

# Treatment of intracerebral haemorrhage

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Apart from management in a specialised stroke or neurological intensive care unit, until very recently no specific therapies improved outcome after intracerebral haemorrhage (ICH). In a recent phase II trial, recombinant activated factor VII (eptacog alfa) reduced haematoma expansion, mortality, and disability when given within 4 h of ICH onset; a phase III trial (the FAST trial) is now in progress. Ventilatory support, blood-pressure reduction, intracranial-pressure monitoring, osmotherapy, fever control, seizure prophylaxis, and nutritional supplementation are the cornerstones of supportive care in intensive care units. Ventricular drainage should be considered in all stuporous or comatose patients with intraventricular haemorrhage and acute hydrocephalus. Given the lack of benefit seen in the recent STICH trial, emergency surgical evacuation within 72 h of onset should be reserved for patients with large (>3 cm) cerebellar haemorrhages, or those with large lobar haemorrhages, substantial mass effect, and rapidly deteriorating condition.

## Introduction

Intracerebral haemorrhage (ICH) is an acute and spontaneous extravasation of blood into the brain parenchyma. ICH accounts for 10–30% of all stroke admissions to hospital, and leads to catastrophic disability, morbidity, and a 6 month mortality of 30–50%.<sup>1</sup> Long-term outcomes are poor; only 20% of patients regain functional independence at 6 months.<sup>1</sup> Although there have been therapeutic advances for aneurysmal subarachnoid haemorrhage and cerebral infarction, treatment for ICH remains limited. Depending on the underlying cause of haemorrhage, ICH is classified as primary or secondary. Primary ICH is when the haemorrhage originates from spontaneous rupture of small arteries or arterioles damaged by chronic hypertension or amyloid angiopathy. Secondary ICH is when haemorrhage results from trauma, rupture of an aneurysm, vascular malformation, coagulopathy, or other causes (panel 1).<sup>2</sup>

ICH is a common disorder, with an estimated frequency of 37 000–52 000 each year in the USA.<sup>3,4</sup> In a recent population-based study, the overall incidence of ICH was 12–15 cases per 100 000 people per year.<sup>5</sup> ICH is most common in men, in elderly people, and in Asian and African Americans.<sup>1</sup>

### Panel 1: Secondary causes of ICH

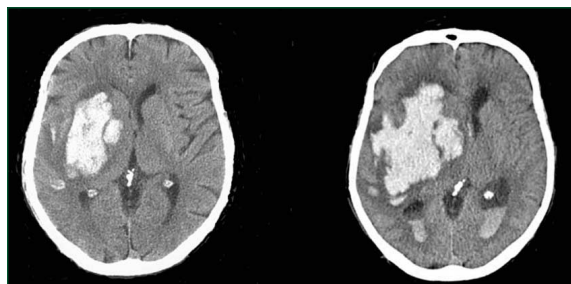
- Trauma
- Arteriovenous malformation
- Intracranial aneurysm
- Coagulopathy
- Haemorrhagic conversion of cerebral infarct
- Dural sinus thrombosis
- Intracranial neoplasm
- Cavernous angioma
- Dural arteriovenous fistula
- Venous angioma
- Cocaine or sympathomimetic drug exposure
- CNS vasculitis

ICH results in staggering medical costs because of acute hospital and chronic care expenses and loss of productivity. The cost of ICH is about US\$125 000 per patient per year, with an overall cost of \$6 billion annually in the USA.<sup>4,6</sup>

## Risk factors

There are several modifiable risk factors for spontaneous ICH. Hypertension is by far the most important and prevalent risk factor, directly accounting for about 60–70% of cases.<sup>7,8</sup> Chronic hypertension causes degeneration, fragmentation, and fibrinoid necrosis of small penetrating arteries in the brain, which can eventually result in spontaneous rupture.<sup>9</sup> Some people have discrete arteriolar microaneurysms (Charcot-Bouchard aneurysms) at the site of vessel rupture. These degenerative changes are most common in the distal portions of medium and small arterioles ranging from 100–600  $\mu\text{m}$  in diameter.<sup>10</sup> Hypertensive ICH typically occurs in the basal ganglia (putamen, thalamus, or caudate nucleus), pons, cerebellum, or deep hemispheric white matter.<sup>2</sup> Non-compliance with antihypertensive treatment increases the risk of ICH<sup>11</sup> and control of blood pressure reduces the risk of ICH.<sup>3,7,12,13</sup>

The second most common cause of primary ICH is cerebral amyloid angiopathy, which accounts for about 15% of cases.<sup>2</sup> This disorder is characterised by the deposition of amyloid- $\beta$  peptide in small to medium-sized blood vessels of the brain and leptomeninges, which results in vascular fragility. The clinical syndrome is typified by spontaneous lobar haemorrhage in elderly patients with a history of cognitive decline. ICH caused by amyloid angiopathy is typically less severe than hypertensive ICH; in some cases, lobar haemorrhages in non-eloquent regions are entirely asymptomatic. Recurrent haemorrhage occurs in 5–15% of patients with lobar ICH and probable amyloid angiopathy each year, and is most common in those with many chronic baseline haemorrhages on gradient echo MRI.<sup>14</sup> However, the risk of recurrent haemorrhage after hypertensive ICH is as low as 2% per year when blood pressure is well controlled.<sup>11</sup>



**Figure 1:** Early haematoma growth in a 48-year-old chronically hypertensive woman

The baseline CT scan (left) shows a moderate-sized right putamen ICH. At this point the patient is in a coma with a left hemiparesis. A follow up CT (right) after she deteriorated to coma with bilateral decerebrate posturing shows massive expansion of the haematoma and new intraventricular haemorrhage and obstructive hydrocephalus; within 24 h she was declared brain dead.

