

Treatment and Prevention of Primary Intracerebral Hemorrhage

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ABSTRACT

Intracerebral hemorrhage (ICH), which constitutes 10 to 15% of all strokes and affects ~65,000 people each year in the United States, has the highest mortality rate of all stroke subtypes. Hypertension, cerebral amyloid angiopathy, and anticoagulation underlie the majority of cases of ICH. Warfarin not only increases the risk but also increases the severity of ICH by causing hematoma expansion. With the advent of gradient-echo magnetic resonance imaging, patients with underlying cerebral amyloid angiopathy or hypertensive vasculopathy can be identified, and measures can be taken to prevent ICH. Initiating an antihypertensive regimen in a patient with nonlobar microbleeds suggestive of hypertensive vasculopathy, and withholding warfarin in patients with lobar microbleeds suggestive of cerebral amyloid angiopathy, are emerging prevention strategies. Although a treatment for cerebral amyloid angiopathy does not exist, agents targeting β -amyloid metabolism and bioactivity are promising candidates. Strategies for preventing warfarin-associated hemorrhage include strict monitoring of anticoagulation levels and using agents such as direct thrombin inhibitors. The future of ICH management lies in therapies targeted at the pathophysiological steps in ICH. Potential treatments include glutamate receptor antagonists for preventing glutamate excitotoxicity, matrix metalloproteinase and thrombin inhibitors for preventing perihematomal edema, and recombinant activated factor VII for preventing hematoma expansion.

KEYWORDS: Intracerebral hemorrhage, cerebral amyloid angiopathy, hypertension, warfarin

Objectives: On completion of this article, the reader will be able to explain the causes, treatment, and prevention of primary intracerebral hemorrhage.

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Stroke Acute Management and Recovery; Editor in Chief, Karen L. Roos, M.D.; Guest Editor, Bradford B. Worrall, M.D., M.Sc. *Seminars in Neurology*, Volume 25, Number 4, 2005. Address for correspondence and reprint requests: Jonathan Rosand, M.D., M.S., Neurology Clinical Trials Unit, 15 Parkman Street, ACC 836, Boston, MA 02114. ¹Vascular and Critical Care Neurology, Massachusetts General Hospital, Boston, Massachusetts. Copyright © 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 0271-8235,p;2005,25,04,445,452,ftx,en;sin00394x.

Primary intracerebral hemorrhage (ICH), spontaneous bleeding into the brain parenchyma, constitutes 10 to 15% of strokes in the United States and 20 to 40% of strokes in Asia.¹ It affects ~65,000 people each year in the United States.² Primary intracerebral hemorrhage is the most fatal stroke subtype, with a 30-day mortality rate of 30 to 50%.³ Furthermore, it causes substantial disability in survivors; of the patients who survive, only 20% live independently at 6 months.⁴

Epidemiological studies suggest that the majority of primary ICH cases are the manifestation of two forms of chronic small-vessel disease, hypertensive vasculopathy and cerebral amyloid angiopathy,⁵⁻⁸ with rarer hemorrhages arising in the setting of vascular malformations and acute vascular injuries such as those associated with acute cocaine intoxication and malignant hypertension. The location of the hemorrhage often provides clues to the underlying cause: long-standing hypertension causes ICH in the basal ganglia, thalamus, brain stem, and cerebellum, whereas cerebral amyloid angiopathy causes lobar and rarely cerebellar ICH.^{5,7-10} Up to 10% of patients with ICH have a family history of ICH,¹¹ and having a first-degree relative with ICH is an independent risk factor for both lobar and nonlobar

hemorrhage,⁵ suggesting that genetic factors may play a role in both types of hemorrhage.

