Clinical Pathways Program

Nephrotic Thromboprophylaxis, Pediatric, Inpatient and Outpatient

Clinical guideline summary

CLINICAL PATHWAY/GUIDELINE NAME: Nephrotic Thromboprophylaxis, Pediatric, Inpatient and Outpatient

PATIENT POPULATION AND DIAGNOSIS: Patients ≤ 18 years of age who are being treated for or suspected to have nephrotic syndrome.

APPLICABLE TO: Helen DeVos Children's Hospital

BRIEF DESCRIPTION: This guideline is to aid in the decision making for thromboprophylaxis (TP) in pediatric patients with nephrotic syndrome (NS) [1] but acknowledges that limited data exists for this population. Patients with nephrotic syndrome are thought to be at risk for bleeding and thrombosis as they lose both pro- and anti-coagulants in their urine. However, bleeding complications are less common than thromboembolism (arterial and venous). Despite this concern, pharmaco-prophylaxis is not warranted in all pediatric patients with NS as only 3% of these patients develop clinically significant venous thromboembolism (VTE) and 25% develop subclinical VTE. [2, 3]

The algorithm outlines factors to consider when deciding on primary TP (preventing a thrombosis) in patients with or suspected to have nephrotic syndrome. Co-existing risk factors for thromboembolism, such as immobility or the presence of a central venous or hemodialysis catheter are weighed against risks of bleeding. This risk/ benefit assessment should be conducted on a regular basis as risk factors for thrombosis and bleeding may change. Treatment modalities affect drug metabolism differently and communication between teams are critical to managing TP. A multidisciplinary discussion and individualized approach are recommended. Shared decision making with patient, family, primary nephrologist, and PHO is critical in developing an individualized care plan.

OVERSIGHT TEAM LEADER(S): Ali Mastin, Chi Braunreiter, Jason Thomas, Jens Goebel

OWNING EXPERT IMPROVEMENT TEAM (EIT): N/A

MANAGING CLINICAL PRACTICE COUNCIL (CPC): Children's Health

CPC APPROVAL DATE: May 1, 2023

OTHER TEAM(S) IMPACTED: This guideline was reviewed with representatives from Pediatric Nephrology and Pediatric Hematology Oncology (PHO), and Pharmacy. Other teams that might be affected are Pediatric Critical Care and Pediatric Surgery.

