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Cerebral Intraparenchymal Hemorrhage
A Review

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IMPORTANCE Although spontaneous intraparenchymal hemorrhage (IPH) accounts for less than 20% of cases of stroke, it continues to be associated with the highest mortality of all forms of stroke and substantial morbidity rates.

OBSERVATIONS Early identification and management of IPH is crucial. Blood pressure control, reversal of associated coagulopathy, care in a dedicated stroke unit, and identification of secondary etiologies are essential to optimizing outcomes. Surgical management of hydrocephalus and space occupying hemorrhage in the posterior fossa are accepted forms of treatment. Modern advances in minimally invasive surgical management of primary, supratentorial IPH are being explored in randomized trials. Hemorrhagic arteriovenous malformations and cavernous malformations are surgically excised if accessible, while hemorrhagic dural arteriovenous fistulas and distal/mycotic aneurysms are often managed with embolization if feasible.

CONCLUSIONS AND RELEVANCE IPH remains a considerable source of neurological morbidity and mortality. Rapid identification, medical management, and neurosurgical management, when indicated, are essential to facilitate recovery. There is ongoing evaluation of minimally invasive approaches for evacuation of primary IPH and evolution of surgical and endovascular techniques in the management of lesions leading to secondary IPH.

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Spontaneous intraparenchymal hemorrhage (IPH) is relatively common and has devastating consequences. Recognition of risk factors (eg, hypertension), early distinction from an ischemic event, and identification of clinical features that can worsen IPH complications is important in optimizing outcomes from IPH. This review examines the pathophysiology of and management options for IPH, with the intent of helping clinicians better manage the condition. IPH accounts for 6.5% to 19.6% of cases of stroke[1,2] but is associated with the greatest rate of mortality; 1-year survival from IPH is approximately 40%,[3-5] and 10-year survival is 24%.[4] Across several studies, the rate of functional independence at follow-up varied from 12% to 39%.[5] A meta-analysis of 36 studies reported an incidence of IPH of 24.6 per 100 000 person-years (range, 1.8-129.6), and the rate was significantly higher in Asian and older populations.[5]

Methods

The PubMed database was searched on September 1, 2018, using the terms intracerebral hemorrhage and intraparenchymal hemorrhage, for English-language studies of the pathophysiology, epidemiology, and management of IPH published after January 1, 2015. Large population epidemiologic studies, randomized trials, and formal treatment guidelines were reviewed. Relevant references published before January 1, 2015, were extracted and also reviewed. Studies providing only aggregate data for all types of hemorrhagic stroke (including subarachnoid hemorrhage) were excluded. This review was based on 77 referenced articles, including 11 clinical trials, 10 meta-analyses, 41 observational studies, 2 guidelines, and 13 other reports.

Epidemiology and Pathophysiology

Primary IPH, accounting for 78% to 88% of cases of IPH, refers to rupture of damaged small arteries or arterioles, most commonly secondary to either hypertension or cerebral amyloid angiopathy (CAA). Secondary IPH can occur secondary to coagulopathy; cerebral venous thrombosis; moyamoya; vasculitis; tumor; hemorrhagic conversion of ischemic stroke; or rupture of a mycotic aneurysm or vascular malformation, such as an arteriovenous malformation (AVM), arteriovenous fistula, or cavernous malformation (**Table 1**).

Primary IPH

Hypertension is the primary risk factor for IPH.[2,4] Hypertension-induced degenerative changes in small, arterial perforators are thought to increase the likelihood of rupture, and hypertensive hemorrhage has a proclivity to occur in the deep brain structures supplied by these vessels (basal ganglia, thalamus, brainstem, and deep

Table 1. Spontaneous Intraparenchymal Hemorrhage (IPH) Etiology

	Treatment
Primary IPH	
Hypertension	BP control, trial enrollment for evacuation[a]
Cerebral amyloid angiopathy	BP control, trial enrollment for evacuation[a]
Secondary IPH	
Coagulopathy	Reversal, remainder as per primary IPH
AVM/AVF	Surgery, embolization, or radiosurgery
Cavernous malformation	Surgery
Distal/mycotic aneurysm	Embolization/surgery
Cerebral venous thrombosis	Anticoagulation and possibly thrombectomy
Moyamoya	Surgical revascularization
Vasculitis	Immunomodulatory medications
Hemorrhagic brain tumor/metastasis	Surgical resection as indicated
Hemorrhagic conversion of stroke	Expectant management

Abbreviations: AVF, arteriovenous fistula; AVM, arteriovenous malformation; BP, blood pressure.

