

Section 1
Chapter

Epidemiology

The epidemiology of intracerebral hemorrhage

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Introduction

Advances in brain imaging have dramatically changed our understanding of intracerebral hemorrhage (ICH). In the pre-CT era, many small ICHs were misclassified as ischemic strokes and patients with massive ICH or subarachnoid hemorrhage (SAH) were often difficult to correctly classify. This chapter reviews the epidemiology of non-traumatic ICH in light of modern neuroimaging and includes discussions of the incidence, etiology, clinical presentation, and natural history of this condition.

Incidence of intracerebral hemorrhage

Intracerebral hemorrhage accounts for 10–15% of all strokes in Western populations and is defined as the non-traumatic, abrupt onset of severe headache, altered level of consciousness, or focal neurological deficit associated with a focal collection of blood within the brain parenchyma on neuroimaging or at autopsy which is not due to trauma or hemorrhagic conversion of a cerebral infarction [1].

The incidence of ICH is defined as the percentage of a population experiencing a first ICH in a given time period (usually a year). When reviewing studies of ICH incidence it is important to consider the criteria utilized, as investigators may include or exclude hemorrhages associated with vascular malformations, anticoagulants, thrombolytic agents, or illicit drugs. Comparisons of incidence rates are further complicated by methodological differences in case ascertainment, imaging rates, variations in population structure, and the range of ages reported.

Given these limitations, incidence rates of ICH in the Western hemisphere during the CT era have generally ranged from 10 to 30 cases per 100 000 persons

[2–11]. Intracerebral hemorrhage incidence rates are higher in eastern Asia, where ICH has historically accounted for a larger percentage of all strokes than in Western populations [12–14]. This balance may be changing due to declining rates of ICH in the East [12,15,16].

The incidence of ICH declined between the 1950s and the 1980s [17–19]. Studies of incidence trends in subsequent years have produced mixed results. There was a trend toward a reduction in ICH incidence in Oxfordshire, England between 1981 and 2006 [20]. Intracerebral hemorrhage incidence also declined during the 1990s in several Chinese cities [12]. However, similar declines have not been seen in other studies [2,8,21,22]. The stabilization of ICH incidence in the last two decades is at least partially attributable to the detection and proper classification of small hemorrhages with modern neuroimaging [8,23,24].

Risk for ICH appears to be marginally greater in men than in women, driven by an excess of deep hemorrhages [11,25,26]. In the United States blacks and Hispanics have significantly higher rates of ICH than whites [11,27]. Among blacks and Hispanics, the excess risk of ICH is most notable in young and middle-aged persons (Table 1.1) [11,27,28].

The predominant location of ICH within the brain varies in different populations (Table 1.2). In the United States, Europe, and Australia, deep cerebral ICH (hemorrhage originating in the periventricular white matter, caudate nucleus, internal capsule, putamen, globus pallidus, or thalamus) is most common, followed closely by lobar hemorrhages originating in the gray matter or subcortical white matter. In a large population-based study in Japan, however, lobar hemorrhage accounted for only 15% of ICHs [13].

Section 1: Epidemiology

Table 1.1. Age-specific risk ratios for ICH defined by location in the Greater Cincinnati Area, black vs. white*

Age	Lobar		Deep		Brainstem		Cerebellum	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
20–34	2.1	0.5–9.3	2.1	0.5–9.3	0	0–20.1	0	0.67
35–54	3.7	2.1–6.7	4.5	3.0–6.8	9.8	4.2–23.0	4.0	1.5–10.8
55–74	1.7	1.1–2.7	2.3	1.7–3.3	3.0	1.2–7.4	0.8	0.2–2.4
75–84	1.2	0.7–2.0	1.1	0.7–1.8	3.6	1.2–11.1	0.7	0.2–2.1
85+	1.0	0.4–2.2	0.9	0.4–1.9	0	0–3.3	0.6	0.1–3.7
All	1.4	1.0–1.8	1.7	1.4–2.1	3.3	2.0–5.5	0.9	0.5–1.6

Notes: *Risk ratio calculated from unadjusted incidence rates.
RR = risk ratio, RR > 1 indicates greater risk among blacks.
Source: From [11].

