

Intracerebral Hemorrhage In Anticoagulated Patients: Evidence-Based Emergency Department Management

Abstract

Spontaneous intracerebral hemorrhage is a true neurological emergency, and its management is made more complicated when patients are anticoagulated, as reversal of anticoagulation must be initiated simultaneously with diagnosis, treatment, and disposition. Recent advances such as newer laboratory testing and rapid computed tomography for diagnosis, blood pressure reduction to reduce hematoma expansion, and new anticoagulant reversal agents may allow for improved outcomes. Management of intracranial pressure is particularly important in anticoagulated patients, as is identifying patients who may benefit from rapid neurosurgical intervention and/or emergent transport to facilities capable of managing this disease.

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CME Objectives

Upon completion of this article readers should be able to:

1. Appropriately reverse a patient who is anticoagulated and found to have ICH.
2. Recognize appropriate blood pressure goals in the setting of ICH.
3. Describe patients who may require neurosurgical intervention.

Prior to beginning this activity, see "Physician CME Information" on the back page.

This issue is eligible for 4 Stroke CME credits.

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Case Presentations

Immediately upon walking into your evening shift, a nurse gets your attention and instructs you to see a patient that she is concerned is having a stroke. The patient is a 78-year-old man with a history of congestive heart failure and a mechanical heart valve who has had 2 hours of headache and dysarthria. His family reports that he had no deficits prior to this. You immediately order a head CT, which demonstrates a small right parietal lobe bleed. The INR returns at 4.0 and you notice in the chart that the patient had a recent echocardiogram with an ejection fraction of 15%. You wonder how well he will tolerate reversal and what should be done about his blood pressure, which is 175/105 mm Hg.

Your second patient is a 65-year-old woman with atrial fibrillation. Her cardiologist put her on dabigatran, and she has been compliant with her medications. Today, she developed a headache and left-sided weakness approximately 1 hour prior to arrival. She is also taken immediately for a head CT, which demonstrates a 15-cc right thalamic intracerebral hemorrhage and a small amount of bleeding into her lateral ventricles. You wonder what the best strategy is for reversal agents for dabigatran.

Later in your shift, a gentleman who appears to be in his mid-50s is brought in after his family noticed that he was sleepier than usual after returning from the grocery store an hour ago. He has a past medical history of atrial fibrillation, and is anticoagulated on rivaroxaban. On your exam, he keeps falling asleep when you try to talk to him, but with painful stimulation, he wakes up and follows commands. He is taken immediately for an emergent head CT, which demonstrates a 3-cm right cerebellar intracerebral hemorrhage. As you step out of the room to speak to the neurosurgeon, the nurse runs out to tell you that the patient has now developed sonorous respirations. As you prepare to intubate the patient, you wonder whether he needs to be hyperventilated and what the best reversal strategy is for rivaroxaban.

Introduction

Intracerebral hemorrhage (ICH), defined as “bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, the subarachnoid space,”¹ is a devastating disease that must be recognized immediately in the emergency department (ED). Unlike ischemic stroke, which has a large body of evidence supporting intravenous tissue plasminogen activator (tPA) and endovascular treatment, ICH has no targeted modalities for treatment.²⁻⁷ Anticoagulated patients with ICH require rapid reversal of coagulopathy to limit hemorrhage progression; however, the optimal approach is debated. Despite the fact that there are no targeted therapies in the treatment of ICH, current strategies to improve outcome rest largely on reducing the risk of hematoma expansion early in treatment, as

each milliliter of expansion decreases the patient’s chances of living independently.⁸

Epidemiology

ICH accounts for 10% to 20% of all strokes, worldwide.⁹ Approximately 25% of these patients are on an oral anticoagulant.¹⁰⁻¹⁶ Outcome data on ICH are clouded with uncertainty, as the cause of death of many of these patients is withdrawal of care. Nonetheless, ICH has a much higher mortality than ischemic stroke.¹⁷ A prospective registry out of Denmark demonstrated that mortality from ICH is significantly higher than in ischemic stroke (hazard ratio [HR], 1.564; 95% confidence interval [CI], 1.4-1.7; $P < .001$).¹⁷ Mortality of ICH at 1 year ranges from 38% to 50%.^{10,18,19}

As the population ages, it is expected that there will be a growing number of patients who are anticoagulated. Oral anticoagulants are most frequently used for stroke prevention in atrial fibrillation or in the treatment of thromboembolic disease, and numerous studies have documented their benefit.^{20,21} Warfarin prescriptions quadrupled between 1988 and 1999, and the incidence of anticoagulant-associated ICH quintupled.²² It is estimated that over the next 50 years, the prevalence of atrial fibrillation will be 2.5 times greater than it is currently.²³ This is reflected in the epidemiology of patients who sustain ICH. Flaherty et al followed a cohort of patients in 1988, and again a decade later. Although the incidence of ICH did not change significantly between the 2 time periods, anticoagulant-associated ICH became more common.¹⁹

When patients are on anticoagulants, their risk of ICH and associated morbidity and mortality increases significantly.²⁴ In a retrospective study of patients with ICH, mortality was 67% in anticoagulated patients versus 55% in those not anticoagulated.²⁵ ICH volume was also statistically larger compared to the nonanticoagulated group.²⁵ An international normalized ratio (INR) > 3.5 nearly doubles the risk of a fatal ICH in patients who are on warfarin when adjusted for age, sex, cardiovascular disease, diabetes, heart failure, hypertension, and type of ICH.²⁶

Since reversal of coagulopathy is a time-sensitive process, emergency clinicians must appropriately diagnose, manage, and disposition patients with ICH. In 2015, a retrospective study in Germany described patients with ICH who were on oral anticoagulants, and it demonstrated a significant survival benefit in patients who had INR reversal to < 1.3 and systolic blood pressure (SBP) to < 160 mm Hg within 4 hours after presentation.²⁷ The results of this study support the critical role played by the emergency clinician in recognition and management of these acute patients.

Critical Appraisal Of The Literature

A literature search was performed in PubMed with the search terms *ICH reversal*, *ICH warfarin*, *ICH anticoagulation*, and *novel oral anticoagulants ICH*. A total of 1738 articles from 1947 to the present were identified, 240 abstracts were reviewed, and 16 papers were selected for full review and referenced. The date of the literature search was May 15, 2015, with additional resources reviewed up to November 2015. The Cochrane Database of Systematic Reviews was searched for systematic reviews using the key term *intracerebral hemorrhage*, and 15 reviews were identified.

The American Heart Association/American Stroke Association (AHA/ASA) published a 2015 update to their 2007 and 2010 guidelines for the management of ICH.^{11,28,29} The European Stroke Organisation published guidelines for the management of spontaneous ICH in 2014.³⁰ With regard to indications for anticoagulation, The American College of Chest Physicians published "Evidence-Based Clinical Practice Guidelines for Management of Anticoagulation Therapy: Antithrombotic Therapy and Prevention of Thrombosis" in 2012.³¹

Using standard evidence-level scales, the majority of clinical evidence of vitamin K antagonist (VKA)-associated ICH falls into the "strong evidence" categories; however, evidence associated with novel oral anticoagulant (NOAC)-associated ICH falls into the "weak evidence" categories. There are several reasons for this. First, ICH is a rare disease, and properly designed clinical trials are often too resource-intensive to perform. Second, NOACs have not been available for sufficient time to quantify the extent of their use within the population and their impact on the clinical evaluation and treatment of ICH. When available, recommendations in this article are evidence-based. Recommendations based on accepted practice or expert consensus are explicitly noted as such.