[a] Empirical surgical evacuation is reasonable outside of trials for cerebellar hemorrhages of at least 3 cm in diameter. It is of consideration in patients with supratentorial IPH and clinical deterioration or coma.

cerebellum). A case-control study from 22 countries of 3000 patients with acute stroke compared with 3000 controls demonstrated that in the 663 patients with IPH (22%), hypertension was the strongest risk factor (odds ratio [OR], 9.18 [95% CI, 6.80-12.39]).[2] Additional significant risk factors included smoking (OR, 1.45 [95% CI, 1.07-1.96]) and alcohol intake (1-30 drinks per month: OR, 1.52 [95% CI, 1.07-2.16]; >30 drinks per month or binge drinking: OR, 2.01 [95% CI, 1.35-2.99]). Another case-control study of 3173 patients aged 55 years and older demonstrated heavy alcohol intake to be associated with deep IPH risk (OR, 1.68 [95% CI, 1.36-2.09]) and overall IPH risk (OR, 1.38 [95% CI, 1.17-1.63]).[6] Increased alcohol intake is postulated to result in platelet dysfunction/coagulopathy and, potentially, endothelial damage.[6] Increased high-density lipoprotein cholesterol, low total cholesterol, and low non–high-density lipoprotein cholesterol are also associated with IPH.[2,7] A 2015 study of 1145 patients with IPH reported annual rebleed rates of 7.8% and 3.4% for lobar and nonlobar primary IPH, respectively.[8] Lobar IPH refers to cortical or subcortical IPH, in contrast to deep or nonlobar IPH, which involves the basal ganglia, thalamus, brainstem, and deep cerebellum.

CAA results from β-amyloid deposition in cortical blood vessels; the vessels are consequently weakened and have an increased tendency to rupture, making CAA an independent risk factor for lobar IPH.[9] It has been shown that the presence of the E2 and E4 alleles of apolipoprotein E are associated with increased deposition of β-amyloid in the vessel wall and, consequently, hemorrhage risk.[10] Distinguishing CAA-related lobar IPH from hypertensive lobar IPH bears clinical and prognostic relevance because the rebleed and dementia risks are significantly higher after a CAA-related bleed.[11,12] A 2017 meta-analysis of 10 studies with 1306 patients with IPH reported a recurrent IPH risk of 7.4% in CAA-related IPH compared with 1.1% in non–CAA-related IPH ($P = .01$).[11]

The modified Boston criteria, serving as diagnostic criteria for CAA, underscores that a definite diagnosis of CAA can only be made following a full postmortem examination demonstrating the vasculopathy.[9] A probable diagnosis is based on supporting surgical pathology with some degree of CAA in the specimen. A probable diagnosis can also be made in a patient who is older than 55 years who does not have another cause of hemorrhage, with multiple bleeds restricted to lobar, cortical, or cortical-subcortical regions or a single bleed with cortical superficial siderosis.[9] A 2018 autopsy study of 110 adults with IPH reported the presence of subarachnoid hemorrhage, *APOEE4*, and "finger-like" projections on computed tomographic imaging to be significant independent predictors for CAA-related lobar IPH.[13] Finger-like projections were defined as elongated extensions arising from the hematoma that were longer than they were wide. The absence of all 3 factors had a negative predictive value of 100%, while the presence of subarachnoid hemorrhage and 1 other factor had a positive predictive value of 96%.[13]

Secondary IPH

Secondary IPH can result from coagulopathy, vascular malformation rupture, cerebral venous thrombosis, mycotic aneurysm rupture, moyamoya, tumor, hemorrhagic conversion of an ischemic stroke, or vasculitis.[14] Vascular malformations capable of rupture include AVMs, arteriovenous fistulas, and cavernous malformations. AVMs are parenchymal webs of dysplastic arteries that shunt into the venous system with an approximate overall prevalence of 0.01%.[15] They harbor a 2% risk of rupture per year that increases to 4% for hemorrhagic AVMs and 6% within the first year of a hemorrhage.[16] High-risk features that may further increase this risk include exclusive deep venous drainage, deep AVM location, and associated aneurysms.[16] Deep venous drainage occurs via the internal cerebral, basal, or precentral cerebellar veins through the vein of Galen, as opposed to cortical (superficial) venous outflow. Arteriovenous fistulae, most often dural arteriovenous fistulae, are acquired, direct arteriovenous connections occurring within the dura mater. If drainage exits from the dura into a pressurized cortical vein, hemorrhage may occur akin to a hemorrhage secondary to cortical vein or venous sinus thrombosis as a result of local venous hypertension. The annual hemorrhage risk for asymptomatic dural arteriovenous fistulas is 3%, increasing to 46% for patients presenting with hemorrhage.[17]