Table 1.2. Proportional distribution of ICH in different studies

	Total ICH	Lobar (%)	Deep (%)	Brainstem (%)	Cerebellum (%)
Greater Cincinnati [11]	1038	359 (35)	512 (49)	65 (6)	102 (10)
Izumo City, Japan [13]	350	53 (15)	242 (69)	30 (9)	25 (7)
Southern Sweden [148]	341	176 (52)	121 (36)	15 (4)	29 (9)
Jyväskylä region, Finland [9]	158†	53 (34)	77 (49)	11 (7)	17 (11)
Dijon, France [149]	87	16 (18)	58 (67)	5 (6)	8 (9)
Perth, Australia [150]	60*	19 (32)	31 (52)	4 (7)	6 (10)

Notes: †Includes 9 intraventricular hemorrhages, here included in the deep group.
*Includes 13 “massive cortical” hemorrhages, here included in the deep group.
Source: From [11].

In most populations, cerebellar hemorrhage accounts for approximately 10% of ICH and brainstem hemorrhage for 5–10% of ICH (Table 1.2). In the United States, the greatest excess risk of ICH in blacks and Hispanics as compared to whites occurs in deep cerebral and brainstem locations (Table 1.1) [11,28].

Risk factors for intracerebral hemorrhage

Age and race

Age is the greatest risk factor for ICH. Incidence rates increase dramatically among persons older than 60 (Fig. 1.1). As discussed previously, there are geographic and racial variations in ICH incidence. Studies to date have not determined whether these variations can be explained entirely by known risk

factors or whether there are additional factors, possibly genetic, which remain undiscovered.

Hypertension

Hypertension is the most important and prevalent modifiable risk factor for ICH. In the biracial population of Greater Cincinnati during 1988, the presence of hypertension among patients with ICH was remarkably similar for whites (73%), African-Americans (71%), men (72%), and women (73%) [29]. Untreated hypertension is a greater risk factor than treated hypertension, and hypertensive patients who discontinue their medications have greater risk than those who continue them [30,31].

Among modifiable risk factors for ICH, hypertension accounts for the greatest attributable risk for hemorrhage in deep hemispheric and brainstem

locations [32]. The role of hypertension in lobar ICH is less clear, but accumulating evidence suggests hypertension is also a risk factor for hemorrhage in this location (albeit less potent) [31,33]. The relative effect of hypertension as a risk factor for ICH is greater in younger patients than the elderly [31,34]. In one case-control study the odds ratio for hypertension in ICH fell from 7.7 among patients age

15–54 years to 1.3 among those aged 65–74 years [31]. Treatment trials for hypertension have shown reduced ICH risk with improved blood pressure control [35,36].

The use of illicit sympathomimetic drugs, particularly cocaine and amphetamines, has been associated with hemorrhagic stroke in some (but not all) studies [37–39]. This relationship may be due to drug-induced hypertension or drug-induced cerebral vasculitis.

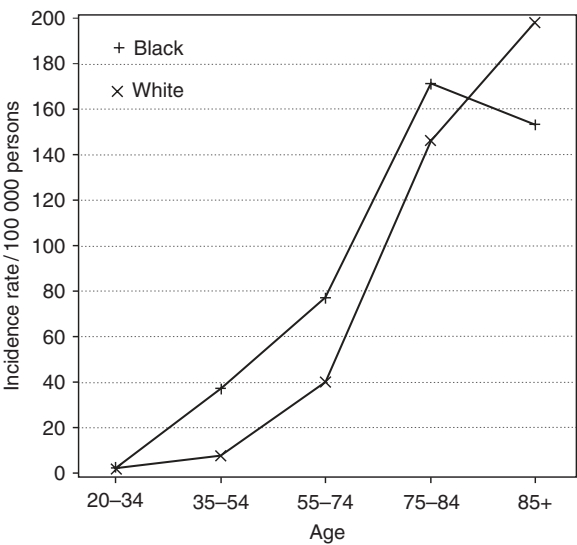


Fig. 1.1 Annual age-specific, race-stratified incidence rates of ICH per 100 000 persons in the Greater Cincinnati/Northern Kentucky region, 1998–2003 (author’s unpublished data).

Cerebral amyloid angiopathy

Once thought to be a rare cause of ICH, cerebral amyloid angiopathy (CAA) is now considered an important cause of lobar hemorrhage in the elderly (Fig. 1.2) [40–42]. Its principal pathological feature is the deposition of amyloid protein in the media and adventitia of leptomeningeal arteries, arterioles, capillaries, and, less often, veins [40–44]. The hypothesized pathogenesis of ICH due to CAA involves destruction of the normal vascular structure by deposition of amyloid in the media and adventitia and subsequent miliary aneurysm formation or double barreling and fibrinoid necrosis [40–42]. The brittle blood vessels and microaneurysms may then be prone to rupture in response to minor trauma or sudden changes in blood pressure [19]. Cerebral amyloid angiopathy may also be responsible for transient neurological symptoms and dementia with leukoencephalopathy [45].