NEUROIMAGING AND THE DIAGNOSIS OF UNDERLYING SMALL-VESSEL DISEASE IN ICH

Although pathological observations have for many years suggested that the hemorrhage location provides a clue to its underlying cause, it was not until the advent of modern computed tomography (CT) and magnetic resonance imaging (MRI) that the clinical significance of ICH location became clear. The recent development of gradient-echo (susceptibility-weighted) MRI allows detection of prior asymptomatic cerebral microbleeds, small areas of signal loss that pathologically correspond to collections of hemosiderin-laden macrophages.¹²⁻¹⁵ The location of microbleeds can distinguish patients with hypertensive vasculopathy from those with cerebral amyloid angiopathy (Fig. 1).^{8,16,17} While microbleed location helps confirm the underlying diagnosis, the number of microbleeds reflects disease severity and risk of recurrence. Increasing numbers of nonlobar microbleeds correlate with other measures of severity and

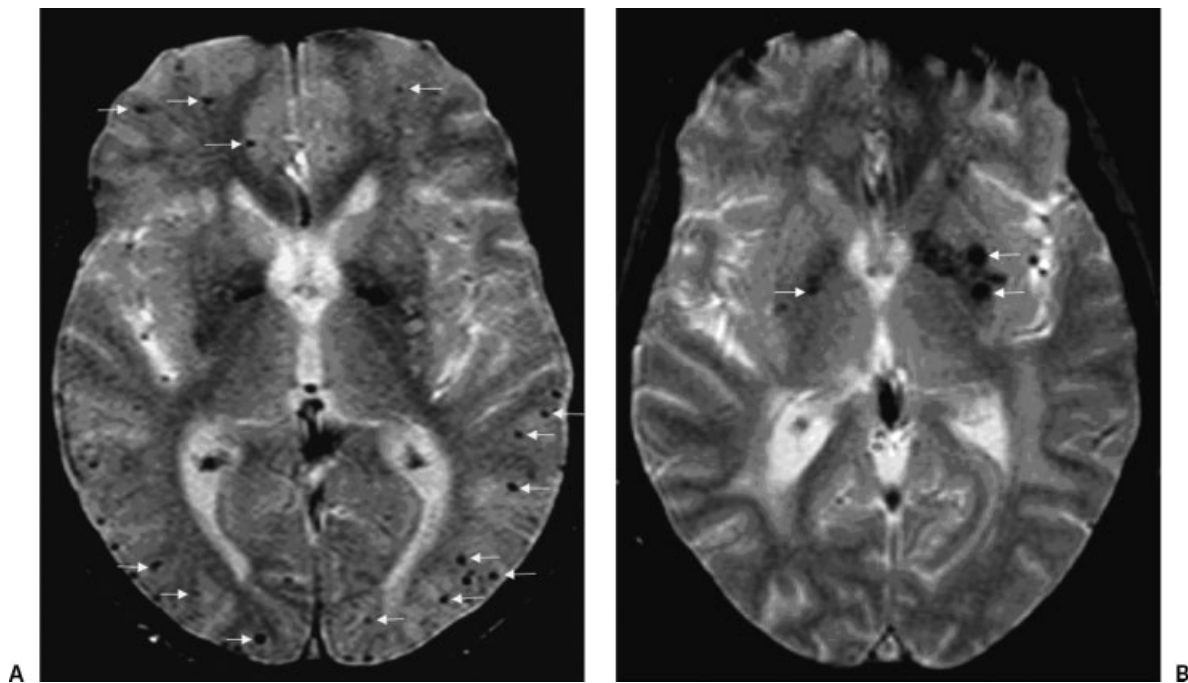


Figure 1 (A) A 73-year-old woman with a 2-year history of worsening cognitive function. Gradient-echo MRI shows multiple foci of signal loss in a cortical or lobar distribution (a subset of these lesions are demarcated by solid arrows). According to the Boston Criteria for diagnosis of cerebral amyloid angiopathy-related ICH, multiple strictly lobar or corticosubcortical hemorrhages, without other known cause, in a patient older than 55 are diagnostic of "probable cerebral amyloid angiopathy."⁸ (B) A 69-year-old woman with history of hypertension. Gradient-echo MRI shows foci of signal loss in bilateral basal ganglia (solid arrows). Deep microhemorrhages such as these are suggestive of long-standing hypertension.¹⁷

duration of hypertension, such as left ventricular hypertrophy,¹⁷ and numbers of lobar microbleeds predict risk of symptomatic lobar ICH in cerebral amyloid angiopathy.¹⁸

