusion of other causes **(C)**; however, renal biopsy is conclusive

R 4.3.d: We suggest for prevention or of recurrence in high-risk types, pre and post-transplant plasma exchange **(C)**

R 4.3.e: We recommend treating recurrence with pulse MPD, CNIs, rituximab, and plasma exchange **(C)**

R 4.3. f: We recommend on recurrence to start RASI re-transplant as the deceased donor is ethically acceptable and considered more appropriate than dialysis **(C)**.

12 Results

This is a guideline, no reported results.

13 Discussion

Through this discussion, we will analyze the panel rational and background behind each of the following three policies: (1) which recommendations the panel decided to include as adopted or exclude from the retrieved guidelines, (2) added good practice points **(EPG-GPP)** with consensus approval related to our local community disease profile, and (3) adaptation and modification of some existing recommendations to suit our facilities and expertise.

14 [1] Adopted recommendations

- The panel has chosen the recommendations with **clearly presented evidence that were common in the three source guidelines** and those that represent the current acceptable and applicable practice addressed to our target users.
- The panel also **considered variation in facilities and expertise** at our local **different health care settings** thus *supported referral* policy to advanced secondary and tertiary levels where specialized care is available.
- All relevant methodology, additional evidence, and **documents** for the development of the source CPGs are available and freely downloadable from their **official websites** stated at the end of the guideline.
- The final version of the adapted CPG was thoroughly reviewed by local and international **external reviewer's panel (KDIGO was presented in the board)**. Final draft was guided by their official recommendations.

Indeed, IPNA 2020, KDIGO 2021, and JAPANESE 2014, our three de novo, systematically developed evidence-based clinical practice guidelines, were very helpful to the panel for making most acceptable statements tailored to suit our local community distinctive pattern, with (1) high rate for consanguineous marriage and (2) where endemic infections are common in some focal hot spots. Facilities and expertise are affordable in many pediatric nephrology centers but are still lacking on the community average, mostly lagging in rural areas. Referral to expert centers is not routinely applied; patient reluctance and insistence of some families to keep their children followed by their practitioners or general pediatricians is a major limitation. All such challenges were considered while developing our recommendations.

IPNA 2020 used flexible recommendations fluctuating between ideal statements, as well those applicable for areas with limited resources lacking genetic testing, renal biopsy, and even cyclosporine. Their panel clinical practice as pediatric nephrologists dealing with children was very evident, especially when discussing genetic types.

KDIGO 2021 recommendations reflect major experience in the management of different types of glomerular diseases based on histopathological types. First and alternative treatment options of immunosuppressives were clear whenever patient intolerance or resistance is present.

Therefore, the **National EPG** used best statements as adopted from either for each topic. We also tailored unavailable recommendations to our highest priority target group and supported referral to secondary and tertiary PNCs with experts and facilities. The following paragraphs will show examples reflecting panel rationale and background behind the following: (1) inclusion and exclusion of recommendation statements, (2) addition of clinical practice points, and (3) modification areas Why and How.

15 [2] Added practice points (GPPs) for local address to our health care settings (R 2.5)

1. **EPG-GPP**. Since general practitioners and pediatricians in our local health settings are the first who diagnose NS among children they are following, therefore, we recommend, upon primary diagnosis of NS, **referral to pediatric nephrologist** for extended evaluation and management. Primary diagnosis is based on the following: nephrotic proteinuria > 1 g/m^2/day in 24 h urine sample or first morning UCPR > 200 mg/mmol corresponding to 3–4 + by urine dip stick, edema, and serum albumin < 3 g/dl).
2. **EPG-G PP**. Since some pediatricians are interested to manage these cases, and some parents prefer to keep their children under their pediatrician care, we recommend the following **red flags for referral to pediatric nephrologists**: infants or young children, positive family history, presence of extra-renal manifestations, hematuria, hypertension, impaired GFR, frequently relapsing, steroid dependent, steroid resistant, progressive decline in renal function, complicated cases with severe edema, infection, and thrombosis.
3. **EPG-GPP**. Since pediatric nephrology centers are the well-equipped areas for proper management, we recommend **sustained support of PNC centers** with all needed facilities: genetic testing, laboratory tests for immunology, infection screen, drug monitoring, renal biopsy, and immunosuppressive drugs, with medical insurance cover.