Heavy alcohol consumption<sup>15,16</sup> and hypocholesterolaemia,<sup>17</sup> also increase the risk of primary ICH. There is meagre evidence implicating cigarette smoking<sup>8</sup> or the use of antiplatelet agents as risk factors for ICH.<sup>18,19</sup>

### Clinical manifestations

About half of spontaneous ICH cases originate in the basal ganglia, a third in the cerebral hemispheres, and a sixth in the brainstem or cerebellum. In 40% of cases, ICH is accompanied by intraventricular haemorrhage, which can cause acute hydrocephalus, high intracranial pressure (ICP), and less chance of a good outcome.

Rapid onset of a focal neurological deficit with clinical signs of high ICP—such as an abrupt change in level of consciousness, headache, and vomiting—suggest a diagnosis of ICH.<sup>20</sup> However, these symptoms can also take place after acute ischaemic stroke. For this reason, CT or MRI is essential for confirming diagnosis. Rapid progression to coma with motor posturing suggests massive supratentorial haemorrhage, bleeding into the brainstem or diencephalon, or acute obstructive hydrocephalus due to intraventricular haemorrhage. Over 90% of patients have acute hypertension exceeding 160/100 mm Hg, whether or not there is a history of pre-existing hypertension.<sup>20</sup> Dysautonomia in the form of central fever, hyperventilation, hyperglycaemia, and tachycardia or bradycardia is also common.

### Diagnosis

ICH is confirmed by CT (figure 1). Careful inspection of the pattern and topography of bleeding can sometimes give important clues about a secondary cause of ICH, such as associated subarachnoid blood (suggestive of aneurysm), multiple inferior frontal and temporal haemorrhages (suggestive of trauma), or fluid-fluid levels within the haematoma (indicative of coagulopathy; figure 2). The volume of the haemorrhage can be rapidly estimated at the bedside from the CT with the ABC/2 method, which involves multiplying the diameter of the haematoma in three dimensions and dividing by two.<sup>21</sup>

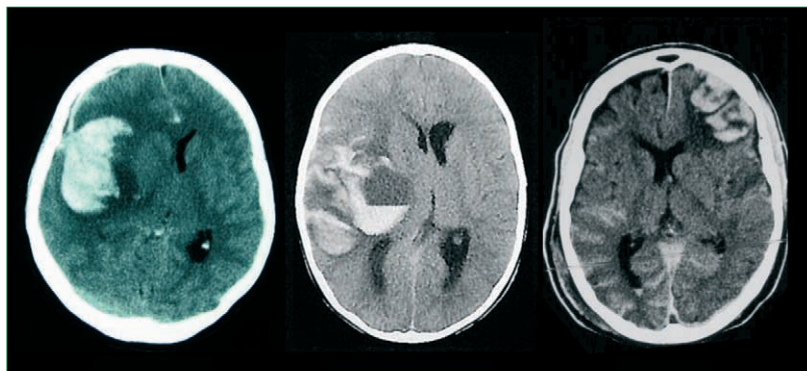
Demonstration of active contrast extravasation into the haematoma with CT angiography might help to predict haematoma expansion<sup>22</sup> and is predictive of poor outcome.<sup>23</sup>

MRI is as sensitive as CT for the detection of ICH in the acute stage,<sup>24</sup> but is most commonly done as a follow-up study to detect of vascular flow voids, which are indicative of an arteriovenous malformation, chronic lobar microbleeds on gradient echo imaging suggestive of amyloid angiopathy, or a contrast-enhancing neoplasm.

Catheter angiography is the diagnostic test for vascular causes of secondary ICH, such as an arteriovenous malformation, dural arteriovenous fistula, cortical-vein thrombosis, or vasculitis. In one study, no vascular malformations were found in people over age 45 years with a history of hypertension and a haemorrhage in a classic hypertensive location (basal ganglia, cerebellum or pons).<sup>25</sup> However, the angiography found vascular malformation in 65% of patients with primary intraventricular haemorrhage and in non-hypertensive patients with lobar haemorrhage. Angiography should always be considered in young non-hypertensive patients with ICH who have no obvious explanation for their haemorrhage, or when the only risk factor is cocaine or sympathomimetic-drug use. When an arteriovenous malformation is diagnosed, there is no particular urgency for surgery or embolisation, because the risk of major rebleeding is as low as 4% per year.<sup>26</sup>

### Pathophysiology

Understanding of the pathophysiology of ICH has changed a lot in recent years. What was thought to be a simple and rapid bleeding event is now understood to be a dynamic and complex process that involves several distinct phases. The two most important new concepts are that many haemorrhages continue to grow and



**Figure 2:** CT clues to common causes of secondary ICH

A thin rim of subdural blood of the right frontal region (left), and sulci adjacent to the medial aspect of the clot, are suggestive of bleeding into the sylvian subarachnoid space, characteristic of a middle-cerebral-artery aneurysm. The presence of fluid-fluid levels, indicative of non-clotting blood, is highly suggestive of coagulopathic haemorrhage (middle). This patient bled during cardiac surgery while receiving anticoagulation therapy for cardiopulmonary bypass. Traumatic contusion of the left frontal lobe (right), which represents contrecoup bleeding in relation to extracranial soft-tissue swelling over the right parietal region. A small amount of subarachnoid haemorrhage is also present within the sulci of the right parietal and bilateral occipital regions.

