Guidelines for the Management of Intracerebral Haemorrhage

AIM: To provide guidance on the management of patients with intracerebral haemorrhage.
SCOPE: All adult ICUs within Brighton and Sussex University Hospitals

EMERGENCY DEPARTMENT

Clinical suspicion of ICH

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Initial ABCDE management and imaging (CTH)

Consider early requirement for mechanical ventilation and sedation

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Systolic BP control 140-160 mmHg

Optimise/reverse coagulation parameters

ICP optimisation

Neurosurgical review and decision for:

- Surgery or conservative
- EVD
- ICP

NEURO ICU

Intracranial pressure monitoring (ICP<20 mm Hg)

CPP 50-70 mmHg

Normocarbia (pCO2 4.5-5 kPA)

SBP 140-170 mmHg

Maintain euvolaemia

Maintain Na 140-150 mmol/L

Optimise coagulopathy

Seizure management/prophylaxis

Normothermia

Further imaging (interval or investigatory for Secondary ICH)

Nutrition

Bowel Management

Mechanical Thromboprophylaxis (in initial stages)

1. INTRODUCTION

Epidemiology

Intracerebral/cerebellar haemorrhage represents approximately 10% of strokes with an incidence of 16 – 33 per 100000 (Rodorf). It often presents like stroke but tends to be more dramatic associated with nausea and vomiting and is more likely to lead to coma. Principal causes are micro-aneurysmal rupture and degeneration of small, deep penetrating arteries, in the context of chronic hypertension. Rarer causes include AVM and Amyloid deposition (Kumar).

Pathophysiology and Risk Factors

Damage is caused initially by direct mechanical damage of the clot itself and cytotoxic peri-lesional oedema. Secondary contributing factors are not well understood but are thought to include disruption of the protective BBB, disrupted cerebral autoregulation leading to local ischaemia, thrombin induced activation of inflammatory cascades leading to local cell damage. Haematoma enlargement is also an issue and is thought to be associated with higher SBP targets, antithrombotic therapy, large haematoma size and extravasation of contrast on CT.

Diagnosis is principally via plain CT which can locate and characterise the lesion and show spread to ventricles and mass effect. Volume in cm^3 can be estimated. In comparison MRI is as effective as CT in detecting acute bleeds but is more effective in detecting chronic bleeds. MRI also has a role to play in detecting underlying causes such as AVM. The role of further investigation for underlying causes is a subtle decision.

If a patient has marked hypertension and haemorrhage affecting a typical part of the brain (Pons, caudate nucleus, putamen/internal capsule, thalamus or cerebellum) then one can declare hypertension or trauma as the probable cause. Otherwise, one may need to investigate for bleeding disorder, tumour or AVM in normotensive patients with lobar haemorrhage.

In cerebellar haemorrhage, signs may indicate the brainstem origin – nystagmus, gaze deviation towards the side of the haemorrhage, uni or bilateral cerebellar signs in an awake patient.

Risk factors: Hypertension, older age, high alcohol intake, Afro-Caribbean descent, low cholesterol, low triglycerides, anti-coagulation with Warfarin, cocaine and methamptamine,