16 [3] Adapted recommendations, rationale and background for adaptation

R 2: Diagnosis workup modification EPG adopted IPNA 2020 recommendations for clinical **(EPG: R2.1)** and laboratory assessment **(R2.2)** (Table 1, 2. IPNA 2020, EPG Tables 1 and 2) of pediatric SRNS

Genetic testing (R2.3): SRNS as recommended by **IPNA 2020** were **customized** to suit our community since they are not affordable for all SRNS. **IPNA 2020** recommends genetic testing to all SRNS if possible **(A)**, at 4–6 weeks steroid therapy **(B)**, and before biopsy **(D)**.

EPG prioritized timing of GT and frame our target group as:

Early testing for infantile onset < 1 year, familial, syndromic with extra renal manifestations 1EPG-GPP; this allows diagnosis of monogenic disorders. Mutations in NPHS1, NPHS2, WT1, COQ2, PLCE1, and LAMB2 account for 50–60% of monogenic disease in children [52, 53].

In **late testing for SR** after 4 weeks steroid therapy since GT for all SR is not possible, we suggest GT for:

EPG-GPP SRNS with FSGS OR DMS, before starting cyclosporine therapy. FSGS is the most prevalent histopathology in genetic types [54–57]. There is correlation between histopathology and age onset of disease; DMS is common at infantile onset, FSGS at 7–25 years of age [5].

EPG-GPP cyclosporine resistant (6months) after standard dose. Those with monogenic etiology have fourfold risk of non-response to CNI [53] and should be excluded from further clinical trials, referred to PNC with genetic experts for TX after WES and pathogenicity tests that confirm genetic variant, and discussed with the family benefit risk of further immunosuppression. **IPNA 2020 (A)**. Certain mutations respond to targeted therapy as coenzyme Q10 [59].

EPG-GPP complement genetic testing for mutations in cases of **C3/DDD** diagnosed with IFM. Mutant protein indicates complement blockade drugs rather than PE and MMF, even after TX. **KDIGO 2021** [49, 50].

EPG-GPP pretransplant GT: All IPNA transplant recommendations for ESRF are adopted since we represent a hot zone of consanguinity applying only live related donor allograft. Inherited kidney diseases (IKD) reported 43% of total kidney transplants in Egyptian children registry 2009–2017 [51].

R 2.4: Renal biopsy for SRNS was more implemented in national CGL as supported by KDIGO recommendations, being more available than GT in our area. When used with laboratory immunology (complement, antibodies, viral serology, infection screen [41–44]), as well as urine and blood biochemistry reflecting renal function, we can identify idiopathic, secondary types and predict genetic types for confirmation with genetic tests [41–44]. Thus, we can put therapy plan and predict disease course and outcome **(EPG biopsy and serology of SRNS (Table B) adapted from KDIGO 2021)**. This was clearly explained while reporting our **EPG recommendations in (Figs. 2, 3, 4, 5, 6 and 7) adapted from KDIGO 2021 and EPG diagnosis workup Fig. 8 adapted from IPNA 2020, KDIGO 021{refer to EPG recommendations guidelines}.**

R.3.Treatment modifications for SRNS after patient evaluation with clinical and lab assessments **EPG modified IPNA 2020**. Treatment recommendations for SRNS to be mainly based on **histopathology**, as well as **genetic testing** whenever possible after exclusion of infections, drugs, malignancy, and systemic autoimmune diseases (lupus, ANCA vasculitis, IgA) **[(Fig. (1.6) adapted from KDIGO 2021, Fig. 8 national CGL adapted from IPNA2020 and KDIGO2021]**.

17 Our reasons

(1) Being an endemic country for some infectious diseases such as hepatitis and currently few focal rural areas for tuberculosis and schistosomiasis, therefore, we suggest our NCGL to support early diagnosis and treatment of infections commonly related to SRNS. **EPG** (Fig. 1 diagnosis workup) [13–15].