The overall strength of evidence supporting correction of coagulopathy in the setting of ICH by replacing appropriate factors or platelets in the setting of severe coagulation factor deficiency or severe thrombocytopenia is strong, with Class I, Level of Evidence C in the 2015 AHA ICH management guidelines.²⁸ These same guidelines give a Class I, Level of Evidence C to withholding VKAs in VKA-associated ICH, receiving therapy to replace vitamin K-dependent factors and correct the INR, and receiving intravenous vitamin K.²⁸ However, in the setting of NOACs, the most rapid and effective ways to reverse coagulopathy are still under study, and no guidelines describe the best method of reversal.

Etiology And Pathophysiology

ICH is categorized by the underlying etiology, if it is known. Although some ICHs may not have an identifiable etiology, they may be caused by trauma, vascular malformations, aneurysms, masses, or hemorrhagic transformation of ischemic stroke. Age and hypertension are the 2 most relevant risk factors for ICH, with hypertension being the most significant reversible risk factor. Common causes and risk factors for ICH are described in **Table 1**.

Primary ICH is frequently caused by essential hypertension, especially in the setting of deep hemorrhages.^{32,33} Hypertension leads to damage of small arteries, making them more prone to rupture.³⁴ Patients with uncontrolled or untreated hypertension do poorly in comparison to patients who have their hypertension treated appropriately.³⁵ In a meta-analysis performed in 2003, the odds ratio (OR) for hypertension as a cause of ICH was found to be 3.68 (95% CI, 2.52-5.38).³⁶

Age is an important risk factor as a causal agent of ICH. A meta-analysis that was undertaken to determine the risk factors of ICH found a relative risk (RR) for age of 1.97 (95% CI, 1.79-2.16) for every 10-year increase in age.³⁶ The mean age of onset of ICH in men is 64.9 years (standard deviation [SD] 11.5) and 69.5 years (SD 11.1) in women.³⁶ As mentioned previously, anticoagulants significantly increase the risk of ICH. However, this risk may be kept lower when INR and blood pressure are both controlled well.¹⁶

Oral Anticoagulants

Vitamin K Antagonists

The most-well-studied oral anticoagulants are VKAs, with warfarin being most commonly used. Vitamin K is used to produce active factors by allowing gamma-carboxylation of factors II, VII, IX, and X, and proteins C and S such that they can participate in clot formation.³⁷ Reversal of VKAs requires regeneration of vitamin K, as well as replacement of the inhibited factors. Current modalities for VKA reversal are fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs), in combination with vitamin K. VKA serum levels are measured by prothrombin time (PT) and converted into the INR.³⁸

Table 1. Common Etiologies And Risk Factors For Intracerebral Hemorrhage

- Coagulopathy: hereditary or medication/drug-induced
- Structural: mass, arteriovenous malformation, aneurysm
- Acquired: amyloid angiopathy
- Traumatic: intraparenchymal hemorrhage, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage
- Advanced age
- Hypertension
- Race

Novel Oral Anticoagulants

The NOACs consist of direct thrombin inhibitors (approved for use in 2010), and factor Xa inhibitors (first approved for use in 2011).^{39,40} Dabigatran (Pradaxa[®]) is currently the only direct thrombin inhibitor approved for stroke prevention. Unlike VKAs, which take days to reach therapeutic serum levels and require bridging, dabigatran attains therapeutic plasma concentration at 1.5 to 2 hours after administration.⁴¹ Dabigatran is excreted renally and has fewer drug interactions compared to VKAs.⁴¹ The RE-LY[®] (Randomized Evaluation of Long-Term Anticoagulant Therapy With Dabigatran Etexilate) trial, which compared 18,113 patients with atrial fibrillation treated with warfarin or dabigatran, found the risk of stroke in warfarin to be 1.69% versus 1.53% in patients who received dabigatran. The risk of ICH in the warfarin group was 0.38% per year, compared to 0.12% per year in the dabigatran group ($P < .001$).⁴² (See Table 2.)

Rivaroxaban (Xarelto[®]), apixaban (Eliquis[®]), and edoxaban (Savaysa[®]) are the 3 approved commercially available factor Xa inhibitors. The half-life of factor Xa inhibitors ranges from 5.7 to 10.4 hours, with peak plasma levels occurring 1 to 4 hours after administration.⁴³⁻⁴⁶ Factor Xa inhibitors are orally metabolized in the gut and, primarily, renally excreted.^{47,48} Large trials have also shown them to be efficacious in the setting of stroke prevention in atrial fibrillation. The ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation, a phase 3 trial, 18,201 patients) compared apixaban to warfarin in patients with atrial

Table 2. Randomized Controlled Trials Of Novel Oral Anticoagulants In Atrial Fibrillation

Trial	Number of Patients	Annual Incidence of Stroke	Annual Risk of ICH
RE-LY [®] (warfarin vs dabigatran)	18,113	Dabigatran: 1.69% Warfarin: 1.53%	Dabigatran: 0.12% Warfarin: 0.38%
ARISTOTLE (warfarin vs apixaban)	18,201	Apixaban: 1.27% Warfarin: 1.6%	Apixaban: 0.24% Warfarin: 0.47%
ROCKET AF (warfarin vs rivaroxaban)	14,264	Rivaroxaban: 1.7% Warfarin: 2.2%	Rivaroxaban: 0.5% Warfarin: 0.7%
ENGAGE AF-TIMI 48 (warfarin vs edoxaban)	21,105	Edoxaban: 1.18% Warfarin: 1.5%	(Major bleeding) Edoxaban: 2.75% Warfarin: 3.43%

Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-TIMI 48; ICH, intracerebral hemorrhage; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy With Dabigatran Etexilate; ROCKET AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation.

fibrillation, and demonstrated a yearly stroke risk of 1.27% in the apixaban group compared to 1.60% in the warfarin group ($P < .001$).⁴⁹ The ROCKET AF trial (Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation, 14,264 patients), also a phase 3 trial, compared rivaroxaban to warfarin, and it demonstrated a 1.7% yearly stroke incidence in the rivaroxaban group compared to 2.2% in the warfarin group ($P < .001$).⁵⁰ The largest phase 3 trial studying any of the NOACs in atrial fibrillation was the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-TIMI 48, 21,105 patients), which compared edoxaban to warfarin, and it demonstrated a 1.18% annualized rate of stroke in edoxaban, compared to 1.50% in warfarin.⁵¹

The ICH rate in ARISTOTLE was 0.24% per year in the apixaban group and 0.47% in the warfarin group ($P < .001$).⁵¹ The ICH rate in the ROCKET AF trial was 0.5% in the rivaroxaban group compared to 0.7% in the warfarin group ($P = .02$).⁵⁰ The ENGAGE AF-TIMI 48 trial demonstrated a major bleeding rate of 3.43% with warfarin and 2.75% with edoxaban ($P < .001$).⁵¹ Thus, 4 large randomized controlled trials have now been conducted that demonstrate the safety and efficacy of NOACs in atrial fibrillation.

