# Update on the Treatment of Spontaneous Intraparenchymal Hemorrhage: Medical and Interventional Management

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## Abstract

*Purpose of review* Spontaneous intraparenchymal hemorrhage (IPH) is a prominent challenge faced globally by neurosurgeons, neurologists, and intensivists. Over the past few decades, basic and clinical research efforts have been undertaken with the goal of delineating biologically and evidence-based practices aimed at decreasing mortality and optimizing the likelihood of meaningful functional outcome for patients afflicted with this devastating condition. Here, the authors review the medical and surgical approaches available for the treatment of spontaneous intraparenchymal hemorrhage, identifying areas of recent progress and ongoing research to delineate the scope and scale of IPH as it is currently understood and treated.
*Recent findings* The approaches to IPH have broadly focused on arresting expansion of hemorrhage using a number of approaches. Recent trials have addressed the effectiveness of rapid blood pressure lowering in hypertensive patients with IPH, with rapid lowering demonstrated to be safe and at least partially effective in preventing hematoma expansion. Hemostatic therapy with platelet transfusion in patients on anti-platelet

medications has been recently demonstrated to have no benefit and may be harmful. Hemostasis with administration of clotting complexes has not been shown to be effective in reducing hematoma expansion or improving outcomes although correcting these abnormalities as soon as possible remains good practice until further data are available. Stereotactically guided drainage of IPH with intraventricular hemorrhage (IVH) has been shown to be safe and to improve outcomes. Research on new stereotactic surgical methods has begun to show promise.

*Summary* Patients with IPH should have rapid and accurate diagnosis with neuroimaging with computed tomography (CT) and computed tomography angiography (CTA). Early interventions should include control of hypertension to a systolic BP in the range of 140 mmHg for small hemorrhages without intracranial hypertension with beta blockers or calcium channel blockers, correction of any coagulopathy if present, and assessment of the need for surgical intervention. IPH and FUNC (Functional Outcome in Patients with Primary Intracerebral Hemorrhage) scores should be assessed. Patients should be dispositioned to a dedicated neurologic ICU if available. Patients should be monitored for seizures and intracranial pressure issues. Select patients, particularly those with intraventricular extension, may benefit from evacuation of hematoma with a ventriculostomy or stereotactically guided catheter. Once stabilized, patients should be reassessed with CT imaging and receive ongoing management of blood pressure, cerebral edema, ICP issues, and seizures as they arise. The goal of care for most patients is to regain capacity to receive multidisciplinary rehabilitation to optimize functional outcome.

## Introduction

The care and management of intraparenchymal hemorrhage (IPH) is a frequent and daunting challenge for providers. It can occur virtually anywhere in the brain and ranges in severity from a short hospital course in some to severe disability and death in many others. Surgical options remain presently limited, and while medical care has certainly improved over recent decades, morbidity and mortality in this disease remain particularly high. A great deal of research has been undertaken recently demonstrating the safety of many approaches, but sadly, very little research has demonstrated definitive improvement in outcomes and mortality.

# Epidemiology of intracranial hemorrhage

Ischemic and hemorrhagic strokes are among the leading causes of death and disability worldwide [1•, 2]. Even though mortality from strokes has decreased in recent decades, the incidence of stroke and stroke-related deaths is increasing, with a disproportionate burden borne by developing and low-income nations [3]. Ischemic stroke remains the most prevalent (80–90%) form of stroke while primary intracranial hemorrhage and subarachnoid hemorrhage (SAH) account for the remaining 10–20% [4]. There were an estimated 5.3 million intracranial hemorrhage (ICH) cases worldwide in 2010 with approximately 3 million deaths of which 84% were borne by low- and middle-income countries [1•]. In the USA, case mortality has fallen over the past four decades from 47 to 29% [5]. Patients who make it to the hospital still face 30-day fatality risk up to 45% in some studies [6]. Those who survive have markedly limited function in activities of daily living, with

only 10–20% regaining functional independence [7, 8, 9••]. Over the recent decades (1980–2006), the overall incidence of IPH has been roughly stable at 24.6 per 100,000 person years [10•].

# Risk factors for intraparenchymal hemorrhage

Spontaneous IPH is the product of a complex interplay of risk factors, the most important of which is hypertension [11, 12]. A meta-analysis of 14 case-control studies demonstrated an increased relative risk for IPH in hypertensive subjects of 3.68 (95% CI, 2.52 to 5.38) over normotensive people [11]. Patients with baseline blood pressure over 160/90 were shown in another meta-analysis to have a 9-fold increased risk of IPH [12]. Even among those with normal blood pressure, increasing blood pressure is related linearly to increasing risk of lobar and non-lobar hemorrhagic stroke [13]. Hypertension has a substantial impact on the likelihood of vessel rupture in the brain. Other identified risk factors are smoking which carries a 1.5-fold relative risk [14, 15], high alcohol intake, low cholesterol levels [16, 17], diabetes with a relative risk of 1.6 [18], and cerebral amyloid angiopathy [19] which alone accounts for roughly 50% of all lobar hemorrhages. Patients taking aspirin [20], warfarin [21], and direct oral anticoagulants (DOACs) (dabigatran etexilate, rivaroxaban, and apixaban) have an increased risk of IPH although this risk is often far exceeded by the benefit provided by the prevention of ischemic strokes [22]. The externally validated and guideline-incorporated HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly) identifies patients in whom the risk of using of oral anticoagulants may equal or outweigh the benefit [23, 24]. Although no prospective studies have evaluated the impact of specific modifiable risk factor management (for example antihypertensive management and smoking cessation on the risk of IPH), such lifestyle modifications are likely to reduce the risk of IPH significantly.