Component	Points
<b>Glasgow Coma Scale score</b>	
3–4	2
5–12	1
13–15	0
<b>ICH volume (mL)</b>	
≥30	1
<30	0
<b>Intraventricular haemorrhage</b>	
Yes	1
No	0
<b>Age (years)</b>	
≥80	1
<80	0
<b>Infratentorial origin</b>	
Yes	1
No	0
<b>30 day mortality at total points:</b>	
5+	100%
4	97%
3	72%
2	26%
1	13%
0	0%

**Table 1: The ICH Score<sup>29</sup>**

expand over several hours after onset of symptoms—a process known as early haematoma growth—and that most of the brain injury and swelling that happens in the days after ICH is the result of inflammation caused by thrombin and other coagulation end-products.

### Early haematoma growth

Early haematoma growth is common and associated with neurological deterioration and poor clinical outcome.<sup>27</sup> In a landmark prospective study, Brott and colleagues<sup>28</sup> showed that, even in the absence of known coagulopathy, about 38% of patients had an increase in haematoma volume of more than 33% shown by CT within 3 h of onset. More importantly, in two-thirds of those patients, haematoma growth was evident within 1 h of the baseline scan, which indicates an active bleeding process. Several retrospective studies<sup>29</sup> have confirmed this observation and shown that only up to 5% of patients have ICH growth when the baseline scan is done more than 6 h after onset. The most consistently identified risk factor for early ICH growth is the time from symptom onset to baseline CT, with shorter intervals associated with a higher risk of subsequent enlargement on a follow-up scan. The location of ICH seems to have no effect on risk of haematoma growth.

The mechanisms that lead to early haematoma growth during the acute stage of ICH remain unclear. A sudden increase in ICP, local tissue distortion and shear forces, and disruption of the normal cerebral anatomy can lead to a multifocal bleeding process in some patients, with enlargement of the haematoma resulting from the addition of discrete “satellite” haemorrhages to the periphery of the existing clot.<sup>29</sup> Other changes in the

surrounding brain tissue that can contribute to early haematoma growth include vascular engorgement related to a reduction in venous outflow, early transient ischaemia, breakdown of the blood–brain barrier, and possibly the transient creation of a local coagulopathy.<sup>29,30</sup>

### Perihaematoma brain injury

Brain-tissue injury and swelling, which can result in increased ICP or herniation related to compartmentalised mass effect, is the primary cause of neurological deterioration after the first day.<sup>31</sup> Although many people think that swelling and oedema “peak” 3 days after onset, clinical studies indicate that the number of patients of neurological deterioration is highest on the day of the haemorrhage, and falls progressively each day thereafter.<sup>31</sup> Radiographic evidence of the extent of oedema and midline shift on CT increases progressively for up to 2 weeks or more, but this is of little clinical consequence.<sup>32</sup>

The possible creation of an ischaemic penumbra in the brain tissue immediately adjacent to an ICH, resulting in secondary neuronal injury and cytotoxic oedema, was a major concern for many years.<sup>33–35</sup> However, PET and MRI studies done as early as 6 h after symptom onset have not shown tissue ischaemia in perihematoma brain regions.<sup>36,37</sup> By contrast, an overwhelming haematoma-induced inflammatory response has been identified in both animal<sup>35,38–40</sup> and human studies.<sup>41,42</sup> In both animals<sup>39,43</sup> and human beings,<sup>44</sup> an ICH that does not clot because of an anticoagulant, an antifibrinolytic agent, or a thrombin inhibitor causes less brain swelling and tissue injury in the adjacent brain tissue. Plasma that is rich in thrombin and other coagulation end-products released by the clotted haematoma seeps into the surrounding brain tissue and is the primary trigger of the inflammatory process.<sup>45</sup> Activation and expression of cytotoxic and inflammatory mediators,<sup>35,38,46</sup> induction of matrix metalloproteases,<sup>40,41</sup> leucocyte recruitment,<sup>40</sup> and disruption of the blood–brain barrier<sup>47</sup> are all implicated in experimental models. These hypothesis-generating insights might lead to the development of anti-inflammatory therapies targeted against the secondary brain injury that evolves over days after the formation of the primary clot.

### Prognosis

Mortality after ICH approaches 50% at 1 year.<sup>48,49</sup> Half of all deaths happen in the first 2 days after symptom onset;<sup>50</sup> whereas most deaths that take place after the first month are the result of secondary medical complications. Independent predictors for 30 day and 1 year mortality include large ICH volume, coma, older age, intraventricular haemorrhage, and infratentorial location.<sup>48–50</sup> A useful clinical grading scale (the ICH score) that incorporates these five elements allows rapid

estimation of 30 day mortality on admission (table 1).<sup>50</sup> Except in the most severe cases, however, caution is warranted when communicating a very poor prognosis after ICH. Physicians tend to underestimate the chances of a good outcome,<sup>51</sup> and poor outcomes might arise from self-fulfilling prophecies: in one study, the implementation of a do-not-resuscitate order within the first 24 h was the single most important predictor of survival after ICH.<sup>52</sup> Observational cohort studies showed that mortality after ICH is reduced in patients cared for in specialist neurological intensive care units;<sup>53,54</sup> this is presumably the result of adherence to the best medical practices, early transition to rehabilitation, and being cared for by a team or healthcare professionals that takes an active interest in promoting recovery.