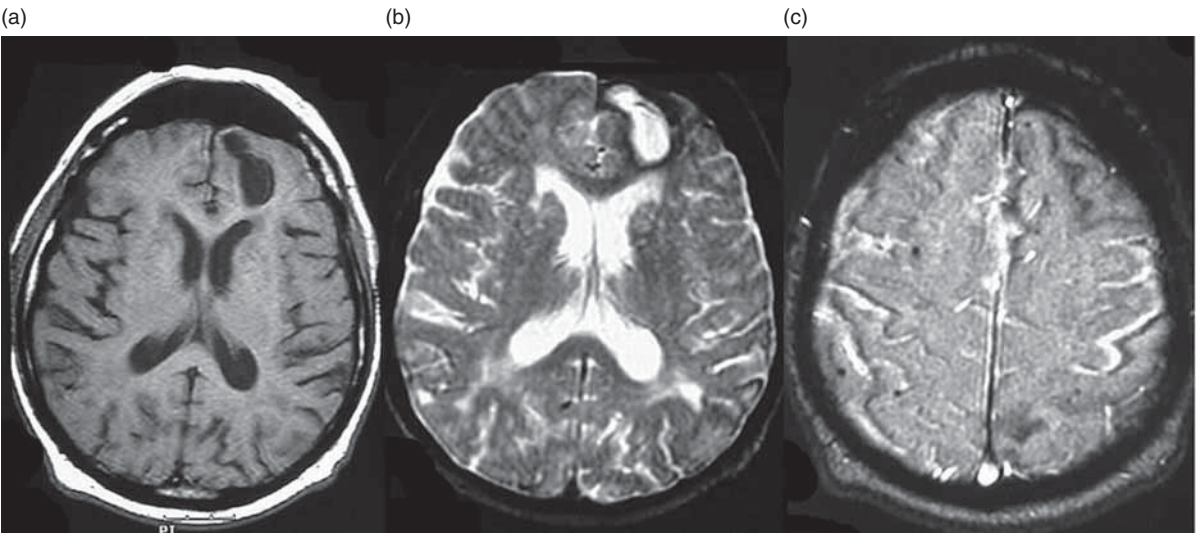


Fig. 1.2 Gradient echo MRI of a patient with previous microhemorrhages in multifocal regions typical of cerebral amyloid angiopathy. (a) T1-weighted image demonstrating an old lesion in the left frontal lobe. (b) T2-weighted image demonstrates a hemosiderin ring around the left frontal lesion. (c) Gradient echo imaging reveals microbleeds in the right frontal and parietal lobes.

Section 1: Epidemiology

Amyloid protein becomes increasingly frequent in cortical blood vessels with advancing age, affecting only 5–8% of persons age 60–69 years but 57–58% of those age 90 years or older [46, 47]. The deposition of amyloid is most prominent in the parieto-occipital regions and is rarely found in the basal ganglia or brainstem [40–43]. Cerebral amyloid angiopathy equally affects men and women [41].

Apolipoprotein E and CAA

The relationship of Apolipoprotein E and CAA is discussed in more detail in Chapter 4. Several studies have examined the relationship of Apolipoprotein E ε2 and ε4 with lobar ICH and CAA [32,33,48–51].

In a population-based, case-control study of hemorrhagic stroke in Greater Cincinnati/Northern Kentucky (the Genetic and Environmental Risk Factors for Hemorrhagic Stroke, or GERFHS, study), cases of lobar ICH were age-, race-, and gender-matched to controls from the same population, allowing investigators to control for putative ICH risk factors and determine the prevalence of Apolipoprotein E genotype in the population from which cases were identified. After controlling for the presence of hypertension, hypercholesterolemia, frequent alcohol use, smoking history, and other risk factors, Apolipoprotein E ε4 was found to be an independent risk factor for lobar ICH but not non-lobar ICH. In addition, haplotypes inferred using 12 markers over the 5' untranslated region, promoter region, and exons of the Apolipoprotein E gene identified significant association with lobar ICH, which suggests that regulation of the gene may affect the risk of disease [33].