HYPERTENSIVE VASCULOPATHY

Long-standing hypertension causes lipohyalinosis of small, deep-penetrating arteries, rupture of which results in deep hemispheric or brain stem hemorrhage.¹⁰ Epidemiological studies support the association between hypertension and nonlobar ICH,⁵ and clinical trials demonstrate a clear decrease in risk of ICH with sustained blood pressure control.^{19–21} Our ability to diagnose underlying hypertensive vasculopathy using gradient-echo MRI allows us to take measures to prevent ICH. Patients incidentally found to have nonlobar microbleeds should be considered likely hypertensive, even in the presence of normal cuff pressures, and should be considered for treatment with antihypertensive medications to prevent symptomatic hemorrhage.^{16,19}

CEREBRAL AMYLOID ANGIOPATHY

Cerebral amyloid angiopathy, defined as amyloid deposition in cerebral vessel walls, affects capillaries, arterioles, and small to medium-sized arteries of the cerebral cortex, overlying leptomeninges, and cerebellum.²² In mild to moderate cerebral amyloid angiopathy, amyloid deposits in the media and adventitia, whereas severe cerebral amyloid angiopathy is characterized by the formation of microaneurysms, perivascular or transmural inflammation, and fibrinoid necrosis.^{22–27} The main constituent of vascular amyloid in sporadic cerebral amyloid angiopathy is the β -amyloid peptide (A β). In rare familial forms, deposition of other proteins such as cystatin C predominates.^{28,29} The only established risk factors for cerebral amyloid angiopathy other than age are genetic: family history of ICH⁵ and possession of the apolipoprotein E (APOE) e2 and e4 alleles.^{5,30–32} Histological studies suggest that APOE e4 increases the deposition of A β in the walls of cerebral blood vessels,^{33–36} and APOE e2 promotes breakdown of vessels containing amyloid deposits.^{32,37}

Cerebral amyloid angiopathy is a common disease in the elderly population, but ICH develops only in a minority of patients with severe disease. According to histological analyses, the prevalence of moderate to severe cerebral amyloid angiopathy increases from 2.3% in patients aged between 65 and 74 to 12.1% in patients older than 85.³⁸ The degree to which cerebral amyloid angiopathy without ICH is symptomatic is currently being studied as there are several clinical manifestations of cerebral amyloid angiopathy, including ischemic infarction, subacute cognitive decline, transient neurolog-

ical symptoms, leukoencephalopathy, vasculitis, and rarely mass lesions (amyloidomas).^{39–50}

ANTICOAGULATION-RELATED ICH

Anticoagulation with warfarin increases the risk of ICH and worsens the severity of hemorrhage, approximately doubling its mortality.^{51–53} The annual risk of ICH in patients undergoing long-term anticoagulation for atrial fibrillation is 0.2 to 0.6%, with higher rates noted in clinical trials using target international normalized ratio (INR) values greater than 4.0.⁵⁴ The excess mortality of ICH when it occurs is likely related to prolonged bleeding, which is commonly observed in patients with anticoagulation-related ICH.⁵⁵