Differential Diagnosis

Patients who present to the ED with acute focal neurologic deficits must be promptly evaluated for ischemic or hemorrhagic stroke, and have a rapid noncontrast head computed tomography (CT) scan obtained. However, hypoglycemia can also mimic stroke-like symptoms, so a fingerstick blood glucose level should be obtained prior to any further work-up.⁵² Acute bleeding in the brain should be ruled out initially. If a patient presents in a comatose state, other causes of altered mental status such as toxic or metabolic encephalopathies, seizures, and trauma must be considered. An abbreviated differential diagnosis is shown in Table 3.

Table 3. Differential Diagnosis In Intracerebral Hemorrhage

Etiology	Diagnosis
Vascular	Transient ischemic attack, ischemic stroke, subarachnoid hemorrhage
Traumatic	Epidural, subdural, subarachnoid
Structural	Mass lesion
Metabolic	Hypoglycemia, hyperglycemia
Infectious	Meningitis, encephalitis, sepsis
Toxicologic	Alcohol, opioids
Other neurologic conditions	Seizure, postictal, migraine

Prehospital Care

Regardless of the etiology of a stroke, the priorities of prehospital care in the setting of suspected ICH are to communicate with the ED, provide appropriate airway support, obtain history from the scene, and rapidly transport patients to the appropriate facility.²⁸ These are not unlike the priorities for ischemic stroke, given that these patients will be undifferentiated from each other prior to hospital arrival.²⁸ Whenever possible, emergency medical services (EMS) should provide hospital prenotification of a possible stroke patient. In the setting of stroke, prenotification has demonstrated a decrease of 17% in the time elapsed between patient arrival to the ED and CT.⁵³

The clinical findings of facial or arm weakness or abnormal speech have a likelihood ratio (LR) of 5.5 that a stroke has occurred, thus forming the base of the prehospital evaluation.⁵⁴ If a patient is not comatose and has focal neurologic deficits, the Cincinnati Prehospital Stroke Scale (CPSS) may be used as a screening tool for stroke-like symptoms. The CPSS demonstrates high reproducibility and validity in this setting, as well as a sensitivity of 88% for anterior circulation infarcts.⁵⁵ The National Institute of Neurological Disorders and Stroke Symposium (NINDS) has published a summary of the CPSS and other stroke scales at: www.ninds.nih.gov/news_and_events/proceedings/stroke_2002/acute_stroke_template_appndx_a.pdf.

Since the time of stroke onset is a key determinant for thrombolytic treatment, EMS providers should obtain a brief history, particularly the “last-seen-normal” time, in any stroke patient transported. A brief medical history, including the use of anticoagulants, is very helpful. If a patient is aphasic or comatose, EMS should ensure that family or friends who know the patient’s past medical history are able to also come to the hospital.

Measures To Control Elevated Intracranial Pressure In The Prehospital Setting

In patients who are comatose and do not present with focal neurologic deficits, basic maneuvers that may decrease intracranial pressure (ICP) should be instituted. Although the benefit of keeping the head elevated has not been specifically studied in the setting of ICH, research performed on patients with traumatic brain injuries does demonstrate that positioning the head of the bed to 30° reduces ICP without decreasing cerebral perfusion pressure.⁵⁶⁻⁵⁹ Given that this is a simple measure that can decrease ICP in the setting of ICH, we recommend that prehospital providers keep the head of the bed elevated during transport.

Pain and anxiety may be present in the setting of ICH, especially in patients who are not comatose, so

alleviating these factors may assist in acutely lowering blood pressure.⁶⁰ Since the etiology of symptoms is unknown prior to a head CT being performed, prehospital medical personnel should use caution when treating pain or anxiety, so as not to obscure the neurologic examination in an awake patient. Although no studies have directly evaluated the use of nonsteroidal anti-inflammatory drugs in ICH, they should not be used in this setting, given their effects on platelet inhibition.⁶¹⁻⁶⁴

Basic Airway Management

Patients with stroke-like symptoms or ICH are at high risk for being unable to protect their airway and many ultimately require intubation and subsequent tracheostomy.⁶⁵ This is of paramount importance in the prehospital setting. Even in patients who are initially protecting their airway, continued neurologic evaluation is important. Patients who require prehospital intubation in the setting of possible stroke should not be given long-acting neuromuscular blockers during transport to the hospital by EMS if this can be avoided. Long-acting paralysis significantly clouds the neurologic examination and causes delays to diagnosis and neurosurgical treatment. Of patients with ICH who are transported by EMS, approximately one-fifth demonstrate neurologic deterioration prior to hospital arrival.^{66,67}

Emergency Department Evaluation

History

If not already determined by EMS, physicians in the ED should determine the last-seen-normal time in the setting of focal neurologic deficits, although this is less important in the acute management of ICH compared to acute ischemic stroke. It should be ascertained whether the patient is anticoagulated, and what type of anticoagulant the patient is taking. Since warfarin is no longer the only anticoagulant available, emergency clinicians need to be cognizant that patients may present taking direct factor Xa inhibitors or direct thrombin inhibitors. Information about the timing of the last dose of anticoagulant should be determined, especially for NOACs, which (at this time) do not have rapid, accurate tests to determine blood levels.

Despite the fact that there has not been an approved, commercially available antidote for reversal of these drugs, patients sustain fewer ICHs when taking NOACs, compared to warfarin.^{42,49-51} (Note: In October 2015, a dabigatran reversal agent, idarucizumab [Praxbind®], received United States Food and Drug Administration [FDA] approval.) Furthermore, the risk of death in the setting of ICH is not higher in patients taking a NOAC compared to warfarin. In 2391 patients who required anticoagulation for atrial fibrillation and subsequently developed an ICH

(2290 on warfarin, 101 on dabigatran), there was no statistically significant increased risk of death when comparing the two (mortality, 22% in warfarin; 20% in dabigatran).⁶⁸

Key portions of the patient's past medical history are important in the diagnosis and management of ICH in the ED. The 2015 AHA guidelines recommend that the ED provide insight into vascular risk factors, medications, recent trauma or surgery, alcohol or illicit drug use, seizures, liver disease, and cancer or other hematologic disorders.²⁸ Other past history that is helpful includes a prior ICH, a known intracranial mass or arteriovenous malformation, or a recent ischemic stroke, as these can provide clues to the cause of the ICH. (See Table 4.)

