Approved by Quality & Patient Safety Committee
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RENAL VEIN THROMBOSIS

This Local Operating Procedure is developed to guide safe clinical practice in Newborn Care Centre (NCC) at The Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this Local Operating Procedure. The following guidelines are based on best available evidence and/or consensus achieved among the neonatologists at the Royal Hospital for Women and the renal and haematology teams at Sydney Children's Hospital.

1. AIM

- To guide management of neonatal renal vein thrombosis

2. PATIENT

- Newborns

3. STAFF

- Medical and nursing staff

4. CLINICAL PRACTICE

Procedure

1. Manage neonatal renal vein thrombosis (RVT) as an emergency.
2. Suspect RVT in any newborn infant with haematuria.
3. Look for classic triad of RVT: (1) haematuria; (2) flank mass; (3) thrombocytopenia.

NOTE:
Consider the following questions to identify potential risk factors for thrombosis

- Is it spontaneous?
- Is it secondary to UVC placement?
- Is it secondary to risk factors associated with hyperosmolar state such as perinatal asphyxia, coagulopathy, maternal diabetes mellitus, dehydration, polycythaemia, acute blood loss, sepsis, shock?
- Is it secondary to inherent prothrombotic risk factors?
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Leiden factor V mutation (heterozygous form X5 to X7 thrombotic risks and homozygous form X80 thrombotic risk)
  - Prothrombin 20210G / A mutation
  - Methylene tetrahydrofolate reductase (MTHFR) 677T genotype
  - Anticardiolipin antibodies
  - Elevated lipoprotein (a)
  - Homocysteinaemia

4. Admit to newborn care centre for close monitoring.
5. Obtain intravenous access and perform FBC, UEC, coagulation profile (APTT, PT) and other blood tests as appropriate.
6. Perform abdominal ultrasound with colour Doppler (Prince of Wales Vascular Laboratory available business hours Monday-Friday) as a priority. An interim abdominal ultrasound without Doppler studies can be requested outside these hours (Royal Hospital for Women Medical Imaging [contact through switch]).

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7. Consider head ultrasound if the infant is considered at risk of intracranial haemorrhage.
8. Consult Sydney Children's Hospital renal and haematology team urgently.
9. Perform prothrombotic risk factor screening: protein C, protein S, plasma antithrombin III activity, lipoprotein (a), factor V Leiden mutation, prothrombin gene mutation and MTHFR thermolabile mutation.
10. Ensure close monitoring of urine output (including catheterisation in case of macroscopic haematuria due to risk of blood clots blocking urination) and fluid balance.
11. Ensure good hydration (guide: 20 ml/kg/day more than regular volume requirement).
12. Determine the extent of RVT on ultrasound and Dopplers:
    - Is it unilateral or bilateral involvement?
    - Is there extension of thromobosis to the contralateral kidney and/or inferior vena cava?
    - Are the kidneys enlarged and echogenic?
    - Is there any evidence of renal and adrenal haemorrhage? (it is not uncommon to see peri-renal fluid collection)
13. Discuss the specific thrombolytic and anticoagulant management with renal and haematology team (see appendix).
14. Perform colour Doppler daily for the first week of hospitalisation. This is to check for:
    - Extension of thrombosis
    - Re-permeabilisation (defined as reappearance of renal vein patency and regression of nephromegaly and hyperechogenicity)
15. Closely monitor blood pressure (minimum 6 hourly) for the first week of hospitalisation to evaluate any transient hypertension.
16. Closely monitor platelets, EUC, urine output and fluid balance.
17. Thrombolytic and heparin therapy (in consultation with renal and haematology team):[1,2]
    - Unilateral RVT without renal impairment or extension to inferior vena cava (IVC):
      - Supportive care with radiologic monitoring
      - If extension occurs, initiate anticoagulation with low molecular weight heparin (LMWH)/Unfractionated Heparin (UFH) or UFH/LMWH in therapeutic dose [duration 6 weeks to 3 months]
    - Unilateral RVT with extension to IVC at diagnosis might benefit from anticoagulation therapy under same modalities as above if there is not a significant risk of bleeding.
    - Bilateral RVT with evidence of renal impairment should be started on UFH and then thrombolytic therapy with tPA, followed by anticoagulation with LMWH/UFH at therapeutic doses.
    - Closely monitor for central nervous system complications by regular cranial ultrasounds as intraventricular 2aemorrhage can occur with thrombolytic/heparin therapy.
    - Therapeutic dosing of LMWH is as follows:[2]
      - The commonly used LMWH in Australia is Enoxaparin
      - Enoxaparin has 110 anti-factor Xa units/mg
      - Newborn infants require higher per-kilogram doses than older children
      - Therapeutic dose in infants <2 months corrected age: 1.5 mg/kg/dose SC 12 hourly
      - Therapeutic dose in infants ≥ 2 months corrected age: 1.0 mg/kg/dose SC 12 hourly
      - The dose is to be monitored to a target range of an anti-Xa level of 0.50 to 1.0 units/mL in a sample taken 4 to 6 h following a subcutaneous injection
      - Watch for adverse effects including major bleeding that can be seen in approximately 10% of newborn infants.
      - Protamine sulfate is used to reverse UFH and some LMWH induced bleeding
    - Therapeutic dosing of unfractionated (otherwise known as standard) heparin is as follows:[2]
      - Loading dose of 75 units/kg IV over 10 minutes followed by initial maintenance dose of 28 units/kg/hour