Cavernous malformations are low-flow collections of dilated, endothelium-lined sinusoids that generally produce relatively small bleeds when they hemorrhage, at a rate of 0.4% to 0.6% per year for incidental lesions and as high as 22.9% per year for previously ruptured lesions, particularly within the first 2 years of a bleed.[18-20] Hemorrhagic morbidity and mortality for vascular malformations are somewhat lower than for overall primary IPH,[21] particularly for cerebral cavernous malformations, where hemorrhagic mortality is rare.[18,19] A 2016 meta-analysis of natural history of cavernous malformation reported posthemorrhage full recovery or minimal disability at 78.5% per person-year and mortality after bleeding at 2.2%.[20]

Cerebral venous thrombosis is estimated to affect 5 people per million, annually, with known predisposing factors including prothrombotic conditions; pregnancy and the puerperium; use of oral contraceptives; cancer; parameningeal infections; and systemic diseases, such as lupus, inflammatory bowel disease, and thyroid

disease.[22] It may cause IPH as a result of venous hypertension, impaired drainage of the cerebral parenchyma, and consequent vein rupture, accounting for 5% of cases of IPH in younger patients.[22,23] As of yet, the prospective risk of IPH from venous thrombosis is poorly quantified in the literature.

While typical saccular aneurysms primarily cause subarachnoid hemorrhage, select aneurysms, such as middle cerebral artery, internal carotid artery terminus, pericallosal, and distal posteroinferior cerebellar artery aneurysms, may cause IPH as well. Atypical distal aneurysms, often mycotic due to septic emboli, may cause IPH. An appropriate index of suspicion is necessary in patient populations more prone to harbor these lesions, such as patients with sepsis or infective endocarditis.[24]

Although it is often a source of ischemic events, moyamoya arteriopathy that results from progressive intracranial arterial stenosis and resultant formation of fragile collateral vessels may result in hemorrhage from rupture of these vessels in adult patients.[25] In a randomized study of hemorrhagic moyamoya in the Japanese population, the rate of recurrent hemorrhage was 7.6% per year, comparing unfavorably to a rate of 2.7% per year for patients treated via surgical direct bypass.[26]

Hemorrhagic transformation of ischemic stroke occurs in approximately 12% of cases, with history of atrial fibrillation and infarct size identified as statistically significant risk factors for its occurrence.[27,28] Two-thirds of cases are petechial hemorrhages (often referred to as hemorrhagic infarction [HI]), and one-third are parenchymal hematomas (PH).[27] PHs are stratified into those involving less than 30% of the ischemic territory with minimal mass effect (type 1; PH1) and those involving at least 30% of the ischemic territory with obvious mass effect (type 2; PH2).

Clinical Presentation

Any patient presenting with an acute-onset headache, seizure, and/or focal neurological deficit should be evaluated for possible IPH. Presentation may resemble an acute ischemic event with similar blood pressure lability or hypertension. The presence of a headache, nausea or vomiting, and a depressed mental state suggests hemorrhagic stroke as opposed to an acute ischemic event. In the original Surgical Trial in Intracerebral Haemorrhage (STICH) of 1033 patients with primary IPH, 60% of patients had arm paralysis, 50% had leg paralysis, and 59% had dysphasia or aphasia. Forty-one percent of patients had Glasgow Coma Scale (GCS) scores (range, 3-15; a higher score indicates a lower severity of brain injury) of 13 to 15, 40% had scores of 9 to 12, and 20% had scores of 5 to 8.[29]

Patients with cavernous malformations or venous sinus thrombosis are more prone to seizures than patients with other causes of IPH.[18-20,23] Patients with secondary IPH, particularly from vascular malformations or venous sinus thrombosis, are younger and generally do not have a history of hypertension. Recent dehydration, pregnancy, or known history of a hypercoagulable disorder may raise suspicion for venous sinus thrombosis.[23] In a 2012 study of IPH, significant risk factors for a secondary etiology were age younger than 65 years, female sex, nonsmoker, intraventricular hemorrhage, and no history of hypertension.[30]

Assessment and Diagnosis

Timely assessment and diagnosis of IPH are crucial; nearly 25% of patients with IPH deteriorate in transport to the hospital[31,32] and an additional 25% deteriorate in the emergency department (ED).[32,33] Risk factors for deterioration in the ED include use of antiplatelet agents, time from symptom onset to ED arrival under 3 hours, initial body temperature of at least 37.5°C, associated intraventricular hemorrhage, and midline shift of at least 2 mm.[33] Rapid computed tomographic scan or magnetic resonance imaging is a class I recommendation[34] to facilitate a timely diagnosis because patients with ischemic stroke are initially treated with permissive hypertension, thrombolytics, and emergent endovascular therapy, while patients with hemorrhage will need aggressive blood pressure control and consideration of surgical intervention to address elevated intracranial pressure, if present. The initial assessment should include obtaining a medical history, with emphasis on determining the time of symptom onset, determining if hypertension and anticoagulant use are present, and performing a neurological examination.