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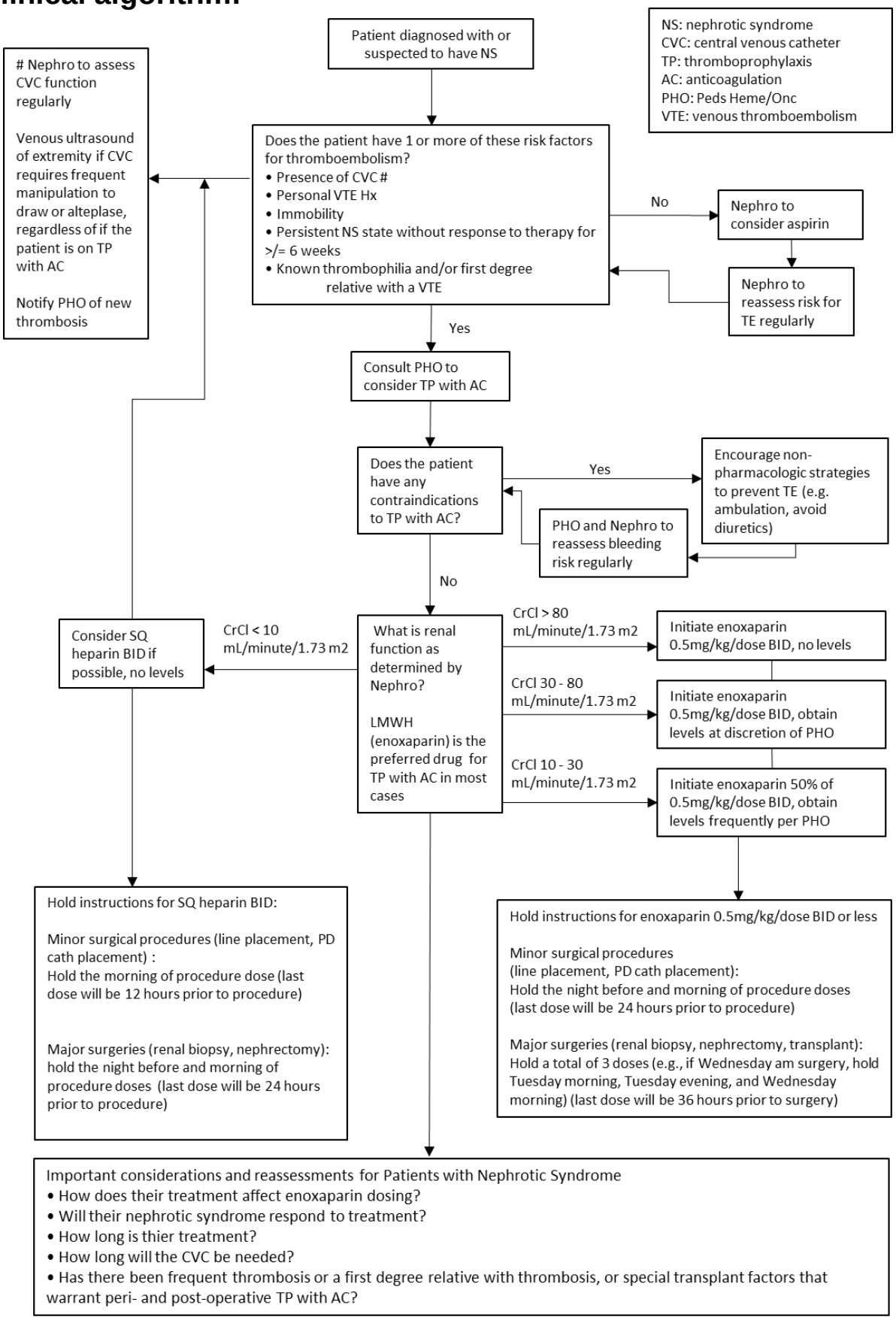
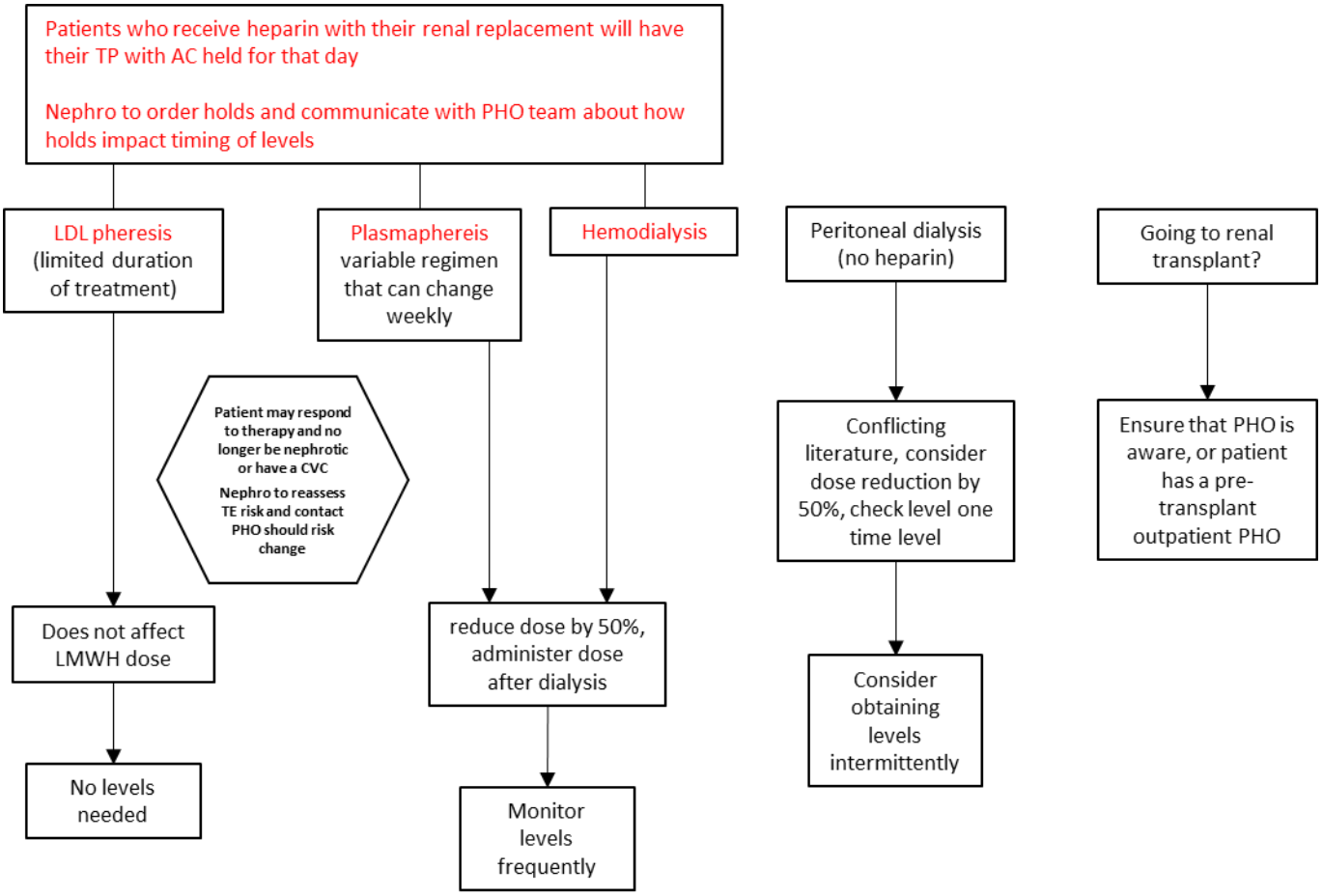
LAST REVISED: May 19, 2023