(2) Since exclusion of secondary types depends on efficient lab for diagnosis of autoimmune diseases, therefore, **referral** recommendations to **pediatric nephrologists** are supported in our local format.

(3) **Genetic labs** are only available in few pediatric nephrology centers. Therefore, identifying our priority group and supporting their referral to centers with genetic expert will be of help in challenging genetic testing limitations in our low resource area [54–58], which is also ranked as hot zone for IKD that is only permitted for life related TX programs [51].

(4) **Renal biopsy** (LM, IF, EM) is available in all PNCs. Light microscopy confirms diagnosis of FSGS, MCD, and DMS podocytopathies for further differentiation between primary, genetic, and secondary. It also diagnoses crescentic types for aggressive immunosuppressives and PE and identifies ESRD for replacement therapy. Immune fluorescent microscopy differentiates secondary FSGS from idiopathic and genetic. Pattern of biopsy deposits with serology findings will identify ANCAV (pauci D), AGBM (linear D), granular deposits in post infectious, LE, IgA, MP, and membranous. Complement D in excess identifies C3/DDD. Electron M can further differentiate between all types of FSGS and report GBM changes related to some hereditary diseases such as Alport [39–42].

18 Immunosuppressive treatment nationally preferred choices (adopted/adapted)

- **Idiopathic FSGS** [EPG Fig. 8]: For identification of genetic types, **in the absence of routine GT, EPG** suggests starting CNI therapy for 6 months for all SR/FSGS **EPG-GPP**. This will identify monogenic types and may identify those known to be cyclosporine resistant **for referral** to genetic expert centers for D/TX. **EPG-GPP** CNI responsive cases will be maintained for 1–2 year; then, MMF is considered. On relapsing, steroid-induced remission with repeat biopsy is recommended. Normal findings suggest extending treatment with CNI while chronicity suggest referral for D/TX **IPNA adopted**. CNI toxicity and resistant cases are suggested for GT, if not previously done **EPG-GPP**, before proceeding to multidrug clinical trials starting with rituximab (RTX) (I**PNA adopted**)
- **Idiopathic ANCA vasculitis**: We suggest CYC in severe cases or RTX in less severe and recurrent cases and if resistant add2 pulses CYC ± PE in severe cases (**KDIGO adopted**). Maintenance with RTX is not available; therefore, MMF or azathioprine is the locally preferred **EPG-GPP**; however, KDIGO supports maintenance with RTX as steroid saving.
- **Lupus nephropathy: Mostly KDIGO 2021 adopted.**

Class 1 and class II are KDIGO **adopted.**

Class III, 1V (proliferative), and V (mixed proliferative and membranous) EPG adaptation:

We adopt KDIGO suggesting IV methyl prednisolone 0.25–0.5 g/day for 3 days, and then oral CS 1 mg/kg/day tapered over 6–12 months. However, we prefer IV monthly CYC 0.5–1 gm/m^2 for 6 months as initial therapy than oral CYC or MPA to ensure patient adherence provided not to exceed toxic cumulative dose and good leucocytic count.

MMF is suggested in resistant or recurrent flares in children with high cumulative dose and risk of infertility **(EPG-GPP)**. Resistant cases not responding to initial therapy at 3 months should be evaluated, and renal biopsy may be considered before shift to any other treatment as switch from CYC to MPA or triple CNI, steroids, and MPA-based initial therapy or RTX **KDIGO 2021.**

We prefer use of triple therapy with CNIs, MPA, and glucocorticoids for those intolerants to MPA or CYC contraindicated or refractory to them **EPG-GPP.**

RTX is suggested in persistent or repeated flares considering its side effects and precautions.