American Heart Association/American Stroke Association guidelines recommend calculation of a baseline severity score as part of the initial assessment (**Table 2**).[34] For general primary IPH, the Intracerebral Hemorrhage Score is simple to use and predicts mortality (**Table 3**).[35] The score is calculated from the patient's presenting GCS score, age, the presence or absence of infratentorial hemorrhage, IPH volume, and the presence of intraventricular hemorrhage. Computed tomographic angiography/venography can identify arteriovenous shunts, venous sinus thrombosis, and aneurysms. In addition, the presence of contrast extravasation on a computed tomographic angiogram, a "spot sign," is predictive of hematoma expansion. In a prospective observational study of 228 patients presenting within 6 hours of symptom onset with IPH, 27% had a spot sign.[36] Hematoma growth by 6 mL or 33% occurred in 61% of patients with a spot sign compared with 22% of patients without a spot sign ($P < .001$). Median hematoma expansion was 8.6 mL vs 0.4 mL ($P < .001$) for patients with and without spot signs, respectively, and 3-month outcomes, as defined by the modified Rankin scale (score range, 0-6; a higher score indicates a higher level of disability), (median of 5 vs 3, respectively; $P < .001$) and mortality (43% vs 20%, respectively; $P = .002$) were significantly worse for patients with a spot sign. Magnetic resonance imaging can be performed to better delineate a cavernous malformation, brain tumor, or ischemic stroke underlying the hemorrhage, and to identify microbleed patterns consistent with CAA or hypertensive microangiopathy (Table 1 and **Figure 1**). For patients suspected of having secondary IPH (no history of hypertension and/or age < 65 years), digital subtraction angiography remains the standard means for the diagnosis of arteriovenous shunts (AVM or dural arteriovenous fistulae) and aneurysms, and it can be of distinctive diagnostic value for moyamoya and vasculitis.

Treatment

American Heart Association/American Stroke Association guidelines for treatment of patients with IPH are summarized in Table 2.[34]

Table 2. Summarized Clinical Practice Recommendations for the Management of Intraparenchymal Hemorrhage (IPH)[a]

	Classification[b]	Level of Evidence[c]
Initial diagnosis and assessment		
Baseline severity score should be performed	I	B
Rapid CT or MR imaging	I	A
More advanced imaging for underlying lesion (CT angiogram, CT venogram, MR, DSA)	IIa	B
Hemostasis and coagulopathy		
Repletion for coagulation factor deficiency or thrombocytopenia	I	C
If taking a VKA and INR is elevated, vitamin K should be administered	I	C
If taking a VKA and INR is elevated, PCC is recommended over FFP	IIb	B
Protamine sulfate to reverse heparin	IIb	C
rFVIIa is not recommended	III	A
Early medical management		
Initial management in ICU or dedicated stroke unit with nurses with nursing neuroscience acute care expertise	I	B
SBP <140 mm Hg, if presenting with SBP 150-220 mm Hg, is safe	I	A
Aggressive reduction of BP via continuous infusion if SBP >220 mm Hg	IIb	C
Monitor glucose; hyperglycemia and hypoglycemia should be avoided	I	C
Seizures should be managed with AED	I	A
Prophylactic AED is not recommended	III	B
Early, formal dysphagia screening before oral intake	I	B
Electrocardiogram and Tn for screening	IIa	C
Steroids are not recommended	III	B
Intermittent pneumatic compression for DVT prophylaxis on admission	I	A
SC heparin or LMWH 1-4 d after IPH ceases for DVT prophylaxis	IIb	B
Surgical management		
Ventricular drainage for hydrocephalus, especially if decreased arousal	IIa	B
Surgical drainage for worsening cerebellar IPH or hydrocephalus	I	B
Surgical drainage for clinical deterioration	IIb	C
Craniectomy for coma, large hematoma with shift or refractory high ICP	IIb	C

Abbreviations: AED, antiepileptic drug; BP, blood pressure; CT, computed tomographic; DSA, digital subtraction angiography; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ICU, intensive care unit; ICP, intracranial pressure; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MR, magnetic resonance; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; SBP, systolic blood pressure; SC, subcutaneous; Tn, troponin; VKA, vitamin K antagonist.

[a] Adapted from American Heart Association/American Stroke Association guidelines.[34]

[b] Classification recommendation of I indicates treatment should be performed; IIa, treatment is reasonable; IIb, treatment may be considered; III, no benefit or harm.

[c] Level of evidence of A indicates data from multiple randomized trials or meta-analysis; B, data from a single randomized trial or nonrandomized studies; C, data from consensus opinion/case studies.

