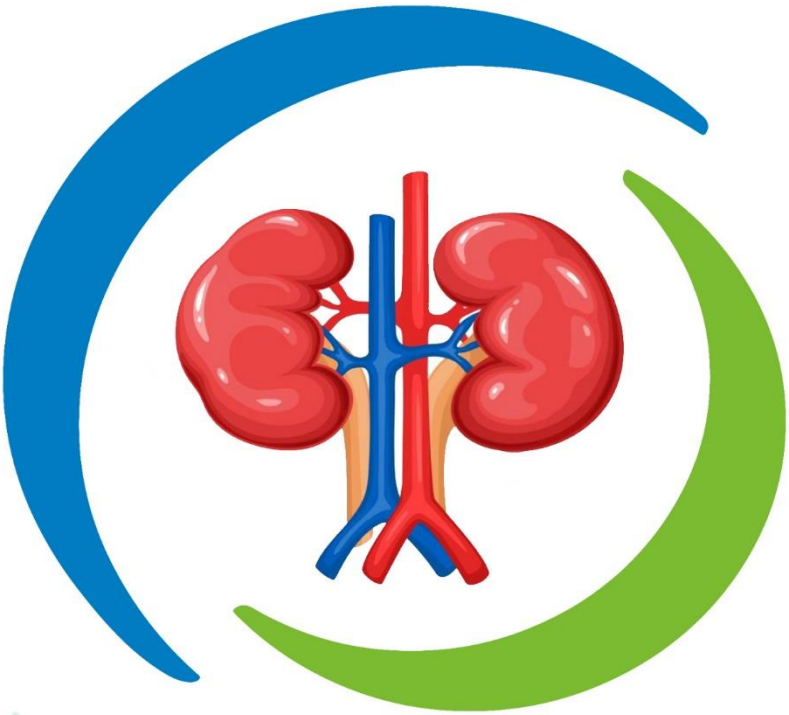
Pediatric Nephrology Protocol of EHA



First Edition 2024

Egyptian Clinical Practice Protocols

in

Pediatric Nephrology

for

Egypt Healthcare Authority

First Edition

2024

Prepared by

Working Group for Development of

Egyptian Clinical Practice Protocols

in

Pediatric Nephrology

for

Egypt Healthcare Authority

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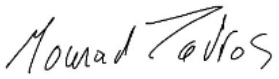

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PREFACE

Recently, there is an increasing need to provide programs with accurate competency-based assessments to ensure the delivery of high-quality healthcare. The aim of developing these Egyptian Clinical Practice Protocols in Pediatric Nephrology is to unify and standardize the delivery of healthcare to any child at all health facilities.

Pediatric Nephrology service is usually offered to children below 16 years of age in Egypt.

The current status of healthcare in which avoidable failures are abound. “We train longer, specialize more, use ever-advancing technologies, and still we fail.” Part of the problem, is that the ever-increasing complexity of medicine makes uniform care delivery impractical or impossible. That is, unless there are protocols, checklists, or care paths that are readily available to providers.

Regarding Pediatric Nephrology, busy clinicians have all felt the need for a concise, easy-to-use resource at the bedside for evidence-based protocols, or consensus-driven care paths.

In this protocol, we offer comprehensive reviews of selected topics and comprehensive advice about management approaches based on the highest level of evidence available in each case. Our goal is to provide an authoritative practical medical resource for pediatricians.

We hope that such an approach will encourage clinicians to apply available evidence to their practice and also track compliance with desired practices. We hope that practicing pediatricians, fellows and practitioners will find this protocol useful in delivering high-quality clinical care to their patients. We remain open to feedback and suggestions about how to improve this resource and how to make it maximally useful to those delivering care at the bedside in for patients in Pediatric Nephrology.

Members of the Working Group

For Development of the Egyptian Clinical Practice Guideline

In Pediatric Nephrology

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Nephrotic Syndrome

Treat-To-Target

- ✓ **Achieve freedom from recurrence**
- ✓ **Minimize side effects**
- ✓ **improve quality of life**

➲ Definitions:

- ☑ ***Nephrotic-Range Proteinuria:*** Urinary protein creatinine ratio (UPCR)≥2 mg/mg in a spot urine, or proteinuria ≥1000 mg/m2 per day in a 24-h urine sample corresponding to 3+or 4+by urine dipstick
- ☑ ***Nephrotic Syndrome:*** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 3gm/dl) or edema if serum albumin not available.
- ☑ ***Complete Remission:*** UPCR (based on first morning void or 24 h urine sample) ≤0.2 mg/mg or <100mg/m2/day, respectively, or negative or trace dipstick on three or more consecutive days.
- ☑ ***Partial Remission:*** UPCR (based on first morning void or 24 h urine sample) >0.2 mg/mg but <2mg/mg and serum albumin ≥3.0gm/dl.
- ☑ ***Steroid-Sensitive Nephrotic Syndrome (SSNS):*** Complete remission within 4 weeks of prednisone (PDN) at standard dose (60 mg/m2 /day or 2 mg/kg/day, maximum 60 mg/day).
- ☑ ***Steroid-Resistant Nephrotic Syndrome (SRNS):*** Lack of complete remission within 4 weeks of treatment with PDN at standard dose.
- ☑ ***Relapse:*** Nephrotic range proteinuria with or without reappearance of edema in a child who had previously achieved complete remission.
- ☑ ***Infrequently Relapsing Nephrotic Syndrome:*** <2 relapses in the 6 months following remission of the initial episode or fewer than 3 relapses in any subsequent 12-month period.

☑ ***Frequently Relapsing Nephrotic Syndrome (FRNS):*** ≥2 relapses in the first 6-months following remission of the initial episode or≥3 relapses in any 12 months.

☑ ***Steroid-Dependent Nephrotic Syndrome (SDNS):*** A patient with SSNS who experiences 2 consecutive relapses during recommended PDN therapy for first presentation or relapse or within 14 days of its discontinuation

☑ ***Steroids Toxicity:***

- New or worsening obesity/overweight, sustained hypertension, hyperglycemia
- Behavioral/psychiatric disorders, sleep disruption
- Impaired statural growth (height velocity <25th percentile and/or height <3rd percentile in a child with normal growth before start of steroid treatment
- Cushingoid features, striae rubrae/distensae, glaucoma, ocular cataract, osteopenia, avascular necrosis

☑ ***Sustained Remission:*** No relapses over 12 months with or without therapy

➲ *Clinical Assessment*

- Spot urine analysis is indicated in any patient with edema or eye puffiness.
- Using spot urine samples, preferably a first morning void, or alternatively a 24-h urine sample to assess proteinuria.

➲ *Initial Diagnostic Work Up*

Clinical Evaluation

☑ ***Relevant Patient History:***

✓ Presence of gravity-dependent edema

✓ Fever episodes, pain, abdominal discomfort, fatigue

✓ Search for risk factors for secondary causes (e.g., lymphoma, systemic lupus erythematosus, medications)

☑ ***Physical Examination***

- ✓ Blood pressure, assess volume status and extent of edema (ascites, pericardial and pleural effusions), lymphadenopathy.
- ✓ Signs of infection (respiratory tract, skin, peritonitis, urinary tract).
- ✓ Extrarenal features, e.g., dysmorphic features or ambiguous genitalia or eye abnormalities (microcoria, aniridia), rash, arthritis. Further work-up is recommended.

☑ ***Anthropometry:***

- ✓ Growth chart: height/length, weight, and head circumference (<2 years).

☑ ***Vaccination Status:***

- ✓ Check/complete according to national standards.
- ✓ This is recommended before starting immunosuppressant medications other than steroids.

☑ ***Family History:***

- ✓ Kidney disease in family members
- ✓ Extrarenal manifestations
- ✓ Consanguinity

☑ ***Biochemistry:***

- ✓ **Spot Urine:**
  - o Protein/creatinine ratio (in first morning void) Recommended at least once before starting treatment of the first episode).
  - o Urine analysis.
- ✓ **Blood:**
  - o Complete blood count, creatinine, eGFR, urea, electrolytes, albumin
  - o Complement C3, C4, antinuclear and anti-streptococcal antibodies, and ANCA in cases suspected to have secondary nephrotic syndrome.

☑ ***Imaging Kidney ultrasound:***

- ✓ Consider a kidney ultrasound in all children with INS to exclude kidney malformations and venous thrombosis and in patients with reduced eGFR, hematuria or abdominal pain and always before kidney biopsy .

☑ ***Kidney biopsy:***

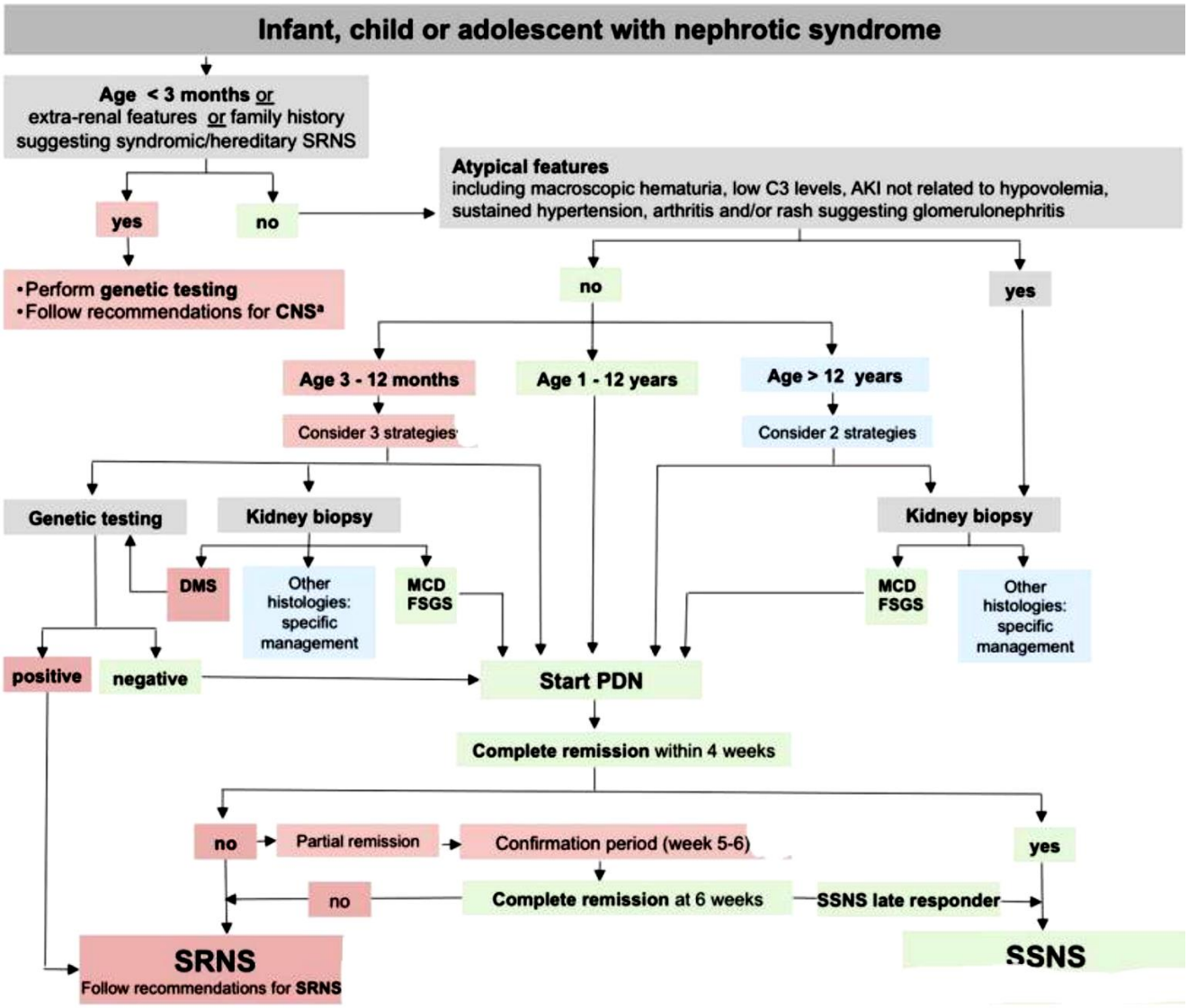
- ✓ Patients with atypical features including macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash
- ✓ Patients with infantile onset NS if genetic screening is not available (age 3–12 months)
- ✓ Patients>12 years of age on a case-by-case basis
- ✓ Patients diagnosed with SRNS

☑ ***Genetic testing:***

- ✓ Congenital NS (nephrotic syndrome in the first 3months of life),
- ✓ Syndromic features and/ or family history suggesting syndromic/hereditary SRNS
- ✓ Infantile onset NS (age 3-12 months)
- ✓ SRNS specially if non-response to CNI,
- ✓ Onset of disease during infancy
- ✓ Before kidney transplant.