# Pathophysiology

IPH occurs after a parenchymal blood vessel in the brain ruptures. Common etiologies include amyloid angiopathy, tumors, ischemic stroke with subsequent hemorrhagic conversion, thrombosis of dural venous sinuses and cortical veins, vasculitis and vascular malformations such as cavernous angiomas, arteriovenous fistulas, arteriovenous malformations, venous angiomas, and aneurysms. Most "primary" cases of spontaneous IPH are thought to be caused by the rupture of Charcot Bouchard aneurysms in the cerebellum, basal ganglia, pons, and thalamus where small penetrating vessels are abundant. Charcot Bouchard aneurysms are presumed to be the result of chronic hypertension-related lipohyalinosis of small arterioles which causes defects in the muscular layer making them prone to rupture [25]. The "primary" etiology is a diagnosis of exclusion, based on a thorough investigation for "secondary" structural causes of IPH. Advanced age, deep location (basal ganglia, thalami, or posterior fossa), or history of hypertension are often taken to suggest primary IPH

although cerebral angiography studies show that these are not always reliable indicators, and patients with these features may have co-existing vascular abnormalities [26, 27].

# Initial management

Medical management is focused on minimizing intracranial pressure, treating hypertension, and primary prevention of clot expansion. With the exception of early blood pressure control, there have been no successful phase 3 trials at the time of this writing that show overall benefit from medical interventions in terms of improved neurological outcome or mortality reduction [28]. Surgical management is focused on clot extraction, removal of toxic blood products, and preventing the sequelae of intracranial hypertension. While there has been some promising early research in this regard, and a recent surge of clinical trials testing clot removal strategies, there is currently a similar lack of successful phase 3 trials showing efficacy.

Initial management should focus on stabilization of airway, breathing, and circulation, including blood pressure, and any coagulopathy should have attempted reversal [9••]. Next, the clinical severity should be scored and documented using the NIH Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) [29–31]. Hourly or more frequent neurologic exams should be scheduled thereafter. The American Heart Association considers neuroimaging with CT (the gold standard) or MRI mandatory, with the use of contrast-enhanced CT angiography (CTA) when available to assess for vascular pathology and likelihood of further clot expansion [26]. Vascular abnormalities are more likely in women, those under the age of 65, those with lobar ICH, intraventricular hemorrhage (IVH), and patients without history of hypertension, smoking, or coagulopathy [32]. Catheter angiography can confirm definitively if there is an underlying vascular lesion [33]. If cerebral venous sinus thrombosis is suspected based on hematoma location, unusual appearance of cerebral sinuses, or increased relative edema volume, then CT venography or MRV should be performed [34]. Volume status should be assessed along with routine monitoring of electrolytes. To avoid exacerbating any brain edema, it is recommended that hyponatremia be avoided. Hyponatremia has been shown to occur in roughly 15% of ICH patients and to worsen outcomes in two retrospective case series, with the syndrome of inappropriate antidiuretic hormone being the most common etiology [35, 36]. Normovolemia should be maintained with isotonic fluids to avoid exacerbating brain edema [37].

# Grading scales

ICH grading scales are routinely used to assess baseline severity, to facilitate communication between providers, and to frame expectations of family members. They should not be used in isolation, however, as reliance on grading scales risks producing a self-fulfilling prophecy in which patients expected to do poorly will have poor outcomes due to limitations of acute interventions [38, 39]. The ICH score [40••] has seen broad clinical adoption as a number of studies have validated its use. The ICH score includes five independent risk factors for 30 day mortality which are assigned weights to derive a score from 0

to 6 (Table 1). The timing of the GCS is important, with studies showing that the GCS assessed once the patient has clinically stabilized has the most utility as compared to an initial assessment [42]. Another useful prognostication tool, the FUNC score, was developed to estimate the likelihood of functional independence at 90 days (Table 1) [41•].