## Emergency management

### Airway

Rapid neurological decline and depressed consciousness lead to loss of normal reflexes that maintain an open airway, which mandates immediate endotracheal intubation and mechanical ventilation.<sup>55</sup> Failure to recognise imminent airway loss can result in aspiration, hypoxaemia, or hypercapnia, which in turn can lead to cerebral vasodilatation and high ICP. For rapid sequence intubation, many practitioners prefer sedatives (such as propofol and etomidate) and non-depolarising neuromuscular paralytic drugs (such as atracurium and vecuronium) that do not raise ICP.<sup>56</sup> Initially the respiratory rate and tidal volume should be set to maintain a pCO<sub>2</sub> of about 35 mm Hg. Aggressive early hyperventilation to pCO<sub>2</sub> below 28 mm Hg should be avoided because of the possibility of excessive vasoconstriction and exacerbation of ischaemia.

### Blood pressure

Single-centre studies and a systematic review have reported a high risk of deterioration, death, or dependency with raised blood pressure after ICH.<sup>57–60</sup> High blood pressure should be corrected immediately to minimise the potential for haematoma expansion and to maintain adequate cerebral perfusion pressure, which is calculated as mean arterial pressure minus ICP.

Extreme hypertension within the first 6 h is common and should be aggressively but carefully treated to avoid excessive reduction of the cerebral perfusion pressure, which might precipitate ischaemia in the perihematoma zone. American Stroke Association guidelines recommend that mean arterial pressure be maintained at or below 130 mm Hg for patients with ICH and a history of hypertension.<sup>3</sup> In patients who have had craniotomy, mean arterial pressure should be maintained at or below 100 mm Hg. In all cases, systolic blood pressure (SBP) should be maintained above 90 mm Hg, and in patients with an ICP monitor, cerebral perfusion pressure should be maintained above 70 mm Hg.

In the emergency department, hypertension can be initially treated with repeated intravenous boluses of labetalol every 10 min, with doses rising from 10 mg to 80 mg. In intensive care units, blood pressure is best controlled with continuous infusions of labetalol, esmolol, or nicardipine (table 2).<sup>3</sup> Sodium nitroprusside should be avoided because of its tendency to cause cerebral vasodilation and high ICP.<sup>61</sup>

There is controversy about the initial treatment of blood pressure in patients with ICH. Two studies found that controlled blood pressure reduction by about 20% has no adverse effects on cerebral blood flow in human beings or dogs.<sup>62,63</sup> Given that this approach seems safe, a recent National Institutes of Health consensus panel gave its highest priority to a trial of aggressive blood pressure control (mean arterial pressure 100–120 mm Hg) within the first 3 h of ICH onset.<sup>64</sup>