Table 3. The Intracerebral Hemorrhage Score[a]

Factors	Points
GCS score	
3-4	2
5-12	1
13-15	0
Age, y	
≥ 80	1
< 80	0
Infratentorial hemorrhage	
Yes	1
No	0
Volume, mL	
≥30	1
< 30	0
Intraventricular hemorrhage	
Yes	1
No	0
Total score	Risk of mortality, %
0	0
1	13
2	26
3	72
4	97
5	100

Abbreviation: GCS, Glasgow Coma Scale.

[a] Adapted from data from Hemphill et al.[35]

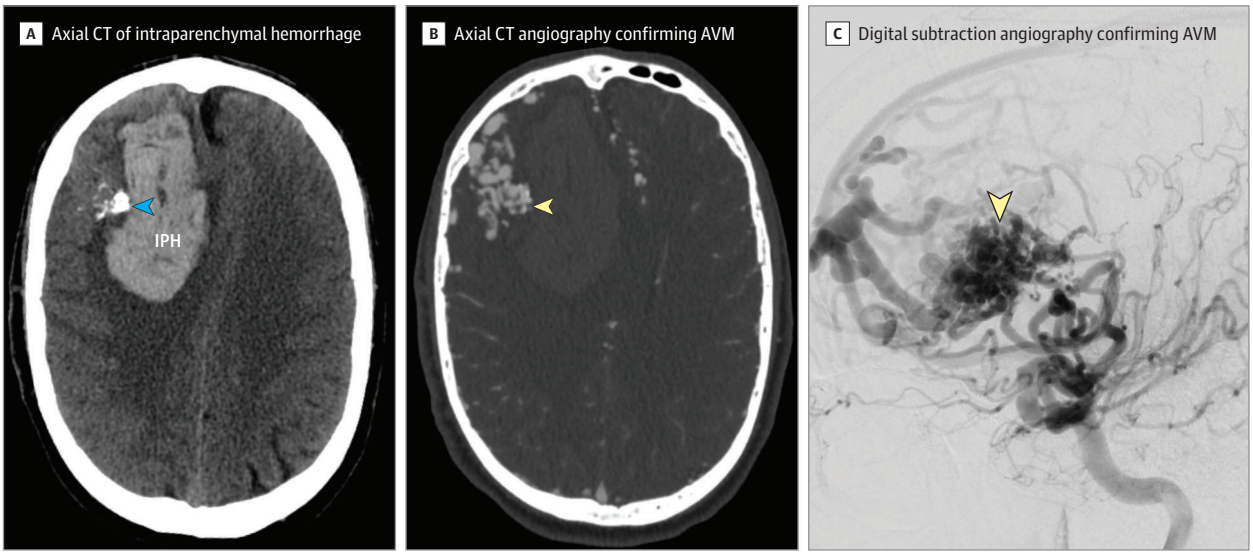
As with any patient presenting with an acute neurological event, airway protection is crucial in unresponsive patients to mitigate the risk of secondary injury from aspiration, hypoxemia, and hypercapnia. Patients with impending herniation can receive ventilation after intubation and be given mannitol to lower intracranial pressure.

Hemostasis and Coagulopathy

Patients with coagulopathy secondary to a coagulation factor deficiency or severe thrombocytopenia should receive factor replacement therapy or platelets, respectively; patients with a high international normalized ratio due to vitamin K antagonist therapy should receive intravenous vitamin K and prothrombin complex concentrate (Class IIb; level of evidence: B).[34,37] Complex concentrates are preferred over fresh frozen plasma because they are more easily reversed, less likely to cause fluid overload, and have comparable thromboembolic complication rates.[37] In one study, the frequency of hematoma growth was 19% in patients treated with prothrombin complex concentrate compared with 33% in patients treated with fresh frozen plasma.[38] Direct thrombin inhibitors can be reversed by administering idarucizumab for dabigatran[39] and andexanet alfa for apixaban, rivaroxaban, or other factor Xa inhibitors.[40] In a study of 67 patients with acute, major bleeding, andexanet alfa administration resulted in median factor Xa activity reduction of 89% and 93% for rivaroxaban and apixaban, respectively.[40]

Empirical recombinant factor VIIa administration is not recommended for patients with IPH.[34] In the Factor Seven for Acute Hemorrhagic Stroke Trial (FAST), 841 patients with primary IPH were randomized to receive a placebo, 20 μg/kg of recombinant factor VIIa, or 80 μg/kg of recombinant factor VIIa within 4 hours of IPH onset.[41]

Figure 1. Secondary Intraparenchymal Hemorrhage (IPH)



Panel A demonstrates a right frontal IPH with an adjacent calcified lesion (arrowhead) and panels B and C show an arteriovenous malformation (AVM; arrowhead). CT indicates computed tomographic.