Physical Examination

A brief physical examination should be performed in concert with the history in a patient presenting with ICH. Specific attention should be paid to the neurologic examination. The Glasgow Coma Scale (GCS) score is well known by healthcare workers across all strata and can widely be reproduced and easily communicated.⁶⁹ The National Institutes of Health Stroke Scale (NIHSS), which was developed for use in ischemic stroke, may be valuable in patients who are awake, and provides information predictive of the risk of in-hospital death following stroke, even when used in the ICH setting.^{70,71} A link to an online calculator for NIHSS may be found at: www.mdcalc.com/nih-stroke-scale-score-nihss/

Diagnostic Studies

Imaging

Head CT will provide the diagnosis of ICH in the ED. Noncontrast head CT can be performed rapidly, and, in many centers, without the patient needing to leave the ED. Although magnetic resonance imaging (MRI) is more sensitive in detecting acute ischemia, it has capability similar to CT in detecting ICH.⁷² Examples of head CTs scans demonstrating ICH are shown in Figure 1 through Figure 5 (pages 6-9). Both blood and bone appear hyperdense on CT. However, their appearance can be distinguished by utilizing Hounsfield units (HUs). The HU scale is a method to measure radiodensity by comparing the image to the radiodensity of distilled water at a standardized pressure and temperature. Bone is

Table 4. Important History To Obtain In Patients With Intracerebral Hemorrhage

- Last-seen-normal time
- Complete medication list
- Prior history of intracerebral hemorrhage
- Chronicity of symptoms (have they gotten worse since onset?)
- History of coagulopathy

> 400 HUs, whereas blood is 30 to 45 HUs.⁷³

The ICH score, which has been derived and externally validated to risk stratify patients with ICH, relies heavily on head CT findings. Other elements of the ICH score, including ICH volume, presence of intraventricular blood, and infratentorial origin, can be determined by the initial noncontrast head CT.⁷⁴ (See Table 5, page 7.)

The noncontrast head CT may help distinguish the cause of an individual's ICH based on location. For example, a deep, nonlobar hemorrhage located in the basal ganglia or thalamus (especially in older individuals with a history of hypertension) is likely related to hypertensive disease.⁷⁵ Lobar hemorrhages in the very elderly are often associated with amyloid angiopathy, and these ICHs are more superficial and limited to the cortex.⁷⁶ In contrast, ICH in a young person or someone without a history of hypertension has a higher potential of being related to a vascular cause and should prompt CT angiography (CTA) or conventional angiography as part of the workup. In patients with the appropriate history and risk factors for venous thromboembolic disease

Figure 1. CT Scan Of A Right Frontal Cortical Intracerebral Hemorrhage



Arrow points to intracerebral hemorrhage.

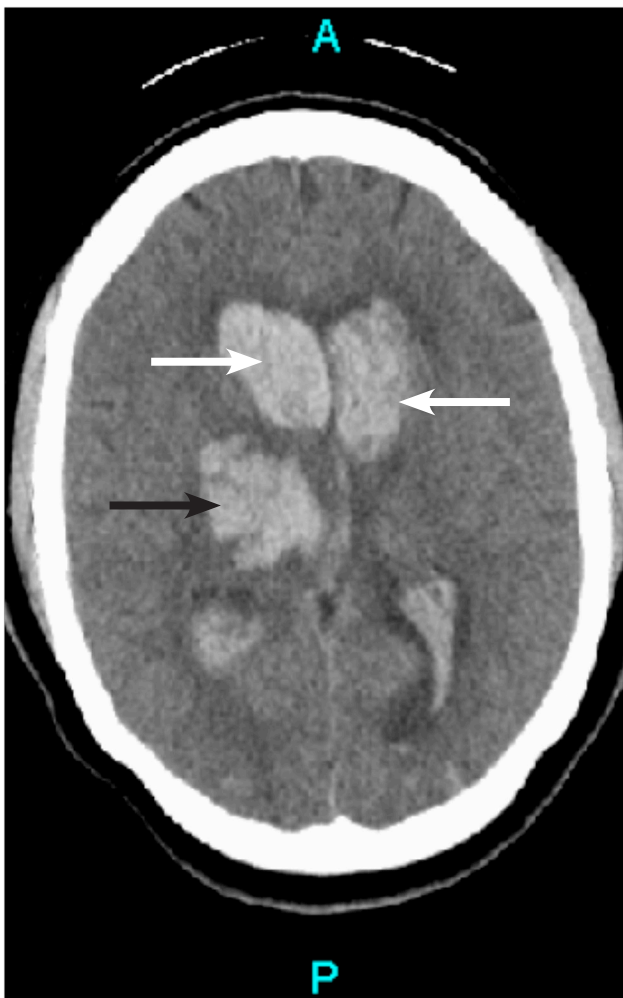
Abbreviation: CT, computed tomography.

Image courtesy of Natalie Kreitzer, MD.

(eg, recent pregnancy, inflammatory bowel disease, or cancer), ICH may sometimes occur in the setting of cerebral venous sinus thrombosis and should prompt cerebral venous imaging (CT venography or magnetic resonance venography). Venous sinus thrombosis may present with an ICH in up to 30% of cases, and the classic imaging finding is of flame-shaped, irregular areas of lobar hemorrhage.⁷⁷

As a general rule, once ICH is identified, head CTA and MRI are considered. Head CTA has taken on an increasingly important role in both diagnosis and prognosis. A “spot sign” on CTA, which is evidence of contrast extravasation within the ICH, is predictive of hematoma expansion (sensitivity 51%, specificity 85%).^{78,79} MRI can generally be delayed to the inpatient setting.^{80,81}

Figure 2. CT Scan Of A Right Thalamic Intracerebral Hemorrhage With Intraventricular Hemorrhage



White arrows point to intraventricular hemorrhage. Black arrow points to right thalamic intracerebral hemorrhage.

Abbreviation: CT, computed tomography.
Image courtesy of Natalie Kreitzer, MD.

Laboratory Studies

Patients with ICH should have complete blood count (CBC), electrolytes, PT (with INR) and activated partial thromboplastin time (aPTT) testing performed; troponin, toxicology screen, urine pregnancy test, and urinalysis are considered on a case-by-case basis.²⁸ A chest x-ray and electrocardiogram are also recommended as part of the 2015 AHA guidelines.²⁸ The PT with conversion to the INR is appropriate to measure the effects of warfarin, but there is more ambiguity in the setting of NOACs.⁸²

Dabigatran, rivaroxaban, and apixaban are the 3 commonly used NOACs. Unfortunately, there is not a widely available rapid method to determine the degree or presence of anticoagulation in patients who are taking these medications. Dabigatran acts as a direct thrombin inhibitor and may prolong the aPTT and thrombin clotting time (TT). Although aPTT can easily be obtained in the ED, dabigatran

Table 5. The Intracerebral Hemorrhage Score

Component	Range	ICH Score Points
Glasgow Coma Scale Score	3-4	2
	5-12	1
	13-15	0
ICH volume, cm ³	≥ 30	1
	< 30	0
Intraventricular hemorrhage	Yes	1
	No	0
Location	Infratentorial	1
	Supratentorial	0
Age	≥ 80 years	1
	< 80 years	0
Total ICH Score		0-6

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume indicates volume on initial CT calculated using ABC/2 method; and IVH indicates presence of any IVH on initial CT.