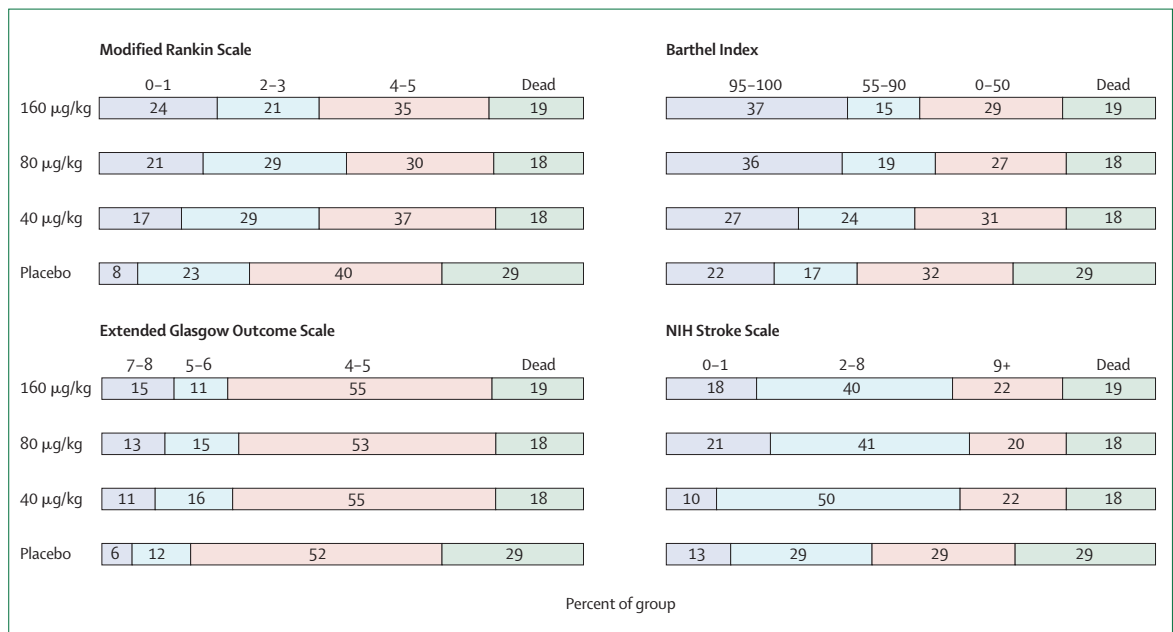
### Emergency ICP therapy

Emergency measures for ICP control are appropriate for stuporous or comatose patients, or those who present acutely with clinical signs of brainstem herniation. The head should be elevated to 30 degrees, 1.0–1.5 g/kg of 20% mannitol should be given by a rapid infusion,<sup>65</sup> and the patient should be hyperventilated to a pCO<sub>2</sub> of 28–32 mm Hg. These measures are designed to lower ICP as quickly and effectively as possible to “buy time” before a definitive neurosurgical procedure (craniotomy, ventriculostomy, or placement of an ICP monitor) can be done.

Drug	Mechanism	Dose	Contraindications
Labetalol	Alpha-1, beta-1, beta-2 receptor antagonist	10–80 mg bolus every 10 min, up to 300 mg; 0.5–2.0 mg/min infusion	Bradycardia, congestive heart failure, bronchospasm
Esmolol	Beta-1 receptor antagonist	0.5 mg/kg bolus; 50–300 µg/kg/min	Bradycardia, congestive heart failure, bronchospasm
Nicardipine	L-type calcium channel blocker (dihydropyridine)	5–15 mg/h infusion	Severe aortic stenosis, myocardial ischaemia
Enalapril	Angiotensin converting enzyme inhibitor	0.625 mg bolus; 1.25–5 mg every 6 h	Variable response, sudden in blood pressure with high-renin states
Fenoldopam	Dopamine-1 receptor agonist	0.1–0.3 µg/kg/min	Tachycardia, headache, nausea, flushing, glaucoma, portal hypertension
Nitroprusside*	Nitrovasodilator (arterial and venous)	0.25–10 µg/kg/min	Increased ICP, variable response, myocardial ischemia, thiocyanate and cyanide toxicity

\*Nitroprusside is not recommended for use in acute ICH because of its tendency to increase ICP

Table 2: Intravenous antihypertensive agents for acute ICH



**Figure 3: Outcome at 3 months according to treatment group in the rFVIIa trial**

Scores of 0-1 on the modified Rankin Scale, 7-8 on the extended Glasgow Outcome Scale, 95-100 on the Barthel Index, and 0-1 on the National Institutes of Health Stroke Scale indicate a favourable recovery. Reproduced with permission from the Massachusetts Medical Society.<sup>67</sup>

### Haemostatic therapy

Eptacog alfa (recombinant activated factor VII [rFVIIa], Novoseven®, Novo Nordisk A/S) is a powerful initiator of haemostasis currently approved for treatment of bleeding in patients with haemophilia who are resistant to factor VIII replacement therapy. However, there is evidence suggesting that rFVIIa might improve haemostasis in patients with normal coagulation systems.<sup>66</sup> In a randomised, double-blind, placebo-controlled study of 399 patients, treatment with rFVIIa at doses of 40 µg/kg, 80 µg/kg, or 160 µg/kg within 4 h of ICH onset limited growth of the haematoma by about 50%. The mean increase was 29% in placebo versus 16%, 14%, and 11% in the 40 µg/kg, 80 µg/kg, and 160 µg/kg rFVIIa groups, respectively, ( $p=0.011$ , rFVIIa vs placebo); this was associated with a 38% reduction in mortality ( $p=0.025$ , rFVIIa vs placebo) and significantly improved functional outcomes at 90 days (figure 3),<sup>67</sup> despite a 5% increase in the frequency of arterial thromboembolic adverse events. A similar pilot trial with aminocaproic acid—an antifibrinolytic agent—has been done but showed no benefit.<sup>68</sup> Although so called ultra-early haemostatic therapy holds great promise as an effective emergency treatment for non-coagulopathic spontaneous ICH, formal approval of rFVIIa for this indication will depend on the result of an ongoing phase III trial (The FAST Trial) comparing placebo with doses of 20 µg/kg and 80 µg/kg.

### Reversal of anticoagulation

Warfarin anticoagulation increases the risk of ICH five to ten times,<sup>69</sup> and about 15% of ICH cases are associated

with warfarin use. Among patients with ICH, warfarin doubles the risk of mortality and increases the risk of progressive bleeding and clinical deterioration.<sup>70</sup> Failure to rapidly normalise the international normalised ratio (INR) to below 1.4 further increases these risks.<sup>71</sup> Patients with ICH receiving warfarin should be reversed immediately with fresh frozen plasma or prothrombin-complex concentrates and vitamin K (table 3). Treatment should never be delayed in order to check coagulation tests. Normalisation of the INR with this approach unfortunately takes several hours in most patients, and clinical results are commonly poor. The associated volume load with fresh frozen plasma might also cause congestive heart failure in patients with cardiac or renal disease.<sup>72</sup> Prothrombin-complex concentrates, a concentrate of the vitamin-K-dependent coagulation factors II, VII, IX, and X, normalises the INR more rapidly than fresh frozen plasma, and can be given in smaller volumes.<sup>71</sup>