# Assessing hemorrhage with imaging

After initial hemorrhage, the hematoma can expand further, with many studies looking at the timing of this expansion but relying on different

**Table 1.  The components of the ICH and FUNC scores presented along with their respective point weights and the mortality and independence implications for each total score, respectively [40••, 41•]**

| ICH score | | FUNC score | |
|---|---|---|---|
| Component | Points | Component | Points |
| Glasgow Coma Scale | | ICH Volume | |
| 3–4 | 2 | < 30 cm$^3$ | 4 |
| 5–12 | 1 | 30–60 cm$^3$ | 2 |
| 13–15 | 0 | > 60 cm$^3$ | 0 |
| Age | | Age | |
| ≥ 80 years | 1 | < 70 years | 2 |
| < 80 years | 0 | 70–79 years | 1 |
| ICH volume | | ≥ 80 years | 0 |
| ≥ 30 cm$^3$ | 1 | ICH location | |
| < 30 cm$^3$ | 0 | Lobar | 2 |
| Presence of intraventricular hemorrhage | | Deep | 1 |
| Yes | 1 | Infratentorial | 0 |
| No | 0 | Glasgow Coma Scale | |
| Infra-tentorial origin of ICH | | ≥ 9 | 2 |
| Yes | 1 | ≤ 8 | 0 |
| No | 0 | Pre-ICH cognitive impairment | |
| | | No | 1 |
| | | Yes | 0 |
| Total ICH score | 30-day mortality (%) | Total FUNC score | Independent at 90 days (%) |
| 0 | 1–10 | 0–4 | 0 |
| 1 | 7–13 | 5–7 | 29 |
| 2 | 30–44 | 8 | 48 |
| 3–4 | 56–78 | 9–10 | 75 |
| 4 | 70–100 | 11 | 95 |
| 5–6 | 100 | | |

time windows between onset and assessment using varying techniques for quantifying hematoma volume [43•]. Hematoma expansion occurs in up to one third of patients and generally occurs within 24 h although delayed expansion is described [44]. Expansion, regardless of definition, is significantly associated with clinical deterioration and worse outcomes, especially when resulting in midline shift or cerebral herniation [8, 45]. The "spot sign" is a hyper dense spot initially defined on CTA source images which is predictive of hematoma growth (Fig. 1) [46]. If a subsequent non-contrast head CT demonstrates extravasation of contrast into the hematoma, this, along with the spot sign, is significantly associated with IPH growth and poor outcome [46]. Although it is possible to assess for both an "early" (30-s post-contrast injection) and "late" (2–5-min post-contrast injection) spot sign on CTA or post-contrast CT, the current utility of this information is not well defined in the absence of therapies specifically targeted to prevent IPH expansion. In the PREDICT study, patients with the spot sign had significantly higher mortality at 3 months (43.4%) as compared to patients who were spot-sign-negative (19.6%) [43•].

The volume of IPH is an important factor in outcomes, with volumes over 30 mL tending to have increased mortality and morbidity [8]. One recent meta-analysis suggested that for each 1-mL increase in hemorrhage volume at hospital admission, the odds of early neurological deterioration increases by 37% [47]. The volume of IPH can be accurately assessed using a range of automated computational techniques if the required software is available, but a quick estimate can be garnered by applying the ABC/2 method to the initial non-contrast CT image. All measurements should be obtained on axial slices, with A being the largest diameter of hematoma seen in any slice and B the diameter taken perpendicular to that on the same slice. C is the slice thickness multiplied by the number of slices. These three values multiplied together and then divided by two give an estimate of the volume of the hematoma assuming a spherical shape.
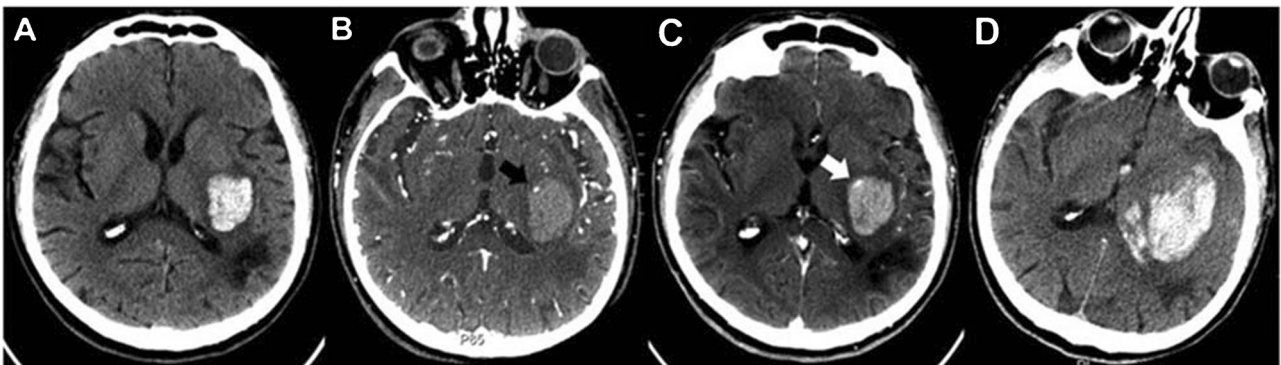


**Fig. 1.** A patient with a spot sign visible in a putaminal IPH. **a** Left posterior putaminal IPH with mild surrounding edema. In **b**, an arrow indicated the small focus of contrast enhancement seen on CTA consistent with the spot sign. **c** The post-contrast CT wherein the white arrow shows the spot sign has enlarged. **d** An unenhanced CT taken 1 day later showing the development of IVH and expansion of the IPH (Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, Symons SP. CT Angiography "Spot Sign" Predicts Hematoma Expansion in Acute Intracerebral Hemorrhage. Stroke. 2007;38:1257-1262).