Interpretation of total score:

- ICH Score 0: no mortality
- ICH Score 1: 13% mortality
- ICH Score 2: 26% mortality
- ICH Score 3: 72% mortality
- ICH Score 4: 97% mortality
- ICH Score 5: 100% mortality
- ICH Score 6: 100% mortality (estimated)

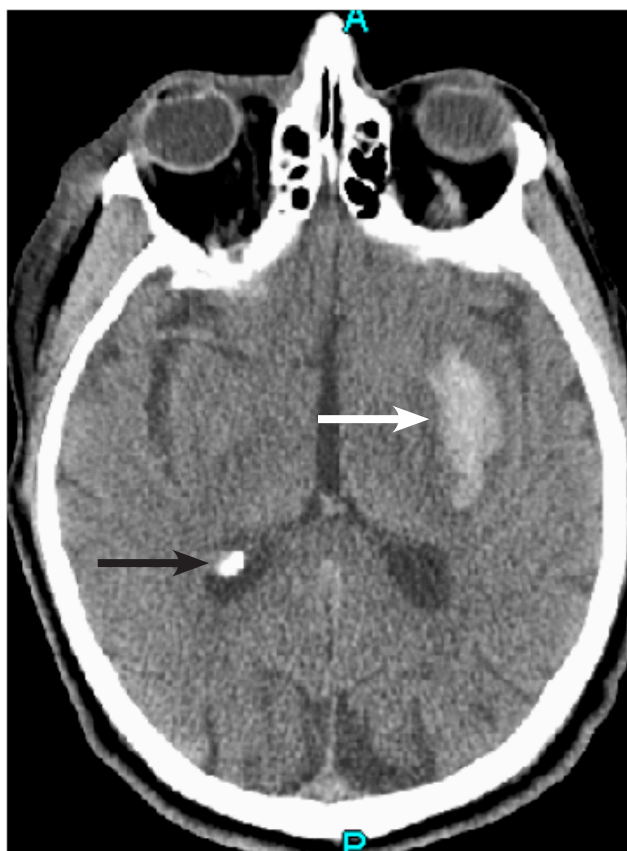
Abbreviation: CT, computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.

J. Claude Hemphill, III, David C. Bonovich, Lavrentios Besmertis, Geoffrey T. Manley, S. Claiborne Johnston. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001. Volume 32, Issue 4. Pages 891-897. Reprinted with permission of Wolters Kluwer Health, Inc.

has a flat dose-response curve to aPTT, thus limiting the use of this as a quantitative measurement.⁴⁰ Although the PT is not sensitive for measuring dabigatran quantitatively, it is able to measure it qualitatively.⁸³ The HEMOCLOT direct thrombin inhibitor assay (HYPHEN BioMed, Neuville-Sur-Oise, France), which combines a TT test with a dabigatran calibration curve, may ultimately become the best option in measuring the plasma concentration of dabigatran; however, in the United States, it is only used for research purposes at this time.⁸⁴

The factor Xa inhibitors present unique challenges in the measurement of anticoagulation in the ED. PT and aPTT are useful in determining a rough estimate of the presence of rivaroxaban, but they are not sensitive tests at lower plasma concentrations.⁸⁵ All factor Xa inhibitors prolong the PT to some degree, but the amount of prolongation is different between test reagents.⁸⁶ The Heptest-STAT assay (HEPTEST Laboratories, Inc., St. Louis, MO), a clot-based antifactor Xa assay and a chromogenic antifactor Xa assay are the best known methods of measuring these

Figure 3. CT Scan Of A Left Basal Ganglia Intracerebral Hemorrhage

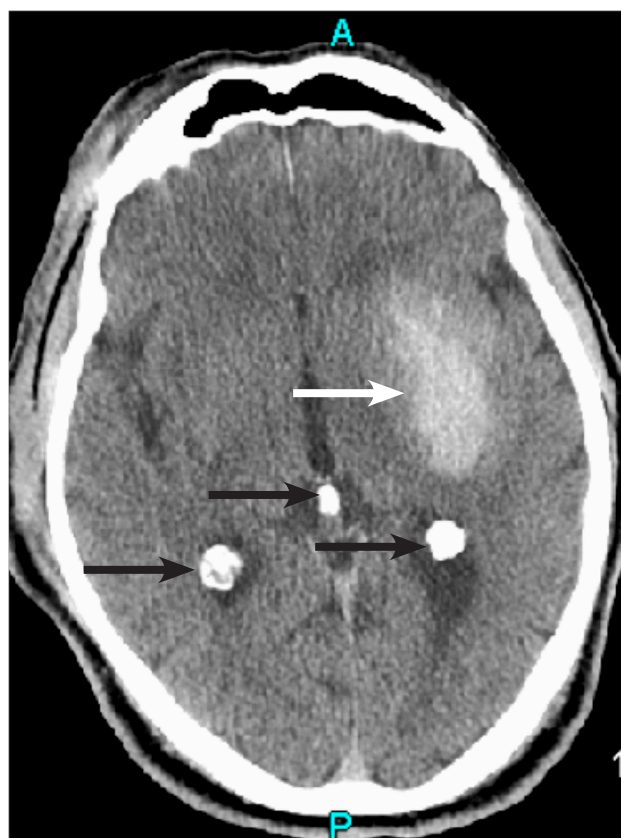


White arrow points to intracerebral hemorrhage, approximately 15 cc.
 Black arrow points to a calcification, shown as a hyperintense area in the right lateral ventricle.
 Abbreviation: CT, computed tomography.
 Image courtesy of Natalie Kreitzer, MD.

drug levels.^{86,87} However, these assays are still very new and are not yet widely available. Although conventional coagulation measurements are unable to provide quantitative measurements of the NOACs, they may be useful as a qualitative measurement of coagulopathy. For instance, a normal thrombin clotting time in patients receiving dabigatran, normal PT in patients receiving rivaroxaban, and normal antifactor Xa level in patients receiving apixaban suggest that coagulopathy is not present in each of the previously mentioned scenarios.⁸⁸

Early research is being conducted on the use of thromboelastography (TEG[®]) to determine whether or not TEG[®] may be of assistance in determining coagulopathy in the setting of VKA and NOAC use. At this time, results are mixed as to whether it will be beneficial. Franchi et al were able to demonstrate an association between TEG[®] times and INR in patients taking VKAs, but Rathbum et al could not find a correlation between patients taking rivaroxaban and TEG[®] findings.^{89,90} Although TEG[®] is immediately

Figure 4. CT Scan Of A Left Basal Ganglia Intracerebral Hemorrhage With Subsequent Enlargement 6 Hours Later



White arrow points to intracerebral hemorrhage at approximately 25 cc, 6 hours later. Black arrows point to calcifications, shown as hyperintense areas in the right ventricle.
 Abbreviation: CT, computed tomography.
 Image courtesy of Natalie Kreitzer, MD.

available in most tertiary EDs, at this time there is not enough evidence for it to be solely used to determine whether or not a patient is anticoagulated, and to what degree he or she is anticoagulated.