Aneurysms and vascular malformations

Although ruptured berry aneurysms typically cause SAH, on occasion bleeding is directed into the brain parenchyma without significant subarachnoid extension [52]. Vascular malformations associated with ICH include arteriovenous malformations (AVMs), cavernous malformations, dural arteriovenous fistulae, venous malformations, and capillary telangiectasias [53]. Reports of ICH mechanism suggest that aneurysms and vascular malformations are particularly important as a cause of ICH among young people [52,54–56]. In a prospective autopsy series, 4% of all brains were found to have vascular malformations, of which 63% were venous malformations. This

Table 1.3. Comparison of the frequency of vascular malformations in autopsy series vs. series of symptomatic ICH patients

	Population-based autopsy [151]	ICH patients autopsy [152]
Venous	105 (63%)	2 (1.3%)
Telangiectasia	28 (17%)	1 (0.6%)
Arteriovenous	24 (14%)	159 (88%)
Cavernous	16 (10%)	6 (3%)
Mixed type	N/A	11 (6%)

Note: Some patients had more than one type of malformation. N/A = not reported.

contrasts starkly with lesions that cause hemorrhage as reported by autopsy (Table 1.3). While venous malformations are the most common lesions in the general population, they are associated with only a small percentage of ICH cases. Similarly, cerebral telangiectasias are more common at autopsy than AVMs or cavernous malformations but rarely hemorrhage. The natural history, clinical evaluation, and management options for intracranial vascular malformations have been recently reviewed [53].

Anticoagulant- and thrombolytic-associated ICH

The use of warfarin for prevention of ischemic stroke among patients with atrial fibrillation increased significantly during the late 1980s and 1990s following publication of the Stroke Prevention in Atrial Fibrillation (SPAF) trials, European Atrial Fibrillation Trial, and other important studies on this topic [57–60]. Warfarin distribution in the United States quadrupled on a per-capita basis during the 1990s [61]. During the same period, the incidence of anticoagulant-associated intracerebral hemorrhage (AAICH) quintupled in the Greater Cincinnati region [61]. Studies from other regions have shown similar trends [62,63].

In most trials of warfarin for treatment of atrial fibrillation or myocardial infarction the risk of AAICH has ranged from 0.3% to 1.0% per patient-year, with risk on the lower end of this spectrum in more recent studies [64,65]. Several trials have tested warfarin for secondary stroke prevention in patients with cerebral ischemia of non-cardiac origin. The Warfarin-Aspirin Recurrent Stroke Study (WARSS)

compared aspirin to warfarin (goal INR 1.4–2.8), and found no difference between groups in effectiveness or risk of major hemorrhage (including ICH) [66]. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) compared aspirin to high intensity warfarin (goal INR 3.0–4.5) [67]. It was stopped before completion because of a 7.0% annual risk of major hemorrhage in the warfarin group, including a 3.7% annual risk of intracranial bleeding [68].

Studies of anticoagulation outside of clinical trials show that well-managed warfarin at conventional INRs can produce acceptable rates of ICH (similar to or slightly higher than in trials); however, the hemorrhage risk must be balanced against the benefit of anticoagulation for each patient [64,69–72]. The relative risk of ICH in anticoagulated patients as compared to the general population is approximately 7–10 [64,69]. Data from clinical trials and community surveillance suggest that clinical factors that increase the risk of AAICH are advanced age, prior ischemic stroke, hypertension, leukoaraiosis, and higher intensity of anticoagulation [64,65,68]. The addition of antiplatelet agents to warfarin probably increases the risk compared to warfarin alone [64,65,73]. Strict management of blood pressure and INR in anticoagulated patients reduces the risk of hemorrhage [65].

Thrombolysis for myocardial infarction carries a small but definite risk of intracranial hemorrhage. Rates of intracranial hemorrhage in this setting have generally ranged from 0.4% to 1.5% of patients treated with various regimens of thrombolytic agents and anticoagulants [74–76]. Risk factors for hemorrhage after thrombolysis for myocardial infarction include older age, female sex, black race, hypertension, prior stroke, excessive anticoagulation, and lower body weight [74,76,77]. In the large GUSTO-1 trial, the majority of such hemorrhages were intraparenchymal (81%) or intraparenchymal plus subdural (15%), with relatively few pure subdural (3%) or pure intraventricular (1%) bleeds [75]. Among intraparenchymal hemorrhages, the majority (77%) occurred in lobar regions of the brain [75]. Intraventricular (49%) and subarachnoid (11%) extension of bleeding was relatively common [75].

Thrombolytic treatment of ischemic stroke carries a greater risk of intracranial hemorrhage than thrombolysis for myocardial infarction, but discussion of this matter is beyond the scope of this chapter [78].