Recent reports have described the use of rFVIIa to speed the reversal of warfarin anticoagulation in patients with ICH.<sup>73</sup> A single intravenous dose of rFVIIa can normalise the INR within minutes, with larger doses producing a longer duration of effect.<sup>74</sup> rFVIIa in doses ranging from 10 µg/kg to 90 µg/kg has been used to reverse the effects of warfarin in acute ICH—primarily to expedite neurosurgical intervention—with good clinical results.<sup>73,75</sup> When this approach is used, rFVIIa should be used as an adjunct to coagulation-factor replacement and vitamin K because the effect will last only several hours.<sup>74</sup> Patients with ICH who have had anticoagulation therapy with unfractionated or low-molecular-weight heparin

should be reversed with protamine sulfate,<sup>76</sup> and patients with thrombocytopenia or platelet dysfunction can be treated with a single dose of desmopressin (DDAVP), platelet transfusions, or both.<sup>77</sup> In most patients with a strong indication for anticoagulation, such as a prosthetic heart valve, full anticoagulation can be safely restarted 10–14 days after ICH.<sup>78</sup>

## Critical-care management

### Positioning of patients

To minimise ICP and reduce the risk of ventilator-associated pneumonia in mechanically ventilated patients, the head should be elevated 30 degrees.

### Fluids

Isotonic fluids such as 0.9% saline (about 1 mL/kg/h) should be given as the standard intravenous replacement fluid for patients with ICH. Free-water given in the form of 0.45% saline or 5% dextrose in water can exacerbate cerebral oedema and increase ICP because it flows down its osmotic gradient into injured brain tissue.<sup>79,80</sup> Solutions containing dextrose should generally be avoided unless hypoglycaemia is present, because hyperglycaemia can be detrimental to the injured brain.<sup>81</sup> Systemic hypo-osmolality (<280 mmol/kg should be aggressively treated with mannitol or 3% hypertonic saline. A state of euvolaemia should be maintained by the monitoring of fluid balance, central venous pressure, and body weight.

Some centres increasingly use hypertonic saline in the form of 3% sodium chloride/acetate solutions (1 mL/kg/h) as an alternative to normal saline in patients with significant perihematomal oedema and mass effect. The goal is to establish and maintain a baseline state of hyperosmolality (300–320 mmol/kg) and hypernatraemia (150–155 mEq/L), which can reduce cellular swelling and the number of ICP crises.<sup>82</sup> When discontinuing treatment, care should be taken to taper the infusion slowly to avoid sharp reductions in

osmolality, which might lead to rebound oedema and increases in ICP. Serum sodium concentration should never be allowed to drop more than 12 mEq/L over 24 h. Further studies are needed to clarify the risks and benefits of hypertonic saline for ICH.

### Anticonvulsant therapy

The 30 day risk of clinically evident seizures after ICH is about 8%.<sup>83</sup> Convulsive status epilepticus may be seen in 1–2% of patients, and the risk of epilepsy is 5–20%.<sup>83</sup> Lobar location is an independent predictor of early seizures.<sup>83</sup> Acute seizures should be treated with intravenous lorazepam (0.05–0.10 mg/kg) followed by an intravenous loading dose of phenytoin or fosphenytoin (15–20 mg/kg), valproic acid (15–45 mg/kg), or phenobarbital (15–20 mg/kg). Patients with ICH might benefit from prophylactic antiepileptic therapy, but no randomised trial has addressed the efficacy of this approach. Some centres prophylactically treat patients with large supratentorial haemorrhages and low consciousness during the first week, based on evidence that this practice reduces the frequency of seizures from 14% to 4% during the first 7 days after severe traumatic brain injury.<sup>84</sup> The American Heart Association guidelines recommend antiepileptic treatment in selected patients for up to 1 month, after which therapy should be discontinued if there are no seizures.<sup>3</sup> This recommendation is supported by the results of an observational study that found a low frequency of seizures in patients with lobar ICH given prophylactic AED therapy.<sup>83</sup>

Continuous electroencephalography detects non-convulsive seizures or status epilepticus in 28% of stuporous or comatose patients with ICH, a finding consistent with studies of patients with other types of severe acute brain injury.<sup>85</sup> Moreover, ictal activity detected by electroencephalography after ICH is associated with neurological deterioration and increased midline shift. We monitor all comatose patients with

Scenario	Agent	Dose	Comments	Level of evidence*
Warfarin	FFP	15 mL/kg	Typically 4–6 units (200 mL) each are given	II
	or Prothrombin complex concentrate	15–30 U/kg	Works faster than FFP, but carries risk of DIC	II
	and IV vitamin K	10 mg	Can take up to 24 h to normalise INR	II
Warfarin and emergency neurosurgical intervention	Above plus rFVIIa	20–80 µg/kg	Contraindicated in acute thromboembolic disease	III
Unfractionated or low-molecular-weight heparin*	Protamine sulfate	1 mg per 100 units of heparin, or 1 mg of enoxaparin	Can cause flushing, bradycardia, or hypotension. Single dose required	III
Platelet dysfunction or thrombocytopenia	Platelet transfusion	6 units	Range 4–8 units based on size; transfuse to >100 000	III
	and/or Desmopressin (DDAVP)	0.3 µg/kg	Single dose required	III

In general anticoagulants should be discontinued immediately, and can be safely restarted approximately 2 weeks after presentation (see text for further discussion). \*Class I=based on one or more high quality randomised controlled trials, class II = based on two or more high quality prospective or retrospective cohort studies, class III = case reports and series, expert opinion; protamine has minimal efficacy against danaparoid or fondaparinux. FFP=fresh frozen plasma; DIC=disseminated intravascular coagulation; INR=international normalised ratio.