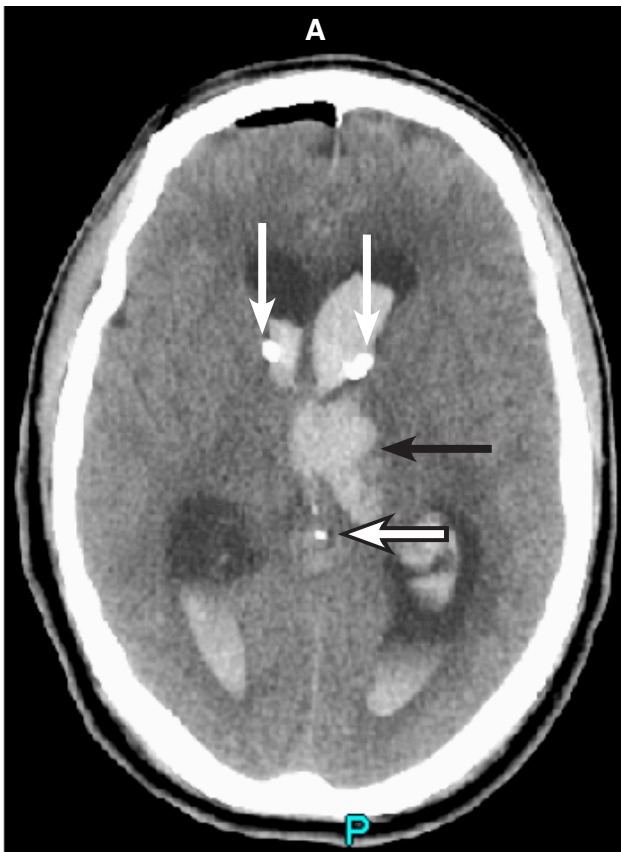
Treatment

Airway And Blood Pressure

ICH is a time-sensitive neurologic emergency. Diagnosis, treatment, and management must be performed in parallel with arranging disposition. One of the key elements of stabilization is airway assessment. Many patients with ICH require endotracheal intubation. Although it was classically taught that hyperventilation was a method to decrease ICP by decreasing CO_2 , this is not indicated unless it is used as a temporary measure prior to definitive operative therapy for decompression.⁹¹⁻⁹⁵

Optimal blood pressure management of patients with ICH has been the subject of numerous studies

Figure 5. CT Scan Of An Intraventricular Hemorrhage With Extraventricular Drain Catheters Placed Bilaterally



White arrows point to extraventricular drains. Black arrow points to a thalamic intracerebral hemorrhage with intraventricular hemorrhage spilling into the third ventricle. Black outlined arrow points to calcification.

Abbreviation: CT, computed tomography.
Image courtesy of Natalie Kreitzer, MD.

in recent years. Unlike ischemic strokes, ICHs do not have a confirmed surrounding area of penumbra (poorly perfused tissue surrounding the clot), and for this reason it is generally safe in ICH to acutely decrease blood pressure.⁹⁶ Furthermore, elevated blood pressures in ICH are independently associated with worsened clinical outcomes (neurological deterioration, hematoma expansion, and unfavorable outcome).⁹⁷ Neither the ATACH I trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage), nor the INTERACT trial (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage) found a safety difference in lowering SBP to < 140 mm Hg.^{98,99}

INTERACT-2, published in 2013, randomized 2839 patients to intensive blood pressure management (SBP < 140 mm Hg within 1 hour) or standard blood pressure management (SBP < 180 mm Hg) with endpoints of 90-day death or disability as primary outcome. Fifty-two percent of patients in the treatment arm compared to 56% in the standard arm experienced the primary outcome (OR, 0.87; 95% CI, 0.75-1.01, $P = .06$). INTERACT-2 demonstrated that intensive blood pressure management was safe, but did not, overall, reduce the likelihood of death, improve functional outcome, or significantly reduce hematoma expansion.¹⁰⁰ ATACH II, currently ongoing, is comparing blood pressure management in ICH patients to a goal of < 140 mm Hg SBP versus < 180 mm Hg SBP.¹⁰¹

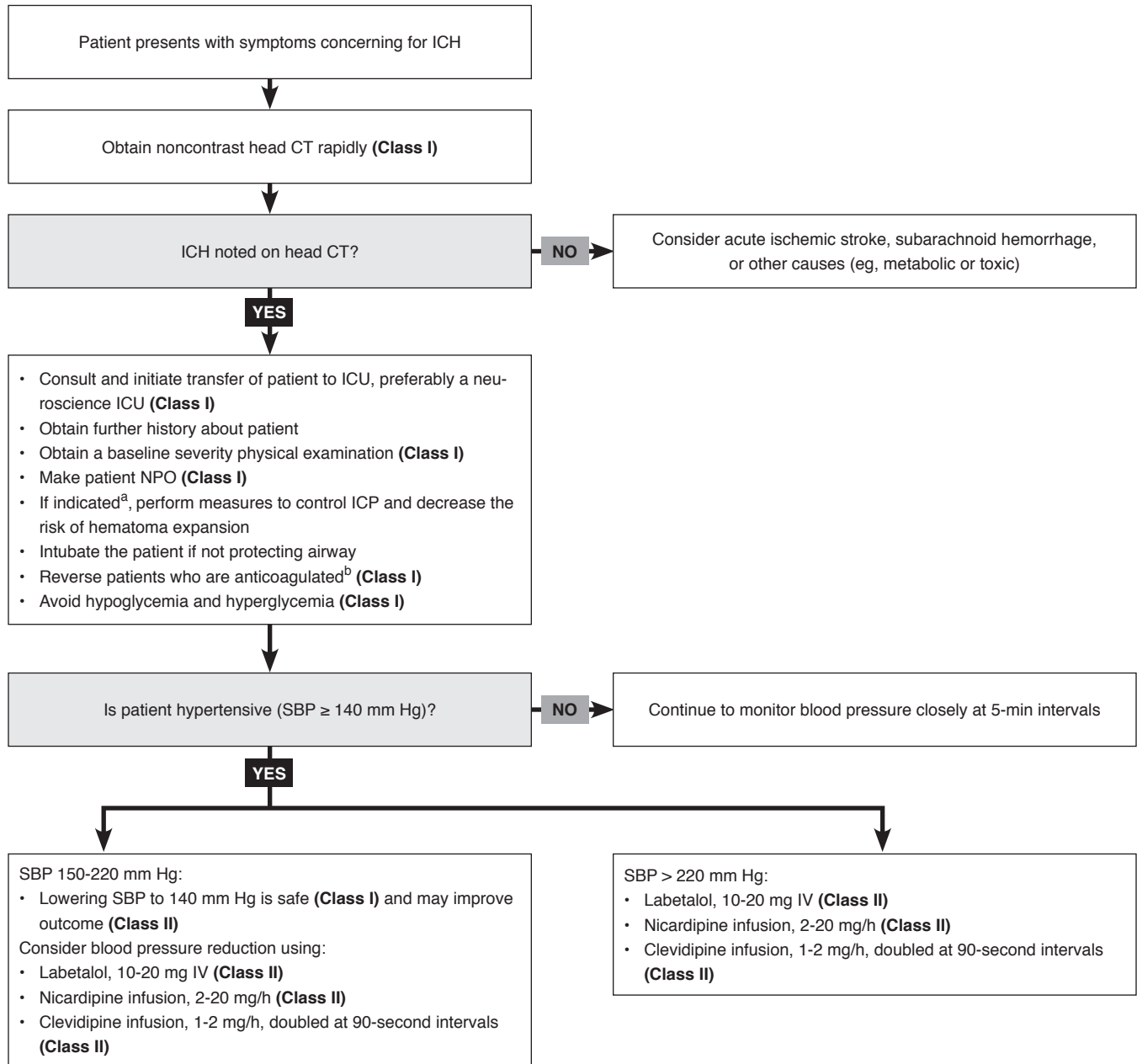
Largely as a result of these trial results, the recent AHA ICH guidelines have given a Class I, Level of Evidence A for acutely lowering SBP to 140 mm Hg as being safe for patients presenting with ICH and SBP between 150 and 220 mm Hg, and a Class IIa, Level of Evidence B that this is effective for improving functional outcome.²⁸ These guidelines were delayed a year to await the trial results, and were somewhat controversial, given that ATACH II is still ongoing. However, based on the best available evidence, emergency clinicians should acutely lower blood pressure in the setting of hypertension and ICH.