The primary outcome, defined as severe disability or death (modified Rankin Scale score of 5 or 6), did not significantly differ between groups (24% in the placebo group, 26% in the 20-µg/kg group, and 30% in the 80-µg/kg group). The mean increase in volume of IPH at 24 hours was 26% in the placebo group, 18% in the 20-µg/kg group (P = .09), and 11% in the 80-µg/kg group (P < .001); however, rates of arterial adverse events were more frequent in the 80-µg/kg group than the placebo group (9% vs 4%; P = .04). Empirical tranexamic acid administration is also not recommended for patients with IPH. A 2018 randomized trial of 2325 patients with IPH randomized to receive tranexamic acid or a placebo reported no significant difference in outcomes or mortality at 90 days; however, there was a lower incidence of serious adverse events in the cohort who received tranexamic acid.[42]

Patients taking antiplatelet medications should not undergo attempted reversal by platelet transfusion. The 2016 PATCH trial randomized 190 patients with IPH receiving antiplatelet therapy to receive either platelet transfusion or no transfusion and demonstrated a greater risk of death or functional dependence at 3 months in patients who underwent transfusion (OR, 2.05 [95% CI, 1.18-3.56]), with a greater risk of serious adverse events during hospitalization (42% vs 29%), than patients who did not undergo transfusion.[43]

Early Medical Management

Hematoma growth is independently associated with worse outcomes and occurs in at least 30% to 38% of cases of IPH.[44-46] To mitigate the risk of secondary brain injury resulting from hematoma expansion, optimal systolic blood pressure goals have been addressed in 2 trials. For patients presenting with systolic blood pressure up to 220 mm Hg, blood pressure should be reduced to less than 140 mm Hg using parenteral medications, such as nicardipine or clevidipine.[34] In the ATACH-2 trial, 1000 patients presenting for care within 4.5 hours of symptom onset with supratentorial IPH were randomized to a systolic blood pressure target of 110 mm Hg to 139 mm Hg (intensive) or 140 to 179 mm Hg (standard) for 24 hours.[47] There was no significant difference in 90-day mortality or severe disability between the groups (modified Rankin Scale score of 4-6 in 38.7% vs 37.7% of patients, respectively). The rate of hematoma expansion was 18.9% in the intensive blood pressure control cohort compared with 24.4% in the standard blood pressure cohort (P = .09); however, the rate of renal adverse events was higher in the intensive group (9% vs 4%; P < .001).

The INTERACT2 trial randomized 2783 patients with IPH within 6 hours of symptom onset to the same blood pressure goals as in the ATACH-2 trial, maintained for a 7-day period.[48] The rate of poor outcomes (modified Rankin Scale score of 3-6) at 3 months was 52% in patients in the intensive blood pressure treatment group compared with 55.6% in the standard blood pressure group (P = .06). Secondary analyses demonstrated better physical and mental health–related quality of life for patients in the intensive group. Careful review of the ATACH-2 trial, however, demonstrated that the mean minimum systolic blood pressure during the first 2 hours was 128.9 in the intensive blood pressure group and 141.1 mm Hg in the standard blood pressure group; in the INTERACT2 trial, mean systolic blood pressure in the first hour was 150 mm Hg in the intensive blood pressure group vs 164 mm Hg in the standard blood pressure group.

Optimally, patients should be admitted to an intensive care unit or dedicated stroke unit.[34,49] In a study comparing 8206 patients with IPH treated in a stroke unit with 2871 patients in a standard hospital ward, the rate of death or functional dependency at 3 months was significantly lower for patients in a stroke unit (59% vs 75%; OR, 0.59 [95% CI, 0.53-0.67]).[49]

Routine prophylactic antiepileptic medications are not recommended and may be associated with worse outcomes for patients with IPH,[50,51] but patients presenting with seizures should be treated with antiepileptic medications. Hyper- and hypoglycemia should be managed and early dysphagia screening and cardiac screening using electrocardiogram results and troponin levels should be performed.[34] Deep vein thrombosis prophylaxis with intermittent pneumatic compression should be administered[52]; subcutaneous

or low-molecular-weight heparin can be started the day after the cessation/stabilization of the bleed.[34,53]

Neurosurgical Management of IPH

Urgent neurosurgical consultation is recommended for assessment for hydrocephalus and the possible need for surgical decompression or hematoma evacuation. In patients with supratentorial IPH and obvious radiographic hydrocephalus and/or decreased level of consciousness, an external ventricular drain is advised.[34] In a large trial of patients with supratentorial IPH, 23% of patients with primary IPH and 55% of patients with associated intraventricular hemorrhage had hydrocephalus.[29,54]