☑ ***Indications of referral:***

- ✓ Congenital NS (nephrotic syndrome in the first 3months of life),
- ✓ Syndromic features and/ or family history suggesting syndromic/hereditary SRNS
- ✓ Nephrotic syndrome secondary to systemic illness
- ✓ Steroid dependent NS
- ✓ Steroid resistant NS



- *CNS: Congenital Nephrotic Syndrome*
- *DMS: Diffuse Mesangial Sclerosis*
- *MCD: Minimal Change Disease*
- *FSGS: Focal Segmental Glomerulosclerosis*
- *PDN: Prednisone*

➲ Therapy for the First Episode

Supportive Care and Management of Complications

☑ ***General measures:***

- ✓ Evaluating the volume status of a child in the acute nephrotic state.
- ✓ Routine fluid restriction is not recommended in SSNS patients, it is only suggested in case of hyponatremia (<130mEq/L) and/or severe edema in a hospital setting
- ✓ Low-salt diet (suggested maximum dose of 2–3 mEq/kg/day) during relapses with moderate or severe edema, and normal salt intake while in remission.
- ✓ Monitoring for hypertension in all children with SSNS and following current hypertension guidelines in children with confirmed, persistent hypertension.
- ✓ It is not recommended to use ACEI (angiotensin converting enzyme inhibitors) or ARBs (angiotensin receptor blockers) in SSNS to control edema or high blood pressure in relapse.

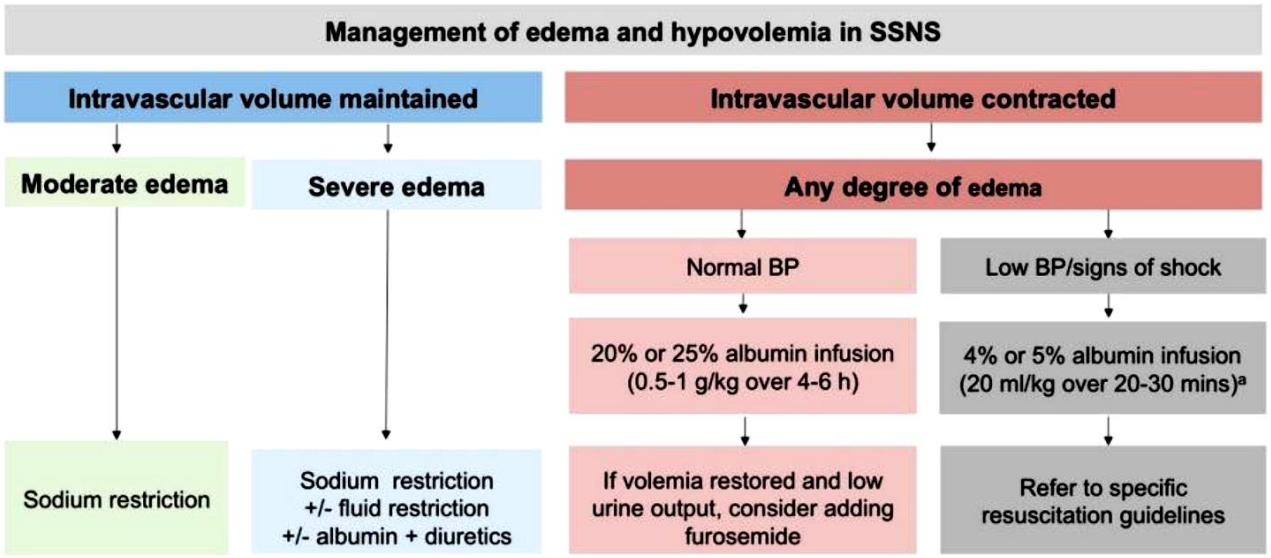
Prednisone therapy

- Daily prednisone for 4 weeks at 60 mg/m2 or 2 mg/kg (maximum dose 60 mg/day), followed by alternate day at the same dose.
- A tapering schedule during alternate day dosing: in the first attack rapid tapering over 1 month is suggested, in subsequent relapses slow tapering is suggested.
- Prednisone dose is calculated by either weight or body surface area based on the estimated dry weight.

Treatment of complications and indications of IV albumin infusion

☑ ***In case of hypovolemia or AKI:***

- ✓ In patients with signs of hypovolemia, withholding diuretics is recommended due to the risk of thrombosis, hypovolemic shock and AKI, and discontinue ACEI or ARBs.
- ✓ Use 20% albumin infusions in patients with signs of hypovolemia (including oliguria, AKI, prolonged capillary refill time, tachycardia, and abdominal discomfort) and add furosemide (1–2 mg/ kg given IV) in the middle and/or at the end of the infusion if volume has been restored and urine output is insufficient.
- ✓ In cases of AKI without hypovolemia, general management of AKI including fluid management, avoidance of nephrotoxic agents and modification of medication dosage when appropriate .



Algorithm for the management of edema and hypovolemia in SSNS. First, the volemic state of the child should be assessed. In case of maintained intravascular volume, we suggest treating moderate edema by low salt diet only, approximately 2 to 3 mEq per day (2000 mg/day in larger children), the amount of sodium required for a growing child, but not fluid restriction. In case of severe edema, fluid restriction is advocated in a hospital setting, with loop diuretics. Fluid restriction is also indicated in case of hyponatremia < 130 meq/L (considering false hyponatremia due to hyperlipidemia). In case of contracted intravascular volume but normal blood pressure, IV albumin infusion (20% or 25% to avoid fluid overload) should be administered over 4–6 h +/– furosemide if volemia is restored. Hypovolemic shock should be treated following specific resuscitation guidelines, starting with volume expansion by 20 mL/kg of 4% or 5% albumin over 20–30 min. [a]Alternatively, isotonic saline can be used if 4% or 5% albumin is not readily available. *BP* blood pressure

Other measures

☑ ***Prevention of thrombosis:***

- ✓ Avoiding immobilization and intravascular volume contraction during acute nephrotic episodes.
- ✓ Routine prophylactic anticoagulation or antiplatelet treatment for children and adolescents in the acute nephrotic stage is NOT recommended.
- ✓ Considering preventive anticoagulation during relapses in case of identified increased risks for thromboembolic complications.

☑ ***Prevention and treatment of viral and bacterial infections***

✓ Antibiotics

- o Antibiotic prophylaxis should not be given routinely to children with SSNS.
- o Prompt antibiotic treatment in the case of a suspected bacterial infection
- o Treating peritonitis with IV antibiotics targeting Streptococcus pneumoniae.

✓ Vaccinations

- o Reviewing the child's vaccination status at disease onset and completing all inactivated vaccinations following the vaccination schedule that is recommended for healthy children without delay, especially for encapsulated bacteria (pneumococcus, meningococcus, haemophilus influenzae).
- o Administering inactivated influenza vaccine annually.
- o Avoid administrating live vaccinations in patients on high-dose immunosuppression and in the first 6 months after RTX treatment.
- o Vaccinating the household against influenza annually, against COVID-19 and with live vaccines if live vaccines are contraindicated in the child with SSNS.

✓ Varicella

- o In case of exposure to chickenpox in children with immunosuppressive treatment who have not been immunized against VZV, prophylactic treatment with specific VZV IVIGs or oral acyclovir or valacyclovir for 5–7 days starting within 7–10 days of the exposure is recommended.
- o VZV infection is treated with intravenous high-dose acyclovir for 7–10 days
- o Vaccinating non-immunized patients while in remission and not on high-dose immunosuppressive medications, as well as vaccinating non-immunized siblings and parents against.

☑ ***Preservation of bone health:***

- ✓ Avoiding prolonged steroid exposure as a risk factor for osteopenia by administering the minimum effective dose, by changing to alternate-day therapy while in remission after relapses, by limiting the duration, and by considering steroid-sparing agents in case of emerging toxicity.
- ✓ Ensuring adequate dietary calcium intake in all children with SSNS and oral calcium supplementation in those with insufficient calcium intake.
- ✓ Assessing 25-OH-vitamin D levels annually in patients with SDNS or FRNS during the remission phase (after three months of remission, if possible) aiming for levels>20 ng/mL (>50 nmol/L).
- ✓ In case of vitamin D deficiency, we recommend follow national treatment guidelines.

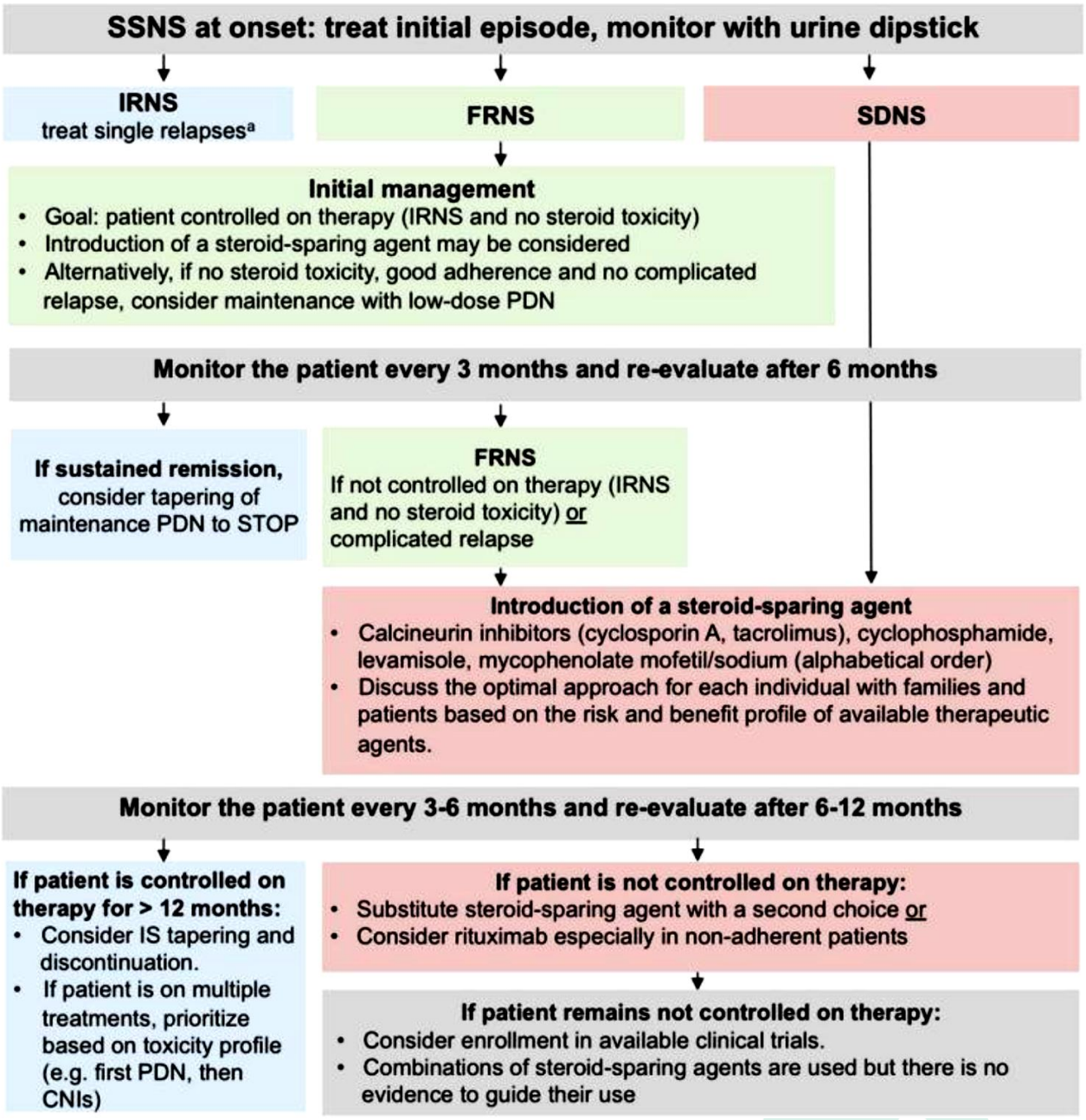
➲ *Therapy of Relapses*

First line therapy of relapsing SSNS

- SSNS relapse is to be treated with single daily dose of prednisone (2 mg/kg per day or 60 mg/ m2 per day, maximum 60 mg) until complete remission (UPCr≤20 mg/mmol (0.2 mg/mg) or negative or trace dipstickon 3 or more consecutive days) and then decreased to alternate day prednisone with slower tapering than the first episode.

Frequent relapses and steroid dependence

☑ ***Algorithm for treatment of SSNS:***



- ✓ In patients with FRNS, either the introduction of a steroid-sparing agent as detailed below or low-dose maintenance PDN given as an alternate-day or a daily dose.
- ✓ Introduction of a steroid-sparing agent in children: – who are not controlled on therapy, or – who suffer a complicated relapse, or – with SDNS
- ✓ The introduction of one of the following steroid-sparing agents: levamisole, cyclophosphamide , calcineurin inhibitors (CNIs) and mycophenolate mofetil (MMF)/ mycophenolic sodium (MPS).
- ✓ RTX as a steroid-sparing agent is recommended in children with FRNS or SDNS who are not controlled on therapy after a course of treatment with at least one other steroid-sparing agent at adequate dose, especially in case of non-adherence .
- ✓ Switching to a different steroid-sparing agent is recommended when a patient is not controlled on therapy with the initial agent.
- ✓ Tapering and discontinuation of maintenance treatment with prednisone and immunosuppressives is recommended in all children in sustained remission for at least 12 months.

