COVID-19 position statement:

Prevention of circuit thrombosis in adult inpatients who are COVID-19 positive and undergoing renal replacement therapy (RRT) on critical care wards

Contents

Introduction

The purpose of this guideline is to provide NHSScotland with advice on the appropriate use of anticoagulation in patients with COVID-19 who are receiving renal replacement therapy (RRT).

This guideline is for:

- health and care practitioners working in critical care areas
- health and care staff involved in planning and delivering services
- national procurement teams.

The recommendations are based on advice from intensive care, renal and haematology specialists working in NHSScotland.

This guidance will be reviewed and updated as new evidence emerges.

This document has been created to answer some of the questions that have arisen in critical care areas regarding the treatment of COVID-19 positive patients receiving renal replacement therapy.

For the purposes of this document, the following definitions apply:

- Patients are classified as COVID-19 positive if they have clinical features of COVID-19 infection and/or test positive for COVID-19 using viral RT-PCR

- Recommendations in this document apply to inpatients who are COVID-19 positive and who are receiving RRT in critical care wards (high dependency or intensive care) for acute kidney injury (AKI) or chronic kidney disease (CKD).

Recommendations

- Consider using a continuous systemic infusion of unfractionated heparin (UFH), instead of citrate and/or low molecular weight heparin (LMWH), for anticoagulation in patients who are COVID-19 positive and receiving renal replacement therapy.

- Use anti-Xa measurements to monitor the effectiveness of UFH in patients who are COVID-19 positive and who are receiving renal replacement therapy (APTTr is unreliable giving either falsely reduced readings, likely due to the very high Factor VIII (FVIII) levels in these patients, or falsely increased readings due to the presence of lupus anticoagulant)

- Site-specific standard operating procedures for anticoagulation in patients who are COVID-19 positive and require renal replacement therapy should be created (for an example, see Appendix 1)

1. Prevention of filtration thrombosis during RRT

Extracorporeal circuit clotting is a major issue with renal replacement therapy (RRT). Significant loss of therapeutic time occurs in replacing clotted haemofilters, which diminishes the efficacy of the treatment.

Anticoagulation options for RRT can be divided into two main categories: regional (circuit) anticoagulation with either citrate, low molecular weight heparin (LMWH) or unfractionated heparin (UFH); and systemic anticoagulation with UFH or LMWH.

Early on in the COVID-19 pandemic there were reports of much more frequent clotting in RRT circuits in patients who were COVID-19 positive than in other patients despite using standard anticoagulation regimens in the circuit, either with citrate or boluses/infusions of LMWH/UFH.[1,2]

This led clinicians to consider whether systemic anticoagulation might be more effective, with a continuous infusion of UFH rather than once daily dosing of LMWH being favoured as the latter results in peaks and troughs of anticoagulation. Anecdotal evidence from centres using systemic UFH seems to support this approach.

There are a number of disadvantages of using UFH infusions including monitoring of anticoagulation using the activated partial thromboplastin time (APTT) ratio or anti-Xa assay, lack of familiarity with UFH dosing and administration amongst clinical staff, and the higher risk of heparin induced thrombocytopaenia (HIT), although the absolute risk of the latter remains low (0.7% in the usual population).[3]

1.1 Anticoagulation of RRT circuits in patients with COVID-19

This section uses a Q&A format to explain the rationale for the use of UFH in patients who are COVID-19 positive and who are receiving RRT, including the limitations of available evidence, the practicalities of administering and monitoring UFH use in this patient population, and the issues and complications that might arise.

An example of the protocol used for such patients in NHS Greater Glasgow and Clyde is included as Appendix 1.

1.1.1 Why are patients who are COVID-19 positive experiencing increased rates of circuit filter thrombosis when undergoing RRT?

There is anecdotal evidence that patients undergoing RRT in critical care who are COVID-19 positive are experiencing a greater frequency of filter thrombosis than patients who are not COVID-19 positive despite the use of recognised methods of anticoagulation in the filter circuit. [1,2,4] Furthermore, patients who are COVID-19 positive appear to have an increased risk of developing systemic venous thrombosis,[5] and laboratory measurements are suggestive of an underlying prothrombotic state, for example high D-dimers, FVIII and fibrinogen.

It is hypothesised that by providing a continuous infusion of systemic anticoagulation with UFH in patients who are COVID-19 positive in critical care, filter thrombosis will be avoided.[1,2] Systemic UFH infusions are a recognised method for providing anticoagulation to a circuit.[4] However, there is currently no evidence that this is more effective than other regimens in patients who are COVID-19 positive and who are receiving RRT.