**Table 3: Emergency management of the coagulopathic ICH patient**

ICH with electroencephalography for at least 48 h and treat nonconvulsive seizures with midazolam starting at 0.2 mg/kg/h.<sup>86</sup> However, the management of nonconvulsive status epilepticus is controversial.

#### Fever control

Fever after ICH is common, particularly after intraventricular haemorrhage,<sup>87</sup> and should be treated aggressively. Sustained fever after ICH is independently associated with poor outcome, and even small rises in temperature exacerbate neuronal injury and death in experimental models.<sup>88</sup> Paracetamol and cooling should be given to all patients with sustained fever in excess of 38.3°C (101.0°F); however, evidence for the efficacy of these interventions in patients with neurological disorders is meagre.<sup>89,90</sup> Adhesive surface-cooling systems and endovascular heat-exchange catheters better maintain normothermia, although whether these measures improve clinical outcome is unclear.<sup>91</sup>

#### Nutrition

As is the case with all critically ill patients with neurological disorders, enteral feeding should be started within 48 h to reduce the risk of malnutrition. A small-bore nasoduodenal feeding tube can lower the risk of aspiration events. A recent trial in dysphagic patients with stroke found a 6% mortality reduction ( $p=0.09$ ) when enteral tube feeding was started as soon as possible compared with avoidance of tube feeding in the first week.<sup>92</sup> No benefits were seen with early versus delayed placement of percutaneous endoscopic gastrostomy tube.<sup>92</sup>

#### Deep venous thrombosis prophylaxis

ICH patients are at high risk for deep vein thrombosis and pulmonary embolism, a potentially fatal complication, because of limb paresis and prolonged immobilised state. Dynamic compression stockings should be placed on admission. In a small prospective trial, low dose subcutaneous heparin (5000 U twice daily) started on day 2 notably reduced the number of these complications, with no increase in intracranial bleeding.<sup>93</sup> Treatment with low molecular weight heparin (ie, enoxaparin 40 mg daily) within the same timeframe is a reasonable alternative.

#### Management of ICP

Large volume ICH is commonly associated with high ICP and brain tissue shifts related to ICP gradients and compartmentalised mass effect. This problem can be exacerbated by intraventricular haemorrhage, which leads to acute obstructive hydrocephalus. As is the case with traumatic brain injury, an ICP monitor or external ventricular drain should generally be placed in all patients with ICH in comas (Glasgow Coma Scale score of 8 or less) with the goal of maintaining ICP below 20 mm Hg and a minimum cerebral perfusion pressure

greater of 60 mm Hg, unless their condition is so poor that aggressive intensive care is not warranted.<sup>94,95</sup> Placement of an external ventricular drain can be lifesaving in patients with intraventricular haemorrhage with acute brainstem herniation.<sup>96</sup> Compared with parenchymal monitors, external ventricular drains have the therapeutic advantage of allowing CSF drainage, but the disadvantage of a substantial risk of infection (about 10% during the first 10 days).

A small retrospective study showed no relation between changes in ventricular size and level of consciousness in patients with ICH and external ventricular drains.<sup>97</sup> Intraventricular administration of the thrombolytic agents urokinase (dose range 5000–25 000 IU) and alteplase (1–3 mg every 6–12 h) after external-ventricular-drain placement might speed clot resolution, minimise the risk of catheter occlusion and chronic hydrocephalus, and potentially improve outcome.<sup>98</sup> However, these benefits may be counterbalanced by a high risk of intracranial bleeding. Phase II trials of this approach are currently in progress.

When ICP is monitored, use of a standard management algorithm (panel 2) results in better control, fewer interventions, and shorter duration of therapy.<sup>99</sup> In general, cerebral perfusion pressure should never be allowed to fall below 60 mm Hg, and interventions to reduce ICP should be increased or initiated whenever it remains above 20 mm Hg for more than 10 min.

An acute and sustained increase in ICP should prompt a repeat CT to assess the need for a definitive neurosurgical procedure. If the patient is agitated or “fighting” the ventilator, an intravenous sedative such as propofol (0.6–6.0 mg/kg/h) or fentanyl (0.5–3.0 µg/kg/h) should be given to attain a quiet, motionless state. Thereafter, if the cerebral perfusion

#### Panel 2: Stepwise treatment protocol for high ICP in monitored patients

- 1 Surgical decompression: consider repeat CT scanning, and definitive surgical intervention or ventricular drainage
- 2 Sedation: intravenous sedation to attain a motionless, quiet state
- 3 CPP optimisation: pressor infusion if CPP is <70 mm Hg, or reduction of blood pressure if CPP is >110 mm Hg
- 4 Osmotherapy: mannitol (0.25–1.5 g/kg IV or 0.5–2.0 mL/kg) and 23–4% hypertonic saline (repeat every 1–6 h as needed)
- 5 Hyperventilation: target pCO<sub>2</sub> 26–30 mm Hg
- 6 High dose pentobarbital therapy: load with 5–20 mg/kg, infuse 1–4 mg/kg/h
- 7 Hypothermia: cool core body temperature to 32–33°C