Anticoagulant Reversal

There are various methods by which to reverse anticoagulation in the setting of ICH. VKAs, factor Xa inhibitors, and direct thrombin inhibitors have different mechanisms of action on the coagulation cascade, and are reversed differently from one another.

VKAs have the most literature describing reversal.¹⁰² In the United States, VKA-associated coagulopathy has traditionally been treated with FFP. However, prothrombin complex concentrates (PCCs) have been in use for more than 20 years in Europe.^{103,104} PCCs generally contain coagulation factors II, VII, IX, and X in various ratios, as well as proteins C, S, Z, and antithrombin 3, whereas FFP contains all factors present in plasma.^{105,106} Although 3-factor PCC (without factor VII) has been

Clinical Pathway For Emergency Management Of Intracerebral Hemorrhage In Anticoagulated Patients



^aClinical indications for ICP management include: herniation syndromes, flexor or extensor posturing, stupor, or coma. Radiographic indications include cerebral edema, hydrocephalus, ventricular compression, cisternal effacement, or significant midline shift.

^bIf patient is anticoagulated, suggested reversal includes:

- Vitamin K antagonist (Coumadin[®]): Administer vitamin K, 5-10 mg, slow IV injection, plus 3- or 4-factor PCC, which corrects INR quickly and with fewer complications compared to FFP. If available, 4-factor PCC should be used. **(Class II)**
- Direct thrombin inhibitor (dabigatran [Pradaxa[®]]): Administer idarucizumab (Praxbind[®]) 5 grams IV; if not available, hemodialysis may be necessary. FEIBA (factor VIII inhibitor bypassing activity) may be of benefit. **(Class III)**
- Factor Xa Inhibitors (rivaroxaban [Xarelto[®]], apixaban [Eliquis[®]], edoxaban [Savaysa[®]]): 4-factor PCC may be necessary.

Abbreviations: CT, computed tomography; FFP, fresh-frozen plasma; ICH, intracerebral hemorrhage; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; IV intravenously; NPO, nothing by mouth; PCC, prothrombin complex concentrate; SBP, systolic blood pressure.

For class of evidence definitions, see page 11.

in use, 4-factor PCC is predominantly used at this time. No head-to-head comparison of 3-factor PCC and 4-factor PCC with a clinical endpoint has been performed; however, 4-factor PCCs are more likely to reverse elevated INR in the setting of VKAs compared to 3-factor PCCs. In a systematic review, Voils and Baird described that the INR was decreased to < 1.5 in 6 of 9 studies using 3-factor PCC versus 12 in 13 studies using 4-factor PCC. It is important to note, however, that the endpoint of these studies was INR, rather than a clinical endpoint.¹⁰⁷

In 2013, the FDA approved Kcentra® (CSL Behring), a 4-factor PCC formulation, for the reversal of VKA-associated acute major bleeding in adults. PCCs have been included in the 2 most recent sets of AHA guidelines for ICH, signaling the increasing strength of evidence supporting their use.^{11,28} There is evidence that PCCs reverse coagulopathy in patients with VKA-associated anticoagulation faster than FFP.¹⁰³ Vitamin K must always be given in conjunction with PCC or FFP in the setting of ICH. In a patient with a VKA-associated ICH, Vitamin K must be administered intravenously, as this has demonstrated a faster reduction in INR when compared to the subcutaneous route of administration.¹⁰⁸

Even when patients are given FFP and vitamin K for anticoagulation reversal, it is not uncommon for patients to not be fully reversed.¹⁰⁹ One of the first studies comparing FFP and PCC was published in 1997, when 41 patients with an INR that was deemed to be dangerously elevated were corrected by either FFP or PCC. Twelve patients received FFP, and their INR did not completely reverse (range 1.6-3.8, mean 2.3). Twenty-nine patients were given PCC, and the INR was completely corrected in 28 of these patients (range 0.9-3.8, mean 1.3). Factor IX levels were also measured in both cohorts following correction of INR, and patients in the FFP group did not achieve appropriate levels.¹⁰⁹

Sarode et al conducted a phase 3b multicenter trial comparing patients with elevated INR due to VKA coagulopathy treated with 4-factor PCC to

those treated with FFP. The primary endpoint was INR correction of at least 1.3 or lower at 0.5 hours after the end of the infusion. Sixty-two percent of patients in the 4-factor PCC group achieved hemostasis, compared to only 9.6% of patients in the plasma group.¹¹⁰ In a retrospective study of patients with VKA-associated ICH, Majeed et al compared 4-factor PCC to FFP for reversal of coagulopathy. This study of 135 consecutive patients demonstrated that the ICH volume was larger in the plasma group (64.5 cc vs 36.0 cc, $P = .021$). Although the 30-day mortality was lower in the PCC group, this was not statistically significant once adjusted for location of hemorrhage, age, and hematoma volume.¹¹¹ These trials demonstrate noninferiority and safety of 4-factor PCC in the setting of VKA antagonists with major bleeding.

Two studies that specifically targeted patients with ICH both determined a benefit to PCCs compared to FFP. Kuwashiro studied 37 patients with ICH on long-term warfarin with an INR > 2.0. Nineteen were given PCC within 7 hours of presentation, and the other 18 were reversed with FFP. The number of patients with hematoma expansion ($P = .017$), poor clinical outcome (modified Rankin Scale score ≥ 3 at 30 days or at discharge; $P = .045$) and inhospital mortality ($P = .042$) were all higher in the FFP group compared to the PCC group.¹¹² Parry-Jones et al pooled data from 16 stroke registries from 9 countries that included 1547 patients on VKA treated with FFP, PCC, both, or neither. Unexpectedly, the patients who received neither modality of reversal fared the worst, followed by FFP alone, then PCC alone, compared to both.¹¹³ These 2 modalities of anticoagulation reversal have not been compared head-to-head in the setting of ICH alone, likely due to the cost of PCC and the inherent difficulties in designing a randomized controlled trial comparing FFP to PCC.¹¹⁴

An study important to emergency practice was conducted by Kuramatsu et al, in which a large number of patients received PCC in the setting of VKA-associated ICH. The majority of patients in this

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II

- Safe, acceptable
- Probably useful

Level of Evidence:

- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate

- Continuing area of research
- No recommendations until further research

Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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retrospective cohort of 1176 patients from 19 German tertiary care centers received PCC, so there were too few patients who received FFP alone to make a direct comparison between the 2 modalities of treatment. However, this study highlights the need for rapid coagulopathy reversal in ICH. Patients who had a combination of INR reversal to < 1.3 within 4 hours of presentation as well as SBP reduction to < 160 mm Hg at 4 hours had a significantly lower rate of hematoma enlargement (18.1% vs 44.2%).²⁷

The only prospective observational study to compare PCC, FFP, and PCC + FFP in the setting of VKA-associated ICH was conducted by Frontera et al. After adjusting for age, admission GCS score, initial INR, and bleed type, patients who received PCC did not have as high a risk of death or severe disability at 3 months ($P = .039$) when compared to FFP alone. PCC corrected INR rapidly in this study without any increase in adverse events when compared to FFP.¹¹⁵

Additional evidence supports the fact that PCCs are at least moderately safe. A meta-analysis of 1032 patients demonstrated an overall thromboembolism rate of 1.4% associated with PCCs.¹¹⁶ Cruz et al described a retrospective review of 70 patients who received PCC for VKA-associated life-threatening bleeding. In this study, 7.1% of patients developed a thrombotic complication, and the 30-day mortality rate was 14.3%.¹¹⁷ The thrombotic potential of PCCs is likely not fully elucidated at this time, due to a lack of data.