1.1.2 Can APTT ratios be used to monitor the effectiveness of this regimen of systemic anticoagulation with UFH?

Recent clinical experience suggests that APTT ratios appear to be insensitive to the effect of UFH in patients who are COVID-19 positive. This is thought to be secondary to the very high levels of FVIII that frequently occur in these patients. Occasionally, patients who are COVID-19 positive will have a prolonged APTT. In almost all of these situations, this is secondary to the presence of a lupus anticoagulant. For these reasons, APTT ratios cannot be used to accurately measure the effect of UFH in patients who are COVID-19 positive.

Anti-Xa levels can accurately quantify UFH concentration in patients who are COVID-19 positive and this approach should be used (personal communication). Anti-Xa levels should be maintained between 0.3-0.7 IU/mL.

1.1.3 How should UFH be administered and monitored?

The dosing of UFH in patients who are COVID-19 positive and who are receiving RRT should be based on that used for anticoagulation in patients who have a venous thrombosis.

- Start the UFH IV infusion at the same time as the episode of RRT commences.
- Give an IV bolus of 5,000 units UFH and commence IV UFH infusion at 1,200 units/hr *(recommended preparation: heparin sodium 20 ml vial of 1000 units/ml; total concentration: 20,000 units/20 ml)*
- Measure anti-Xa activity 6 hours after the start of infusion. During RRT, target anti-Xa is 0.3-0.7 IU/mL (refer to Table 1 in Appendix 1 for recommended dose adjustments).
- If RRT is planned to last >8 hours, anti-Xa activity must be measured urgently (as this will inform dose change for the remainder of RRT). If RRT is planned to last <8 hours, anti-Xa activity will inform the infusion rate +/- bolus for the next episode of RRT.
- If the UFH infusion rate requires adjustment during RRT, anti-Xa level activity should be measured 4 hours after the change in infusion rate.

1.1.4 In patients who are COVID-19 positive, can the anticoagulation methods usually employed when providing RRT continue to be used?

In some critical care wards, RRT is provided by nursing staff who are familiar with using infusions of citrate or boluses of LMWH or UFH to maintain circuit flow and prevent thrombosis. If these usual methods are found to be effective in a patient who is COVID-19 positive, then there is no obligation to switch to a systemic UFH infusion. This is an important issue as, during the pandemic, redeployed staff are often working in clinical environments with which they are not familiar, and they should not be asked to manage new regimens of medication that are not essential.

1.1.5 Should all patients who are COVID-19 positive, including those receiving RRT in renal units and in renal wards, receive systemic anticoagulation with UFH?

No. Patients who are COVID-19 positive and in critical care units are most at risk of developing filter thrombosis. There is currently no indication that patients receiving RRT for acute kidney injury or chronic renal failure in medical wards, renal units or haemodialysis centres need anything other than normal measures for maintaining circuit patency.

1.1.6   What method of anticoagulation should be used if a patient develops thrombocytopaenia?

There is an increased risk of heparin induced thrombocytopaenia (HIT) in patients who receive UFH compared to LMWH, with an incidence of approximately 0.7% in the usual population. If thrombocytopaenia develops in a patient receiving systemic UFH, a HIT score must be calculated. If this is >3, a HIT assay must be performed urgently and the patient converted to an alternative anticoagulant. In patients with renal failure, this should be with argatroban.

1.1.7   Argatroban levels are usually measured using an APTT ratio. Is this a valid method of measurement in patients who are COVID-19 positive?

This is not known. Argatroban is a direct thrombin inhibitor and the effect of high FVIII levels on APTT ratios, which are normally used to measure the effect of argatroban may not be accurate.

The laboratory at Glasgow Royal Infirmary uses a dilute thrombin time assay to measure argatroban levels and concurrently measures APTT ratios to assess their accuracy in patients who are COVID-19 positive.

Laboratories that cannot measure argatroban can contact the laboratory at Glasgow Royal Infirmary for advice (Contact: Mrs Caroline Lawrence 0141 211 4461 caroline.lawrence@ggc.scot.nhs.uk).

1.1.8   If continuous haemofiltration is not being used, do patients require ongoing anticoagulation to prevent systemic thrombosis?

Continuous haemofiltration is commonly used in critical care areas. However, in critical care, approximately one third of patients who are COVID-19 positive require RRT and filter resource may be limited, resulting in the need for RRT to be provided intermittently.