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- Loading bolus is to be withheld or reduced if there is a significant risk of bleeding (discussion with haematologist is recommended)
- The dose is adjusted to target the APTT in the range of 60-85 seconds (assuming this reflects anti-Xa level of 0.35-0.7 units/mL) [refer to table below for dose adjustment]
- Obtain bloods for APTT 4 hours after loading dose and 4 hours after every change in the infusion rate
- Monitor for adverse effects including: (i) major bleeding from both therapeutic dosing and accidental overdosing; (ii) heparin induced thrombocytopenia; (iii) osteoporosis with prolonged usage
- Protamine sulfate is used to reverse heparin induced bleeding

Table 1. Systemic heparin dosing and adjustment

Loading dose: heparin 75 units/kg IV over 10 minutes
Initial maintenance dose: 28 units/kg per hour
Adjust heparin to maintain APTT of 60-85 seconds (equivalent to an anti-Xa level of 0.35-0.70)
Obtain blood for APTT 4 hours after administration of the heparin loading dose and 4 hours after every change in the infusion rate
When APTT values are therapeutic, perform daily FBC and APTT

APTT (seconds)	Bolus (units/kg)	Pause (minutes)	Rate change (%)	Repeat APTT
<50	50	0	+10	4 hours
50-59	0	0	+10	4 hours
60-85	0	0	0	Next day
86-95	0	0	-10	4 hours
96-120	0	30	-10	4 hours
>120	0	60	-15	4 hours

- Thrombolysis (Fibrinolysis) with tPA:
  - Prior to prescribing tPA, ensure fibrinogen level >1.0 g/L and platelets >100x10^9/L and correct any other coagulopathy with FFP and/or vitamin K
  - Recommended dose of tPA is 0.5 mg/kg/hr for 6 hours
  - Commence unfractionated heparin at therapeutic dosing after tPA finishes (with no loading bolus)
  - Fibrinolytic therapy, is associated with a risk of bleeding, specifically if there is an associated adrenal haemorrhage (significant risk of adrenal, intraabdominal and intraventricular haemorrhage).
  - Monitoring during thrombolysis:
    - There is no therapeutic range for thrombolytic agents
    - Maintain fibrinogen levels at least 1.0 g/L and platelets >100x10^9/L
    - Monitor D-Dimer level to determine if effective thrombolysis is present

18. RVT secondary to UVC placement:[2,3]
    - It is unclear whether anticoagulation should immediately be started. The UVC should be removed 3-5 days after starting anticoagulation. Alternatively, remove the UVC and provide supportive therapy with radiologic monitoring.
    - If the UVC is removed and there is extension of thrombus, start anticoagulation. Use either LMWH or UFH followed by LMWH. Therapy duration: 6 weeks to 3 months.
    - If thrombolysis is required, tPA is recommended (see table).
19. Post-discharge follow-up:
    - Infants may be at risk of long term morbidities including systemic hypertension, tubular dysfunction, renal atrophy and chronic kidney disease.[7]
    - Arrange regular follow-up by renal team, paediatrician, haematologist and other teams as appropriate.

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- Periodic monitoring of blood pressure and renal function as appropriate in the follow-up visits.
- Periodic ultrasound review by paediatrican/renal team.
- If anticoagulant therapy is prescribed beyond discharge, monitor as per haematology and renal teams.