Clinical algorithm:



Treatment modalities that might affect TP with AC



Clinical pathways clinical approach

DEFINITIONS

1. Nephrotic syndrome (NS)[1]: a manifestation of glomerular diseases that increase permeability across the glomerular filtration barrier. NS is characterized by[4]
    - proteinuria (urinary protein excretion > 40mg/m2/day in pediatrics or > 3.5 g/d in adults
    - hypoalbuminemia (serum albumin < 2.5 gm/dL)
    - dyslipidemia, and
    - edema

PERTINENT INFORMATION

1. Comparison of thromboembolism and TP literature for pediatric vs adult NS[4].
    - Appendix 1

2. When is Pediatric Hematology and Oncology (PHO) consulted?
    - PHO should be consulted to manage prophylactic enoxaparin and subcutaneous (SQ) heparin
        - monitor dosing due abnormal renal function
        - to assist with holding enoxaparin for procedures
        - to assist with bridging anticoagulation prior to a procedure when a patient is on aspirin
        - to assist with ordering medications as some pharmacies may not carry smaller doses or SQ heparin
    - Communication is key. EPIC will be the primary tool to communicate between PHO and Nephrology teams regarding TP
        - Peds Nephro Nurse Triage (pool) to assist with anti-Xa levels, and to coordinate visits
        - Peds Nephro Transplant Coordinator (pool) to be included in renal transplant related discussions
        - Peds Hem Onc Coag Nurse (pool)
        - APP for PHO
        - Primary nephrologist
        - Primary hematologist
    - If PHO is managing enoxaparin, patient should be seen by PHO every 4-6 months for follow up

3. Role of inherited thrombophilia testing
    - Thrombophilia testing is not recommended as a screening test for NS patients to determine TP need. Obtaining a detailed family history of VTE in first degree relatives, and/or a personal history of VTE is more important. Thrombophilia testing is obtained at the discretion of Nephrology prior to renal transplant.

4. As the literature for TP and pediatric NS are limited, the following scenarios should prompt a reevaluation of the ongoing need for TP:
    - the patient is no longer considered "nephrotic" as determined by their primary nephrologist,
        - While some types of NS are not amenable to immunosuppression, which results in a chronic nephrotic state (and chronic risk of thrombosis), some NS can be treated
            - Patients undergoing treatment with pheresis (plasma or LDL) may respond to therapy.
    - the patient no longer has a dialysis line or CVC
    - the factors associated with thromboembolism is no longer an issue

PHARMACOLOGIC PROPHYLAXIS MEDICATION RECOMMENDATIONS
See also Pediatric VTE Prophylaxis, Inpatient, Guideline

- Choice of medication requires a multidisciplinary discussion and shared decision making with patient and family.
  - Aspirin use should be directed and managed by Nephrology
  - Antiplatelet and anticoagulation are rarely used concurrently in this patient population
- Use appropriate dosing (dry) weight for medication dosing, as determined by nephrology
- GFR (to be calculated by Nephrology) will determine what medication to use/avoid and what dosages for renally dosed anticoagulation (discuss with Nephrology and Pharmacy)
- Timely communication with all teams is critical to managing TP. Tasks, reminders, and notifications can be communicated via EPIC (see Pertinent Information #2)