➲ Steroid Resistant Nephrotic Syndrome

Definition

Lack of complete remission despite 4 weeks daily therapy with prednisone.

The guidelines advise that patients with partial remission at 4 weeks be followed up for an additional 2 weeks, with intensified or similar therapy.

Patients showing complete remission following additional therapy are labeled as late steroid responder.

“SRNS is an indication for referral to Pediatric Nephrologist”

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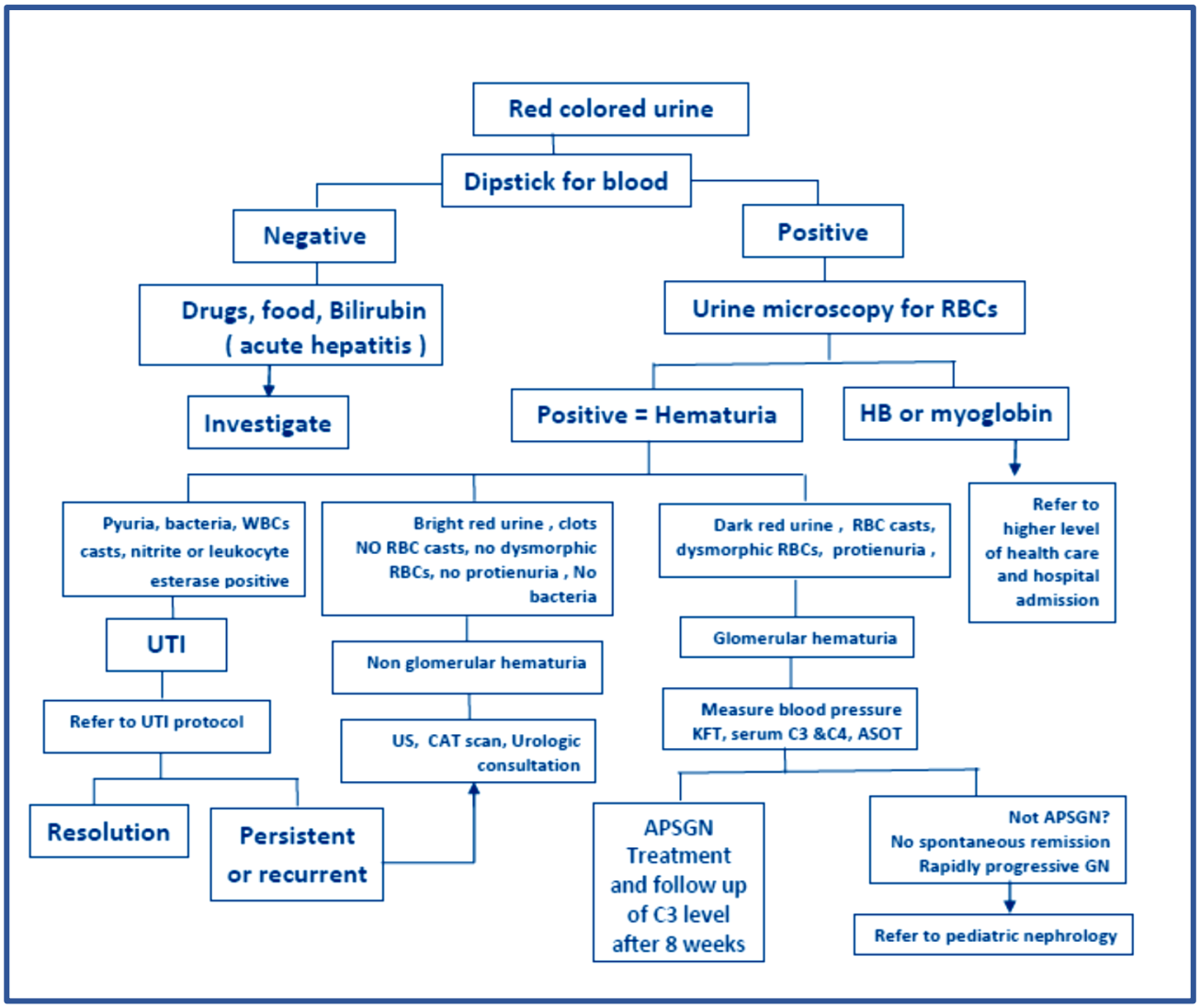


- ***Hematuria: presence of > 5 RBCs/HPF of 10 ml freshly voided centrifuged urine sediment (microscopic), if the urine by naked eye is red (usually RBCs > 100/HPF) its gross or macroscopic hematuria.***
- ***Proteinuria: presence of protein in urine > 4 mg/m2/h or 1st sample urinary protein/creatinine ratio > 0.2 mg/mg (200 mg/g).***

Acute Glomerulonephritis

Essentials for Diagnosis

- Hematuria (dark brown urine, tea or Cola colored), proteinuria (significant= 4 – 40 mg/m2/h), oedema, hypertension and oliguria

Post Streptococcal GN is diagnosed by

1. Evidence of streptococcal infection in throat (1 – 2 weeks ago) or skin(2-4 weeks ago) by history or high ASOT or throat culture.
2. Low serum level of C3 and normal C4. Normalization of C3 level after 8 weeks.

History

1. True bright red blood in the urine is more likely a consequence of non glomerular cause as urolithiasis.

2. Urine color in AGN is uniform throughout the stream.

3. The gross hematuria of AGN is virtually always painless, dysuria accompanying gross hematuria points to acute hemorrhagic cystitis.

4. A history of recurrent gross hematuria would point to an exacerbation of a chronic process such as IgA nephropathy and must be referred.

5. The family history for autoimmune disorders, as SLE is essential.

6. A family history of renal failure (asking about dialysis and kidney transplantation) may be the first clue to a process such as Alport syndrome, which may initially present with an AGN picture.

Systemic Review: To Exclude Other Causes of AGN.

1. Particular attention should be paid to rash, joint discomfort, recent weight change, fatigue, appetite changes, respiratory complaints, and recent medication exposure.

2. Complicated cases may present with shortness of breath or exercise intolerance from fluid overload or headaches, visual disturbances, or alteration in mental status from hypertension.

➲ *Workup at Presentation*

1. Blood pressure monitoring Q 6h.
2. 24h urine collection for volume and protein content
3. Urine analysis
4. Blood urea and creatinine
5. Serum electrolytes, CBC
6. Serum albumin
7. Body weight and edema monitoring daily
8. ASOT or throat culture
9. C3 and C4 serum levels
10. Renal ultrasound

❖ Notes:

1. The presence of red blood cell casts is diagnostic of GN if present.
2. The combined presence of glomerular hematuria and proteinuria is diagnostic of GN.
3. AGN is an inflammatory process, so it is common to see white blood cells in nephritic urine (sterile pyuria). Unfortunately, this occasionally leads to an inappropriate diagnosis of urinary tract infection.
4. The microscopic hematuria in poststreptococcal AGN may persist for a long time, even a year.
5. The best indicator of resolution of the disease is the return of the C3 level to normal. This generally occurs within 6 to 8 weeks.
6. Persistent decrease in C3 by this time merits consultation of pediatric nephrologist, as this could be an indicator of the initial presentation of a more chronic process such as MPGN.

Treatment

1) Children with AGN will require immediate referral or consultation of a pediatric nephrologist in the following situation

- Severe hypertension (more than 5mm above the 99th percentile)
- Significant renal insufficiency
- AGN is accompanied by a nephrotic syndrome (nephrotic range proteinuria in a child with nephritis)

2) Beyond these situations AGN can be managed in the primary care setting

- The APSGN is self-limited but requires good monitoring
- For hypertension (blood pressure between the 95th and 99th percentiles): restrict fluid and salt intake, Antihypertensives ; diuretics (lasix 1-2 mg/kg Q 12h orally or slowly IV), Ca channel blockers, ACI and others as indicated
- Hypertensive emergency (sublingual nifedipine, IV lasix or nitroprusside, nitroglycerine or labetolol) then referral.
- Antibiotics : Penicillin or erythromycin to limit spread of streptococci although it does not change disease course

➲ Other Causes of Acute Glomerulonephritis

Work up

1. **Routine as APSGN**
2. **ANA, anti ds DNA**
3. **Anti GBM antibodies**
4. **Serology for HBV, HCV, HIV and EBV**
5. **Serum C3 and C4 levels**
6. **Renal biopsy is indicated in**

   - Persistent low C3 levels > 8 weeks (MPGN, C3 GN, Lupus, hepatitis B or C and immune complex mediated as endocarditis or shunt nephropathy).
   - GN with normocomplementemia (IgA nephropathy , IgA vasculitis or ANCA associated vasculitis).
   - Rapidly declining renal function = rapidly progressive GN(pauci immune GN or anti GBM disease, Goodpasture disease).

Recommendations

☑ ***Refer to pediatric nephrologist***

Treatment

☑ ***As per diagnosis protocols***

Rapidly Progressive GN

☑ ***Rapidly progressive glomerulonephritis (RPGN) is a syndrome of the kidney that is characterized by a rapid loss of kidney function, (usually a 50% decline in the glomerular filtration rate (GFR) within 3 months) with glomerular crescent formation seen in at least 25% of glomeruli seen on kidney biopsies.***

❖ **Recommendation**

1) **Refer to or consult pediatric nephrology unit with dialysis facility.**
2) **Don't wait renal biopsy results, it's medical emergency.**

Chronic Kidney Disease

- Renal disease in pediatric population may be asymptomatic and detected accidentally during a routine physical examination.
- Unexplained symptoms like fever, pains, unexplained anemia, gastrointestinal symptoms, abdominal mass, edema, hypertension, and metabolic acidosis maybe early signs of renal disease.
- Chronic kidney disease (CKD) may present by anorexia, lassitude, anemia, growth failure and/or hypertension.
- **CKD nomenclature as defined by KDIGO**
- **CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.**

☑ ***Green, low risk (if no other marker of kidney disease, no CKD);***
☑ ***Yellow, moderately increased risk;***
☑ ***Orange, high risk;***
☑ ***Red, very high risk.***
☑ ***GFR; glomerular filtration rate***

➲ *High risk populations at risk for CKD*

i. Prematurity and being small for gestational age.
ii. Congenital abnormalities of the kidney and urinary tract.
iii. H/o poor growth or failure to thrive.
iv. Family history of kidney diseases and relatives on dialysis or transplant.
v. Electrolyte or acid-base abnormalities.
vi. Body mass index (BMI) > 95th percentile.
vii. Blood pressure greater than the 95% recorded on multiple visits.
viii. Polyuria or inappropriately dilute urine.
ix. Gross hematuria.
x. Dysfunctional voiding, urinary incontinence, or prolonged enuresis.
xi. H/o recurrent UTI.

➲ *Work-Up*

- Initial testing in a child with suspected chronic kidney disease (CKD) must include an examination of the urine and estimation of the glomerular filtration rate (GFR).
- Plasma creatinine, arterial blood gases, complete blood picture.
- Imaging studies such as ultrasonography and radionuclide studies help in confirming the diagnosis of chronic kidney disease and may also provide clues to its etiology.
- Bone age can help differentiate AKI from CKD
- Blood pressure measurement
- Echocardiography

➲ *Refer children and adolescents to specialist kidney care services in the following circumstances*

- An ACR of 30 mg/g [3 mg/mmol] OR a PCR of 200 mg/g [20mg/mmol] or more, confirmed on a repeat first morning void sample, when well and not during menstruation,
- Persistent hematuria,
- Any sustained decrease in egfr,
- Hypertension,
- Kidney outflow obstruction or anomalies of the kidney and urinary tract,
- Known or suspected CKD,
- Recurrent urinary tract infection.

➲ Precautions when dealing with CKD patients

Vascular access

- Vein preservation is of particular importance for future AVF creation.
- Upon diagnosis of CKD in a child, patients and families should be educated on the importance of protecting veins, especially in the non-predominant arm.
- Venipunctures for blood samples and intravenous lines should be performed at distal sites of the dominant arm whenever possible.

Medication Prescription

- Some medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) and radiocontrast agents are contraindicated in children with chronic kidney disease (CKD) because of the risk of deterioration of kidney function.
- Dose modification is required for a wide variety of drugs belonging to different categories.

➲ Anemia in CKD

Diagnosis and evaluation of anemia in CKD

- Diagnose anemia in children with CKD if Hb concentration is <11.0g/dl in children 0.5–5years, <11.5 g/dl in children 5–12 years, and <12.0 g/dl in children 12–15 years.