5. DOCUMENTATION

- eMR
- Daily Care Plan
- Neonatal Observation Chart
- NICUS database

6. EDUCATIONAL NOTES

- RVT is one of the most common non-catheter-related thrombosis in newborn period.
- Incidence:1.3-2.2 per 100,000 livebirths.[3,4]
- More common in male infants (67.2%) and term infants (71%).[4]
- Age of presentation: 7% in-utero, 67% within 3 days and 26% after 3 days after birth.[4]
- 70% unilateral (66% left kidney); 30% bilateral.[4]
- Thrombus extends into IVC in 44% of cases and adrenal haemorrhage in 15% of cases.[4]
- Most thromboembolic events including RVT in preterm infants are secondary to treatment procedures (central catheters, umbilical vessels catheterization etc). However, in term infants, the majority of RVT cases are spontaneous, accounting for up to 80% cases.[3] RVT can be secondary to acquired or inherited perinatal risk factors including: (1) increased blood viscosity state (perinatal asphyxia, hypovolemia, septicaemia, dehydration, shock, polycythemia, cyanotic heart disease, infant of diabetic mother) or (2) inherent prothrombotic risk factors identified in 0.5% - 8.2%.[3]
- In spontaneous forms, thrombus starts in an arcuate or interlobular vein and may spread in both directions to involve main renal cortex and main renal vein. In RVT secondary to procedure such as UVC insertion, thrombus starts forming at the site of endothelial injury from the UVC and then spreads centrifugally into renal vein.
- Genetic prothrombotic factors include:[4]
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Leiden factor V mutation
  - Prothrombin 20210G / A mutation
  - Methylene tetrahydrofolate reductase
  - Anticardiolipin antibodies
  - Elevated lipoprotein (a)
  - Homocysteinemia
- Genetic prothrombotic risk factors: Among patients with RVT in whom prothrombotic factors were investigated, 53% (79 of 149) had at least 1 risk factor identified. About 7% of these neonates with RVT had a second thrombotic event, occurring during puberty.[4]
- Pathognomic triad: (1) macroscopic haematuria, (2) palpable abdominal mass, and (3) thrombocytopenia.[3-5]
- Diagnosis: Abdominal ultrasound with colour Doppler is the modality of choice. US findings include globular enlargement of kidneys, increase in echogenicity, loss of corticomedullary boundary, echogenic streaks and loss of normal sinus echoes.[3-5]

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- General principles of treatment[1,2,4]: Renal outcomes are similar between supportive treatment and heparin therapies. A similar proportion of affected kidneys became atrophic in neonates who were managed supportively or with heparin.[4] RVT in neonates often leads to irreversible damage and anticoagulant therapies may not have an impact on the long-term outcomes.[1,3-5]
- In the majority of cases, the affected kidney becomes atrophic.
- Re-permeabilisation in the neonatal period is not a good prognostic factor.
- Management should involve a multidisciplinary team that includes neonatologists, radiologists, haematologists, and nephrologists.
- During the acute phase, supportive management of electrolytes and fluid balance especially maintaining the good hydration is important. The haematologists should be consulted on whether and when the neonates require anticoagulation or fibrinolytic treatments. The response to the treatment should be monitored by the clinical team in conjunction with the radiologists, nephrologists and haematologists.
- Unilateral involvement: Most neonatal renal venous thrombosis is unilateral and does not respond to fibrinolytic therapy and heparin. It is also not clear whether an associated inferior vena cava clot is an indication for anticoagulation because no embolic complications have been observed.
- Bilateral involvement: Although evidence is not conclusive, fibrinolytic and heparin therapy should be used in an attempt to prevent renal failure. In such patients therapy should begin as early as possible within 24 hours of recognition of the thrombus to prevent irreversible damage. Fibrinolytic therapy, however, is associated with a risk of bleeding, specifically if there is an associated adrenal haemorrhage.[1] The optimum length of therapy with fibrinolytics is not known. In the absence of definite criteria it seems reasonable to suggest that at least 24 hours (and up to 7 days) of therapy can be attempted, while closely monitoring for associated abdominal and intracranial bleeding.[1] Fibrinolytic therapies are tPA and urokinase. Heparins include UFH or LMWH.[1]
- Plasminogen is the zymogen of plasmin, the major enzyme that degrades fibrin clots. Plasminogen must be activated to plasmin to dissolve fibrin. tPA is released by endothelial cells in damaged blood vessels. tPA catalyses the conversion of plasminogen into plasmin.
- tPA is the agent of choice for clot lysis (fibrinolysis). Urokinase is another agent but is not currently used for this purpose.
- Affected neonates must be followed closely for renal complications such as hypertension, atrophy, functional loss, and chronic renal insufficiency.[4]
- Outcomes: The long-term RVT morbidity includes systemic hypertension, tubular dysfunction, renal atrophy and chronic kidney disease. Regardless of the treatment received, irreversible damage was found in approximately 70% of affected kidneys. In patients treated with UFH/LMWH or supportive care, 75.3% and 72.5% of the affected kidneys were found to be atrophic at last follow-up respectively. 19% of neonates with unilateral RVT and 22% of the neonates with bilateral RVT had persistent elevated blood pressure.[4]

7. RISK RATING

- Low

8. NATIONAL STANDARD

- Standard 1 Clinical Governance
- Standard 4 Medication Safety
- Standard 5 Comprehensive Care
- Standard 6 Communicating for Safety
- Standard 8 Recognising and Responding to Acute Deterioration

RENAL VEIN THROMBOSIS cont'd

9. ABBREVIATIONS AND DEFINITIONS OF TERMS

NCC	Newborn Care Centre	PT	Prothrombin Time
RVT	Renal Vein Thrombosis	IVC	Inferior Vena Cava
UVC	Umbilical Venous Catheter	LMWH	Low Molecular Weight Heparin
MTHFR	Methylene tetrahydrofolate reductase	UFH	Unfractionated Heparin
FBC	Full Blood Count	tPA	Tissue Plasminogen Activator
EUC	Electrolytes Urea Creatinine	FFP	Fresh Frozen Plasma
APTT	Activated Partial Thromboplastin Time		

10. REFERENCES

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