While not as accurate as image analysis software available commercially, it is an effective method for quickly assessing hematoma volume [48].

# Blood pressure management

A number of trials have tried to arrest the further expansion of IPH by managing hypertension or by supplementing clotting factors. INTERACT1 was a feasibility study that demonstrated the safety and feasibility of INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage. This led to INTERACT2, an international, multicenter, prospective, randomized, open label, blinded end-point trial of patients with hypertension and IPH occurring in the prior 6 h which randomly assigned 2839 patients to receive either intensive treatment of systolic BP to less than 140 mmHg or guideline recommended targeting of systolic BP to less than 180 mmHg [49••]. The primary outcome was death or major disability as assessed by mRS at 90 days. A total of 52.0% (719) of the participants in the intensive treatment group achieved the primary outcome as compared to 55.6% (785) of patients receiving guideline-recommended treatment. Mortality was comparable between the two groups (11.9% in intensive treatment group and 12.0% in the guideline-recommended treatment group). This intensive treatment of blood pressure failed to result in significant reduction in hematoma volume or improvement in outcomes on the primary outcome although concurrent ordinal analysis showed significantly lower modified Rankin Scale (mRS) scores with intensive treatment (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; $P = 0.04$) [49••]. The slight reduction in death and disability and hematoma size in this trial may be attributed the smaller initial average hematoma volumes (11 mL) of patients included in the study along with the average of 4-h delay from onset of symptoms to treatment and 6 further hours on average to achieve the blood pressure goal (with only 34% of patients getting intensive treatment achieving the goal in under 60 min). Taken together, these time windows imply that the average participant in INTERACT 2 had 10 h from hemorrhage onset until they achieved blood pressure parameters, a period during which most ICHs will have expanded already if that was going to happen.

Another large intensive blood pressure lowering trial was ATACH 2 [50••]. This randomized, multicenter, open-label trial looked at patients with IPH volume < 60 mL and GCS score of 5 or more, randomizing them to either an intensive SBP target of 110 to 139 mmHg or a standard target of 140 to 179 mmHg using intravenous nicardipine. The primary outcome was death or disability at 3 months which was equivalent between the two groups: 38.7% of the intensive treatment group (186 of 481) and 37.7% (181 of 480) of the standard-treatment group. Aggressive treatment of blood pressure in ATACH 2 did not improve outcomes.

ATACH 2 and INTERACT 2 were similar trials in that they looked at blood pressure lowering, but there are a number of important differences in the protocols and goals of the studies that should be considered. While INTERACT 2 had a 6-h recruitment window, ATACH 2 was considerably narrower at 4.5 h. ATACH-2's intervention lasted for 24 h while in INTERACT 2, blood pressure was targeted 6 days longer. Further, the baseline blood pressures differed at the outset, with average systolic blood pressure of 179 mmHg in ATACH 2 and

201 mmHg in INTERACT 2. The average systolic blood pressure of the intensive treatment group in INTERACT 2 after 1 h was 150 mmHg, not far from the 141.1 mmHg that was the average systolic blood pressure of the standard treatment group in ATACH 2 within 2 h. The intensive treatment group in ATACH 2 had an average systolic pressure of 128.9 ± 16 mmHg after 2 h, which was roughly 12 mmHg lower than the 141.1 ± 16 seen in the standard treatment group and perhaps importantly 21 mmHg lower than the intensive treatment group from INTERACT 2 and almost 36 mmHg lower than the standard group from INTERACT 2. ATACH 2 had significantly higher (9%) rate of adverse renal events in the intensive treatment group than in the standard group (4%). The hematomas in both studies on average were relatively small (10 mL) resulting in a lower propensity for expansion. This makes generalizing these results to patients with larger hematomas causing mass effect, intracranial pressure elevation, and consequent decrease in cerebral perfusion pressure problematic. While a goal SBP of 140 mmHg seems to be a safe target, it does not represent an evidence-based target proven to improve outcomes or reduce mortality and SBP < 140 mmHg may cause adverse effects in some patients.

# When to use and not use hemostatic therapy

The FAST trial focused on reducing clot burden by increasing the propensity of blood to coagulate at the site of hemorrhage [51•]. Recombinant activated factor VII (rFVIIa) acts upon factor X in the extrinsic pathway of the clotting cascade facilitating the conversion of prothrombin to thrombin. Prior studies had shown that administering rFVIIa within 4 h of IPH onset reduced mortality and was associated with better functional outcomes after 3 months [52•]. FAST randomly assigned 841 IPH patients to receive 20 μg/kg of rFVIIa, 80 μg/kg, or placebo within 4 h after onset. The primary outcome was severe disability on mRS or death at 90 days. The highest dose group had statistically significant but clinically minor reduction in IPH growth (a difference of only 2.6 mL in the group receiving 20 μg/kg and 3.8 mL in the group receiving 80 μg/kg) as compared with the placebo group. All three groups had equivalent percentages of patients with poor outcomes (24% placebo group, 26% 20 μg/kg of rFVIIa, and 29% 80 μg/kg). The administration of rFVIIa failed to improve functional outcomes or reduce mortality.