Investigations of anemia

- In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia:

  - ✓ **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
  - ✓ **Absolute reticulocyte count**
  - ✓ **Serum ferritin level**
  - ✓ **Serum transferrin saturation (TSAT)**
  - ✓ **Serum vitamin B12 and folate levels**

➲ *CKD-Mineral Bone Disorder (CKD-MBD)*

Diagnosis of CKD-MBD: biochemical abnormalities

1. We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity in children beginning in CKD G2.
2. In patients with CKD G3a–G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD.

Reference

1) ***Guidelines based on kdigo 2023 clinical practice guideline for the evaluation and management of chronic kidney disease, public review draft july 2023.***

Pediatric Acute Kidney Injury

➲ Scope

- Designed for individuals up to 18 years of age. Many concepts are similar in adolescents
- Applicable to the broader spectrum of acute kidney injury (AKI). AKI can occur due to acute renal disorders, in patients with chronic kidney disease (CKD) as well as in various acute care settings.
- While those with known kidney disease will often have been under the care of a pediatric nephrologist, many patients with AKI will not. Early involvement of nephrologists is desirable, and will be essential in some cases:

  ✓ **When Managing Intrinsic Kidney Disease**
  ✓ **In Those with CKD And Transplant Recipients**
  ✓ **When Dialysis Is Needed?**

- Because AKI is frequent in critically ill patients, management of AKI could constitute part of the system support integral to critical care. Higher level intensive care units should generally be capable of providing acute dialysis. Qualified personnel and equipment are needed and logistic plans should be present to address cases of AKI.
- The specific treatment of intrinsic renal and urological diseases causing AKI is not included in this protocol, neither are the details of dialysis modalities.

➲ Disclaimer

- Protocols and guidelines outline the recommended or suggested clinical practice; however, they cannot replace sound clinical judgment by appropriately trained and licensed physicians.
- The physician is ultimately responsible for management of individual patients under their care.

AKI is defined by acute increase in serum creatinine &/or oliguria-anuria

- A recent increase in creatinine of >1.5x or 0.3mg/dL
  - ☑ *From a previous baseline; or*
  - ☑ *Above the upper limit of the reference interval for age*
- Usually associated with a fall in urine output <0.5ml/kg/hr for at least 8 hours

Oliguria is not essential for diagnosis of AKI

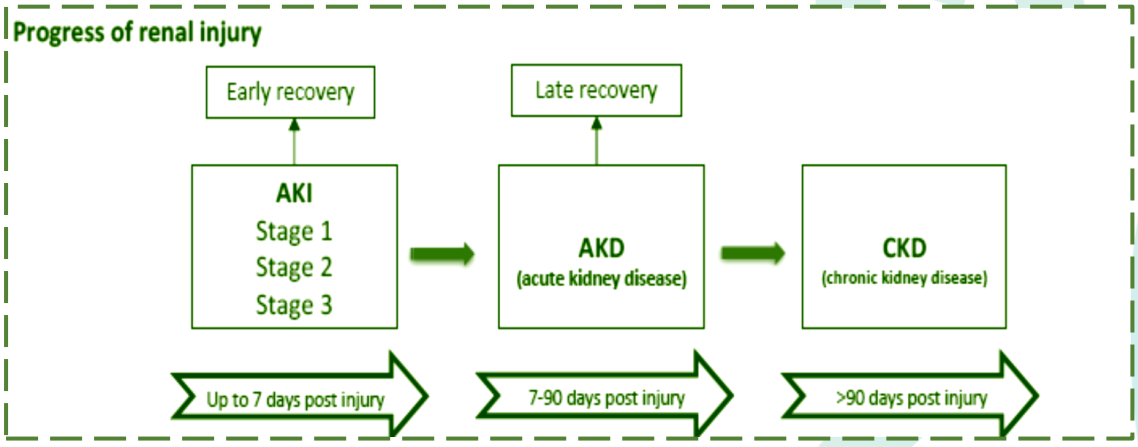
- ☑ *The cut-off for oliguria may be higher (up to 1mL/Kg/h) in infants.*
- ☑ *Inappropriate polyuria is also an abnormal urine output and may be associated with tubular injury or tubulointerstitial nephritis.*

Acute reduction in GFR is essential to diagnose AKI

- ☑ *GFR = glomerular filtration rate.*
- ☑ *Despite that creatinine rise could take some time after GFR loss, diagnosis and staging of AKI based on GFR or estimated GFR is NOT recommended.*
- ☑ *This is due to difficulties in measurement and inaccuracy of formula-based estimates with acute changes in creatinine*

- *Stages of AKI (KDIGO)*

Stage	Serum Creatinine	Urine Output
1	↑SCr ≥ 26.5µmol/l (≥ o.3 mg/dl) Or ↑SCr ≥ 1.5-2x	<0.5ml/kg/h (>6h)
2	↑SCr >2-3x	<0.5ml/kg/h (>12h)
3	↑ SCr > 3x Or ↑SCr to ≥ 353.6 µmol/l (≥4 mg/dl) Or initiation of renal replacement therapy	<0.3ml/kg/h (24h) Or anuria (12h)



➲ Reference values for serum creatinine according to age

Age Group	Reference Range		AKI Cut-Off*
	µmol/L	mg/dL	mg/dL
Preterm Neonates	29-87	0.33-0.99	1.50
Full Term Neonates	27-77	0.31-0.87	1.30
Infants	14-34	0.16-0.39	0.60
1- <3 yrs	15-31	0.17-0.35	0.53
3- <5 yrs	23-37	0.26-0.42	0.63
5- <7 yrs	28-52	0.32-0.59	0.90
7- <9 yrs	35-53	0.40-0.60	0.90
9- <11 yrs	34-65	0.39-0.74	1.10
11- <13 yrs	46-70	0.52-0.80	1.20 (1.10)
13- <15 yrs	50-77	0.57-0.87	1.30 (1.17)
15y +; female	44-80	0.50-0.91	1.37 (1.20)
15y +; male	62-106	0.70-1.20	1.80 (1.50)

- **1.5x upper limit for age. Values between parentheses are based on 0.3mg/dL rise**
- **Serial Measurements of serum creatinine may be more important than single values, particularly when these values are close to the upper limit/ cut-off value**
- **Neonatal values refer to those at birth. Normally, a decline occurs over a few days reaching values similar to those of infants**

➲ High Risk Patients

Vast Venom

- ☑ **Vasoactive Medications***
- ☑ **Sepsis**
- ☑ **Thrombocytopenia**
- ☑ **Ventilation/Volume Depletion**
- ☑ **Nephrotoxic Medications**
- ☑ **O2 Low (Hypoxia)**
- ☑ **Multiorgan Failure**

➢ **Monitor urine output and serum creatinine in these cases, who are at an increased risk for AKI**

"It is the pathological process requiring vasopressors that causes the risk and withholding necessary vasopressor support could increase the risk further"

Causes	Considerations in the history
Pre-renal • Hypovolaemia • Impaired Cardiac output • Renal vessel occlusion • Hepato-renal syndrome	• Signs and symptoms of hypovolaemia e.g. vomiting or diarrhoea, decreased UO, dizziness, lethargy • FH of renal artery stenosis • PMH: biliary atresia, cardiac disease
Intrinsic renal disease • Glomerulonephritis • Involvement of renal microvasculature- HUS, HSP • Interstitial nephritis • Drugs • ATN • Tumour lysis syndrome	• Recent viral illness • Change in urine colour e.g. red or "coca cola" coloured • History of transplant or nephrotoxic drugs
Post-renal or obstructive • Posterior urethral valves • Bilateral ureteric obstruction (trauma, calculi) • Urethral obstruction (trauma, calculus)	• Abdominal pain • Reduced UO • History of trauma • History of kidney stones • Frequent UTI's

➲ *Etiology of AKI*

❖ **Prolonged hypovolemia (pre-renal) may lead to ATN (intrinsic renal)**

➲ Initial Assessment

Etiology

- ☑ **History of renal disease or transplantation**
- ☑ **History or signs of dehydration**
- ☑ **History of polyuria or other losses particularly with limited access to fluids**
- ☑ **Shock, low cardiac output, sepsis or tissue hypoxia**
- ☑ **Recent viral illness, sore throat or skin infection**
- ☑ **Urinary tract, cardiac, liver or systemic autoimmune disease**
- ☑ **Drug exposure**
- ☑ **Malignancy, chemotherapy**
- ☑ **Trauma, myoglobinuria or hemolysis**
- ☑ **Change in urine amount or color (esp. brown, smoky or tea-colored urine)**
- ☑ **Dysuria, suprapubic or loin pain**

Manifestations

- ☑ **Fluid assessment: oedema, dehydration, urine output, fluid intake and recent weight changes (eg since admission)**
- ☑ **BP, pulse, perfusion, pallor, cardiac exam and signs of HF**
- ☑ **RR and chest exam (metabolic acidosis, pulmonary congestion or oedema, effusion)**
- ☑ **Neurological exam (uremic or hypertensive encephalopathy, electrolyte disturbances or associated stroke)**

Investigations

- ☑ **All Cases**
  - ✓ Urea, creatinine, blood gases, Na, K, Ca, P, ALP/ PTH, albumin in oedematous patients
  - ✓ CBC
  - ✓ Urinalysis, and culture if pyuria or clinically suspected infection
  - ✓ Abdominal ultrasound : Urgent to rule out obstruction, size, echogenicity and differentiation

☑ **Stage II-III**

- ✓ Chest X-ray/ Echocardiography/ bedside functional US:
  - **Cardiac size & contractility, effusions, fluid status at IVC and lungs**
- ✓ Other tests for etiology
  - **Glomerulonephritis: complement C3, C4, ANA, ANCA, AntiGBM, ASOT**
  - **Hemolysis/ TMA: Reticulocytic count, T & D bilirubin, LDH, Coomb's and fragmented RBCs in blood film**
  - **Vascular causes: Renal Duplex**

❖ **N.B. children with undiagnosed CKD, even ESKD, may present with apparently AKI due to:**

- **An acute insult on top (eg infection, drug) ; or**
- **Neglected ckd presenting with complications**

☑ **Differentiation depends on**

- ✓ Past history suggestive of CKD (anorexia, bony pains, growth failure, anemia, oedema, urinary abnormalities as hematuria, recurrent UTI, polyuria or secondary enuresis)
- ✓ Family history of genetic renal disease or renal failure
- ✓ Clinical signs of growth failure, bone deformities, unexplained pallor or earthy look
- ✓ Small echogenic kidneys with impaired/ absent corticomedullary differentiation by ultrasound

➲ ***Indications for referral to/ management by pediatric nephrologist***

Immediate consultation/ referral

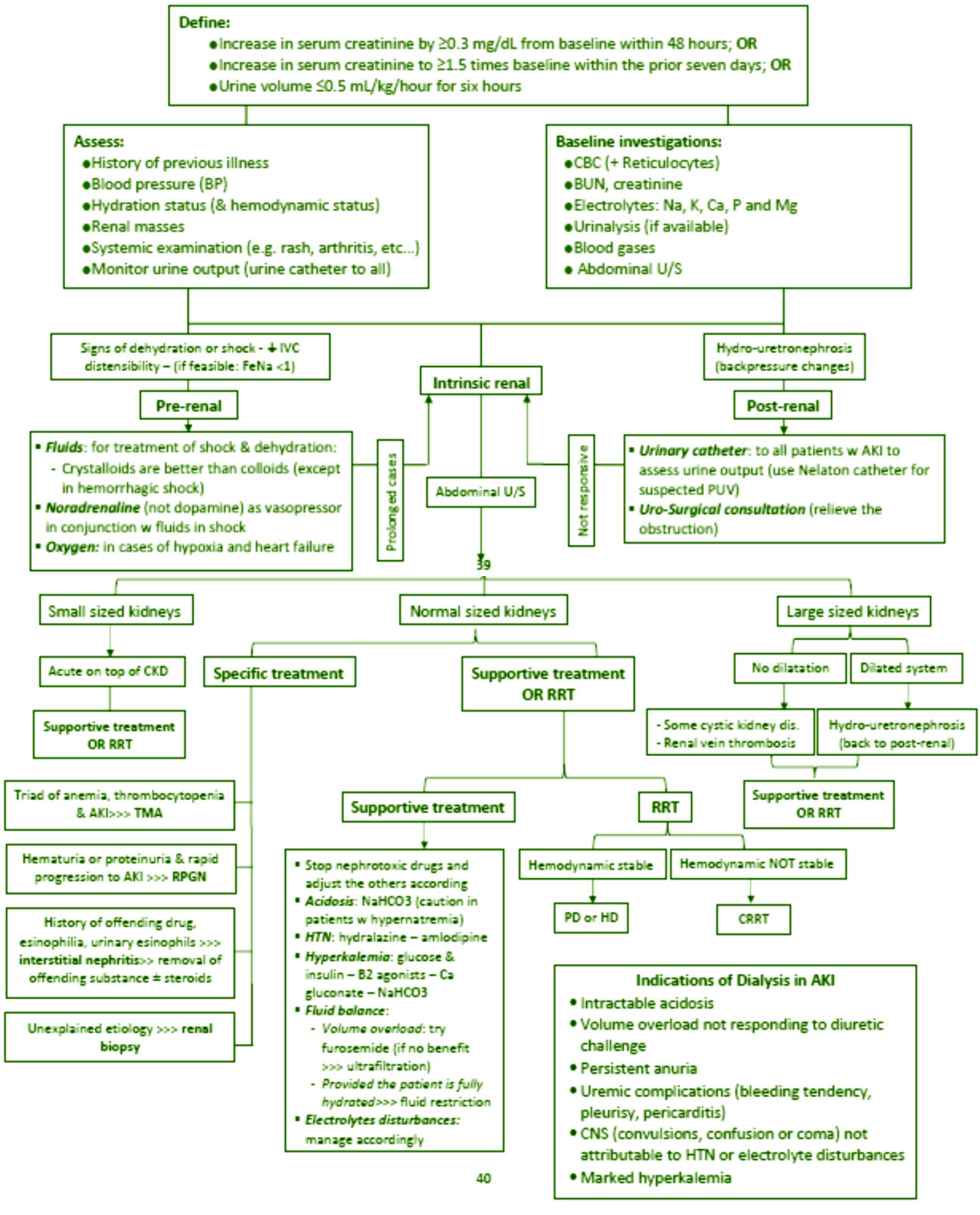
- ☑ **K> 6.5 mmol/L**
- ☑ **Na< 125 mmol/L with anuria or oliguria**
- ☑ **Persistent or worsening metabolic acidosis**
- ☑ **Pulmonary oedema or hypertension not responding to diuretics**
- ☑ **Urea >240 mg/dL (40mmol/L) not responsive to fluid challenge**