CPP= cerebral perfusion pressure  
Reproduced with permission from Sage Publications.<sup>94</sup>

pressure is low (<70 mm Hg), vasopressors such as dopamine (5–30 µg/kg/min) or phenylephrine (2–10 µg/kg/min) can lead to ICP reduction by decreasing the cerebral vasodilation that sometimes occurs in response to inadequate perfusion.<sup>95</sup> Alternately, if cerebral perfusion pressure is high (generally more than 120 mm Hg) and has overwhelmed the brain's capacity to autoregulate, blood pressure reduction with intravenous labetalol, nicardipine, or a similar agent (table 2) can sometimes lead to a parallel reduction in ICP.

Mannitol and hyperventilation should be used if sedation and cerebral perfusion pressure optimisation do not normalise ICP. The initial dose of mannitol is 1.0–1.5 g/kg of a 20% solution, followed by bolus doses of 0.25 to 1.0 g/kg as needed. Additional doses can be given as frequently as once an hour, based on the initial response to therapy. Hypertonic saline, such as 23.4% saline solution, can be used as an alternative to mannitol, particularly when cerebral perfusion pressure augmentation is desirable.<sup>100</sup> However, care should be taken to avoid fluid overload in patients with heart or kidney failure. Hyperventilation is generally used sparingly and for brief periods in monitored patients, because its effect on ICP tends to last for only a few hours. Good long-term outcomes are possible when the combination of osmotherapy and hyperventilation reverses transtentorial herniation.<sup>101</sup> Haemorrhages that are large enough to lead to intracranial hypertension refractory to these measures are fatal in most patients. Corticosteroids such as dexamethasone are not suggested in the management of ICH, based on the results of randomised trials that have failed to demonstrate their efficacy in ICH.<sup>102,103</sup> Steroids have the potential to cause hyperglycaemia, immunosuppression, impaired wound healing, and protein catabolism.

### Surgical management

The STICH trial, a landmark trial of 1033 ICH patients, showed that emergent surgical haematoma evacuation within 72 h of onset does not improve outcome in comparison to a policy of initial medical management.<sup>104</sup> These results are consistent with those of a meta-analysis of all prior trials of surgical intervention for supratentorial ICH, which showed no benefits.<sup>105</sup> Although the STICH trial has rightfully dampened the enthusiasm of neurosurgeons for surgery, it must be remembered that the trial was based on the principle of clinical equipoise; patients who the local investigator felt would most likely benefit from emergency surgery were not enrolled in the study. Thus, the STICH trial may not be applicable to certain subsets of patients who traditionally are thought to be good candidates for surgery, particularly young individuals with large lobar haemorrhages rapidly deterioration due to mass effect. A small retrospective study showed the best results with emergency craniotomy in exactly this subset of patients.<sup>106</sup> Because the mean interval from onset to

### Search strategy and selection criteria

References for this review were identified by searches of Ovid, MEDLINE, and PubMed from 1966 until April 2005 for the term "intracerebral hemorrhage". Articles were also identified through searches of the authors' own files, and from reference lists of articles identified in the literature search. Only papers published in English were reviewed.

surgery in the STICH trial was greater than 24 h, it is also possible that earlier surgery might improve outcome.

One small trial of minimally-invasive endoscopic surgery showed better outcomes with this intervention than with medical management.<sup>107</sup> Other minimally invasive surgical approaches are also feasible.<sup>108–110</sup> Clinical trials will be needed to determine whether these interventions can improve outcome.

In contrast to supratentorial ICH, most neurosurgeons feel that cerebellar haemorrhages larger than 3 cm in diameter benefit from emergency surgical evacuation. Sudden deterioration to coma can occur within the first 24 h of onset in these patients;<sup>111</sup> for this reason, it is generally unwise to defer surgery in these patients until further clinical deterioration occurs.

### Future directions

For decades, the prevailing attitude toward the treatment of ICH has been one of therapeutic nihilism. There is a need for more evidence to place aggressive intensive-care-unit treatment for ICH on firmer scientific footing. The results of the phase II trial of rFVIIa for ICH are encouraging; an effective emergency treatment for ICH may soon be available. If this is the case, future efforts could be directed at testing the efficacy of combining very early surgery with acute haemostatic therapy, which might minimise the risk of postoperative bleeding that occurs when surgical intervention is done within 4 h of onset.<sup>112</sup> There is a pressing need to study the effectiveness of very early, aggressive blood pressure reduction in acute ICH. Other promising approaches that deserve further study include thrombolytic therapy for intraventricular haemorrhage, and the development of new anti-inflammatory drugs that target coagulation-induced perihematoma brain injury. These advances will hopefully lead to new optimism for what has historically been one of the most devastating illnesses in clinical medicine.

### Authors' contributions

FR did the primary reference search and wrote the article; SAM provided key conceptual themes, did a secondary reference search, and co-wrote the review.

### Conflicts of interest

SAM has received research support, consulting fees, and speaking honoraria from Novo Nordisk A/C, and has received speaking honoraria from ESP Pharma, is also on the scientific advisory board and has stock options in Radian Medical; has received research support, consulting fees and stock options from MediVance, Inc. FR has no conflicts of interest.

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