Patients with abnormalities of platelets, coagulation factors, or who are taking anticoagulants have an increased likelihood of IPH expansion due to their decreased propensity to form stable clot. Ultra-early hemostatic therapy with replacement of the deficient factors or transfusion with functional platelets is indicated. Patients on oral anticoagulants account for up to 20% of patients with IPH [53]. Patients on vitamin K antagonists should have their drug withheld and should receive vitamin K, but as this takes up to 24 h to work, they benefit from prothrombin complex concentrate (PCC) since this corrects the INR more quickly (5.7 vs 11.8 h, respectively) and has a better safety profile than fresh frozen plasma (FFP) [54, 55]. If PCC is unavailable, FFP can be administered. Direct oral anticoagulants including direct thrombin inhibitors (DTIs) and factor Xa inhibitors (FXa-Is) are increasingly used due to their apparent advantages over warfarin and increased indications for anticoagulation. Currently, only dabigatran has a reversal agent (idarucizumab,

a humanized monoclonal antibody fragment against dabigatran), and for the others, there is no high-quality evidence for drug removal from the circulation, pro-hemostatic therapies like DDAVP or anti-fibrinolytic agents, or the administration of prothrombin complex concentrates [51•]. Andexanet alfa is a factor Xa inhibitor antidote intended for patients presenting with major bleeds who are taking FXa-Is. FDA approval is pending at the time of this review. Most hospital protocols include the administration of PCC for the reversal of FXa-Is, while there is currently no randomized prospective data to base this decision on there are case series and some animal experiments [56–59].

There is considerable controversy surrounding patients on antiplatelet agents. In the recent past several reports, worse clinical outcomes and increased hematoma expansion in these patients had been described [60, 61]. Recent studies show that rates of hematoma expansion and outcome are independent of antiplatelet use [62, 63]. A number of recent observational studies suggested that platelet transfusion could be of benefit in IPH, so a randomized phase 3 trial (the PATCH trial) was recently completed in Europe looking at whether platelet transfusion in IPH patients improved outcomes [64, 65••]. Patients who received platelets were actually more likely to have poor outcomes at 3 months than those who did not (OR 2.5, 95% CI 1.18–3.56, $p = 0.0114$). Further, 42% of patients who got platelets had serious adverse events compared to 29% in the control group. Platelet transfusion is not currently indicated in IPH patients pending further clinical trials and can only be considered as a risk reduction measure in patients planned for urgent neurosurgical intervention [66, 67].

# Venous thromboembolism prophylaxis

The priority of stopping the bleeding in IPH and avoiding triggering further bleeding must be balanced against the need to prevent deep venous thromboembolism (DVT). The incidence of symptomatic DVT in patients with IPH has been reported in retrospective case series to be on the order of 1–3% [68, 69], with symptomatic pulmonary embolism in 0.5–1% of IPH patients [70]. Previously, recommendations regarding the use of compressive stockings and intermittent pneumatic compression (IPC) devices in IPH were extrapolated from data in similar settings (post-neurosurgical patients, ischemic stroke patients) but a randomized trial considered this setting specifically, showing that in a group of 151 patients, 15.7% with compression stockings alone and 4.7% of those with IPC and stockings developed DVT (relative risk 0.29, 95% CI 0.08 to 1.00) [71]. The CLOTS3 trial showed an absolute risk reduction of 3.6% (95% confidence interval 1.4–5.8) of DVT in patients with the use of IPC [72]. It is therefore recommended that patients receive DVT prophylaxis with pneumatic compression devices (with or without compression stockings) immediately upon hospital admission and continuing until discharge [73]. The evidence for the use of DVT prophylaxis with subcutaneous unfractionated (UFH) or low molecular weight (LMWH) heparin in ICH relies on two small prospective randomized trials which were limited by their small size on low frequency of hemorrhagic or thromboembolic events [74, 75]. A comprehensive meta-analysis of these and two other observational studies showed the use of UFH or LMWH to be effective in reducing PE (RR 0.37, 95% CI 0.17–0.80) but no effect

on the incidence of DVT, expansion of hematoma, or death [75]. Current guidelines recommend the use of subcutaneous UFH or LMWH in those ICH patients with lack of mobility who have stable hematomas after 1 to 4 days from onset [73].

# Seizure management

Most patients with spontaneous IPH do not experience seizures, but in the first 7 days, up to 16% experience clinical seizures and up to 31% have electrographic seizures [76–78]. Current guidelines support continuous EEG monitoring in patients with clinical seizures or patients with mental status deterioration out of proportion to their IPH [9••]. Seizures are the product of cortical irritation and are most likely in patients with cortical extension of their ICH [79, 80]. Of note, while a large single center study has shown that prophylaxis decreases the risk of seizures in IPH, prospective studies report that seizures do not seem to effect mortality or neurologic outcome [81, 82•, 83]. In fact, the available data seems to suggest that antiepileptic prophylaxis is associated with worse outcomes and increased mortality in particular with phenytoin [84, 85]. In response, leviteracetam use for seizure prophylaxis has been on the rise despite limited knowledge about its potential effects on outcomes [86]. Present guidelines do not support the use of anti-seizure medications for prophylaxis in ICH but do recommend treating patients who have seizures accompanied by a change in mental status.