Antiplatelet drugs

Antiplatelet drugs probably increase the risk of ICH by a small amount [79]. The absolute risk of intracranial hemorrhage among elderly persons taking aspirin has been estimated at 0.2–0.3% annually (vs. 0.15% in similar persons not taking antiplatelets or anticoagulants) [65]. This risk increases with age and aspirin doses > 325 mg daily [79,80]. In trials comparing the antiplatelet agents clopidogrel or ticlopidine to aspirin among patients at high risk of vascular events, rates of intracranial hemorrhage were similar between groups [81]. However, the combination of aspirin plus clopidogrel led to more intracranial hemorrhages than clopidogrel alone when used for secondary stroke prevention in the MATCH trial [65,82]. A meta-analysis of trials using dipyridamole for secondary stroke prevention found the combination of aspirin and dipyridamole did not cause more bleeding than aspirin alone, although specific rates for intracranial hemorrhage were not reported [83].

Cerebral microbleeds

The use of gradient echo MRI to detect small, asymptomatic hemorrhages in the brain parenchyma (“microbleeds”) has received considerable recent attention. Gradient echo MRI accentuates signal dropout from chronic blood products and is more sensitive at detecting small hemorrhages than standard T2 sequences [84,85]. The prevalence of microbleeds in the general population is best estimated from two studies of middle-aged and elderly adults without known cerebrovascular disease or dementia, in which microbleeds were found in 6.4% and 4.7% of the respective populations [86,87]. Microbleeds are associated with both ischemic (especially lacunar) and hemorrhagic cerebrovascular disease as well as hypertension, leukoaraiosis, advancing age, and male gender [86–89]. Microbleeds are common in hemorrhagic stroke, occurring in 54–71% of ICH patients (Fig. 1.2) [90]. They appear to be equally prevalent in cases of deep cerebral and lobar hemorrhage, and are therefore not specific for amyloid angiopathy or hypertensive ICH; however, in some studies the location of microbleeds has correlated with the site of symptomatic hemorrhage (i.e., deep cerebral microbleeds are associated with deep cerebral ICH while lobar microbleeds are associated with lobar ICH) [91,92]. Many clinicians consider microbleeds to be markers of small-vessel disease and a hemorrhage-prone state.

Section 1: Epidemiology

Although microbleeds have been associated with a variety of demographic variables and disease states, their practical value in predicting hemorrhage risk is less clear. A small, prospective Chinese study scanned 121 acute stroke patients with gradient echo MRI and found that 35.5% had microbleeds. Over a mean follow-up of 27.2 months, 4 patients (9.3%) with microbleeds had a subsequent ICH, compared to 1 patient (1.3%) without microbleeds ($p = 0.053$) [93]. Additionally, in a referral-based study of lobar ICH patients, increasing burden of microbleeds was shown to predict recurrent hemorrhage [94]. However, these studies are too small to guide patient management at present. The power of microbleeds to predict subsequent hemorrhagic and ischemic cerebrovascular disease and the value they might add to risk-benefit analyses for antiplatelet or anticoagulant use are important questions which remain unanswered.

Prior cerebral infarction

Prior cerebral infarction is associated with a 5- to 22-fold increased risk of ICH [32,95,96]. The strong relationship between ICH and cerebral infarction is not surprising since hemorrhage and infarction share similar risk factors, such as hypertension. In the GERFHS case-control study in Greater Cincinnati 15% of ICH patients had a history of previous ischemic stroke; the multivariate odds ratio for ICH in patients with prior stroke compared to controls was 7.0 [32].

Hypocholesterolemia

While hypercholesterolemia is a risk factor for cardiac disease and ischemic stroke, hypocholesterolemia appears to increase risk of ICH. Data from case-control studies have been mixed, but the preponderance of evidence supports an inverse relationship between cholesterol levels and ICH risk [26,97–102]. This relationship is also supported by several cohort studies [26]. Potential explanations for the association of low cholesterol and ICH include reduced platelet aggregation, increased fragility of the cerebral vasculature, and confounding by medical illness or nutritional deficiencies [98]. Given these findings, there is theoretical concern that widespread use of cholesterol lowering medications may increase rates of ICH. Analysis of the GERFHS study showed that hypercholesterolemia was protective for ICH, but that statin use was not associated with increased ICH risk [97].

Large randomized trials of statin drugs for primary and secondary prevention of cardiovascular disease have not shown increased ICH rates [103,104]. However, a randomized trial of high-dose atorvastatin versus placebo for patients with transient ischemic attack or stroke did find a trend toward more hemorrhagic strokes among the atorvastatin group during follow-up [105].

Heavy alcohol use

Numerous studies have identified a relationship between alcohol use and the risk of hemorrhagic stroke [26,37,106,107]. There is probably a dose-response relationship with increased risk among heavy but not light drinkers [26,107]. Heavy alcohol use has also been implicated in early hematoma expansion, possibly due to adverse effects upon platelet and liver function [108].

