Who should read this document?

- All clinical medical and nursing staff involved in the administration of thrombolysis in acute ischaemic stroke
- All anaesthetic, critical care and theatre recovery unit staff
- All cardiac arrest and resuscitation-team staff
- All blood-bank/haematology/transfusion staff
Key Practice Points

- Thrombolysis with iv tissue plasminogen-activator (tPA) for ischaemic stroke is usually administered in a level 1 care environment (Emergency Department and/or Acute Stroke Unit), as there is no specific recommendation otherwise.

- Angioedema, manifesting as hemi-facial/orolingual swelling is a recognised complication of stroke thrombolysis with tPA which may progress to life-threatening airway compromise.

- Preceding treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and presence of insula/frontal cortical ischaemia on pre-treatment CT increase the likelihood of angioedema developing.

- All patients eligible for thrombolysis will be assessed for their risk of developing angioedema by the attending senior stroke team doctor. This risk should be discussed and documented with the patient and/or family.

- In those patients eligible for tPA identified as at-risk of developing angioedema, the second on-call anaesthetist will be informed of the patient details, location and timing of tPA treatment.

- Patients developing angioedema will receive appropriate urgent medical treatment and timely anaesthetic review in an appropriate environment, as outlined in this policy.

Scope and Background

Scope of the policy
Patients receiving thrombolysis with tPA for ischaemic stroke may develop the potentially life-threatening complication of hemi-facial/orolingual angioedema.

The purpose of this protocol is to consolidate best evidence-based guidance to inform the assessment of risk of angioedema, and its management, in patients receiving thrombolysis for acute ischaemic stroke. The protocol aims to provide:

1. A Trust framework facilitating urgent assessment of risk
2. An agreed management algorithm for patients developing angioedema
3. Governance and audit systems to ensure protocol adherence and to monitor processes of care.

Background
The incidence of angioedema in patients receiving tPA for ischemic stroke has been reported as 1.3 to 8%\(^2\). It usually manifests as mild, transient painless hemifacial swelling starting in the tongue, usually contralateral to the ischaemic hemisphere, and resolves within 24 hours.\(^2\)
Data from observational studies suggest life-threatening airway compromise requiring anaesthetic intervention is rare; occurring in around 0.2 to 1% of all patients receiving tPA, or around 13% of those developing angioedema\(^2,3,5,6\).

In a recent single-centre study at Salford Royal, the incidence of angioedema at SRFT was approximately 8%, ranging from 5 to 189mins after initiation of tPA\(^5\).

The pathophysiological basis of angioedema following tPA in stroke is unclear. tPA generates plasmin, which leads to formation of bradykinin, a powerful vasodilatory peptide\(^7\) metabolised by angiotensin converting-enzyme (ACE). ACE-inhibitors (ACE-I) have been associated with non-hereditary angioedema and may therefore enhance the risk of tPA-induced angioedema in stroke by potentiating bradykinin levels.

Autonomic dysregulation associated with acute stroke has also been proposed as a contributory factor although the mechanisms and importance remain unclear.

Existing treatment with ACE-I (RR 13.6; 95% CI 3 to 62.7) and signs of acute insula/frontal ischemia (RR 9.1; 1.4 to 30) predicted development of angioedema\(^2\) in one relatively small study of patients receiving tPA in acute ischaemic stroke. A subsequent study confirmed the association between ACE-I and angioedema\(^5\).

**What is new in this version?**

Published data for angioedema complicating stroke thrombolysis at SRFT have been incorporated into the background section, and the citation added to the references

Statins are no longer considered risk factors for angioedema complicating stroke thrombolysis. In the Salford Royal study, only ACE-I, but not statins, were independently associated with angioedema in multifactorial analyses.

The long-range pager for the second-on call anaesthetics registrar is no longer used and has been removed from the protocol. **Emergency contact is via the wireless baton mobile phone (61852).** Other relevant contact details (including addition of stroke registrar on-call baton pager and ward B3 extension numbers) have also been updated.
**Clinical Guidance**

**FIGURE 1**

**ACUTE ISCHAEMIC STROKE PATIENT ELIGIBLE FOR THROMBOLYSIS**

**STROKE TEAM BRING THROMBOLYSIS BOX**

? **AT RISK OF ANGIOEDEMA?**

Existing treatment with ACE-I
Ischaemia involving insula

**INFORM SECOND ON-CALL ANAESTHETIST:**

*Wireless baton mobile 61852*

Commence thrombolysis observations including:
? STRIDOR
HEMIFACIAL/LINGUAL ANGIOEDEMA CHART