# Medical complications

IPH is associated with a number of medical complications which must be managed along with the primary insult. In the 607 patient Cerebral Hematoma and NXY Treatment trial, 88% of patients had at least one adverse event [87]. These included in order of frequency pneumonia, pulmonary embolism, respiratory failure, aspiration pneumonia, sepsis, and urinary tract infection. Given that medical complications of stroke cause up to 50% of mortality in this context, aggressive management of these complications is imperative. Dysphagia is a risk factor for aspiration and consequent aspiration pneumonia or chemical pneumonitis, but formal bedside swallow screening for all stroke patients has been shown in a prospective multicenter study to reduce the absolute risk of pneumonia from roughly 5 to 2% [88]. A Cochrane meta-analysis of 33 studies looking at nutrition and swallowing in stroke showed that avoiding malnutrition is possible with placement of an orogastric or nasogastric feeding tube and that PEG placement reduces treatment failures and GI bleeding while increasing food delivery [89]. Up to 21% of patients with IPH require mechanical ventilation for inability to protect their airway [90]. Ventilated patients are at risk for in hospital mortality as high as 48% and should be surveilled for ventilator-associated pneumonia and acute respiratory distress syndrome [91]. To minimize risk of aspiration pneumonia, the head of the bed should be kept at 30°, frequent oral care should be instituted, and the duration of intubation should be minimized when possible [92]. In non-intubated patients without concerns for elevated intracranial pressure, the recently published Head PoST trial which included 930 patients with acute intracerebral

hemorrhage determined whether laying patients flat improves cerebral perfusion and outcomes without increasing the risk of pneumonia versus positioning of at least 30°. Rate of pneumonia in patients kept flat was not statistically different from the rate in patients with the head of bed elevated [93]. Of note, the trial excluded intubated patients and did not provide a description or stratification of the clinical severity of the IPH. Supine positioning did not provide outcome benefit in this trial and is therefore not required or encouraged in IPH patients.

## Glycemic management

Hyperglycemia is an independent risk factor for death and poor outcomes in patients with IPH, regardless of whether there is underlying diabetes mellitus [94]. Intensive control of glucose to 80–110 mg/dL has been shown to both increase incidence of hypoglycemia and intracranial hypertension in one study [95] and to decrease it in another [96]. At present, there is no large randomized controlled trial demonstrating the effectiveness of strict normoglycemia in IPH and it is not recommended [97]. IPH patients should have frequent monitoring of glucose to avoid extreme hypo and hyperglycemia, but normoglycemia should not be an aggressively pursued goal.

## Avoiding hyperthermia and hypothermia

Fever is common after IPH and has an established relationship with worse outcomes and hematoma growth [98]. While a causal relationship has not been established between the complex inflammatory, neurohumeral, and metabolic cascades involved in temperature management and their derangement in the context of IPH, it seems intuitive that targeting normothermia could improve outcomes. However, maintenance of normothermia has not been shown to have an impact on improving outcomes [99]. In the broader context of neurologic injury, there have been a number of animal studies showing neuroprotective effects of hypothermia, but in humans and particularly in the setting of IPH, cooling is only recommended in the context of ongoing trials as controversy exists regarding the optimal temperature to target, the speed of cooling, its duration, and speed of rewarming along with management of side effects [100]. There are no trials looking at outcomes of hypothermia in IPH, but a small (80 patients) case controlled study of normothermia in IPH showed no difference in outcomes and increased length of ICU stay, increased duration on ventilator, and reduced clearance of sedation, suggesting that benefits of normothermia must be balanced against several risks [101]. Present guidelines therefore leave targeted hypothermia in IPH relegated properly to investigational use and state that management of fever "may be reasonable" [9••].

## Disposition

Upon stabilization, patients with IPH should be dispositioned to dedicated neurological intensive care or stroke units, especially in the initial 24 h of care [102••]. Diringer et al. analyzed 36,986 IPH patients and showed that

placement outside of a dedicated neurointensive care unit increased the likelihood of mortality (OR 3.4; 95% confidence interval 1.65–7.6) while care under a full time intensivist was associated with lower mortality (OR, 0.388; 95% CI, 0.22–0.67). Patients requiring ventriculostomy drainage or mechanical ventilation will necessarily require ICU care, ideally in a dedicated neurological unit.