Tobacco use

There may be a weak association between tobacco use and ICH but data have been conflicting [26,37]. Several recent studies suggest that current smoking (as opposed to past smoking or never smoking) increases the risk of ICH in a dose-dependent manner [38,109,110].

Diabetes

Diabetes is associated with greater risk of ICH in some case-control studies. A review of available data produced an overall risk ratio of 1.3 with borderline statistical significance [26]. The association of diabetes and ICH may vary by age group and location of hemorrhage [38]. Clarification of the role of diabetes as a “minor risk factor” for ICH will require larger studies [111].

Heritability

There is a genetic component to ICH risk but its absolute value is small. Among probands in the GERFHS case-control study, 6% of patients had an affected first-degree relative and 6% an affected second-degree relative. Among cases the odds ratio for an affected first-degree relative was high (6.3) but the population attributable risk was low (0.05) [32]. The association of apolipoprotein genotypes with lobar ICH was previously discussed.

Clinical presentation and natural history of intracerebral hemorrhage

The Harvard Cooperative Stroke Registry reported on the clinical findings associated with stroke [112]. The clinical features used to define ICH were presentation with a gradual progression (over minutes or days) or sudden onset of focal neurological deficit, usually accompanied by signs of increased intracranial pressure such as vomiting or diminished consciousness. As many as 91% of patients were hypertensive (blood pressure 160/100 mmHg or higher) at the onset of their stroke.

Vomiting was far more common in ICH and SAH (51% and 47% respectively) than for ischemic stroke (4–10% of cases). While SAH presented with headache at onset in 78% of cases, 33% of cases of ICH also had a headache at onset compared to 3–12% of ischemic stroke subtypes. Finally, SAH and ICH both presented with coma in 24% of cases compared to 0–4% of ischemic stroke subtypes. A particular characteristic of ICH was the smooth or gradual progression of stroke in 63% of cases, with sudden onset in 34% of cases (Table 1.4). A smooth or gradual onset of stroke was seen in only 5–20% of ischemic stroke subtypes and 14% of SAH. Thus, ICH is the stroke subtype most likely to worsen significantly in the first 24 hours.

Hematoma growth

Intracerebral hemorrhage was traditionally viewed as a monophasic event with a brief episode of bleeding

followed by increasing edema and clinical deterioration. This view is no longer accepted. A prospective, population-based study of spontaneous ICH in 1993 showed that among hemorrhages imaged within 3 hours of onset 26% increased by > 33% in volume in the next hour and 38% increased by > 33% volume within the first day (Fig. 1.3) [113]. The importance of ICH expansion has been confirmed by other studies which demonstrate that most hematoma growth occurs within six hours of onset, and that growth is associated with worse outcomes [108,114–116]. Based upon these findings, the use of ultra-early hemostatic therapy to reduce hematoma growth and potentially improve outcome following ICH has become an active area of research [117]. Clinical predictors of early hematoma growth have been difficult to consistently identify. In one retrospective study hypertension (systolic blood pressure ≥ 160) was associated with enlargement [116]. This finding has

Table 1.4. Clinical presentation of symptoms by subtype of stroke

	Thrombosis	Lacune	Embolus	ICH	SAH
Maximal at onset	40%	38%	79%	34%	80%
Stepwise	34%	32%	11%	3%	3%
Gradual	13%	20%	5%	63%	14%
Fluctuating	13%	10%	5%	0%	3%

Source: From [112].

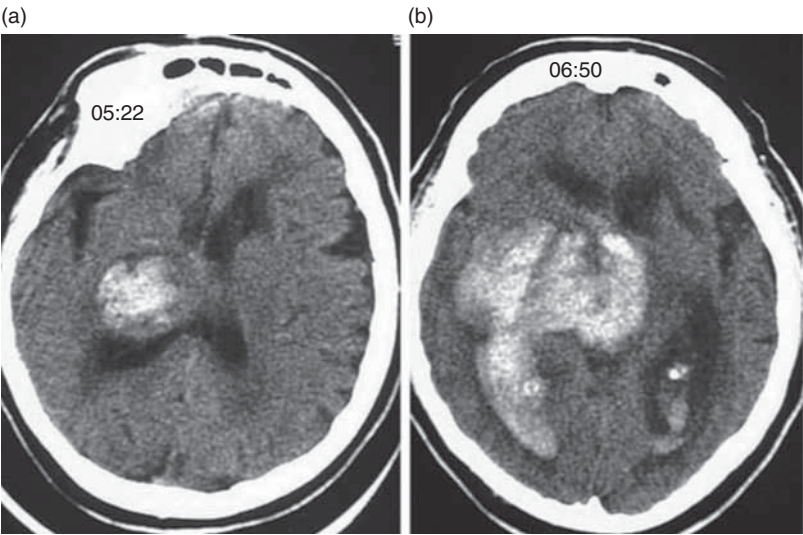


Fig. 1.3 Increase in hemorrhage size. A thalamic ICH (a) is seen in this patient with a history of hypertension. The patient’s condition deteriorated over the next hour and repeat imaging (b) demonstrates enlargement of the hematoma and rupture into the ventricles.