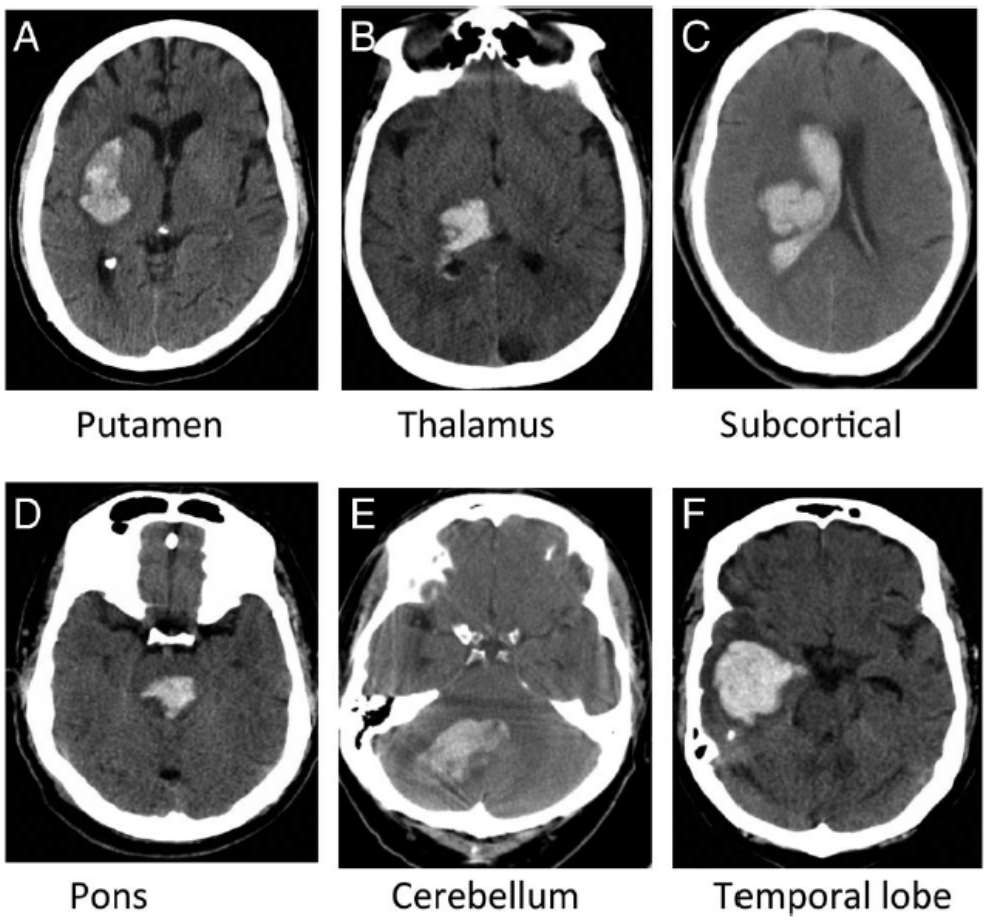

Figure 1 Typical locations of hypertensive ICH are putamen (A), thalamus (B), subcortical white matter (C), pons (D) and cerebellum (E). Thalamic and subcortical haemorrhages often extend into ventricles (B and C). CAA, drug abuse or vascular anomaly often causes lobar haemorrhage (F). ICH, intracerebral haemorrhage; CAA, cerebral amyloid angiopathy.

Table 1: Scoring systems

Clinical scoring (Hemphill):

Component		ICH Score Points
GCS	**3-4**	2
	5-12	1
	13-15	0
ICH volume cm3	**>30**	1
	<30	0
IVH	**Yes**	1
	No	0
Infra-Tentorial origin of ICH	**Yes**	1
	No	0
Age	**>/= 80**	1
	<80	0
	Total ICH score	**0-8**

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT

2. PROCESS

Scoring systems and diagnosis

Recommendation (Action)	Justification (Rationale)
The use of a scoring system predicts mortality (see table 1)	Thirty-day mortality rates for patients with ICH Scores of 1, 2, 3, and 4 were reported as 13%, 26%, 72%, and 97%, respectively. Overall mortality is in excess of 40%.

Recommendation (Action)	Justification (Rationale)
Diagnosis is principally via plain CT	CT can locate and characterise the lesion and show spread to ventricles and mass effect. Volume in cm^3 can be estimated. In comparison MRI is as effective as CT in detecting acute bleeds but is more effective in detecting chronic bleeds. MRI also has a role to play in detecting underlying causes such as AVM. The role of further investigation for underlying causes is a subtle decision. If a patient has marked hypertension and haemorrhage affecting a typical part of the brain (Pons, caudate nucleus, putamen/ internal capsule, thalamus or cerebellum) then one can declare hypertension or trauma as the probable cause. Otherwise, one may need to investigate for bleeding disorder, tumour or AVM in normotensive patients with lobar haemorrhage. In cerebellar haemorrhage, signs may indicate the brainstem origin – nystagmus, gaze deviation towards the side of the haemorrhage, uni or bilateral cerebellar signs in an awake patient.