**DEVELOPMENT OF ANY SIGNS OF ANGIOEDEMA:**

**STOP tPA IMMEDIATELY**

Administer first-line Rx:
- HIGH-FLOW OXYGEN
- CHLORPHENAMINE 10mg iv
- HYDROCORTISONE 200mg iv
- 5ml of 1:1000 NEBULISED ADRENALINE driven by 100% oxygen (repeat as required 2-3 hourly) *

- Assess severity and risk of airway compromise
- Contact the CARDIAC ARREST TEAM immediately (2222)
- Inform second on-call anaesthetist (or ICU SpR)
- Inform stroke consultant if not already present

**TRANSFER TO POST-ANAESTHESIA CARE UNIT (PACU)**
**LEVEL 3 THEATRE RECOVERY (65079/64663)**

Consider **C1-esterase inhibitor** 1000units iv over 10-15mins, followed by further 500units iv PRN;
0.5ml of 1:1000 **ADRENALINE IM**

**ONGOING MANAGEMENT**

Review on a case by case basis with senior medical staff

Continue for a minimum of **24 hours:**
- Chlorphenamine 10mg iv tds
- Hydrocortisone 100mg iv tds
- Nebulised adrenaline PRN*

Consider discontinuing ACE-I/statin longer-term
Complete Trust audit form, yellow card reporting, EPR coding

* ENSURE EYE PROTECTION APPLIED TO PATIENT (see text)
FIGURE 2

<table>
<thead>
<tr>
<th>Acute Stroke Unit (ASU)</th>
<th>Extension 64788/62149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute Stroke Unit (HASU) B3</td>
<td>Extension 61913/61903</td>
</tr>
<tr>
<td>On-call stroke consultant</td>
<td>Pager via switchboard or ASU</td>
</tr>
<tr>
<td>On-call stroke registrar</td>
<td>Baton pager 07623 606 541</td>
</tr>
<tr>
<td>Second on-call anaesthetist</td>
<td>Baton wireless mobile 61852</td>
</tr>
<tr>
<td>ICU SpR</td>
<td>Extension 65045/65046</td>
</tr>
<tr>
<td>PACU, level 3 theatres</td>
<td>Extension 65079/64663</td>
</tr>
<tr>
<td>Emergency room: resus area</td>
<td>Extension 64849/62451</td>
</tr>
<tr>
<td>Blood bank (0900-1730)</td>
<td>Extension 64994</td>
</tr>
<tr>
<td>On-call haematology technician</td>
<td>Bleep 3077</td>
</tr>
<tr>
<td>(1730-0900)</td>
<td></td>
</tr>
</tbody>
</table>

1. Assessment of patients at-risk of angioedema

The drugs required for empirical urgent first-line treatment of angioedema\(^8\) (FIGURE 1) are contained within the thrombolysis packs. These are kept on the ASU and routinely taken when assessing suitability for thrombolysis.

All patients eligible for thrombolysis will be screened for risk of angioedema.

Known treatment with an ACE-I (any dose or formulation; if the full drug history is unknown assume the patient is taking ACE-I until proven otherwise) and/or those with clear evidence of early ischemia involving the insula cortex will trigger the following:

The second on-call anaesthetist will be contacted using the baton mobile phone (see FIGURE 1 and 2) to inform them:
- That tPA is commencing in a patient potentially at-risk of angioedema
- The exact location of the patient

2. Commencing thrombolysis with tPA

Monitoring of thrombolysis will proceed as usual with the addition of the facial/lingual swelling observation chart (APPENDIX 1) for ALL patients.

Note that maintenance of normal oxygen saturations should NOT be interpreted as absence of laryngeal oedema/early airway compromise.
3. If ANY features of angioedema develop (FIGURE 1)

- Stop tPA immediately (if not already)
- Commence first-line medical treatment⁷ (see FIGURE 1 and below)
- Contact the cardiac arrest team urgently (2222)
- Contact the second on-call anaesthetist. Contact the ITU SpR if the second on-call anaesthetist is unavailable
- Contact the senior stroke team doctor if not already present

1) Adrenaline, 5ml of 1:1000 (=5mg), should be given nebulised in 100% oxygen. Staff must ensure eye protection (wet swab/paper towel/goggles) for any patients that receive nebulised adrenaline.