During the periods when RRT is not required, it is recommended that the UFH infusion continue at a reduced rate of 500 U/hr until the next episode of RRT *(off label use)*. During this time no monitoring of anti-Xa activity is required and subsequent boluses of UFH, prior to each RRT, should be 4,000 units.

This 'off label' use of UFH is recommended to avoid the need to administer boluses of UFH or LMWH for systemic thromboprophylaxis during the period when systemic anticoagulation with UFH is not being given.

1.2 Procurement

Providing systemic anticoagulation with UFH safely for patients who are COVID-19 positive and receiving RRT in critical care units will require close collaboration between critical care teams, senior renal healthcare providers, haematologists and senior haematology laboratory staff to determine capacity, including staffing and training.

Issues to be considered include:

- sufficient supply of UFH
  - Boards should liaise with National Procurement Commodity Manager, Hazel Johnstone, hazel.johnstone@nhs.net to highlight any change in anticipated usage to enable discussions with all suppliers regarding their capacity to support additional requirements. Whilst there is expected to be sufficient capacity to support an increase in usage, co-ordination at national level will help manage requirements across all four home nations.
- sufficient supply of syringe pumps to administer UFH
- availability of anti-Xa monitoring
- availability of laboratory testing for HIT
- availability of argatroban in the event of a presumed/confirmed case of HIT.

2. Methodology

This Guidance has been produced on behalf of the Scottish Government's Chief Medical Officer in response to the COVID-19 pandemic situation and so has not followed the standard process used by SIGN to develop guidelines. The recommendations are based on expert opinion, with rapid expert peer review as assurance.

2.1 Updating the guidance

The guidance will be reviewed and updated if significant new evidence emerges.

2.2 Contributors

Dr Catherine Bagot	Consultant Haematologist, NHS Greater Glasgow & Clyde
Ms Beatrice Cant	Programme Manager, SIGN
Dr Colin Church	Consultant Respiratory Physician, NHS Greater Glasgow & Clyde
Dr Martin Johnson	Consultant Respiratory Physician, NHS Greater Glasgow & Clyde

2.3 Peer review

This document was reviewed by the **Clinical Guidance Cell**.

2.4 Editorial review

As a final quality check, the guideline was reviewed by an editorial group, as follows:

Professor Tom Evans	Professor of Molecular Microbiology, Institute of Infection, Immunity & Inflammation, University of Glasgow and Consultant Infectious Disease Physician, NHS Greater Glasgow & Clyde
Dr Roberta James	Programme Lead, SIGN
Dr Safia Qureshi	Director of Evidence, Healthcare Improvement Scotland

Appendix 1

Prevention of thrombosis in COVID-19 +ve[‡] adult inpatients (pregnant and non-pregnant) undergoing renal replacement therapy (RRT) on Critical Care Wards[‡‡]

NHS
Greater Glasgow and Clyde

[‡]Patients are classified as COVID-19 +ve if they have clinical features of COVID-19 infection and/or test positive for COVID-19

[‡‡]Includes COVID-19 +ve inpatients receiving RRT in Critical Care wards (High Dependency or Intensive Care) for Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD)

- There is significant anecdotal evidence that patients who are COVID-19 +ve are at increased risk of thrombosis, both in RRT circuit lines and systemically
- Usual anticoagulation measures during RRT, including citrate and/or boluses of LMWH, may be ineffective in this patient population
- A continuous infusion of UFH, instead of citrate and/or LMWH, may be more effective
- AntiXa measurements are required to monitor the effectiveness of unfractionated heparin (UFH) in COVID-19 +ve patients (APTTr is unreliable, likely due to the very high FVIII levels in these patients)

Recommendation
Patients who are COVID-19 +ve, and require RRT in Critical Care, should be considered for continuous IV infusions of Unfractionated Heparin (UFH) [¶]

- Start the UFH IV infusion at the same time as the episode of RRT commences.
- Give an IV bolus of 5000 units[#] UFH and commence IV UFH infusion at 1200 units/hr *[recommended preparation: heparin sodium 20ml vial of 1000 units/ml (total concentration: 20,000 units/20ml)]*
- Measure antiXa 6 hours after start of infusion (request 'antiXa UFH' on Trakcare stating time sample taken). During RRT, target antiXa is 0.3-0.7 - refer to Table 1 overleaf for recommended dose adjustments.
- If RRT is planned to last >8 hours, antiXa level must be requested urgently (as this will inform dose change for remainder of RRT). If RRT is planned to last <8 hours, antiXa level will inform infusion rate +/- bolus for next episode of RRT.
- If UFH infusion rate requires adjustment during RRT, an antiXa level should be measured 4 hours after the change in infusion rate.
- Once RRT is complete, switch UFH infusion rate to 500 units/hr and continue until next episode of RRT *(off label)*
- Subsequent boluses of UFH, prior to each RRT, should be 4000 units[*]
- AntiXa monitoring is only required <u>during</u> RRT
- APTTr monitoring should not be used at <u>any</u> time
- Do NOT give additional thromboprophylaxis with UFH or LMWH whilst the above regimen is being used