Any AKI

- ☑ **In patient with CKD or renal transplant**
- ☑ **Suspected intrinsic renal disease (e.g. nephritis / HUS)**

AKI stage 2 or 3 or AKD

Approach to a child with Acute Kidney Injury (AKI)



➲ *Conservative Management of AKI*

1) Establish and maintain appropriate renal perfusion (BP, CO & tissue perfusion) and oxygenation.

"Do Not Keep Any Patient Hypovolemic and Do Not Withhold Necessary Vasopressors!! Hypoxia And Anemia Should Be Corrected"

2) Urinary tract obstruction needs to be ruled out quickly

- Patients with suspected retention or UT obstruction and those in whom accurate monitoring of urine output is not otherwise possible should be catheterized

3) Manage fluid balance

4) Monitor electrolytes and manage disturbances

- Significant metabolic acidosis is corrected with NaHCO3. Maintenance bicarbonate (starting at 2 mEq/Kg/day divided q6h) may be needed. Concerns: volume, Na content, will lower Ca & K
- Dilutional hyponatremia is managed by fluid restriction; only severe symptomatic or resistant cases need hypertonic saline if bicarbonate correction will not be given (contains more Na than hypertonic saline!)
- Maintenance K is avoided in anuric or oliguric patients but cautious correction of hypokalemia can and should be done
- Moderate & severe hyperkalemia warrant emergency medical treatment; which should be initiated even when dialysis is being arranged
- Severe or symptomatic hypocalcemia should be corrected with IV calcium
- Phosphate binders may be necessary

5) Medications

- Control of BP with antihypertensives may be needed. Age-appropriate references should be used. Excessive (<50th centile) or too rapid reduction of BP should be avoided. The use of ACE inhibitors may exaggerate renal ischemia and hyperkalemia
- Control of convulsions if present
- Avoid nephrotoxic agents (unless critically needed), use less toxic alternatives (when possible) and adjust doses of renally-excreted medications
- Others as indicated

6) AKI is not a contraindication for feeding

- Adequate caloric intake, age-appropriate protein intake should be targeted.
- Sodium restriction in hypertensive, oliguric or oedematous patients.
- Potassium and phosphorous restriction unless/ until losses are present.

7) Identify & manage conditions with specific treatment eg aHUS, RPGN, etc

➲ Fluid Management During AKI

Assessment of Fluid Status

- ☑ **Oedema**
- ☑ **Systemic and pulmonary congestion: jugular venous pressure, new/ tender hepatomegaly, chest crepitations, bedside U/S (lung, IVC and heart)**
- ☑ **Signs of dehydration**
- ☑ **Weight changes and previous fluid balance if available**
- ☑ **BP: Hypotension (late) and hypoperfusion can denote hypovolemia, hypertension can be a sign of overload (poor sensitivity and not specific)**

Initial volume administration (avoided in presence of intravascular fluid overload):

- ☑ **Correct shock if present (refer to shock guideline)**
- ☑ **In euvolemic patients, a 10mL/ Kg challenge with normal saline may be given over 30-60 min**

Furosemide (avoided in dehydration and UT obstruction):

- ☑ **In case of fluid overload (from the start)**
- ☑ **In case of euvolemia with persistent anuria/ severe oliguria not responsive to fluid challenge (expect response in 2h)**
  - ✓ 3-6 mg/ Kg (max 250 mg)
  - ✓ May be repeated q6-12h or followed by continuous infusion (0.5-1mg/Kg/hr) to maintain response, but NOT in initial non-responders. Max total dose 1 g in 24h
  - ✓ On-going treatment with furosemide needs to be followed by a senior clinician

"The use of Dopamine or mannitol to induce diuresis is not recommended and may be harmful"

Subsequent fluid management

- ☑ **Maintenance requirements should be based on**
  - ✓ Insensible loss 400mL/m2/24h; more in fever and spontaneous hyperventilation, less on MV/ humidified oxygen
  - ✓ Actual urine output (based on last known output; per hr or last 24h, may be zero in anuric patients, update based on monitored urine output)
  - ✓ Any abnormal losses eg diarrhea, vomiting, drains

"These requirements should be revised frequently based on measured urine output, other losses and state of hydration. Type of fluids should depend on Na and glucose required"

Patients with intravascular or extravascular fluid overload ➔ A NEGATIVE balance is necessary *Give 50-70% of required maintenance, restrict further to essential requirements (eg medications, to avoid hypoglycemia, essential transfusions) during treatment of pulmonary*
Patients with normovolemia ➔ A ZERO balance is necessary. *Intake = maintenance*
Patients with dehydration ➔ Deficit amount should be ADDED until euvolemia is achieved
Recovery may be associated with diuresis and electrolyte losses *that must be replaced with adequate fluids, Na & K taking in consideration oral/ enteral intake*

➲ *Ongoing Management "Monitor, Maintain, Minimize"*

1) Monitor

- ☑ **Initial weight and height on a growth chart**
- ☑ **At least daily weight,** at the same time of the day
- ☑ **Strict and accurate input / output and hydration status.** At least 4-hourly in those with dehydration, intravascular overload, critical or rapidly changing status. At least daily in all others
- ☑ **Blood pressure,** initially at least 4-hourly

❖ **Investigations:**

- Electrolytes and serum bicarbonate. Initially at least daily, more frequently when following or correcting abnormalities
- Urea and creatinine. Initially daily
- Others as needed

2) Maintain

- ☑ **Ensure adequate circulatory volume – address hypoperfusion urgently with fluid boluses (10 ml/kg) and inotropic support once volume is restored.**

3) Minimize

- ☑ **Further harm should be reduced by stopping nephrotoxic drugs when possible, dose adjustments and avoiding intravenous contrast.**

➲ *Indications of Dialysis*

1) AKI

- ☑ **Fluid overload:**
  - ✓ Hypervolemia, pulmonary edema
  - ✓ Refractory extravascular overload >10%
  - ✓ Potential overload: persistent oliguria with +ve balance if not tolerated eg cardiac condition or obligatory fluid needs such as transfusions, nutritional support, etc
- ☑ **Severe/ refractory electrolyte imbalance**
  - ✓ (Mainly hyperkalemia, sometimes extreme hyperphosphatemia, rarely others)
- ☑ **Metabolic acidosis when correction with bicarbonate is ineffective or not possible**
- ☑ **Clinically significant uremia (eg with bleeding, encephalopathy, etc)**
- ☑ **There is no absolute cut-off value for urea or creatinine. However, high or rapidly increasing values should be considered in view of the overall patient's condition**

2) CKD

- ☑ **Acute indication (as AKI) in a patient with CKD (on conservative treatment or just diagnosed)**
- ☑ **ESKD**

Acute Dialysis Options

Choice is guided by:

- ☑ Patient characteristics (disease/symptoms, hemodynamic stability)
- ☑ Goals of therapy (fluid removal, electrolyte correction)
- ☑ Availability, expertise, and cost

Peritoneal dialysis (PD)

- ☑ Fluid removal follows an osmotic gradient, therefore more dependent on concentration of dialysis solution. A short dwell time increases fluid removal.
- ☑ Clearance achieved by PD depends on volume of dialysis fluid, size of molecule, dwell time and number of exchanges
- ☑ Simple, inexpensive, not equipment-dependent, possible in hemodynamically unstable patients. The easiest to achieve competency
- ☑ Contraindications: defect in peritoneal membrane, abdominal problems
- ☑ Treatment is slow and moderately predictable

Intermittent hemodialysis

- ☑ Extracorporeal exchange of fluid and solute that occurs across an artificial semipermeable membrane between blood and dialysis fluid moving in opposite directions
- ☑ Children have to be hemodynamically stable and be able to tolerate interval between dialysis runs. Not suitable for small infants (except with special circuits)
- ☑ Predictable fluid removal that can be rapid if needed
- ☑ Most rapid solute clearance
- ☑ Precautions are needed to avoid disequilibrium with rapid urea clearance in severely uremic patients
- ☑ Vascular access & anticoagulation needed (but sessions can be done with high flow, repeated saline flush & no anticoagulation)
- ☑ Moderate needs in terms of equipment, cost & required expertise. But a HD machine & water treatment unit is needed in the ICU or the patient should be fit for transport to the hospital HD unit

Continuous Renal Replacement Therapy (CRRT)

- ☑ Extracorporeal therapy using a special machine that's transportable and not dependent on HD or water treatment unit
- ☑ Treatment is well controlled, continuous and slow (most physiological). Rapid fluid removal is still possible if needed
- ☑ Better tolerated than HD and not dependent on abdominal cavity
- ☑ Different treatments are possible in various combinations (dialysis, hemofiltration with replacement or a combination)
- ☑ Vascular access & anticoagulation needed
- ☑ High cost, human resource intensive and needs expertise

Prolonged intermittent renal replacement therapy (sustained low efficiency dialysis)- PIRRT or SLED

- ☑ Prolonged daily (6-23hrs), but not continuous, extracorporeal therapy using a HD machine and circuit
- ☑ Treatment is applied slowly to approximate CRRT at a lower cost and using existing HD machines when there is a HD unit and trained HD staff

References

Primarily Adapted From:

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5) *McCaffrey J, Dhakal AK, Milford DV, Webb NJ, Lennon R. Recent developments in the detection and management of acute kidney injury. Arch Dis Child. 2017;102(1):91-6.*
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7) *Sutherland SM, Kwiatkowski DM. Acute Kidney Injury in Children. Adv Chronic Kidney Dis. 2017;24(6):380-7.*
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9) *https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance_for_paediatric_patients_Final.pdf*
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Urinary Tract Infection in Pediatrics for Pediatricians