Although long-term anticoagulation clearly increases the risk of developing ICH, the mechanisms by which anticoagulation leads to bleeding are by no means clear. The risk of ICH doubles with each 0.5 point increase in the prothrombin time ratio above the recommended limit of 2.0.⁵⁶ This relationship between the degree of anticoagulation and the risk of ICH suggests that any individual may develop ICH if the anticoagulant effect is sufficiently high. Nonetheless, the majority of anticoagulant-related ICH occur when the INR is 2.0 to 3.0,⁵³ suggesting that there are other factors predisposing to hemorrhage. The current leading hypothesis is that in most cases, warfarin does not affect hemorrhage occurrence, but rather hemorrhage severity. Thus, a hemorrhage that might remain subclinical in the absence of anticoagulation enlarges to become a devastating hemorrhagic stroke in an anticoagulated patient.⁵¹ The role of underlying small-vessel disease is supported by several observations. First, age is a risk factor for ICH on warfarin, suggesting that age-related diseases, such as hypertensive vasculopathy and cerebral amyloid angiopathy, may play a role.^{2,57} Second, leukoaraiosis, indicative of small-vessel disease, is associated with a higher risk of ICH in patients treated with warfarin.^{58,59} Finally, cerebral amyloid angiopathy itself has been identified as a risk factor for lobar warfarin-ICH.⁶⁰

ACUTE ICH

Although hematoma formation sets off a series of reactions in the involved tissue that contribute to neurological injury,^{61–65} the mass effect of the ICH itself appears to be the primary mechanism of injury. The damage caused by ICH is proportional to the volume of blood that extravasates from the ruptured vessel or vessels.^{55,66,67}

Intracerebral hemorrhage was once thought to be a brief event lasting seconds to minutes; however, several studies suggest that as many as 30 to 40% of patients experience ongoing bleeding while in the emergency room, particularly if they are on warfarin

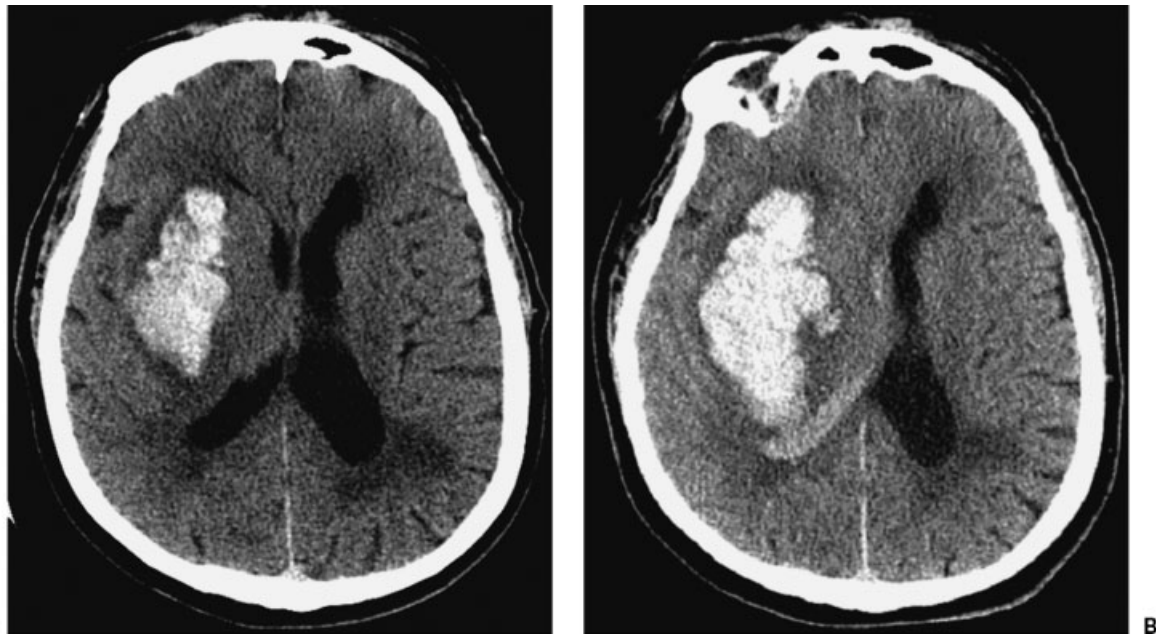


Figure 2 (A) A 59-year-old man on warfarin for atrial fibrillation (INR 3.5) presented with slurred speech and left hemiparesis. Head CT 120 minutes after onset of symptoms showed right basal ganglia hemorrhage measuring 40 mL. Volume of hemorrhage was calculated using the formula: volume = (ABC)/2, where A = largest diameter, B = largest diameter perpendicular to A, and C = the number of slices containing ICH \times thickness of each slice.⁸² (B) Repeat head CT 180 minutes after original CT shows expansion of the hematoma, which now measures 82 mL, and extension into the lateral ventricle.