[¶] Some critical care areas may wish to continue to use tinzaparin boluses during RRT, rather than switch to UFH. If using tinzaparin and RRT lasts <8 hours, standard thromboprophylaxis should be given during the remaining 16 hours e.g. enoxaparin 20mg 6-8 hours after episode of RRT ends.

[#] Omit bolus if patient has received prophylactic dose LMWH/UFH in the last 6 hours.

[*] If there continues to be episodes of circuit thrombosis during RRT, this bolus dose of UFH can be increased, up to a maximum of 5000 units.

Prevention of thrombosis during RRT in COVID-19 +ve critical patients v6, 27/4/20, CBagot, B Miles, G Chalmers, D McCarey, C Geddes

Appendix 1 (continued)

Use Table 1 to calculate change in dose of UFH for ongoing/next RRT episode

Table 1. Recommended UFH dose changes based on AntiXa levels
Modified from Normogram from University of Wisconsin, USA (available here)

AntiXa level (IU/ml)	Infusion rate change	Other recommendations
<0.1	Increase by 400 units/hr	Consider bolus 2000 Units
0.1-0.19	Increase by 200 units/hr	-
0.2-0.29	Increase by 100 units/hr	-
0.3-0.7	No change	-
0.71-0.8	Decrease by 100 units/hr	Discontinue infusion for 30 minutes
0.81-1.7	Decrease by 200 units/hr	Discontinue infusion for 1 hour
>1.7	Decrease by 300 units/hr	Discontinue infusion for 1 hour

Contraindications against thromboprophylaxis with UFH
- Platelet count ≤ 50 x10^9/l
- Receiving anticoagulation for another reason
- Patient considered to be at high bleeding risk e.g. recent intracranial haemorrhage, untreated inherited/acquired bleeding disorders
- Trauma with high bleeding risk
- Active bleeding
- Heparin induced thrombocytopaenia – see details in page 2
- Acute stroke (use IPC if immobile & contact stroke team for guidance)
- Within 6 hours of procedures e.g. surgery, lumbar puncture
- Acute bacterial endocarditis
- Persistent hypertension (BP ≥230/120)
- Liver failure <u>and</u> INR>2

Heparin Induced Thrombocytopaenia

If platelet count falls by more than 50% baseline, or there are any other indications to suggest the development of Heparin Induced Thrombocytopaenia (HIT), calculate HIT score (using this link) and discuss urgently with consultant haematologist.

Systemic Venous Thrombosis

If a patient develops a systemic venous thrombosis during their inpatient stay, use the following anticoagulation regimens:

- Renal impairment (CrCl <30ml/min) **with** ongoing RRT
  - Therapeutic IV UFH and antiXa measured using the regimen described above i.e. first measurement at 6 hours with measurements taken 4 hours after every change in infusion rate. When no change in infusion rate is required, antiXa should be measured daily.

- Renal impairment (CrCl <30ml/min) but **no longer** on RRT
  - Therapeutic dose SC dalteparin and an antiXa level measured 4 hours post 3rd dose (aiming for target antiXa 0.5-1.2 [request 'AntiXa LMWH' on Trakcare]) as per GGC guideline.

References

1   Anecdotal reports locally and internationally: https://www.era-edta.org/en/covid-19-news-and-information/#toggle-id-21 (see under 'Additional Local Protocols', article by Casper Franssen, Nephrologist, University Medical Center Groningen, The Netherlands, 2 April 2020. CVVH and frequent filter clotting in patients with COVID-19.l)

2   Thomas et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. Thromb Res. 2020 Apr 25 doi: 10.1016/j.thromres.2020.04.028

3   Watson H, Davidson S and Keeling D. Guidelines on the diagnosis and management of heparin induced thrombocytopenia: second edition. British Journal of Haematology, 2012, 159: 528–540

4   Ahmed A R, Obilana A, and Lappin, D. Renal Replacement Therapy in the Critical Care Setting. Clinical Care Research and Practice (2019) https://doi.org/10.1155/2019/6948710

5   Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med (2020). https://doi.org/10.1007/s00134-020-06062-x