Medical Management

Recommendation (Action)	Justification (Rationale)
Airway	Early mechanical ventilation with sedation is advised in the following patients: • Worsening cerebral agitation • fluctuating GCS • Deteriorating GCS • Developing focal neurology • Evidence of seizures • Evidence of rising intracranial pressure • GCS less than or equal to 8
Ventilation	Normocarbia (4.5-5) should be maintained

Recommendation (Action)	Justification (Rationale)
Blood pressure control	Aim SBP 140-179 but discuss with neurosurgeryEnsure there are no contraindications for lowering blood pressure and **AVOID HYPOTENSION.** The actual blood pressure targets are controversial and should be discussed with neurosurgery as hypotension may cause ischemia but hypertension may result in extension of the haematoma. INTERACT 2(1) The INTERACT 2 trial looked at immediate blood pressure control to SBP < 140 within 1 hour of presentation and maintained for the first 7 days on admission in patients with ICH who presented with a SBP of 150-220, compared to standard therapy (SBP <180). There was a statistically significant benefit in the reducing SBP to <140 improving functional outcome (modified Rankin Scores). Please note that it excluded patients with structural etiology for ICH, GCS <5, massive haematoma with poor prognosis, or those planned urgent evacuation of haematoma. (1) ATACH2 (2) The ATACH 2 trial showed that patients whose systolic blood pressure was reduced to the standard levels used to treat acute stroke (140 to 179 mm Hg) fared as well as patients who underwent intensive blood pressure reduction (110 to 139 mm Hg) with intravenous nicardipine. Primary outcomes (death and severe disability were observed in 38.7% of participants in the intensive treatment group versus 37.7% in the standard treatment group. Serious adverse events that occurred with 72 hours of blood pressure reduction that were determined to be a result of treatment occurred in 1.6% of patients in the intensive treatment group and in 1.2% of those in the standard treatment group. The intensive treatment group had a significantly higher rate of renal adverse events within 7 days compared with the standard treatment group (9.0% versus 4.0%).

Recommendation (Action)	Justification (Rationale)
Antihypertensive Medication	The American Heart Association have recommended the following antihypertensives in ICH(3) • Labetalol • Esmolol • Nicardipine • Enalapril In our unit the antihypertensive of choice is Labetalol as an IV Infusion. Initially 20mg/hthen increased in 20 minute increments to 40mg/h,80gm/h up to a maximum of 160 mg/min. Labetalol is usually prepared in 5% dextrose or sodium chloride and dextrose diluted to 1mg/min but ? may need to be more concentrated if problems with fluid balance. ? need to check with pharmacy. ***NB If patient intubated and sedated make sure sedation is adequate before initiating antihypertensive therapy***. Patients with premorbid hypertension will need more long term management of blood pressure as they recover from initial injury as poorly controlled blood pressure is associated with recurrence. (Biffi et al).
ICP monitoring	ICP monitoring is recommended in the following patients who are under sedation and unable to be neurologically assessed.(2) • GCS low (<8) at time of intubation • Large volume ICH • Evidence of mass effect on imaging • Intraventricular blood • Hydrocephalus • Tentorial herniation or at risk of it.

Recommendation (Action)	Justification (Rationale)
Target ICP	Aim for ICP< 20mmH20 Ensure ICP is well controlled with the following: • Optimised cerebral venous return and venous return o Ensure 30 degree head elevation o Loosen ETT ties, loosen hard collar if too tight o Avoid hip flexion beyond 90 degrees o Avoid hyperextension of neck • Adequate sedation • Normothermia • Good ventilator synchrony
Manage raised ICP	There may be clinical signs of intracranial pressure (3rd or 6th nerve palsy, bradycardia, hypertension, ICP >20). If ICP > 20mmH_20 sustained for > 5 minutes, call neurosurgeons (CTH/EVD/surgical intervention to be considered) Please refer to the appendix for the protocol for managing raised ICP.
Cerebral Perfusion Pressure	Aim for cerebral perfusion pressure 50-70mmHg.
Tranexamic acid	There is currently no evidence for the use of tranexamic acid in ICH small unrandomised studies have suggested a beneficial effect and this is currently subject large RCT. (4)