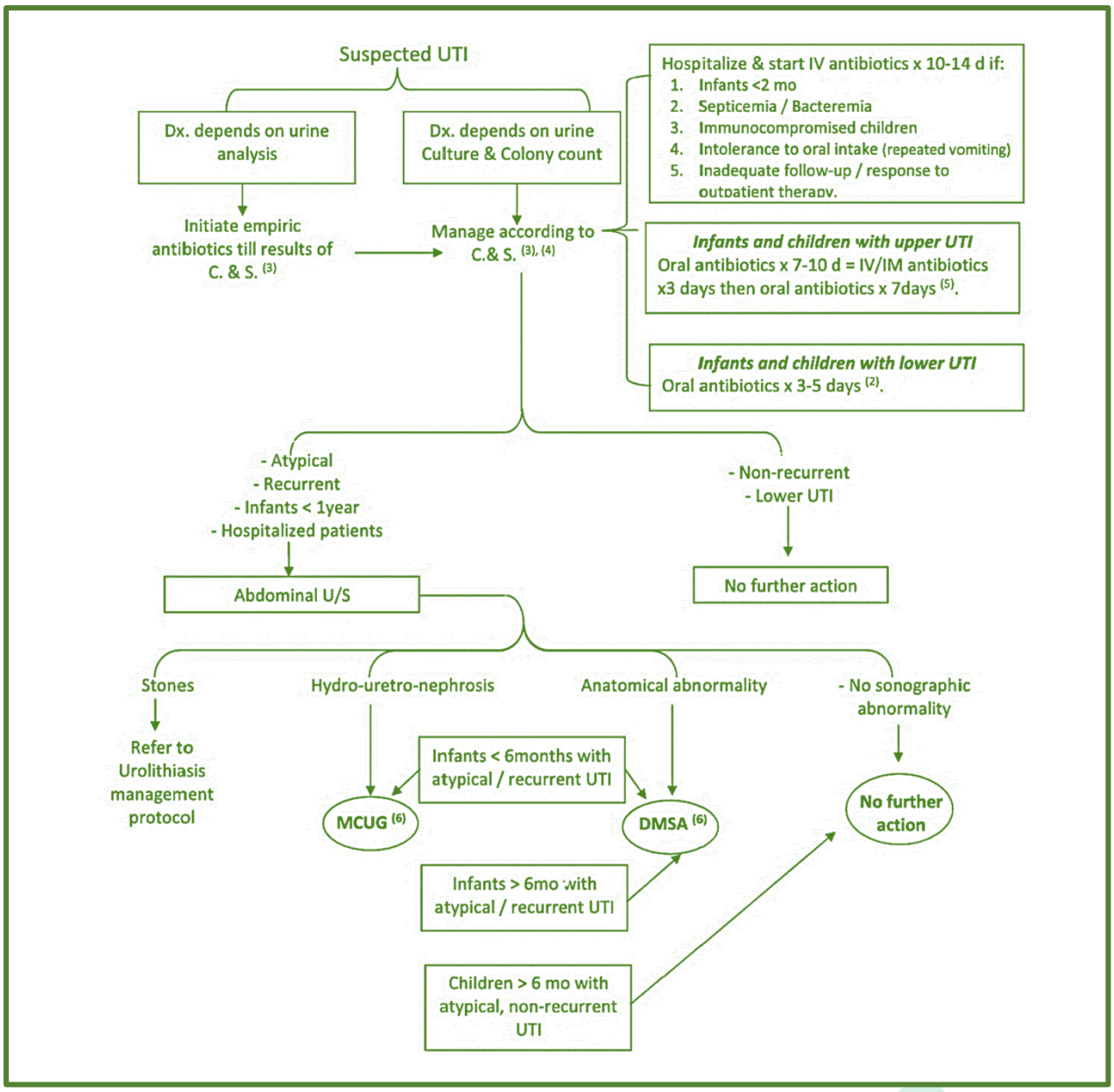
- Urinary tract infection is a common health problem in children and presentation can vary in different age groups within Pediatric and Adolescent cohort.
- Identifying this type of infection (not confusing UTI with other infections) can prevent faulty treatment and point out at risk group.

➲ *Definition of UTI: Prescence of symptoms* +*

☑ **Urine CFU >50.000/ml if catheterized or mid-stream clean-void in circumcised boy**
☑ **Urine CFU >100.000/ml if uncircumcised boy or mid-stream clean-void in girls.**
☑ **Supra-pubic sample with growth of any organism except 2000-3000 CFU/ml**

Symptoms				
Age Groups		**Most Common** →		**Least Common**
Infants< 3 mo		Fever Vomiting Lethargy irritability	Poor feeding Failure to thrive (FTT)	Abdominal pain Jaundice Offensive urine Hematuria
Infants and Children >3 mo	**Pre-Verbal**	Fever	Abdominal pain Vomiting Poor feeding	Lethargy Irritability FTT
	Verbal	Frequency Dysuria	Voiding dysfunction Abdominal pain	Fever vomiting Malaise Cloudy urine

➲ How to approach a case of UTI



➲ *Reliable methods of Urinary collection*

- ☑ **Clean-catch sample is an easy and quick method of urinary collection (quick wee in infants)**
- ☑ **Catheterization is a more accurate but invasive method**
- ☑ **Sonar guided supra-pubic aspirate is the method of choice (most accurate but also most invasive).**
- ☑ **Urine bag collection is only good for screening but not for urine culture and sensitivity (can't document a UTI).**

❖ **N.B.**

- **Whatever the accepted method for urinary collection, stick to the colony count accepted for each method.**

➲ ***Important Notes***

I. Differences between Upper and lower UTI

	Upper UTI (Pyelonephritis)	*Lower UTI (Cystitis)*
Symptoms	Fever, rigors, vomiting and loin pain.	Dysuria, urgency, frequency, incontinence and enuresis
Investigations	☑ WBCs elevated ☑ CRP positive ☑ Poor urine concentrating ability ☑ DMSA study confirms upper UTI	☑ Normal WBCs ☑ CRP negative ☑ Good urine concentrating ability ☑ DMSA study is non revealing

II. Empiric management of UTI (prior to culture)

☑ **Early initiation of antimicrobial therapy is particularly important if:**

- ✓ Fever (especially >39°C or >48 hours)
- ✓ Ill appearance
- ✓ Costovertebral angle tenderness
- ✓ Known immune deficiency
- ✓ Known urologic abnormality

Antibiotic	Dose	Frequency	Route
Cefpodoxime	5 mg/kg/dose	Q12h	Oral
Cefixime	8 mg/kg/d§	Q12h (or single)	Oral
Cefdinir	14 mg/kg/d	Q12h	Oral
TMP-SMX	8mg (TMP)/kg/d	Q12h	Oral
Nitrofurantoin	5-7 mg/kg/d	Q 6-8h	Oral
Amoxicillin	25-50 mg/kg/d	Q8h	Oral
Amox. + clav.	25-50 mg/kg/d	Q8-12h	Oral

III. When to refer to a pediatric Nephrologist

A. High Risk Group

1. **Known Patient With:**
   - Structural abnormalities
   - Stones
2. **VUR**
3. **Abnormal Voiding pattern.**
4. **Abdominal mass.**
5. **Previous UTI.**

B. Recurrent UTI

- **Two or more episodes of UTI documented on proper urine culture.**

C. Atypical UTI

- **Seriously ill child or infant / septicemia.**
- **Abnormal voiding pattern.**
- **Impaired kidney function tests.**
- **Mechanical/ functional obstruction of urinary tract.**
- **Failure to respond to treatment with suitable antibiotics within 48 hours.**
- **Infection with non E-coli organisms.**

Urinary Incontinence

➲ ***Monosymptomatic nocturnal enuresis (NE):*** ***is also known as bedwetting. There is a gender difference in the incidence: two boys to one girl at any age.***

Enuresis: ***Intermittent incontinence while asleep in a child >5 years of age***

Monosymptomatic enuresis: ***Enuresis with no other lower urinary tract symptoms***

Non-monosymptomatic enuresis: ***Enuresis with other, mainly daytime, lower urinary tract symptoms or bowel dysfunction.***

- Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry (six months).
- The term "secondary NE" is used when a child or adult begins wetting again after having stayed dry.

❖ **The Pathophysiology** of enuresis is complex, involving the central nervous system (several neurotransmitters and receptors), circadian rhythm (sleep and diuresis), and bladder function derangements.

➲ ***Causes:***

☑ **Congenital anatomical abnormalities such as ectopic ureter, or bladder exstrophy.**
☑ **Neurologic abnormalities as myelomeningocele (MMC).**
☑ **Functional bladder problems.**
☑ **Deep poor sleepers due to high arousal thresholds and frequently disturbed sleep: the child does not wake up when the bladder is full.**

➲ ***Management***

Diagnostic evaluation

The diagnosis is mainly obtained by:

☑ **History-taking.**
✓ Focused questions to differentiate; monosymptomatic vs. non-monosymptomatic.
✓ Primary Vs. Secondary.
✓ Comorbid Factors Such as Behavioral Or Psychological Problems and Sleep Disorder Breathing.

❖ In addition, a two-day complete micturition and drinking diary, this records day-time bladder function and drinking habits.

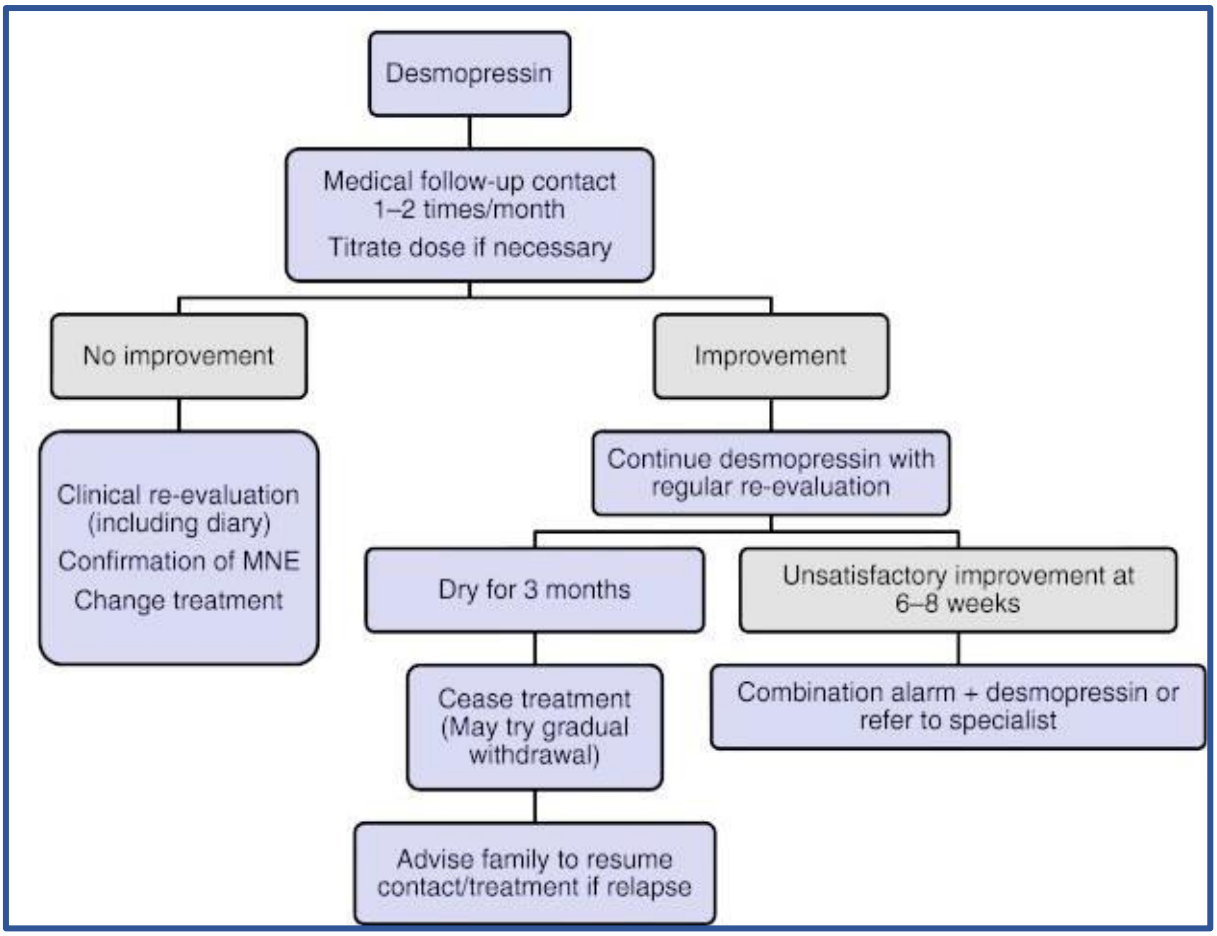
☑ **Physical examination should be performed with special attention to:**

- ✓ The Back Of The Child (To Exclude Any Neurological Problem)
- ✓ The external genitalia and surrounding skin, as well as to the condition of the clothes (wet underwear or encopresis).
- ✓ Urine analysis is indicated if there is a sudden onset of bedwetting, a suspicion or history of UTIs, or inexplicable polydipsia.