# Surgical management

Surgical management usually follows a trial of conservative medical therapy [103]. Intracranial blood is neurotoxic. The disruption of the local anatomy leads to ischemia, glutamate release and consequent excitotoxicity, vasogenic edema, oxidative stress, inflammation, and necrosis [104]. Secondary injury is caused by erythrocytes, plasma proteins, and inflammatory mediators released locally [105]. Further, the volume of blood in the brain can increase ICP or prove obstructive, leading to intracranial pressure elevation. Inflammatory cells vital for removal of cellular debris contribute to ongoing inflammation. The cytotoxic pro-oxidative and pro-inflammatory environment created by these cells and molecules is further augmented by the breakdown of hemoglobin and activation of the coagulation pathway. The final outcome is disruption of the blood-brain barrier, perihematomal edema, and destruction of damaged and healthy tissue. The initial removal of the hemorrhage should theoretically interrupt or at least mitigate the secondary destruction of tissue in the brain, improve elevated ICP, prevent brain herniation, and lead to improved survival and outcomes.

The recommendations for ICP monitoring in IPH is largely borrowed from the traumatic brain injury literature, where ICP monitor placement is recommended in patients with a GCS of 8 or less, with a goal of maintaining ICP < 20 and CPP at 50 to 70 mmHg [106]. The use of ICP monitoring would seem to make intuitive sense in patients with an IPH, but ICP monitoring exposes patients to non-negligible risk for hemorrhage and infection, and the present literature is limited in the setting of IPH [107]. In a cohort study of 243 IPH patients, 57 (23%) underwent ICP monitoring and of those 70% had at least one episode of elevated intracranial pressure but this did not negatively impact mRS scores (OR 0.8, 95% CI 0.3–2.3) [108].

In analysis of 100 patients from two prospective multicenter trials of patients with intraventricular hemorrhage (IVH) who underwent placement of EVD for injection of intraventricular alteplase or saline, most (91.5%) of the transduced ICP readings were within normal range, demonstrating the effectiveness of CSF drainage for controlling ICP [109]. ICP readings > 30 mmHg in this analysis were an independent predictor of 30-day mortality after adjustment for other outcome predictors. ICP monitoring and treatment should be considered in IPH patients with evidence of herniation, significant IVH or hydrocephalus, or GCS ≤ 8 [9••].

Intraventricular extension of IPH (IVH) is seen in almost half of patients with IPH [110]. The presence of IVH doubles the likelihood or poor outcomes in spontaneous IPH [111]. Meta-analysis has shown that IPH with IVH increases the risk of mortality from 20 to 51% [112]. Removing the blood from the ventricles via catheter alone is difficult as blood tends to occlude the catheter and the speed of drainage is slow [113]. The use of adjunctive thrombolytic

agents makes catheter-assisted drainage a viable treatment option and has been demonstrated to be safe and effective in the large randomized, double blind, placebo-controlled CLEAR-III trial [114•]. In the trial, 500 patients with hypertensive IPH (volume < 30 mL) and obstructive hydrocephalus from IVH were randomized to receive up to 12 doses of alteplase 1 mg or 0.9% saline through an extraventricular drain every 8 h. The treatment group had significantly lower mortality (18 vs 29% in the saline-treated group) but a greater proportion with mRS 5 (17 vs 9% in the control group). Only 2% of subjects in both treatment and control groups had symptomatic bleeding. At present, this protocol is the only one demonstrated via a large multicenter randomized controlled trial to be safe. Intraventricular alteplase cannot currently be recommended for the routine management of IVH although ongoing studies are evaluating conditions under which this treatment may have long-term functional benefit which may be related to more complete reduction of ventricular clot burden.

A number of studies have compared standard craniotomy vs. conservative treatment. A recent meta-analysis of 10 randomized controlled trials (2059 participants) showed that craniotomy reduced the odds of death or disability at final follow-up (OR 0.74) [115]. Most often craniotomy is offered to patients who are having rapid neurological decline, but none of the included trials specifically considered these patients. The Surgical Treatment of Intracerebral Hemorrhage (STICH) trial compared early surgical evacuation of IPH to medical therapy [116••]. The trial did not show a survival advantage in patients with early surgery. Utilizing the extended Glasgow Outcome Scale (eGOS) at 6 months, 26% of the surgically treated patients and 24% of those randomized to conservative medical treatment had a favorable outcome (OR = 0.89, 95% confidence interval [CI] = 0.66–1.19, $p = 0.41$; note that the difference between groups was not statistically significant); the absolute benefit was 2.3% (– 3.2–7.7%), and the relative benefit 10% (– 13–33%). Analysis of the subgroups of the STICH I trial comparing lobar vs. deep hemorrhages showed that cortical IPH location (within 1 cm from cortex) had a better prognosis in surgically treated patients [117]. The cross-over rate in this trial was 25% of medical subjects who underwent late surgery for clinical deterioration [118]. It appears that neither early surgery in all patients nor surgery only on decompensating patients was of benefit at the time of trial completion. STITCH II investigated the subgroup of patients from STICH I who appeared to have improved outcomes: those with superficial hematomas with no IVH present and with GCS between 8 and 15. STICH II randomized 601 patients to receive either craniotomy within 12 h (307 of 601 patients) or best medical care (294 patients) with the goal of improved functional outcome [119]. Median hematoma volume was 36 mL (23.0–55.5 mL). At 6 months, 59% of the surgery group had an unfavorable outcome versus 62% in the initial conservative group (absolute difference = 3.7%, 95% CI = – 4.3–11.6, OR = 0.86, 95% CI = 0.62–1.20, $p = 0.367$). The crossover rate from initial conservative to surgical treatment was 21%. Despite the demonstration of non-inferiority in STICH II, the surgical technique did not demonstrate statistically significant clinical improvement using existing surgical techniques employing open craniotomy with resection of the hemorrhagic tissue. From these studies, one could conclude that craniotomy to remove clots may only be effective in a select subset of patients and generally has clinical equipoise with medical management.