Reversal of patients on anticoagulation/antiplatelets: Specific advice

Recommendation (Action)	Justification (Rationale)
Patients on vitamin K antagonists (Warfarin)	• Withholding of anticoagulation and rapid correction of anticoagulation has been recommended in ICH. • Vitamin K 5-10mg (IV) and FFP is given as soon as possible. Vitamin K has an onset in 2 hours, and maximal effect in 24 hours assuming adequate liver function(5). Goldstein et al. showed that every 30 minute delay in FFP administration was associated with a 20% reduction in odds of reversal of INR in patients with ICH in the first 24 hours of admission(6). • The use of prothrombin complex concentrate has been assessed through a Cochrane review. Although INR corrects faster and earlier administration of the product is possible (no thawing or cross-matching needed), there seems to be no difference in mortality or difference in transfusion requirements. However, none of the RCTSs used were powered to detect mortality, benefit, and harm(7). As such, further research is required. • The use of rFVIIa has also shown to reverse INR much faster than FFP, however higher powered studies are needed to show improved outcomes in ICH(8;9).
Patients on unfractionated Heparin	• Protamine is used to reverse heparin. Please contact Pharmacy for the calculated dose (dose is dependent on the amount of heparin that the patient has had.)
Patients on anti platelet therapy	• Medical Management: The PATCH study (RCT of 190 patients with spontaneous supratentorial ICH) concluded that platelet transfusion therapy cannot be recommended in patients with ICH on antiplatelet therapy(10). A meta-analysis of 6 studies of the use of platelets in ICH revealed no difference in survival outcomes (11). • Neurosurgical intervention: The use of platelets in patients who require urgent neurosurgical intervention should be decided by the neurosurgeon and haematologist. Traditionally, neurosurgical intervention requires a platelet count of greater than 100.

Recommendation (Action)	Justification (Rationale)
Patients on other anticoagulants e.g.LMWH, fondoparinaux, rivaroxaban, apixaban, dabigatran,)	**Requires consultation with haematologist (2)** • Commonly used agents include Tranexamic acid, PCC and rFactor VII • All patients on the following drugs should have levels done with a clotting sample sent at the same time. Initial clotting results should be discussed with the haematologist oncall as they will give an indication of how much systemic anticoagulant is remaining as well as the type of anticoagulant (if this is unknown). The name of the drug, the dose and time of the last dose must be provided when sending the sample (if known). a. Dabigatran (renally excreted): TT and APTT are prolonged b. Apixaban: can prolong INR, however no abnormality is seen normally. c. Rivaroxaban: Very sensitive to INR, thus INR will be very high • **Specific anticoagulants** **a. Anti Xa inhibitors**: A factor Xa inhibitor antidote (Andexanet alpha) is currently in phase 3 clinical trial (ANNEXA-4) and will hopefully be available shortly (apixaban, rivaroxaban, edoxaban or enoxaparin). In the meantime, the following may be considered on discussion with the haematologist. Subcutaneous: 1. Low molecular weight heparin (dalteparin, enoxaparin, tinzaparin): Protamine, however reversal may be partial. Please contact Pharmacy for the dose. 2. Fondoparinaux: rFVIIa may be considered Oral 1. Rivaroxaban: PCC may be considered 2. Apixaban: PCC may be considered **b. Anti IIa** i. Dabigatran: Reversal (Praxbind: idarucizumab) is available from blood transfusion or with Octaplex in the A &E department. Haemodialysis may be considered

Other medical measures

Recommendation (Action)	Justification (Rationale)
Anticonvulsants	Prophylaxis: The incidence of seizures has been reported as low as 6.2 % and as high as 40%, depending on the location and extent of ICH. An observational study has suggested that phenytoin prophylaxis is associated worse outcomes. However there has been not been a large study yet to systematically elucidate the correlations between size, location, timing of ICH with seizure prophylaxis. ICHs with subarachnoid extension, and cortical involvement have been associated with higher risk for seizures (12-14). **Prophylaxis** Consider prophylaxis with the following although not recommended (3): • Subarachnoid extension • Cortical involvement in lobar ICH We would recommend one of the following antiepileptics: • Levetiracetam 500mg BD • Phenytoin 15-20mg/kg followed by 300mg OD **Management of seizures**: (continuous EEG monitoring is recommended) • First line: benzodiazepine. If the patient is sedated, ensure pt is fully sedated • Second line: Phenytoin loading or Levetiracetam (dosage as above). Levetiracetam: in resistant seizures, a 250mg bolus followed by an increase by 250mg BD up to 1500mg BD. • Third line: Phenytoin or Levetiracetam (which ever has not been used yet) • Fourth line: Sodium Valproate • Fifth line: Consider thiopental (discussion with ICU consultant first)