Section 1: Epidemiology

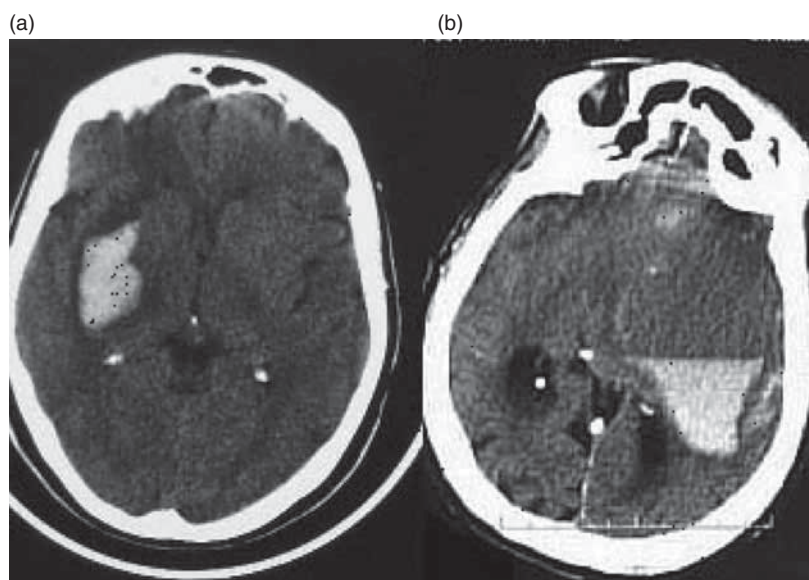


Fig. 1.4 (a) Spontaneous ICH with perihematomal edema. (b) Coagulopathy-associated ICH with minimal perihematomal edema despite greater hemorrhage size.

not been prospectively confirmed [113,118]. Another retrospective study identified earlier patient presentation, heavy alcohol consumption, reduced level of consciousness, and an irregularly shaped hematoma as predictors of enlargement [108]. The authors did not include hypertension after admission in their multivariate model because of concern that hypertension was an effect rather than a cause of hematoma growth [108]. Serum factors associated with hematoma growth have included low fibrinogen levels and elevated levels of interleukin-6 and cellular fibronectin [108,119].

Conflicting reports have compared the size of AAICH and bland ICH at presentation to medical care; some find no difference in size and some find larger hemorrhages in anticoagulated patients [120–122]. After presentation, hematoma enlargement and clinical deterioration are more common in anticoagulated patients [64,120,123]. Failure to promptly correct elevated INRs has been associated with hematoma enlargement [124].

Perihematomal edema

With the advent of CT technology, much has been learned about perihematomal edema. When whole blood is infused into the cerebral lobes of pigs, perihematomal edema develops within one hour of infusion [125]. Yet when packed red blood cells (no serum) are injected, edema does not develop for nearly 72 hours. This suggests that factors within serum are responsible for acute perihematomal

edema, while lysis of red blood cells contributes to edema at approximately 72 hours [125,126]. Studies have subsequently demonstrated that edema formation can occur when clotting factors alone (without serum or red blood cells) are injected into animal brains [127,128]. Thrombin and the fibrinogen cascade have been implicated in edema formation [127].

In humans, most hemorrhages due to thrombolysis are large and have little perihematomal edema [75]. Thrombolysis-related ICH has visible perihematomal less often than spontaneous ICH and has lower absolute and relative volumes of edema [129]. Figure 1.4 compares a case of spontaneous ICH to a case of ICH with coagulopathy.

Among patients not receiving anticoagulants, absolute edema volume generally doubles within the first day, while relative edema volume (defined as absolute edema volume divided by hematoma size) increases by a lesser amount [130]. One study found that greater relative edema volume in the hyperacute period paradoxically predicted better clinical outcomes, possibly because such edema resulted from successful hematoma clotting, but this finding has not been replicated [115,131]. Significant delayed edema may occur days to a week after initial bleeding and has been associated with neurological deterioration [132].