Open surgical evacuation does not hold significant advantage over medical therapy. This may be due to the damage cortex that suffers when violated. Newer minimally invasive techniques are currently being tested which aim to decrease the damage to cortex and cortical tracts while at the same time offering increased access to the region of IPH. These include stereotactic-guided placement of brain catheters with aspiration followed by chemical thrombolysis to slowly evacuate hematomas to single pass stereotactically targeted tubes with gently sloped obturators which allow for tissue to be pushed aside gently without injury as opposed to cut through or damaged.

A Cochrane meta-analysis of four randomized controlled trials of acceptable quality (2996 participants) showed that aspiration of IPH clot decreased the likelihood of death or dependence significantly (OR 0.80, 95% CI: 0.69–0.93; $P = 0.004$) when compared to open craniotomy [120]. The Minimally Invasive Surgery and rtTPA for Intracerebral Hemorrhage Evacuation (MISTIE) trials I and II showed that IPH clot can be targeted and drained safely using serial alteplase injections through a stereotactically targeted catheter [121]. The ongoing MISTIE III trial is investigating whether minimally invasive clot evacuation with thrombolysis improves functional outcomes at 180 days compared with conservative management (Clinical Trials.gov identifier NCT01827046).

According to the American Heart Association guidelines, patients with cerebellar hemorrhage causing brainstem compression and rapid neurologic deterioration should undergo surgical removal of the hemorrhage if aggressive management is pursued [9••]. Treatment of cerebellar IPH patients with ventricular drainage alone is not recommended. Evacuation of a supratentorial hematoma or decompressive hemicraniectomy can be considered life-saving for deteriorating patients, but early hematoma evacuation is not clearly beneficial for otherwise stable patients. The effectiveness of minimally invasive techniques for clot evacuation has not been proven with a randomized controlled trial, and surgical evacuation has been associated with excellent clinical outcomes. Moreover, posterior fossa hemorrhage is often quickly followed by decompensation in 25 to 75% of patients [122]. Retrospective series have suggested that suboccipital decompression significantly lowers mortality [122, 123]. Patients with cerebellar hemorrhage $> 3$ cm$^3$, those with brainstem compression or symptomatic hydrocephalus, have better outcomes with surgical decompression. Treatment with ventricular drainage alone is ineffective [123].

Current studies are evaluating a number of new devices placed via stereotactic guidance which enable enhanced drainage of intraparenchymal clots. One device, the Penumbra Apollo system (Penumbra Inc., Alameda, California, USA), uses a guided wand which uses vibration in combination with irrigation and suction to maximize the amount of IPH and IVH evacuated [124]. The NICO Brainpath system (NICO Corporation, Indianapolis, Indiana, USA) uses a larger caliber tube with a blunt obturator tip that when inserted through a brain sulcus is designed to sweep aside rather than cutting white matter tracts. The Brainpath system was shown recently to achieve a mean volume reduction of 95.7% ± 5.8% (range 0–14 mL, $P < 0.001$) in a series of 35 patients with initial mean ICH volume of 52.7 mL ± 22.9 mL and post-evacuation volumes of 2.2 mL ± 3.6 mL. Notably, this technology enabled direct visualization of the surrounding clot area such that in 65% of patients, a bleeding source was identified and treated. The Minimally invasive Subcortical Parafascicular Access for Clot Evacuation (MiSPACE) studies have so far shown successful evacuation of clot, and a randomized multicenter trial

(ENRICH, ClinicalTrials.gov NCT02880878) is currently underway [125•, 126]. It remains to be seen whether the successful volumetric reduction of clot is matched with improvement in patient outcomes, but as techniques with increasingly low morbidity emerge, it is hoped that appropriately selected patents will increasingly benefit from such treatment.

For patients who are able to make it out of the acute window after IPH and survive to discharge from hospital, recovery of function continues for many months after IPH and cannot be fully assessed until 6 to 12 months post-injury [127]. Unfortunately, up to half of IPH patients who survive will not achieve functional independence, with families and caregivers bearing that burden for the rest of their lives [41•]. The present AHA guidelines advocate that all patients with ICH benefit from well-organized, multidisciplinary rehabilitation during hospitalization and after discharge [128]. Earlier discharge and rehabilitation have been shown in prospective cohort studies to result in improved functional outcomes [129, 130].

# Conclusion

The management of IPH is a challenge shared by emergency providers, neurologists, neurosurgeons, and intensivists throughout the world. Clinical decision-making is increasingly supported by evidence-based practices that decrease mortality, minimize harm, and increase the likelihood of functional outcome.

# Compliance with Ethical Standards

### Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

# References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
•       Of importance
••      Of major importance

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