Recommendation (Action)	Justification (Rationale)
Temperature Control	• Normothermia is recommended. • Fever is common in ICH and is associated with poor neurological outcome (15;16). An observational study has correlated fever with increased ICH volume and third ventricular shift (15). • Further randomised multicentre trials are awaited to look at the role of mild hypothermia in ICH(17).
Glucose Control	Normoglycaemia is recommended (6-10mml/L)
Further imaging	CTA, CT with contrast or MRI may be useful in investigating the underlying cause of the ICH. (eg. Vascular malformation or tumours)
Thromboprophylaxis	Intermittent pneumatic compression stockings arerecommended from the first day of admission (CLOTS 3)(18) Early thromboprophylaxis with heparin or low molecular weight heparin has been shown to reduce the risk of PE however its effect on haematoma enlargement remains equivocal. (19). As such, early thromboprophylaxis can be advised once neurosurgeons can recommend so and there is no high risk of re-bleed or high risk for neurosurgical intervention.

Surgical Management

Recommendation (Action)	Justification (Rationale)
Craniotomy:Supratentorial ICH	• Evacuation of spontaneous ICH (Craniotomy) The STICH (20) and STICH II(21) trials looked at whether early neurosurgical intervention improved outcomes in patients with spontaneous ICH. • In the STICH trial, there was no significant difference in outcome between early surgical and medical management. • In the STICH II trial, patients with lobar haemorrhage without intraventricular haemorrhage were assessed and a non-significant advantage to outcome was noted in patients in the early intervention arm. In patients with poor prognostication subgroup analysis suggested early surgical intervention was associated with better neurological outcome (p=0.02). Overall, the study was unable to prove that early surgery was associated with significantly improved outcomes. • When all trials of surgical intervention in ICH were analysed together by the STICH authors, significantly improved outcomes were noted however the heterogeneity of ICH makes this result difficult to assess in the context of clinical applicability. Further RCTs are required.

Recommendation (Action)	Justification (Rationale)
Craniotomy:Posterior fossa ICH	***Cerebellar ICH*** The main factors contributing to mortality are compression of the brainstem, compression of the fourth ventricle (causing hydrocephalus), oedema surrounding the haematoma and expansion of the haematoma. ***Brainstem ICH*** Brainstem ICH is associated with very poor prognosis and it is unlikely to improve with surgical intervention(2) • Compression of the brainstem or compression of the fourth ventricle • The American Stroke Association have recommended evacuation of the haematoma if any of the following are present o hydrocephalus from ventricular obstruction o brainstem o It has been suggested that the need for an EVD due to hydrocephalus from an obstructed 4rth ventricle suggests the requirement of surgical decompression (22)
Decompresive craniectomy	Decompressive craniectomy has been used to alleviate resistant raised intracranial pressure in TBI(23), SAH(24) and malignant ischaemic stroke(25). It may have a role in severe ICH however as shown in a systematic review by Takeuchi et al, a good quality RCT is required to show clinical effectiveness (26;27).
Minimally invasive surgery	Minimally invasive surgery has shown some promising results and may be implemented in the future Perihaematomal oedema is a contributor or morbidity. In the MISTIE trial, medical management revealed 52% higher perihaematomal oedema than with minimally invasive surgery. In the surgical arm, a catheter was placed at the ICH site from where the haematoma was evacuated with the use of alteplase.(28) A phase III trial is currently being held.

Recommendation (Action)	Justification (Rationale)
Surgical management of Intraventricular extension of ICH or Intraventricular Haemorrhage (IVH)	Intraventricular extension of an ICH is associated with a much worse mortality than ICH alone(29). • Discuss insertion of EVD with neurosurgeons is recommended. • Alteplase in IVH: The CLEAR III trial has compared the use of alteplase and EVD with saline washout and EVD in patients with IVH and small parenchymal haemorrhage (<30cc). Results are due in 2016 (30). The endoscopic evacuation of IVH is also unknown at present.

3. GLOSSARY

SAH Sub-Arachnoid Haemorrhage

TBI Traumatic Brain Injury

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The use of this guideline is subject to professional judgement and accountability. This guideline has been prepared carefully and in good faith for use within the Department of Critical Care at Brighton and Sussex University Hospitals.The decision to implement this guideline is at the discretion of the on-call critical care consultant in conjunction with appropriate critical care medical/ nursing staff.