2) The severity of angioedema and threat of impending airway compromise should be evaluated as follows (and documented on EPR):

- **Mild**: unilateral involvement, without progression to involve bilateral structures or airway compromise
- **Moderate**: bilateral involvement but without progression to impending or actual airway compromise
- **Severe**: impending or actual airway compromise

3) If there is no response to nebulised adrenaline within 5 minutes of administration or if symptoms worsen, consider adrenaline IM at a dose of 500mcg (0.5ml of 1:1000) and early use of C1 esterase inhibitor (see below). If a patient is being treated in the Emergency Dept. and staff with the skills required to provide advance airway management are immediately available then the decision to call the cardiac arrest team rests with the senior clinician in attendance. However, the on call anaesthetist should be called. If the skills for advanced airway management are not immediately available, then proceed as below in section 4).

4) If the second on-call anaesthetist or ICU SpR is able to attend, they should assess the patient's airway prior to transferring the patient to the Post-Anaesthesia Care Unit (PACU) in level 3 theatres for further management. If they are unable to attend urgently, the patient should be transferred to the PACU without delay where the anaesthetist is likely to be able to assist.

5) If angioedema becomes refractory to first-line treatment, or there is any concern regarding impending airway compromise, iv C1 esterase inhibitor concentrate 1000units should be obtained urgently from blood bank and administered over 10-15mins, with a further 500units iv if necessary. During office hours the blood bank should be contacted directly (ex: 64994). The on-call Haematology technician should be contacted out-of hours (bleep 3077).

6) There is a lack of evidence to inform whether to continue or stop ACE-I or statins in the longer-term in this situation. The decision should therefore be made on an individual patient basis, documented appropriately on EPR and communicated to the GP/ receiving medical team if repatriated.
4. Standards

A. Thrombolysis with iv tPA is usually administered in a level 1 care environment (Emergency Department and/or the Acute Stroke Unit) as there is no specific recommendation otherwise.

B. The thrombolysis box, containing the appropriate first-line drugs for treatment of angioedema, will be taken to the bedside whenever stroke unit staff assess patients for suitability of thrombolysis.

C. All patients eligible for thrombolysis will be assessed for their risk of developing angioedema by the attending senior stroke team doctor. This MUST be discussed with the patient and/or family and documented on EPR.

D. In those patients eligible for tPA identified as at-risk of developing angioedema, the second on-call anaesthetist will be informed of the patient details, location and timing of tPA treatment.

E. Patients developing angioedema will receive appropriate medical treatment and timely anaesthetic review in an appropriate environment.

5. Explanation of terms

Please refer to text.

6. References and Supporting Documents

To be read in conjunction with the following documents:
NICE guidance – diagnosis and initial management of Stroke and TIA

References
(6) Engelter ST, Fluri F, Buitrago-Téllez C, et al. Life-threatening orolingual...


7. Roles and responsibilities

**Stroke clinical staff**: to be aware of (1) the risk and potential consequences of angioedema following tPA and to advise patients and families of the risk; (2) the existence of this policy including urgent drug management and liaison with anaesthetic colleagues.

**Anaesthetic/ critical care/ theatre recovery unit staff**: to be aware of this policy and the potential need to provide resuscitation skills, in particular airway management in patients at risk of, or developing angioedema following tPA.

**Cardiac arrest/resuscitation team**: to be aware of this policy including urgent drug management and liaison with anaesthetic/ ICU and stroke colleagues.

**Stroke ward manager & nursing staff**: to ensure awareness of (1) this policy;
(2) its implications for patient monitoring and safety; (3) indications for alerting senior medical/anaesthetic staff; (4) liaison with pharmacy.

**Blood bank/ Haematology staff**: to be aware (1) of the indication for use of C1 esterase inhibitor as a second-line treatment for refractory angioedema; (2) that a request for C1 esterase inhibitor concentrate may be received from stroke unit staff.
8. Appendix 1

We are very grateful to Sister Sally Marshall for kindly contributing the angioedema observation chart

Indicate extent of any area of swelling to the face/ lips/ tongue by shading the picture. Stop tPA urgently and refer to the angioedema protocol.

<table>
<thead>
<tr>
<th>Time/Date.................</th>
<th>No Swelling noted □ Name:</th>
<th>Time/Date.................</th>
<th>No Swelling noted □ Name:</th>
</tr>
</thead>
<tbody>
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</table>

Patient Name:                                                Hospital No: