Intracerebral Hemorrhage: An Overview of Etiology, Pathophysiology, Clinical Presentation, and Advanced Treatment Strategies

24

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Introduction

Spontaneous intracerebral hemorrhage (ICH) represents direct intraparenchymal bleeding, usually from rupture or leakage of the arterioles or small arteries of the brain. Extension or bleeding into the ventricles or subarachnoid space is common. The annual incidence for the United States ranges from 10 to 30 per 100,000. ICH accounts for 10–30% of stroke-related hospital admissions, with an overall 50% 30-day mortality. Hispanic, African Americans, and Native Americans have a higher incidence in North America. Similarly, Asiatic populations have a much higher incidence, most likely secondary to poor control of hypertension [1–9].

Etiologically, ICH can be grouped into primary spontaneous ICH, which is mainly associated with hypertension (70%) and amyloid angiopathy (30%). Secondary causes include hemorrhages due to oral anticoagulant therapy, neoplasms, vascular malformations, or aneurysms [6, 7].

Several risk factors have been identified over the last several decades for spontaneous ICH, consisting mainly of genetic aspects, pre-existing medical conditions, and lifestyle factors. Two different apolipoprotein E alleles (e2/4) have been related to an increased risk and a greater recurrence of ICH. Further genetic associations relate to ethnic differences. The most relevant prior medical history is the diagnosis of arterial hypertension which—if treated—may lead to a risk reduction of ICH in patients with cerebrovascular disease. Moreover, ICH-associated lifestyle factors include a history of smoking, drug abuse, or heavy alcohol intake. Predictive factors of poor outcome may be divided into non-modifiable or modifiable (potentially treatable) features. The initial hematoma volume, age, neurological status on admission, and ICH location are non-modifiable, whereas potentially treatable factors are avoiding hematoma growth, treating acute hydrocephalus, reducing brain edema, and managing medical comorbidities and complications [1–6, 9].

Pathophysiology

Regional Cerebral Blood Flow and Metabolism in ICH

In ICH, a localized hematoma can enlarge over time. Growth of the hematoma occurs within the first 6 h but may continue up to 24 h. Blood may dissect along white matter pathways, until regional pressure increases limit the spread of the hematoma or until the hemorrhage relieves this pressure gradient by emptying into the ventricles or the cerebrospinal fluid (CSF) space on the pial surface of the brain. Damage from the enlarging hematoma may develop directly through physical compression of the hematoma or indirectly from perihematomal ischemia (Fig. 24.1) [4–6].

Regional cerebral blood flow is also affected during ICH and occurs in specific phases (Fig. 24.1).

- The first phase, referred to as the hibernation phase, occurs within the first 48 h. During this phase, there is decreased cerebral blood flow and metabolism in both ipsilateral (predominantly in the perihematoma region) and contralateral hemispheres.
- The second phase, referred to as the reperfusion phase, occurs anywhere from 48 h to 14 days and is described by a combination of areas of hypo- and hyperperfusion in the perihematoma regions.
- The third phase, referred to as the normalization phase, occurs more than 14 days later and is characterized by normal cerebral blood flow in the localized surrounding tissue [4–6].

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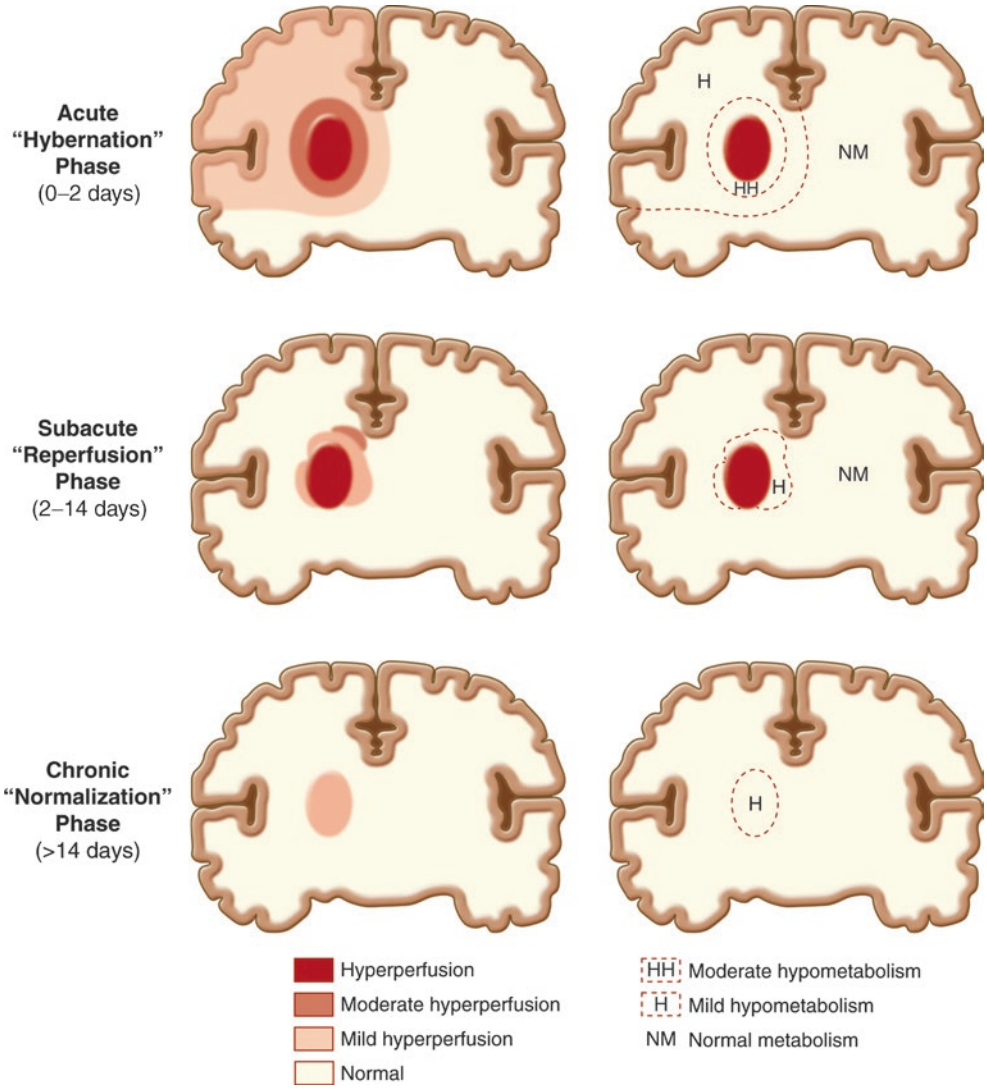

Fig. 24.1 Diagrammatic representation of the three phases of cerebral blood flow and metabolism changes in the acute, subacute, and chronic phases after intracerebral hemorrhage. (From Alqadri and Qureshi [6])

Pathophysiology

Primary ICH secondary to long-standing hypertension commonly affects the deep white matter, the basal ganglia, the thalamus, the brain stem (predominantly the pons), and the cerebellum as a result of ruptured vessels affected by hypertension-related degenerative changes. Most bleeding in hypertension-related ICH is at or near the bifurcation of small penetrating arteries that originate from basilar arteries or the anterior, middle, or posterior cerebral arteries. Small artery branches of 50–700 μm in diameter often have multiple sites of rupture; some are associated with layers of platelet and fibrin aggregates. These lesions are characterized by the breakage of elastic lamina, atrophy, and fragmentation of smooth muscle, dissections, and granular or vesicular cellular degeneration. Severe atherosclerosis including lipid deposition can affect elderly patients. Fibrinoid necrosis of the subendothelium with subsequent focal dilatations (microaneurysms) may lead to rupture in a small proportion of patients [4–6].

ICH secondary to cerebral amyloid angiopathy most commonly leads to cortical hemorrhages. Cerebral amyloid angiopathy is characterized by the deposition of amyloid-β peptide and degenerative changes (microaneurysm formation, concentric splitting, chronic inflammatory infiltrates, and fibrinoid necrosis) in the capillaries, arterioles, and small- and medium-sized arteries of the cerebral cortex, leptomeninges, and cerebellum. Cerebral amyloid angiopathy leads to sporadic ICH in elderly people, commonly associated with variations in the gene encoding apolipoprotein E. A similar syndrome exists in young patients with mutations in the gene encoding amyloid precursor protein. White matter abnormalities (e.g., leukoaraiosis) seem to increase the risk of both sporadic and familial ICH, suggesting a possible shared vascular pathogenesis.

Anticoagulant-induced ICH typically affects patients with vasculopathies related to either chronic hypertension or cerebral amyloid angiopathy [4–6].

The region surrounding hematomas are characterized by inflammation, edema, apoptosis, and necrosis. Hematomas induce injury (Fig. 24.2) by the mechanical disruption of neurons and glia. Mechanical deformation of local tissue causes secondary oligemia with subsequent neurotransmitter release and membrane depolarization, which culminates in mitochondrial dysfunction. Depending on the severity of mitochondrial dysfunction, the results of injury range from temporary metabolic suppression (hibernation phase) to cellular swelling and necrosis.

A secondary cascade of injury is initiated through the by-products of coagulation and hemoglobin breakdown. Thrombin generation activates microglia within a few hours of injury. Activated microglia release products that induce breakdown of the blood–brain barrier. This leads to the development of vasogenic edema, and direct and indirect cell death in neurons and glia.

Perihematomal edema increases in volume by about 75% in the first 24 h after ICH, peaks around 5–6 days, and lasts up to 14 days. Large edema volume relative to hematoma volume portends worse neurological outcome.

The initial size of the hemorrhage and the rate of hematoma expansion are important prognostic variables in predicting neurologic deterioration. Hematoma size >30 mL is associated with increased mortality. Following the expansion, cerebral edema forms around the hematoma, secondary to inflammation and disruption of the blood–brain barrier. This perihematoma edema is the primary etiology for neurological deterioration and develops over a period of days following the initial insult. In up to 40% of ICH cases, the hemorrhage extends into the cerebral ventricles, causing intraventricular hemorrhage (IVH). This is associated with acute obstructive hydrocephalus and also worsens prognosis. ICH and accompanying edema may also disrupt or compress adjacent brain tissue, leading to neurological dysfunction.

Displacement of brain parenchyma may cause elevation of intracranial pressure (ICP), with the potential for the development of herniation syndromes. Figure 24.3 illustrates the progression of hematoma and edema on computed tomography (CT) [4–6].

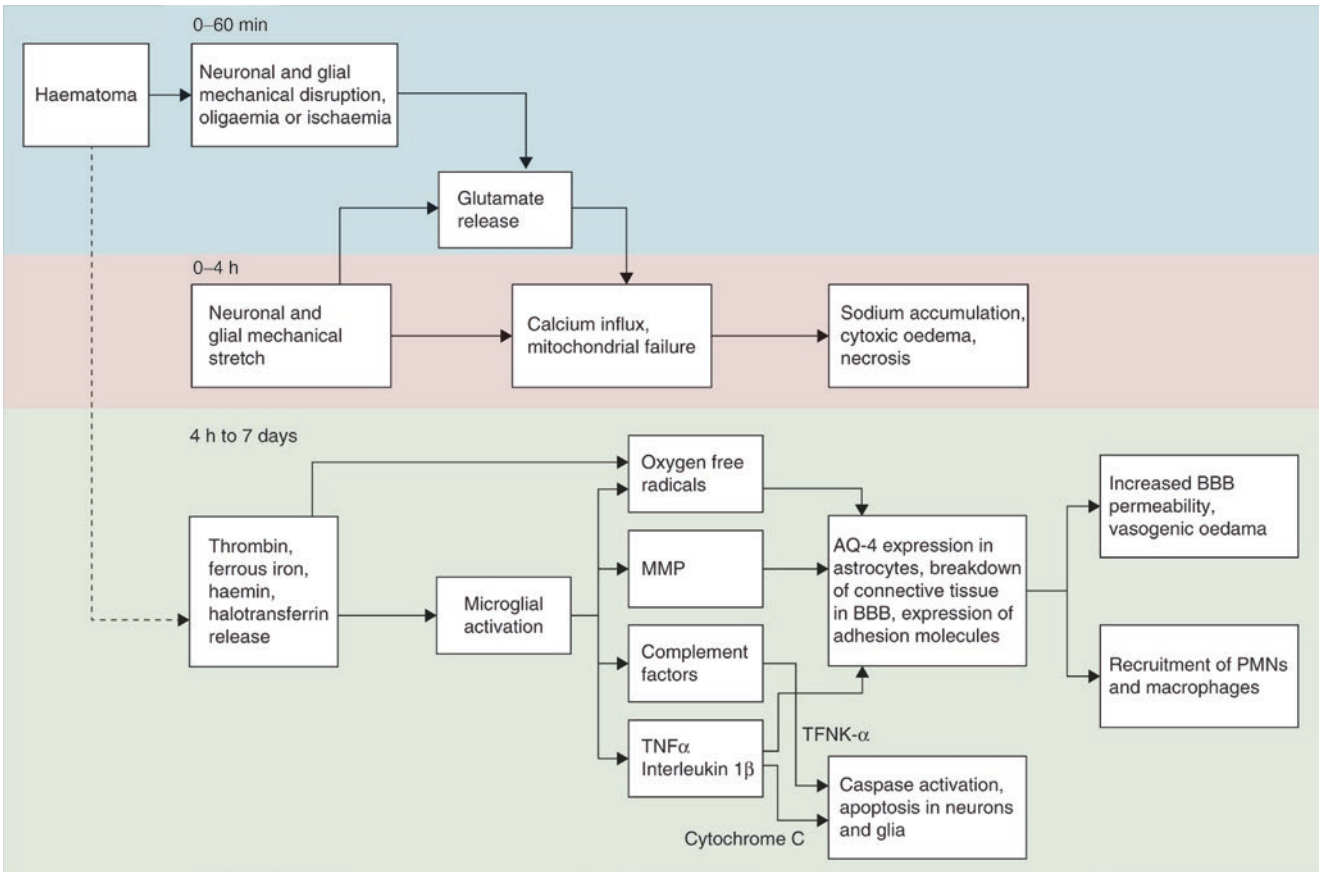

Fig. 24.2 Cascade of neural injury initiated by intracerebral hemorrhage. The initial process in the first 4 h is related to the direct effect of the hematoma, while later steps are accounted for through the release of products from the hematoma. *BBB* blood–brain barrier, *MMP* matrix metallopeptidase, *TNF* tumor necrosis factor, *PMN* polymorphonuclear cells. (From Qureshi et al. [26]. With permission from Elsevier)

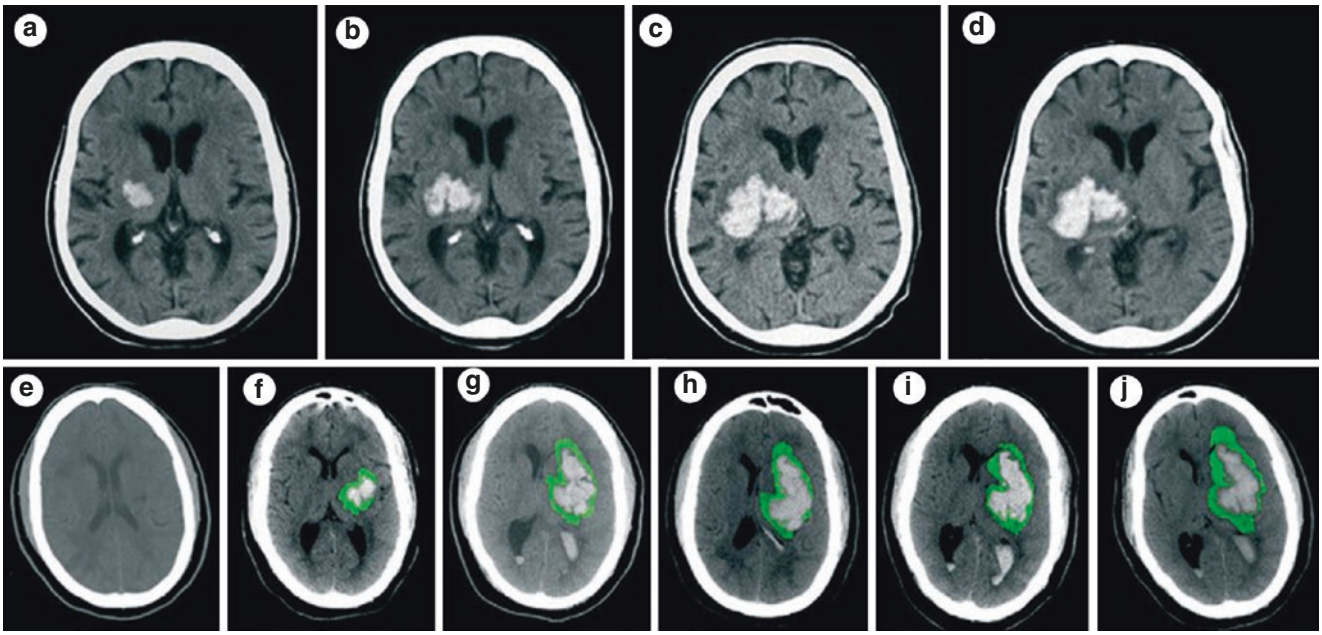

Fig. 24.3 Progression of hematoma and edema on computed tomography (CT): hyperacute expansion of hematoma in a patient with intracerebral hemorrhage on serial CT scans. Small hematoma detected in the basal ganglia and thalamus (**a**). Expansion of the hematoma after 151 min (**b**). Continued progression of the hematoma after another 82 min (**c**). Stabilization of the hematoma after another 76 min (**d**). Bottom: progression of hematoma and perihematomal edema in a patient with intracerebral hemorrhage on serial CT scans. The first scan (**e**) was acquired before the intracerebral hemorrhage. Perihematoma edema is highlighted in green to facilitate recognition of the progression of edema. At 4 h after symptom onset, there is a small hematoma in the basal ganglia (**f**). Expansion of hematoma with extension into the lateral ventricle and new mass effect and midline shift at 14 h (**g**). Worsening hydrocephalus and early perihematomal edema at 28 h (**h**). Continued mass effect with prominent perihematomal edema at 73 h (**i**). Resolving hematoma with more prominent perihematomal edema at 7 days (**j**)

Clinical Manifestation

Rapid recognition of ICH is crucial. Rapid clinical progression during the first several hours can quickly lead to neurological deterioration and cardiopulmonary instability. The classic presentation in ICH is the progressive onset of focal neurological deficits in minutes to hours, with accompanying headache, nausea, vomiting, decreased level of consciousness, and elevated blood pressure. Compared to ischemic stroke and subarachnoid hemorrhage, there is typically a more abrupt progression of focal deficits. Symptoms of headache and vomiting are also observed less often in ischemic stroke compared with ICH. Large hemorrhages may increase ICP, as evidenced through the presence of Cushing's triad—hypertension, bradycardia, and irregular respiration. Dysautonomia is also frequently present in ICH, accounting for hyperventilation, tachypnea, bradycardia, fever, hypertension, and hyperglycemia. Classic neurological deterioration is common before and during hospital admission and is related to early hematoma enlargement or late worsening of edema. Several descriptors of disease severity are predictive of early death, including age, initial score on the Glasgow Coma Scale (GCS), hematoma volume, ventricular blood volume, and hematoma enlargement [6].

The GCS is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 15 (Table 24.1).

Table 24.1 Glasgow coma scale

	1	2	3	4	5	6
Eye	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys

Stroke can often be confused with other neurological conditions that mimic stroke in their clinical presentation. The most common stroke mimics are seizure, syncope, and sepsis. Sensory symptoms such as vertigo, dizziness, and headaches are non-discriminatory between stroke and non-stroke. Furthermore, ICH is particularly difficult to diagnose because symptoms of syncope, coma, neck stiffness, seizure, diastolic blood pressure (BP) of >110 mmHg, nausea, vomiting, and headache are typically present. As a result, early neuroimaging becomes vital in the diagnosis of ICH. The most common symptoms of hemorrhagic and ischemic stroke are acute onset, limb weakness, speech disturbances, and facial weakness.

Mortality in patients with ICH is high. Various studies have reported mortalities of 31% at 7 days, 59% at 1 year, 82% at 10 years, and more than 90% at 16 years. Subsequent risk of other cardiovascular events is 2%. Lobar hemorrhages have a high rate of recurrence (4% per patient-year). Recurrent bleeding can be changed by antihypertensive treatment; whether progressive functional impairments are equally treatable is unknown. Asymptomatic disease progression is particularly common when microbleeds and white matter abnormalities are taken into account [6].

Diagnosis and Assessment

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial because early deterioration is common in the first few hours after ICH onset. More than 20% of patients will experience a decrease in the GCS score of 2 points between the pre-hospital emergency medical services assessment and the initial evaluation in the emergency department. For those patients with pre-hospital neurological decline of greater than 6 points, the mortality rate is 75%. The risk for early neurological deterioration and the high rate of poor long-term outcomes underscore the need for aggressive early management. The crucial resources necessary to manage patients with ICH include neurology, neuroradiology, neurosurgery, and critical care facilities [6].

Neuroimaging

The abrupt onset of focal neurological symptoms is presumed to be vascular in origin until proven otherwise. However, it is impossible to know whether symptoms are due to ischemia or hemorrhage based on clinical characteristics alone. Vomiting, systolic BP 220 mmHg, severe headache, coma or decreased level of consciousness, and progression over minutes or hours all suggest ICH, although none of these findings are specific; neuroimaging is, thus, mandatory. CT and magnetic resonance imaging (MRI) are both reasonable for initial evaluation. CT is very sensitive for identifying acute hemorrhage and is considered the gold standard; gradient echo and T2 susceptibility weighted MRI are as sensitive as CT for the detection of acute blood and are more sensitive for the identification of prior hemorrhage. Time, cost, proximity to the emergency department, patient tolerance, clinical status, and MRI availability may, however, preclude emergent MRI in a sizeable proportion of cases [6–8].

The high rate of early neurological deterioration after ICH is, in part, related to active bleeding. The closer symptom onset is to the first neurological image, the more likely subsequent images will demonstrate hematoma expansion. Among patients undergoing head CT within 3 h of ICH onset, 28–38% have hematoma expansion of greater than one-third on follow-up CT. Hematoma expansion is predictive of clinical deterioration and increased morbidity and

mortality. As such, identifying patients at risk for hematoma expansion is an active area of research. CT angiography and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast extravasation within the hematoma.

MRI/angiogram/venogram and CT angiogram/venogram are reasonably sensitive at identifying secondary causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis. A catheter angiogram may be considered if clinical suspicion is high or non-invasive studies are suggestive of an underlying vascular cause. Clinical suspicion of a secondary cause of ICH may include a prodrome of headache, neurological, or constitutional symptoms. Radiological suspicions of secondary causes of ICH should be invoked by the presence of subarachnoid hemorrhage, unusual (non-circular) hematoma shape, the presence of edema out of proportion to the size of the hematoma, an unusual location for hemorrhage, and the presence of other abnormal structures in the brain, like a mass. An MRI or CT venogram should be performed if hemorrhage location, relative edema volume, or signal abnormalities in the cerebral sinuses suggest cerebral vein thrombosis [6–8].

Medical Management of ICH

Acute Hemostatic Treatment

For patients being treated with oral anticoagulants (OACs) who have life-threatening bleeding, such as intracranial hemorrhage, the general recommendation is to correct the international normalized ratio (INR) as rapidly as possible. Infusions of vitamin K and fresh frozen plasma (FFP) have historically been recommended but, in general, take too long to administer and be effective in anticoagulation reversal for ICH and can have significant side effects [10–14].

More recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies. PCCs are plasma-derived factor concentrates primarily used to treat factor IX deficiency. Because PCCs also contain factors II, VII, and X in addition to factor IX, they are increasingly recommended for warfarin reversal. PCCs have the advantages of rapid reconstitution and administration, having high concentrations of coagulation factors in small volumes, and processing to inactivate infectious agents. Though different PCC preparations differ in relative amounts of factors, with factor VII the most likely to be low, several studies have shown that PCCs can rapidly normalize the INR (within minutes) in patients taking OACs. Reviews and study have shown more rapid correction of the INR with vitamin K and PCC than vitamin K and FFP, with differences in the clinical outcome as well. In fact, the US Food and Drug Administration (FDA) approved, in 2013, the use of a certain PPC (Kcentra™) which contains higher concentrations of factor VII compared to other PCCs for the urgent reversal of warfarin therapy in adult patients with acute ICH. Although PCCs may theoretically increase the risk of thrombotic complications, this risk appears to be relatively low. Despite the lack of large, well-controlled, randomized trials, PCCs are being increasingly recommended as an option in guidelines promulgated for warfarin reversal in the setting of OAC-associated life-threatening or intracranial hemorrhages. Table 24.2 provides a list of several products for factor replacement in warfarin reversal that are commercially available in the United States at the present time [10–14].

rFVIIa is also used in spontaneous ICH, as studies have shown that it reduced growth of the hematoma and improved survival and functional outcomes. However, it is not commonly used in acute warfarin reversal.

The use of antifibrinolytics was also studied for the treatment of acute ICH with a pilot study carried out to investigate their effects in halting ICH enlargement. Aminocaproic acid (Amicar™) is a derivative and analog of the amino acid lysine, which makes it an effective inhibitor for enzymes. Such enzymes include proteolytic enzymes like plasmin, the enzyme responsible for fibrinolysis. For this reason, it is effective in the treatment of certain bleeding disorders. The study concluded it was unlikely that the rate of ICH enlargement in patients given Amicar within 12 h of ICH is less than the natural history rate, although the treatment appeared to be safe.

A direct antibody has been developed to reverse the effects of dabigatran. Further studies with these types of agents are warranted [10–14].

Current Guidelines on the Management of Acute Hypertensive Response

The current guidelines for hypertension in ICH are based on incomplete evidence, since there are still ongoing trials of BP intervention. However, certain factors are generally taken into account, such as chronic hypertension, age, time of onset and presentation, maintaining mean arterial pressure (MAP) between the therapeutic range of 90 and 130 mmHg, and targeting cerebral perfusion pressure maintenance at >70 mmHg if there is evidence of increased ICP [14–20]. Suggested guidelines for treating elevated BP in spontaneous ICH, as recommended by the American Stroke Association (ASA) and the American Heart Association (AHA), include the following:

– If a patient presents with a systolic blood pressure (SBP) of >200 mmHg or MAP of >150 mmHg, then aggressive

Table 24.2 Products for factor replacement in warfarin reversal

Product	Factor(s)	Dose (consultation with a hematologist is recommended for specific dosing)	Uses
Fresh-frozen plasma	I (fibrinogen), II, V, VII, IX, X, XI, XIII, antithrombin	10–15 mL/kg with ideal recovery would raise factor levels by 15–20%	OAC reversal
			Consumptive coagulopathy Hepatic dysfunction
Cryoprecipitate	I, VIII, XIII, VWF	1–2 U/10 kg	Hypo/a-fibrinogenemia
			Lack of factor-specific products for factor VIII deficiency or VWD factor XIII deficiency
Prothrombin complex concentrates			
	II, IX, X (small amounts of VII)	Assayed in factor IX activity	Factor IX deficiency (hemophilia B)
Bebulin VH (Baxter), Profilnine SD (Grifols), Kcentra (CSL Behring)		Both Bebulin and Profilnine are three-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. Kcentra is a four-factor PCC	OAC reversal (not FDA-approved)
		Dosing for factor IX deficiency—1 U/kg raises activity by 1%	
		Dosing for OAC reversal has not been well established	
NovoSeven RT (Novo Nordisk)	Recombinant activated VII	Higher risk of thromboembolic complications with higher doses	Factor VIII or IX deficiency with inhibitors to factor VIII or IX
		For hemophilia A or B patients with inhibitors, 90 μg/kg every 2 h	Congenital factor VII deficiency
		For factor VII-deficient patients, 15–30 μg/kg every 4–6 h	Not recommended for spontaneous ICH or OAC reversal
Factor VIII concentrates			
Plasma-derived	VIII	Each factor VIII unit/kg raises the plasma factor VIII level by 2% (typically, a 50-U/kg dose is used to raise the factor VIII level to 100%)	Factor VIII deficiency (hemophilia A)
Alphanate (Grifols)[a,b]			
Humate-P (CSL-Behring)[a,b]			
Koate-DVI (Bayer)[a]			
Wilate (Octapharma)[a,b]			
Immunoaffinity purified			
Hemofil-M (Baxter)			Wilate is not indicated for hemophilia A
Monarc-M (Baxter)			
Monoclate-P (CSL-Behring)			
Recombinant			
Advate (Baxter)			
Helixate FS (CSL-Behring)			
Kogenate FS (Bayer)			
Recombinate (Baxter)			
Xyntha (Wyeth)			
Factor IX concentrates			
Plasma-derived	IX	Each factor IX unit/kg raises the plasma level by 1% (typically, a 100-U/kg dose is used to raise the level to 100%)	Factor IX deficiency (hemophilia B)
AlphaNine SD (Grifols)			
Mononine (Baxter)			
Recombinant			One unit of BeneFix raises the plasma level by 0.83%, so 120 U/kg raises the activity to 100%
BeneFix (Wyeth)			

From Morgenstern et al. [37]

VWD von Willebrand disease, *FDA* US Food and Drug Administration, *PCCs* prothrombin complex concentrates

[a]Also contains von Willebrand factor

[b]Indicates for von Willebrand disease (dose by ristocetin cofactor units; ratio of factor VIII to ristocetin cofactor unit varies by product)

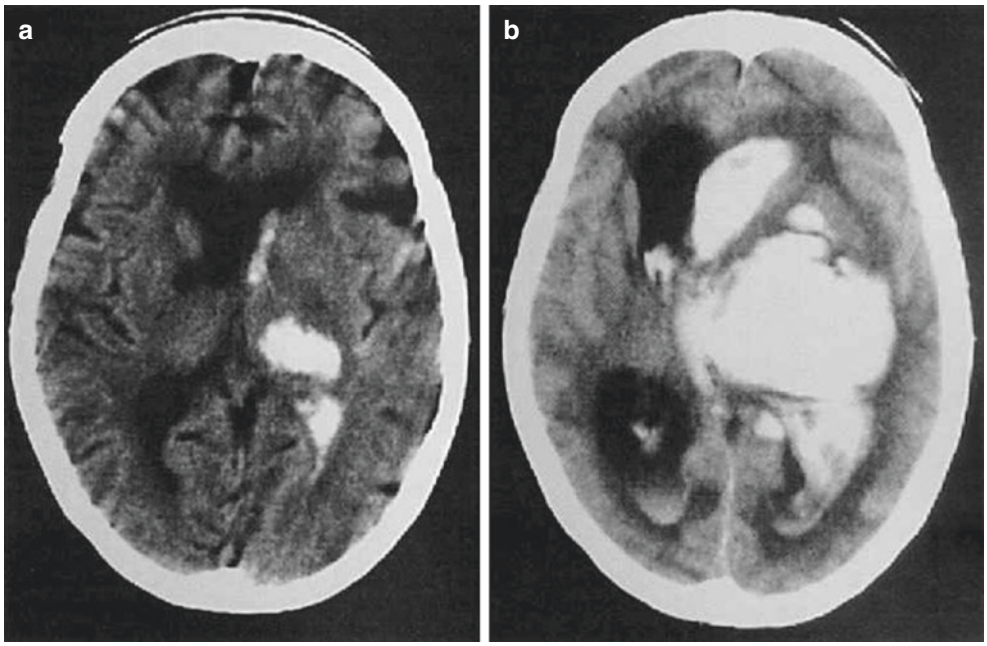

Fig. 24.4 Illustrates lack of BP control. (**a**) Initial head CT, (**b**) head CT in the same patient whose SBP was consistently more than 140 mmHg

lowering of BP is recommended with continuous intravenous (IV) infusion of antihypertensive medications (i.e., labetalol, nicardipine, esmolol, hydralazine, nitroprusside, or nitroglycerine). If the patient presents with an SBP of >180 mmHg or MAP of >130 mmHg with suspected increased ICP, monitor ICP and use intermittent or continuous IV antihypertensives mentioned above to maintain cerebral perfusion pressure at a safe range of >50–70 mmHg. If a patient presents with an SBP of >180 mmHg or MAP of >130 mmHg with no increase in ICP and then moderately reduce BP using intermittent or continuous IV antihypertensives.

– In patients presenting with a systolic BP of 150–220 mmHg, acute lowering of systolic BP to 140 mmHg is probably safe and desirable (new recommendation).

Acute hypertensive response is defined as "SBP≥140 mmHg or diastolic BP of ≥90 mmHg demonstrated on two recordings taken 5 min apart within 24 h of symptom onset." A large prevalence study showed that 75% of ICH patients presented with SBP more than 140 mmHg. Recent data have highlighted the importance of acute hypertensive response as a therapeutic target. The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial and Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) have shown that reducing the SBP to 140 mmHg is well tolerated and associated with reduction of hematoma expansion. The effect of lowering BP on death and severe disability was evaluated by both the phase III ATACH II and INTERACT 2 trials and showed both outcomes to be similar in both the control and experimental groups [15–21].

Figure 24.4 illustrates the importance of aggressive SBP control. Table 24.3 provides the major trials looking at BP management in ICH.

Seizure in ICH

Eight percent of patients with ICH have clinical seizures within 1 month of symptom onset, associated with lobar location or hematoma enlargement. However, continuous electroencephalographic monitoring in an observational study showed that 28% of patients with ICH had (predominantly subclinical) seizures within the first 72 h of admission. Seizures were associated with neurological worsening, an increase in midline shift, and poorer outcomes. Therefore, a low threshold for obtaining electroencephalographic studies and the use of anticonvulsants in patients with ICH might be advisable. Patients who have a seizure more than 2 weeks after ICH onset are at greater risk of recurrent seizures than those who do not and might need long-term prophylactic treatment with anticonvulsants [22–25].

Management of Intraventricular Hemorrhage and Hydrocephalus

Clinical trials have confirmed that IVH and hydrocephalus are independent predictors of poor outcome in spontaneous ICH. Impaired flow of CSF and direct mass effects of ventricular blood lead to obstructive hydrocephalus. External drainage of CSF through ventricular catheters reduces intracranial

Table 24.3 Major trials assessing BP management in ICH [6]

Time period	ATACH I 2004–2008	INTERACT 1 2005–2007	ATACH II 2010–2015	INTERACT 2 2008–2012
Study design	Prospective, multicenter, randomized, safety, efficacy study, open-label	Randomized, active-control, parallel-assignment, safety, efficacy study, open-label	Randomized, multicenter, parallel-assignment, treatment efficacy study, open-label, phase III	Randomized, multicenter, parallel-assignment, safety, efficacy study, open-label
No. of cases	60	404	1280	2800
Inclusion criteria	ICH on CT	ICH on CT	ICH on CT	ICH on CT
	<6 h of symptom onset	<6 h of symptom onset	<3 h of symptom onset	<6 h of symptom onset
	SBP ≥170 mmHg	SBP 150–220 mmHg on ≥2 readings	SBP ≥180 NIHSS score ≥4	SBP 150–220 mmHg on ≥2 readings
	GCS ≥8		GCS score ≥5	
	Hematoma volume <60 cc		Hematoma volume <60 cc	
Intervention	Patients randomized to three tiers of SBP reduction with IV Nicardipine:	Patients randomized to two target groups with IV antihypertensives:	Patients randomized to two target BP groups with IV Nicardipine +/− IV Labetalol for 24 h:	Patients randomized to two target groups with IV antihypertensives:
	170–200 mmHg 140–170 mmHg 110–140 mmHg	Control: BP ≤180 mmHg	Control: 140–180 mmHg	Control: BP ≤180 mmHg
		Intensive therapy: BP ≤140 mmHg	Intensive therapy: 110–140 mmHg	Intensive therapy: BP ≤140 mmHg
Outcomes	Target treatment goals maintained and achieved for 18–24 h post-ictus. Safety and tolerability achieved	Target treatment goals maintained for 24 h. Safety and tolerability achieved	Ongoing trial	Ongoing trial

ICH intracerebral hemorrhage, *CT* computed tomography, *SBP* systolic blood pressure, *GCS* Glasgow Coma Scale, *NIHSS* National Institutes of Health Stroke Scale, *IV* intravenous, *BP* blood pressure

pressure but has an inherent risk for developing infections and clotting off. Shortening the length of external ventricular drainage with early ventriculoperitoneal shunt placement or lumbar drainage for communicating hydrocephalus might lower the rate of infections. Substitution of lumbar drainage for external ventricular drainage in patients with communicating hydrocephalus might also lessen the need to change temporary ventricular catheters [18, 26–28].

IVH is a dynamic process that follows ICH. The presence of IVH at any time and growth of this hemorrhage increase the likelihood of death or severe disability by 90 days. To facilitate early and effective clearance of blood in the ventricles, recent efforts have focused on the intraventricular use of thrombolytic drugs in patients who have IVH in association with spontaneous ICH. Clinical trials have not clearly shown improved neurological outcome in survivors of IVH. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR-IVH) trial is investigating this issue [18, 26–28].

Deferoxamine

Hemoglobin degradation products, in particular iron, have been implicated in secondary neuronal injury following ICH. The iron chelator deferoxamine (DFO) mesylate exerts diverse neuroprotective effects, reduces perihematoma edema and neuronal damage, and improves functional recovery after experimental ICH in animal models. It is hypothesized that treatment with DFO could minimize neuronal injury and improve outcome in ICH patients. As a prelude to test this hypothesis, a phase I, open-label study to determine the tolerability, safety, and maximum tolerated dose (MTD) of DFO in patients with ICH was done. Intravenous infusions of DFO in doses up to 62 mg/kg/day (up to a maximum of 6000 mg/day) were well tolerated and did not seem to increase serious adverse events or mortality. As a result, a multicenter, double-blind, randomized, placebo-controlled, phase II clinical trial [Intracerebral Hemorrhage Deferoxamine (iDEF) trial] was initiated to determine if it is futile to move DFO forward to phase III efficacy evaluation. It is currently in phase II [29].

Surgical Evacuation

Surgical evacuation may prevent expansion, decrease mass effects, block the release of neuropathic products from hematomas, and, thus, prevent the initiation of secondary injury. The Surgical Trial for Intracerebral Hemorrhage (STICH) compared early surgery (median time of 20 h from presentation to surgery) with medical treatment. Overall, the results did not show any improvement with open surgery; however, hematomas extending to within 1 cm of the cortical surface had a trend toward more favorable outcome with surgery within 96 h. STICH II was designed to evaluate this subgroup,

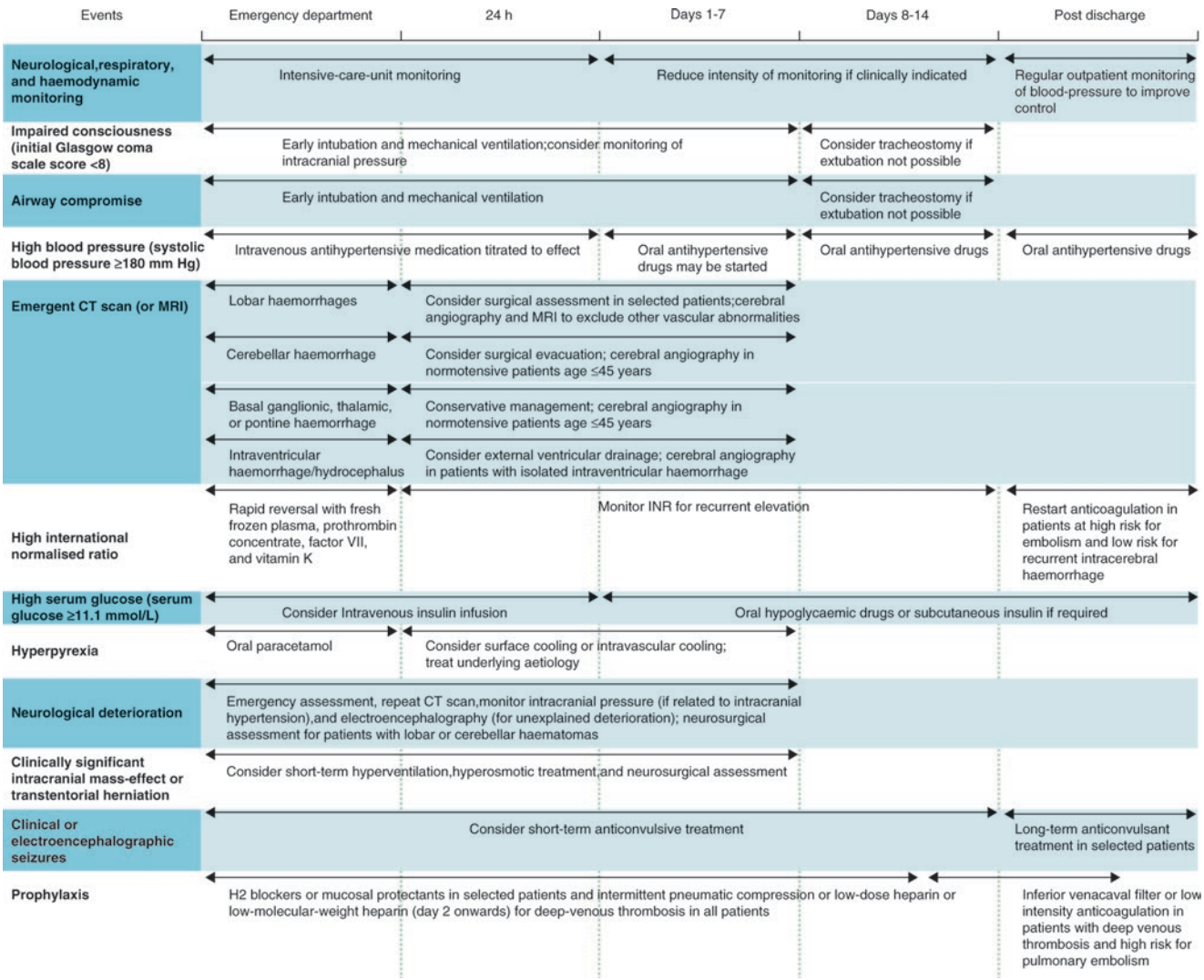

Fig. 24.5 Management algorithm for patients with intracerebral hemorrhage

which revealed only a marginal benefit in this subgroup. The failure of open surgery to provide significant benefit has led to the study of minimally invasive techniques to remove deep hematomas. Preliminary work has been encouraging and phase III trials are currently being developed [30–36].

Cerebellar hemorrhages, however, are treated differently to supratentorial hemorrhages. According to the AHA/ASA guidelines, patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible. Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (new recommendation). To limit neural damage and the risk of recurrent bleeding associated with open craniotomy, studies are now focusing on less invasive stereotactic and endoscopic evacuation with the use of thrombolytic drugs [30–36] (Fig.24.5).

Conclusion and Future Studies

Clinical evidence suggests the importance of three management tasks in ICH: limiting hematoma expansion, removing the clot or preventing secondary injury from developing, and controlling cerebral perfusion pressure. The precision needed to achieve these goals and the degree of benefit attributable to each clinical goal will be clarified as the results of trials in progress become available. An NIH workshop identified the importance of animal models of ICH and of human pathology studies. The use of real-time, high-field MRI with three-dimensional imaging and high-resolution tissue probes

is another priority. Trials of acute BP treatment and coagulopathy reversal are also medical priorities. Trials of minimally invasive surgical techniques including mechanical and pharmacological adjuncts are surgical priorities. A better understanding of methodological challenges, including the establishment of research networks and multispecialty approaches, is also needed. New information created in each of these areas should add substantially to our knowledge about the efficacy of treatment for ICH [37].

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