A common strategy supported by small population studies is to proceed with surgical decompression and evacuation of cerebellar hemorrhage at least 3 cm in size.[55,56] There is less certainty about the efficacy of evacuation for supratentorial IPH, though patients with sizable hematomas, clinical deterioration, or coma should be considered for craniectomy and/or clot evacuation.[34,57,58] In the original STICH, 1033 patients from 83 centers with primary supratentorial IPH were randomized to receive early surgical or initial conservative management.[29] Favorable outcome, defined as good recovery or moderate disability on the Glasgow outcome scale, did not significantly differ between the groups (26% in the surgical management group vs 24% in the conservative management group; $P = .41$). In the STICH II trial, 601 conscious (GCS>8) patients with 10- to 100-mL superficial, supratentorial IPH without intraventricular hemorrhage were randomized to undergo surgical hematoma evacuation or conservative management.[59] However, a statistically significant difference in favorable outcome at 6 months between the groups was not observed (41% in the surgical management group vs 38% in the conservative management group; $P = .37$).

As a means to reduce the morbidity of open surgical approaches, minimally invasive approaches are being investigated. These approaches use small incisions and bony openings (burr hole), and insert either a catheter into the clot for drainage or a small tube into the clot for direct evacuation. Zhou et al found a significantly lower rate of death or dependence (modified Rankin Scale score >2) with minimally invasive surgery compared with craniotomy or conservative management in a meta-analysis of patients with supratentorial IPH.[60] The benefits of minimally invasive surgery were achieved in patients younger than 80 years who had superficial bleeds, a GCS score of at least 9, hematoma volume between 25 mL and 40 mL, and underwent the surgical procedure within 72 hours of symptom onset. A 2018 meta-analysis of 5 randomized trials and 9 prospective studies involving 2466 patients with supratentorial IPH found a statistically significant difference in mortality rate between patients who underwent minimally invasive surgery and craniotomy (OR, 0.76 [95% CI, 0.60-0.97]) and a lower rate of rebleeding (OR, 0.42 [95% CI, 0.28-0.64]) and a higher rate of good recovery (OR, 2.27 [95% CI, 1.34-3.83]) for minimally invasive approaches.[61]

Ongoing Minimally Invasive Surgery Studies for Primary IPH

In the Minimally Invasive Surgery Plus rt-PA in Intracerebral Hemorrhage Evacuation (MISTIE) II trial, 54 patients with IPH were randomized to undergo stereotactic placement of a catheter into the hematoma and administration of recombinant tissue plasminogen activator and 42 were randomized to receive routine medical care.[62] The authors found similar rates of 30-day mortality (9.5% vs 14.8%; $P = .54$), 7-day mortality (0% vs 1.9%; $P = .56$), symptomatic hemorrhage (2.4% vs 9.3%; $P = .23$), and infection (2.4% vs 0%; $P = .43$) in the routine care vs the surgical care group. The MISTIE III trial will compare functional outcome between the 2 groups at 180 days, as defined by the modified Rankin Scale. Innovative approaches for catheter insertion are ongoing, with recent reports of robot-assisted catheter insertion (**Figure 2**).[63]

The ongoing multicenter ENRICH (NCT02880878) study randomized patients aged 18 to 80 years with a GCS score of 5 to 14 and an IPH volume of 30 mL to 80 mL to receive surgical evacuation via an endoport or routine medical care within 24 hours. The primary outcome is functional improvement on the utility-weighted modified Rankin Scale score at 180 days. An initial single-arm surgical evaluation of this endoport system in 39 patients with primary IPH reported functional independence in 52% of patients at follow-up and no mortality.[64]

Secondary IPH

While the early treatment of patients with secondary IPH remains consistent with primary IPH, medically and in terms of managing early hydrocephalus, diagnosing and addressing the etiologic cause of the IPH is important. Given their increased risk of repeat hemorrhage after a bleed, surgically accessible ruptured AVMs should be excised with or without adjunctive embolization.[15] The Spetzler Martin grading scale is used to stratify surgical risk based on AVM size (<3 cm, 1 point; 3-6 cm, 2 points; >6 cm, 3 points), presence of deep venous drainage (+ 1 point), and eloquent locale (+ 1 point).[65] Grade 1 to 2 AVMs are generally considered reasonable surgical targets; grade 3 AVMs are of intermediate surgical risk, and grade 4 to 5 AVMs are associated with higher surgical morbidity.[15,65] Surgically inaccessible or high-risk ruptured AVMs should be considered for radiosurgery (focused radiation)[66]; rarely, small ruptured AVMs can be managed with embolization, though embolization is generally viewed as an adjunctive measure.[67] Recent advances in transvenous embolization may ultimately broaden the spectrum of AVMs amenable to endovascular therapy with curative intent.[68]