(Fig. 2).^{55,68,69} The proposed theories for hematoma expansion include secondary bleeding at the periphery of the hemorrhage,⁷⁰ potentiation of hemorrhage by fibrin degradation products and plasmin exuded from the clot,^{61,62,65,71} and continued bleeding from the primary ruptured vessel.⁷²

Prothrombotic treatments such as aminocaproic acid, tranexamic acid, and aprotinin have all been considered as potential preventative treatments for ICH expansion, but the only agent to demonstrate promising results to date is activated recombinant factor VII (rFVIIa).^{73,74} FVIIa, a natural initiator of hemostasis, functions in regions of endothelial disruption by forming a complex with tissue factor and initiating the conversion of factor X to Xa.⁷⁵ Pharmacological doses of rFVIIa amplify this pathway in the absence of tissue factor.⁷⁶ A recent dose-ranging study of rFVIIa administered to patients with primary ICH within 4 hours of symptom onset demonstrated that the drug reduced hematoma expansion and improved clinical outcome with a small increase in the frequency of thromboembolic adverse events.⁷⁴ A phase 3 clinical trial of rFVIIa in acute ICH is now underway.

Another important contributor to mass effect is perihematomal edema, which increases by \sim 75% during the first 24 hours.⁷⁷ Serum proteins, such as thrombin, seem to play a substantial role in perihematomal edema, extruding into the interstitial space as clotting occurs.^{78–80} Intracerebral injection of a thrombin inhibitor reduces edema formation in a rat model of ICH.⁶¹

Matrix metalloproteinases contribute to edema by causing breakdown of the blood–brain barrier.⁷¹ Matrix metalloproteinase inhibitors decrease edema in rat models of ICH.⁷¹ Hyperglycemia causes more profound brain edema and perihematomal cell death in a rat model of ICH, which, when considered together with evidence linking hyperglycemia to increased mortality in ICH in humans, suggests that tight glucose control may be important in reducing the morbidity of ICH.⁸¹

Intracerebral hemorrhage elicits neuronal excitation mediated by glutamate, which may also contribute to neuronal injury.⁶³ Glutamate, released from damaged cells and the circulation, causes astrocyte cell death⁶⁴; its toxicity is magnified by substances such as thrombin that potentiate glutamate receptors.⁶³ Glutamate receptor antagonists and thrombin inhibitors are candidates for preventing the tissue damage that occurs as a result of perihematomal excitotoxicity.

TREATMENT OF ACUTE ICH

Current management of ICH focuses on preventing hematoma expansion, reducing mass effect, taking steps to minimize secondary neurological injury, and preventing nosocomial complications (refer to www.stopstroke.org). The most important steps in the emergency department are measuring hematoma volume,⁸² reversing any coagulopathy, controlling blood pressure,⁸³ treating hyperglycemia,⁸⁴ and managing intracranial pressure.⁸⁵ Although there appears to be a

region of reduced cerebral blood flow surrounding ICH,^{86,87} accumulating evidence suggests this region is not ischemic.^{88–90} Studies of moderate blood pressure reduction have not demonstrated a significant change in either global or perihematomal cerebral blood flow.⁹¹ Current guidelines suggest that surgery be offered to patients with cerebellar hemorrhage > 3 cm in diameter, clinically deteriorating young patients with moderate or large lobar hemorrhage, and patients whose ICH is associated with a surgically accessible structural lesion.⁸³ Approximately 28% of patients with hemorrhages develop seizures within the first 72 hours⁹²; therefore, prophylactic antiepileptic therapy may be reasonable in critically ill patients.⁸³ Prophylactic anticoagulation for prevention of deep venous thrombosis may be started 24 to 48 hours after ICH, when there is no evidence of ongoing hematoma expansion.⁹³