Morbidity and mortality

Intracerebral hemorrhage is often clinically devastating. Thirty-day case fatality rates in most studies

Chapter 1: Epidemiology of intracerebral hemorrhage

Table 1.5. Mortality of ICH based on volume and location of hematoma

	Overall 30-day mortality (n = 188)	≤ 30 cm ³ ICH	30–60 cm ³ ICH	≥ 60 cm ³ ICH
Lobar (n = 66)	39%	23%	60%	71%
Deep (n = 76)	48%	7%	64%	93%
Pontine (n = 9)	44%	43%	100%	N/A
Cerebellum (n = 11)	64%	57%	75%	N/A

Note: N/A = not applicable.
Source: From [137].

range from 40% to 50%, with approximately half of deaths occurring within two days of onset [133–135]. Patients with ICH fare worse than those with ischemic stroke, and few are left without disability [133, 134]. Mortality after ICH was reportedly as high as 90% in the pre-CT era [17]. The lower mortality in more recent studies likely reflect a combination of identification bias in the pre-CT era (with mild hemorrhages misclassified as ischemic infarcts) and improved supportive care [23,135]. A study comparing mortality after ICH in 1988 and the late 1990s found no improvement in outcomes during that period [135].

Prognostic indicators

A variety of reports have examined clinical and radiographic factors associated with prognosis after ICH. Predictors of poor outcome include advanced age, poor neurological status at presentation (as measured by Glasgow Coma Scale [GCS] score), larger hematoma size, early hematoma growth, intraventricular extension of hemorrhage, anticoagulant use, and brainstem location of hemorrhage [13,121,135–138].

In a population-based study in Greater Cincinnati, the volume of ICH in combination with the GCS predicted overall 30-day mortality with 96% sensitivity and 98% specificity (Table 1.5). Patients with a volume of 60 cm³ and a GCS score ≤ 8 had a predicted mortality of 91% while those with a volume of ≤ 30 cm³ and a GCS score ≥ 9 had a predicted mortality rate of 19%. For ICH with a volume of ≥ 60 cm³, the 30-day mortality for deep hemorrhages was 93% and for lobar hemorrhages was 71% (Table 1.5) [137]. Several prediction models for outcome after ICH have been developed but have not gained widespread clinical use [136,138]. Nonetheless, in a recent study more deaths caused by ICH were associated with withdrawal of care or a “comfort care”

approach (68%) than progression to brain death (29%) or medical complications (3%) [139]. The “self-fulfilling prophecy” in neurological catastrophes like ICH has been described as the preconceived notion that medical care is futile, followed by withdrawal of care and death of the patient [140]. The complicated determinants of morbidity and mortality following ICH, together with expectations of the patient, family, and physicians require careful consideration in each case.

Risk of ICH recurrence

Because ICH is less common and more deadly than ischemic stroke, studies estimating ICH recurrence risk have been more difficult to perform. A review of studies tracking ICH recurrence found an aggregate risk of 2.4% per patient-year [141]. The studies selected excluded patients with “secondary” causes of ICH such as vascular malformations or anticoagulation. Most studies have found ICH recurrence is more common following lobar ICH than non-lobar ICH. In the cited review, risk of recurrence among patients presenting with lobar ICH was 4.4% per year, compared to 2.1% annually for those with non-lobar hemorrhage [141]. Risk of new cerebral ischemia (1.1% per year) was lower than the risk of recurrent ICH [141]. One study found that Apolipoprotein ε2 or ε4 genotypes increase the risk of recurrence following lobar ICH, presumably because of their association with amyloid angiopathy [142]. The 21% two-year recurrence risk after lobar ICH in this study was greater than other reports and likely reflects the highly selected patient cohort [142]. A recent population-based study of ICH in Izumo City, Japan, documented an annual recurrence risk of 2.3% among 279 patients [143]. Location of ICH did not predict recurrence in this population, consistent with epidemiological data showing that lobar hemorrhage

Section 1: Epidemiology

(and presumably amyloid angiopathy) is less prominent in Asian populations than in the United States or Europe.

Primary intraventricular hemorrhage

Primary intraventricular hemorrhage (IVH) is rare among adults, comprising 2–3% of ICH admissions [144–147]. Study of this subject has been limited to small case series [144–147]. Signs and symptoms of IVH frequently include headache, vomiting, and altered level of consciousness. Many patients are hypertensive or coagulopathic and some have vascular malformations defined by angiography. Hydrocephalus and elevated intracranial pressure are frequent and potentially fatal complications.

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