➲ *The Treatment*

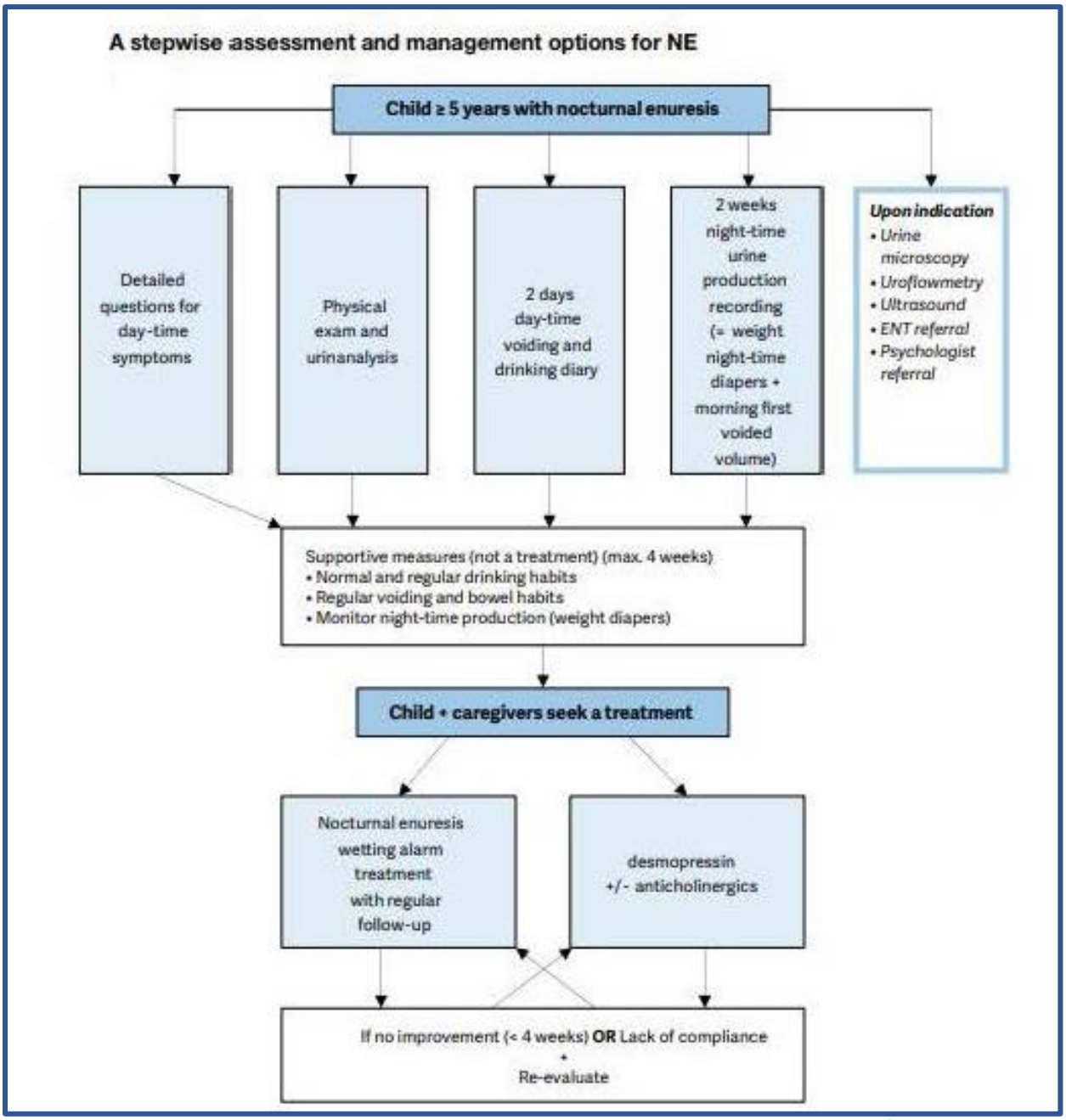
☑ **A multimodal approach, involving strategies such as**

- ✓ Management of underlying and potentially complicating conditions such as constipation and UTIs.
- ✓ Supportive treatment measures Initially:
  - ➢ Normal and regular eating and drinking habits should be reviewed.
  - ➢ Stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep.
- ✓ Medical management
  - ➢ Desmopressin either as tablets (200-400 µg), or as sublingual Desmopressin oral lyophilisate (120-240 µg).
  - ➢ A nasal spray is no longer recommended due to the increased risk of overdose.
  - ➢ Medication should be taken 1 h before the last void before bedtime to allow timely enhanced concentration of urine to occur.
  - ➢ Fluid intake should be reduced from 1 h before desmopressin administration.
  - ➢ Desmopressin is only effective on the night of administration; therefore, it must be taken on a daily basis.
  - ➢ If patients are dry on treatment after this initial period, breaks are recommended to ascertain whether the problem has resolved and therapy is no longer necessary.
  - ➢ If the child does not achieve complete dryness, or if wetting resumes once treatment is withdrawn, it should be resumed.
  - ➢ If a second voiding diary indicates nocturnal urinary production is not reduced, consider a dose increase (if maximum recommended dose has not been reached); otherwise, refer the child to a specialist.

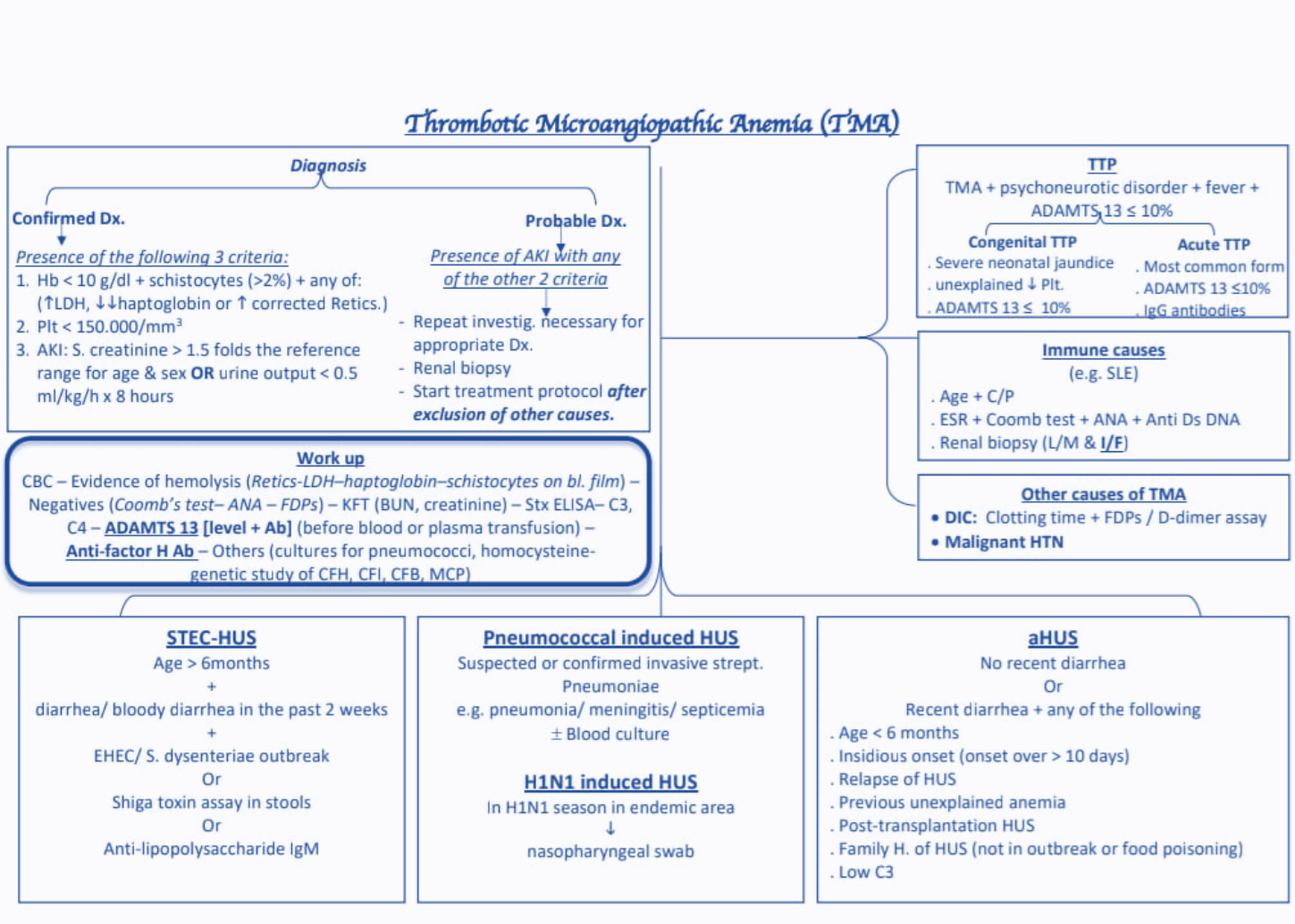


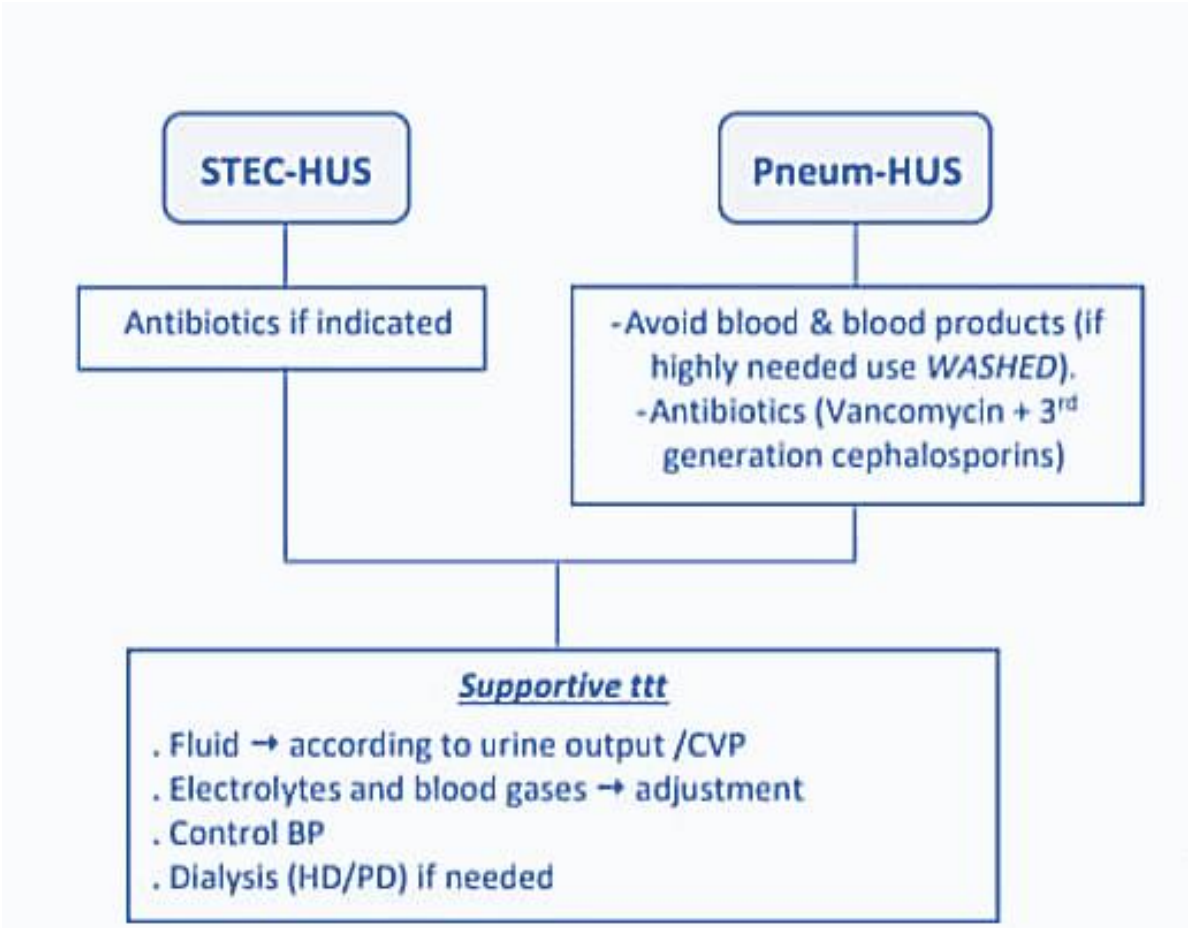
- ✓ Behavioral modification, is a term which covers all non-pharmacological and non-surgical treatment modalities.
  - ➢ Standardization of fluid intake
  - ➢ Bowel management; timed voiding and basic relaxed voiding education.
  - ➢ Referral for psychological support should be advised and followed-up for patients with NE and their families, especially if the NE comorbid factor is developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child are observed.