Ruptured dural arteriovenous fistulae are generally managed via embolization as first-line curative therapy; open neurosurgical resection is reserved for fistulae that cannot be effectively embolized.[69] A 2017 study of 260 patients with dural arteriovenous fistulae treated via embolization reported an 80% occlusion rate with an overall 8% complication rate.[69] Hemorrhagic cavernous malformations are surgically excised if accessible.[18] Modern advances in advanced imaging, such as tractography, and improving neurosurgical approaches continue to reduce operative risk.[18,70-72] Ruptured aneurysms that cause isolated IPH are often atypical, distal mycotic aneurysms that are generally managed with embolization.[24] Patients with venous sinus thrombosis and associated hemorrhage should be considered for transvenous thrombectomy, or, with stability of small hemorrhages, anticoagulation may be used.[23] A systematic review of 17 studies with a total of 235 patients undergoing transvenous thrombectomy reported radiographic resolution in 69% of patients; worsening or new intracranial hemorrhage was reported in 8.7% of cases.[73] Anticoagulation is thought to reduce rather than elevate IPH risk by averting thrombus propagation and exacerbation of venous hypertension and requires close monitoring to avoid worsening hemorrhage. Patients with vasculitis are often treated medically once a diagnosis is achieved; patients with moyamoya vasculopathy may

be considered for surgical revascularization.[25,74] Hemorrhagic neoplastic lesions may be surgically excised as indicated once the patient is stabilized.

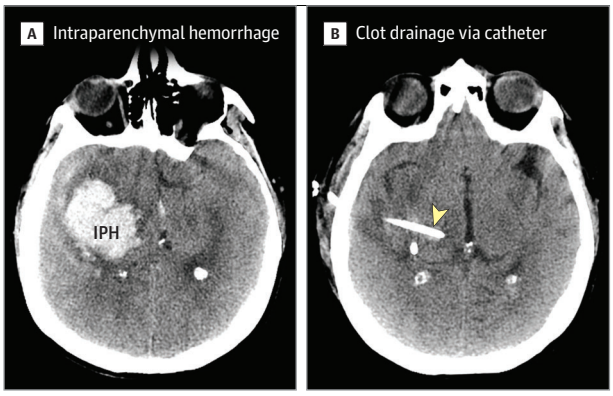
Recovery

Patients recovering from IPH are optimally treated in specialized neurorehabilitation facilities.[34] Control of hypertension, alcohol intake, and smoking cessation should be pursued, given their effect on IPH risk.[2,8] For patients needing antiplatelet therapy, it can be resumed within days after primary IPH,[34] while resumption of anticoagulation therapy should be delayed by 1 to 2 months, particularly for patients with deep, non–CAA-related primary IPH. A 2017 meta-analysis regarding resumption of anticoagulation therapy after IPH showed that resuming anticoagulation therapy is associated with a significantly lower risk of thromboembolic complications (risk ratio, 0.34 [95% CI, 0.25-0.45]), but a comparable risk of recurrent IPH (risk ratio, 1.01 [95% CI, 0.58-1.77]).[75] A study that evaluated optimal timing for resumption of anticoagulation therapy demonstrated that the combined risk of recurrent stroke or IPH reached a nadir if anticoagulation therapy was restarted between 10 and 30 weeks after the initial hemorrhage.[76] Nevertheless, patients at higher risk for recurrent IPH, such as patients with lobar and/or CAA-related IPH, should be evaluated on an individual basis. A Markov decision model demonstrated that withholding anticoagulation in a case of a 69-year-old man with nonvalvular atrial fibrillation resulted in improving quality-adjusted life expectancy by 1.9 quality-adjusted life-years.[77] In patients with secondary IPH from a vascular malformation, mycotic aneurysm, vasculitis, or brain tumor, anticoagulation therapy can often be initiated after therapeutic cure of the etiologic lesion.

Limitations

This review is limited by its inclusion of predominantly observational studies supporting management options for both primary, and particularly secondary, IPH etiologies. Given the rarity of vascular malformations, moyamoya, and most etiologic causes of secondary IPH, it will be difficult to obtain substantial high-quality evidence to guide the management of these conditions. Even rarer secondary IPH causes, such as reversible cerebral vasoconstriction syndrome, cerebral proliferative angiopathy, and encephalitides, were not specifically addressed in this review.

Figure 2. Robot-Assisted Catheter Insertion for Minimally Invasive Intraparenchymal Hemorrhage (IPH) Evacuation



A noncontrast, axial computed tomographic image showing a 60-mL spontaneous IPH (panel A) managed via robot-assisted insertion of a catheter (panel B, arrowhead) for administration of tissue plasminogen activator with resultant significant drainage of the clot.

Conclusions

IPH remains a considerable source of neurological morbidity and mortality. Rapid identification, medical management, and neurosurgical management, when indicated, is essential to facilitate recovery. There is ongoing evaluation of minimally invasive approaches for evacuation of primary IPH and evolution of surgical and endovascular techniques in the management of lesions leading to secondary IPH.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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