PRIMARY PREVENTION OF ICH

Our ability to diagnose asymptomatic hemorrhagic vasculopathy has important clinical implications. In the case of hypertensive vasculopathy, patients with nonlobar microbleeds on MRI may be started on an antihypertensive regimen, even if cuff pressures are not frankly elevated. Although we currently do not have medications to prevent cerebral amyloid angiopathy-related hemorrhage, there are multiple potential targets for therapies aimed at altering the metabolism or bioactivity of A β . One approach to reach early clinical trial is to use a low-molecular-weight anionic molecule that interferes with the interaction of A β with sulfated glycosaminoglycans in the basement membrane of vessel walls.⁹⁴ A safety, tolerability, and pharmacokinetic study identified no major safety issues in cerebral amyloid angiopathy subjects over 12 weeks of treatment.⁹⁴

New imaging techniques and novel treatment strategies also offer hope in the prevention of warfarin-ICH. Through imaging we can identify patients potentially at risk for warfarin-ICH, such as patients with lobar microbleeds suggestive of cerebral amyloid angiopathy⁹⁵ and patients with a history of prior stroke and evidence of leukoaraiosis.⁵⁸ Future studies may identify specific subgroups in whom warfarin should be withheld.⁹⁶ Although APOE genotype can identify patients with ICH who are at increased risk for hemorrhage recurrence,⁹⁷ it is neither sensitive nor specific for the primary diagnosis of cerebral amyloid angiopathy, and therefore may not be useful for determining which patients can be safely anticoagulated. Several strategies for ICH prevention in patients undergoing chronic anticoagulation are on the horizon, including home INR machines to facilitate tight control of the INR and antithrombotic medications that do not need monitoring, such as direct thrombin inhibitors.^{98–101} One such agent, ximelagatran, was shown to be comparable to

warfarin for the prevention of stroke in patients with atrial fibrillation but was not approved by the Food and Drug Administration due to excess hepatotoxicity.^{100,101}

SECONDARY PREVENTION OF ICH

Secondary prevention strategies differ depending on whether the index ICH was lobar or nonlobar. The recurrence rate for lobar hemorrhage is considerably higher than that for nonlobar hemorrhage.^{97,102} Although careful control of hypertension reduces the risk of recurrent nonlobar hemorrhage,²¹ it probably has little effect on recurrent lobar hemorrhage.⁹⁷ According to a decision analysis model, the risk of recurrent hemorrhage outweighs the benefit of anticoagulation in patients with both nonvalvular atrial fibrillation and a history of lobar hemorrhage, although patients with a history of nonlobar hemorrhage may benefit from anticoagulation if their ischemic stroke risk is high.⁹⁶ Although the risk of aspirin in patients with atrial fibrillation and previous lobar ICH may outweigh the benefits in patients at low risk for ischemic stroke, the cardiovascular benefits of aspirin must also be taken into account.

CONCLUSION

Recent developments in our understanding of the pathophysiology of ICH form the basis for novel prevention and treatment strategies. Gradient-echo MRI allows the identification of the major etiologies of ICH, hypertensive vasculopathy and cerebral amyloid angiopathy. Careful blood pressure management can prevent nonlobar hemorrhage, and the judicious selection of patients for long-term anticoagulation will likely decrease the occurrence of anticoagulant-related ICH. Promising though unproven treatments such as rFVIIa for acute ICH and glycosaminoglycan mimetics for cerebral amyloid angiopathy prevention represent the first generation of pharmacological agents specifically targeted to prevent and treat ICH, offering hope for reducing the burden of disease.

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