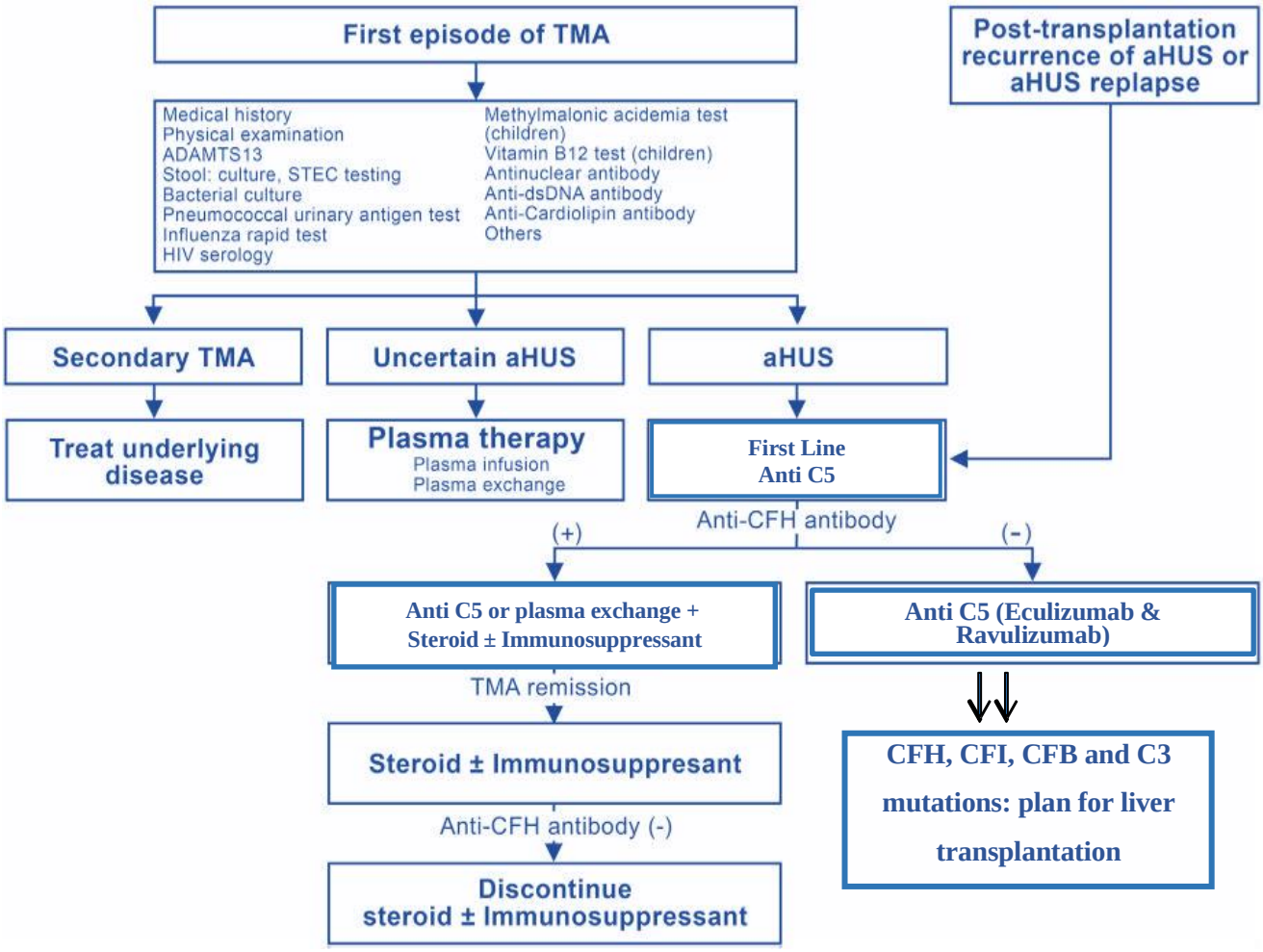
- ✓ Wetting alarm treatment; the nocturnal alarm treatment relies on the use of a device that is activated by getting wet.
  - ➢ The goal of this therapeutic approach is that the child wakes up by the alarm, which can be acoustic or tactile, either by itself or with the help of a caregiver.
  - ➢ Their method of action is to repeat the awakening and therefore change the high arousal to a low arousal threshold, specifically when a status of full bladder is reached.
  - ➢ The recommended length of therapy with the alarm treatment continues to be uncertain, varying from 8-12 weeks to 16-20 weeks.


A stepwise assessment and management options for NE
Child ≥ 5 years with nocturnal enuresis
Detailed questions for day-time symptoms
Physical exam and urinanalysis
2 days day-time voiding and drinking diary
2 weeks night-time urine production recording (= weight night-time diapers + morning first voided volume)
Upon indication
• Urine microscopy
• Uroflowmetry
• Ultrasound
• ENT referral
• Psychologist referral
Supportive measures (not a treatment) (max. 4 weeks)
• Normal and regular drinking habits
• Regular voiding and bowel habits
• Monitor night-time production (weight diapers)
Child + caregivers seek a treatment
Nocturnal enuresis wetting alarm treatment with regular follow-up
desmopressin +/- anticholinergics
If no improvement (< 4 weeks) OR Lack of compliance
+
Re-evaluate

Hemolytic Uremic Syndrome (HUS)

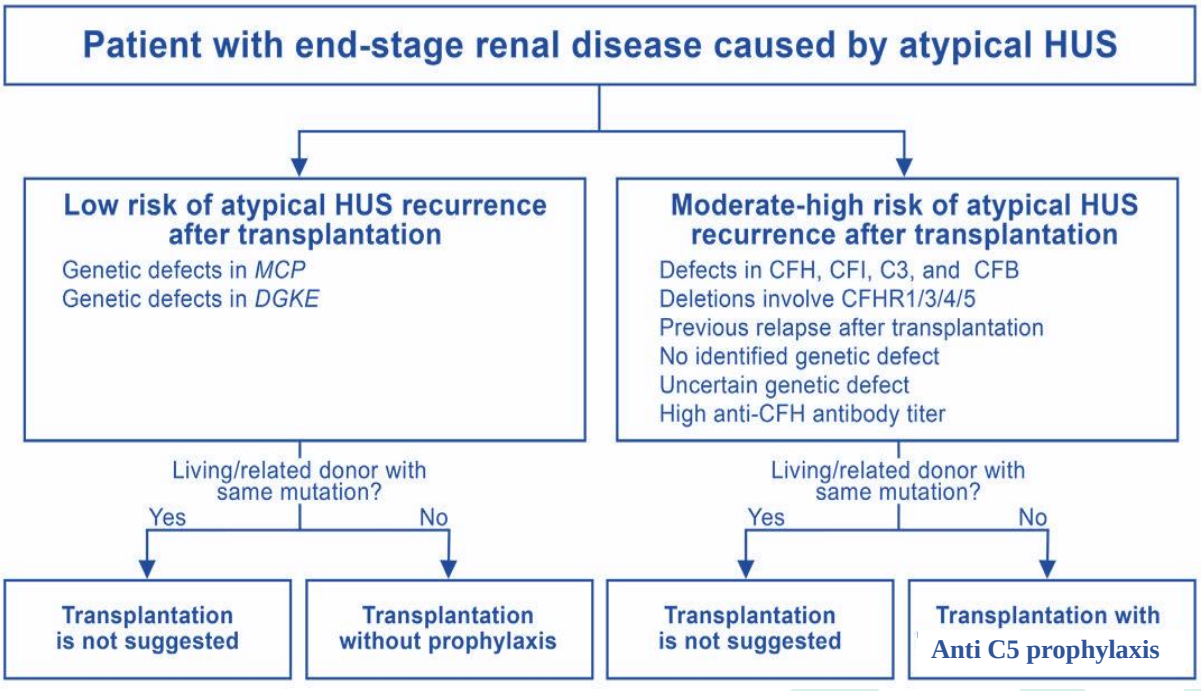



STEC-HUS
Pneum-HUS
Antibiotics if indicated
-Avoid blood & blood products (if highly needed use WASHED).
-Antibiotics (Vancomycin + 3rd generation cephalosporins)
Supportive ttt
. Fluid → according to urine output /CVP
. Electrolytes and blood gases → adjustment
. Control BP
. Dialysis (HD/PD) if needed


First episode of TMA
Post-transplantation recurrence of aHUS or aHUS replapse
Medical history
Physical examination
ADAMTS13
Stool: culture, STEC testing
Bacterial culture
Pneumococcal urinary antigen test
Influenza rapid test
HIV serology
Methylmalonic acidemia test (children)
Vitamin B12 test (children)
Antinuclear antibody
Anti-dsDNA antibody
Anti-Cardiolipin antibody
Others
Secondary TMA
Uncertain aHUS
aHUS
Treat underlying disease
Plasma therapy
Plasma infusion
Plasma exchange
First Line
Anti C5
Anti-CFH antibody
(+)
(-)
Anti C5 or plasma exchange + Steroid ± Immunosuppressant
Anti C5 (Eculizumab & Ravulizumab)
TMA remission
Steroid ± Immunosuppresant
CFH, CFI, CFB and C3 mutations: plan for liver transplantation
Anti-CFH antibody (-)
Discontinue steroid ± Immunosuppressant

➲ *Transplantations in atypical HUS patients with end stage renal disease*

- ☑ **There are three main strategies of transplantations for patients with atypical HUS:**
  - ✓ Combined liver kidney transplantation
  - ✓ Isolated liver transplantation
  - ✓ Isolated kidney transplantation
- ☑ **The majority of complement regulatory proteins, including CFH, CFI, CFB, and C3, are synthesized in the liver; therefore, liver transplantation is a rational therapeutic option for patients with aHUS caused by defects in these genes.**
- ☑ **Renal transplantation offers a functional graft kidney and prevents the morbidity and mortality of patients with aHUS with ESKD on chronic dialysis.**
- ☑ **However, transplantation and chronic immunosuppressant use carry the risks of infection, complement overactivation, and aHUS relapse. Therefore, the advantages and risks of transplantation should be weighted in patients with aHUS.**



Source:

- **Min-Hua Tseng a, Shih-Hua Lin b, Jeng-Daw Tsai c, Mai-Szu Wu d,e, I-Jung Tsai f, Yeu-Chin Chen g, MinChih Chang h, Wen-Chien Chou i, Yee-Hsuan Chiou j,**, Chiu-Ching Huang k . Atypical hemolytic uremic syndrome: Consensus of diagnosis and treatment in Taiwan. Clinical Practice**

- ☑ **Anti-C5 therapy (Ravulizumab/Eculizumab) should be started as rapidly as possible in all children with aHUS at a standard dose.**
- ☑ **Vaccination status should be evaluated for all meningococcal strains and for Streptococcus pneumoniae and Hemophilus influenzae; these vaccinations are completed as soon as possible, and subsequently kept up to date during prolonged complement blockade.**
- ☑ **If vaccination is not possible or until 15 days after it is completed, antibiotic prophylaxis against meningococcal infection must be administered.**
- ☑ **In children < 5 years of age, in immunosuppressed individuals, and in those who live in communities, low- dose prophylactic antibiotics may be advisable even with a complete vaccination schedule.**
- ☑ **Patients receiving anti-C5 treatment should be advised of the risk of meningococcal infection, albeit low, instructed on early identification of warning signs and symptoms, and provided with an information card to carry at all times allowing for prompt recognition of their disease and treatment upon hospital admittance.**
- ☑ **For patients with aHUS triggered by autoantibodies, in addition to anti-complement therapy at disease presentation, an antibody reduction strategy is done.**
- ☑ **This entails either use of plasma exchange or therapy with immunosuppressive medications (cyclophosphamide, rituximab.**

➲ *Transplantation:*

- ☑ **aHUS patients may require some combination of plasma therapy and/or anti-C5 therapy prior to and post-transplant; prophylactic treatment should be based on the risk of recurrence.**
- ☑ **Prophylactic PE/PI (started just before transplantation) has been recommended and should be used when anti complement therapy is not available.**
- ☑ **Whenever possible, anti-complement therapy should be used to prevent recurrence starting just prior to renal transplantation in all forms of aHUS based on quantification of the risk of recurrence.**
- ☑ **High-risk patients are defined as those with a previous recurrence of aHUS on a renal allograft, or harboring pathogenic variants of FH, C3, or FB genes;**
- ☑ **Moderate risk are patients with a negative complement screening or with a pathogenic variant in FI gene or with detectable circulating anti-FH antibodies;**
- ☑ **Low-risk patients are those with undetectable circulating anti-FH anti bodies who previously were positive and patients harboring MCP or DGKE isolated mutation.**
- ☑ **The use of prophylactic anti-C5 therapy should be done starting immediately prior to transplant in patients with a moderate and high risk of recurrence.**
- ☑ ***Liver transplantation* corrects the complement abnormality and prevents disease recurrence in patients with defects in genes encoding circulating complement proteins that are synthesized in the liver.**
- ☑ **IT is an attractive option for treatment of atypical HUS in patients who cannot afford long-term treatment with complement factor 5 inhibitors, and also in resource-limited conditions.**

Eligibility for combined liver and kidney transplant or liver transplant alone

- ☑ **CH or CFI mutation**
- ☑ **Less than 10% normal CFH levels in plasma Patients who have identified mutations of genes encoding and have aHU recurrence after isolated kidney transplantation or have a family member who had the same mutation and had aHUS recurrence after isolated kidney transplantation**
- ☑ **HUS recurrence after isolated kidney transplantation in patients with identified mutations of genes that may have both hepatic and nonhepatic sites of expression and protein synthesis.**

Eligibility for isolated kidney transplantation

- ☑ **No evidence of CPH, CF, CFB, or C3 gene mutations**
- ☑ **MCP mutation**
- ☑ **Mutations associated with successful isolated kidney transplantation in affected family members**
- ☑ **Anti-factor H autoantibodies**

"Split or whole liver transplantation is indicated adequate liver mass must be provided. Auxiliary liver transplantation is not recommended. Living related donation is not recommended."

References:

- **Saland, Jeffrey M.; Ruggenenti, Piero; Remuzzi, Giuseppe and the Consensus Study Group. Liver-Kidney Transplantation to Cure Atypical Hemolytic Uremic Syndrome. Journal of the American Society of Nephrology 20(5):p 940-949, May 2009. | DOI: 10.1681/ASN.2008080906**

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