Azathioprine is suggested for intolerance, high cost, or unavailability of other drugs. **EPG-GPP.** Maintenance therapy with MPA or AZA for 1–3 years is suggested for all patients as adopted from **KDIGO 2021.**

Class V (pure MN): We adopt **KDIGO 2021** for patients with nephrotic range of proteinuria and or extra renal manifestations. **KDIGO2021** suggests glucocorticoids with one other agent (e.g., MPA, CNI, CYC, RTX, and AZA). **KDIGO 2012** previously graded CYC, CNI **(2C)**, and MMF and AZA as **(2D). EPG** prefer MMF in class V, being effective and tolerant in most of our cases. CNI is suggested for resistant cases or those contraindicated for CYC. RTX is limited to resistant cases being expensive, unavailable of high risk in the presence of infection **EPG-GPP.**

- **IgA N and IgAV KDIGO adopted**, **C3G/DDD KDIGO adopted**
- **Idiopathic MN:** We prefer CYC and steroids in severe cases provided no toxic load and suggest CsA in less severe and to be supported with 2 pulses RTX if resistant unless slowing GFR indicating switch to RTX or CYC **(EPG-GPP).**

19 On conclusion

Adaptation guidelines are very helpful for countries with limited resources. The ADAPTE process is a comprehensive tool for development of high-quality CPGs for health care institutions in developing countries. Our collaboration and adaptation of CPG produced by relevant organization such as KDIGO or international specialized society such as IPNA aim to optimize patient care with the most beneficial and least harmful interventions (evidence-based) customized to our culture, considering patient values and references, with identification of priority areas for address, priority questions, transparency for evidence grades, expert clinical and methodology panel trained in EB, continuous communication through virtual meetings, workshops and webinars, critical appraisal, and peer reviewing for drafts. All these factors aimed for proper final statements despite all challenges including the continuous update for major high-quality scored EB CPGs.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
ACR	American College of Rheumatology of SLE
ARF	Acute renal failure
AHUS	Atypical hemolytic uremic syndrome
AGBM	Anti-glomerular basement membrane antibodies
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
CRF	Chronic renal failure
CS	Corticosteroid
CSF	Cerebrospinal fluid
CYC	Cyclophosphamide
CYS R	Cyclosporin resistant
CVD	Cardiovascular disease
DDD	Dense deposit disease
DMS	Diffuse mesangial sclerosis
ESKD	End-stage kidney disease
EULAR	European League Against Rheumatism/American College of Rheumatology
EM	Electron microscopy
EMA	European Medicines Agency
ESRD	End-stage renal disease
FR	Frequent relapse
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GIT	Gastroenteritis
GT	Genetic tests
Glucocorticoids	Steroids
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IF	Immunofluorescopy
IFTA	Interstitial fibrosis tubular atrophy
INR	International formalized ratio
IgAV	IgA vasculitis
IgAN	IgA nephropathy
ISKDC	International Study Kidney Disease in Children
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IPNA	International Pediatric Nephrology Association
I.V	Intravenous
IV CYC	Intravenous cyclophosphamide
IV MP	Intravenous methyl prednisone
KDIGO	Kidney Disease International Global outcome
LM	Light microscopy
LN	Lupus nephritis
MP	Methylprednisolone
mg/kg	Milligram of medication per kilogram of body weight
MCD	Minimal change disease
MCNS	Minimal change nephrotic syndrome
MDR	Multidrug resistant
MN	Membranous nephropathy
MP	Membranoproliferative
MMF	Mycophenolate mofetil
NCGL	National Clinical Guideline
NGS	Next-generation sequencing
PP	Practice point
PR	Partial remission
PDN	Prednisone
PE	Plasma exchange
PLA2R	Phospholipase A2 receptor antibodies
PNC	Pediatric nephrology center
PSGN	Post streptococcal glomerulonephritis
RASI	Renin angiotensin system inhibitor
RPGN	Rapidly progressive glomerulonephritis
SCr	Serum creatinine
SD	Steroid dependent
SLE	Systemic lupus erythematosus
SLEDAI	Diffuse activity index for lupus patients
SSNS	Steroid-sensitive nephrotic syndrome
SRNS	Steroid-resistant nephrotic syndrome
TTP	Thrombotic thrombocytopenic purpura
UPCR	Urine protein creatinine ratio
VZIG	Varicella-zoster immune globulin
TMA	Thrombotic microangiopathy
TX	Transplantation
WES	Whole exon sequencing
WGS	Whole genome sequencing

Supplementary Information

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Additional file 1. Supplementary File. Appendix: EPG Methodology List of Figures & Tables; IPNA 2020 & KDIGO 2021 Tables.

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