1. Unfractionated Heparin (when CrCl < 10 mL/minute/1.73 m2, as calculated by Nephrology)

Table 1: Prophylactic Unfractionated Heparin (UFH) Dosing & Monitoring		
Patient type/age	**UF Heparin dosing**	**Monitoring / Notes**
≤ 60 kg	75 units/kg/dose SQ Q12 hours	Consider CBC monitoring
> 60 kg	5000 units SQ* every 12 hours	
> 18 yrs or > 125 kg	5000 units SQ every 8 hours	
Continuous infusion	≤ 10units/kg/hr	
Renal dysfunction	No adjustment required	

* SQ: subcutaneous
** Outpatient/ home SQ heparin may not be available for all patients.

2. Low Molecular Weight Heparin (e.g., enoxaparin)

Table 2: Prophylactic Enoxaparin Dosing & Monitoring		
Patient type/age	**Enoxaparin dosing**	**Monitoring / Notes***
< 2 months	0.75 mg/kg/dose SQ Q12 hours	Monitoring of anti-Xa levels indicated/recommended
2 months or < 60 kg (up to 18 years)	0.5 mg/kg/dose SQ Q12 hours (max starting dose of 30 mg/dose)	Monitoring of anti-Xa levels *may be* indicated if enoxaparin continued ≥ 3 days
> 18 years or ≥ 60 kg (up to 125 kg)	40 mg SQ once daily OR 30 mg SQ every 12 hours	Monitoring of anti-Xa levels *may be* indicated if enoxaparin continued ≥ 7 days
> 125 kg	40 mg SQ every 12 hours	Monitoring of anti-Xa levels indicated/recommended
Renal dysfunction	Consider decreasing dose, switching to UFH, and/or consult pharmacy	Monitoring of anti-Xa levels indicated/recommended

* Anti-Xa levels should be drawn 4 hours post the 3rd or 4th SQ dose and should be 0.13-0.3 units/mL (as of Feb 2023; please refer to lab reference range for most up-to-date reference range) for prophylaxis. Consult lab for the most recent anti-Xa reference range.

Appendix 1.

	Pediatric NS	Adult NS [4]
Who to prescribe TP for	Congenital NS seem to be confer a higher VTE rate, but may be secondary to the presence of CVC.[5] Adolescents with NS are more likely to develop VTE than younger children with NS.[6] Membranous disease in children (membranous nephropathy and/or class-V lupus nephritis) and secondary NS are more likely to develop VTE.[6] Patient with active nephrotic syndrome with CVC	MGN, for unclear reasons, appears to confer an especially high risk for thrombosis among NS. [7]
When to prescribe TP	Worsening proteinuria is correlated with increase VTE probability. [6] In contrast to adult studies, hypoalbuminemia in pediatrics NS, was reported not to be a significant marker for VTE. [6] In pediatric patients, the majority of clinical VTE are diagnosed with the first 3 months after NS diagnosis. [6]	The first 6 months from diagnosis of NS may have higher rates of TE. [8] Serum albumin appears to be a strong predictor of TE. Recommend starting TP in adult MPGN when serum albumin falls < 2.5 gm/dL in the presence of other thrombotic risk factors. [9] It is unclear if depressed serum albumin is applicable to other subtypes of NS. [4] If bleeding risks are high, TP may not be beneficial regardless of serum albumin levels.
How to prescribe TP	Non-pharmacologic strategies, such as ambulation, appropriate hydration, and avoidance of CVC when possible should be encouraged.	Vitamin K antagonist for MGN-related venous TE [9], with a INR goal of 2.0-3.0 for prevention of thrombosis in non-NS population. [10] LMWH is an alternative agent, but the loss of antithrombin III may lead to heparin resistance. [11] Despite this theoretical concern, the use of LMWH as TP agent has been reported in small, observational studies. Low dose ASA was used for low-risk patients in one study.[1] Data for DOACs and the treatment of TE is conflicting. [4]
How long should TP be prescribed	Regular assessment of risk factors and status of NS is needed to determine if TP should continue	Continuation with TP while patient remains nephrotic or with serum album < 3.0 gm/dL. [9]

NS: nephrotic syndrome; VTE: venous thromboembolism; CVC: central venous catheter; ASA: aspirin; DOAC: direct oral anticoagulants; TP: thrombophrophylaxis; MGN: membranous glomerulonephropathy; MPGN: membranoproliferative glomerulonephropathy; LMWH: low molecular weight heparin; TE: thromboembolism

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