There are advantages and disadvantages associated with the use of both PCCs and FFP. PCCs are able to be stored at room temperature, thus making preparation much faster in emergencies.¹⁰⁵ PCCs have a much smaller volume of infusion, and are ideal for patients with heart failure, as these patients may not be able to tolerate a large volume. FFP combined with vitamin K has been the traditional method by which INR is reversed in VKA-associated ICH. When coagulopathy is corrected in this manner, a dose of 15 mL/kg needs to be used to ap-

propriately correct the INR, which may be a large volume. FFP can cause transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and transfusion allergic reactions. Infections may also be transmitted. The risks of these processes are relatively low.^{118,119} Suggested reversal agents are listed in **Table 6**.

Guidelines And Recommendations For Vitamin K Antagonist-Associated Major Bleeding

Current CHEST guidelines recommend that patients with VKA-associated major hemorrhage receive 4-factor PCC rapidly rather than FFP (Grade 2C). They furthermore suggest that patients should also receive 5 to 10 mg of vitamin K intravenously, slow IV injection (Grade 2C).³¹ The 2015 AHA/ASA guidelines state that "...patients with ICH whose INR is elevated should have VKA withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K (Class I, Level of Evidence C)." They also state that "PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (Class IIb, Level of Evidence B)."²⁸ Based on evidence available, we think that all ICH in the setting of VKA represents a life threat, and we favor the use of PCCs for reversal.

Reversal Of Antiplatelet Medications In Intracerebral Hemorrhage

Data are currently mixed regarding the reversal of antiplatelet medications in the setting of ICH, and studies are ongoing to determine the answer to this question. The majority of literature reports that patients with ICH who are on antiplatelet therapy have increased hemorrhage growth and potentially worsened outcomes compared to those who are not on antiplatelet therapy.^{120,121} The CHANT trial (Cerebral Hemorrhage and NXY-059 Treatment) did not demonstrate that patients on antiplatelet therapy do worse in the setting of ICH. This trial contained 70 patients who were taking an antiplatelet medication at the time of ICH. It demonstrated no association between antiplatelet medications, volume of ICH at presentation, initial edema volume, edema growth, or hematoma expansion. There was no difference in clinical outcome at 90 days (OR, 0.67; 95% CI, 0.39-1.14; $P = .14$) between patients who were taking antiplatelet therapy and those who were not.¹²²

Aspirin and clopidogrel combined were found to increase the rate of ICH by 61% ($P = .06$) compared to clopidogrel alone in a recent randomized trial of patients with recent stroke or transient ischemic attacks.¹²³ Typically, even in studies where an increase in ICH rates are shown in patients taking antiplatelet therapy, the benefits of risk reduction in myocardial infarction outweigh the risks, as shown

Table 6. Recommended Reversal Agents For Anticoagulation

Agent	Reversal Options
Warfarin (vitamin K antagonist)	<ul style="list-style-type: none"> Vitamin K plus Either fresh-frozen plasma or PCC
Dabigatran (direct thrombin inhibitor)	<ul style="list-style-type: none"> Idarucizumab (approved October 2015) Hemodialysis or FEIBA Consider PCC if dialysis initiation will be a lengthy process
Rivaroxaban/apixaban/edoxaban (factor Xa inhibitors)	<ul style="list-style-type: none"> PCC

Abbreviations: FEIBA, factor VIII inhibitor bypassing activity; PCC, prothrombin complex concentrate.

in a meta-analysis by He et al of 55,462 patients. This study demonstrated that there was a risk reduction of 137 events per 10,000 persons of myocardial infarction ($P < .001$), but a slight increase in ICH, at an increased risk of 12 per 10,000 persons ($P < .001$).¹²⁴ However, it is unknown whether platelet transfusions are beneficial for reversing antiplatelet therapy, as study results have been mixed. In a recent retrospective review of 5 studies of patients on antiplatelet therapy with traumatic ICH, the results were mixed with regard to treatment. One study reported higher mortality for patients with platelet transfusion (RR, 2.42; 95% CI, 1.2-4.9). Another study showed a lower mortality for patients who received platelets (RR, 0.21; 95% CI, 0.05-0.95), and the other 3 studies showed no difference in mortality.¹²⁵ Naidech et al described a series of 45 patients who received a platelet transfusion for ICH. In all patients, platelet function testing showed improved platelet function. Patients who received platelets within 12 hours of symptoms had a smaller hemorrhage size on follow-up, as well as increased odds of independence at 3 months ($P = .01$).¹²⁶

Current AHA guidelines state that the “usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain,” and give this a Class IIb, Level of Evidence C.²⁸ The ongoing PATCH study (Platelet Transfusion in Cerebral Hemorrhage) may provide further information.¹²⁷ This trial is a randomized controlled trial in which patients on antiplatelet therapy receive platelet transfusions or standard care within 6 hours.

Desmopressin may be another avenue for reversal in patients on antiplatelet therapy with ICH. Naidech et al performed a study of 14 patients with ICH and demonstrated that desmopressin was well-tolerated and improved platelet activity, as shown by platelet function testing.¹²⁸ Larger studies will need to be performed to determine whether desmopressin may be an avenue for reducing hematoma growth or improving survival in ICH in patients on antiplatelet therapy.

Reversal Of Novel Oral Anticoagulants In Intracerebral Hemorrhage

Compared to evidence available for VKA-associated bleeding, far less evidence is available regarding the reversal of coagulopathy caused by the NOACs. As of October 2015, idarucizumab has been approved by the FDA for the urgent reversal of dabigatran under the accelerated approval program, but is not yet widely available for use. Direct thrombin inhibitors can generally be removed by hemodialysis, since it is (largely) renally cleared.¹²⁹ Based on case series, hemodialysis for 4 hours reduces plasma concentrations by 62% to 68%, but a rebound increase is noted at the termination of dialysis.¹³⁰ Animal studies have demonstrated a benefit of PCC in the setting of dabigatran reversal.¹³¹ Although dialysis is recom-

mended for the reversal of direct thrombin inhibitors, it often takes hours before it is even started. These early hours are critical for hematoma expansion in ICH, so we recommend an attempt at PCC in patients with ICH taking dabigatran if idarucizumab is unavailable.

Factor VIII inhibitor bypassing activity (FEIBA), also known as activated 4-factor PCC, has been used for more than 40 years in patients with hemophilia who have antibodies against factor VIII or factor IX.¹³² FEIBA has also been described as another possibility for the reversal of dabigatran in very small case series. In 8 patients taking dabigatran, FEIBA administration was able to reverse coagulopathy based on thrombin generation measurements caused by dabigatran.¹³³ NOAC reversal was studied in a randomized crossover ex vivo study of 10 healthy individuals treated with dabigatran initially and rivaroxaban 2 weeks later, in which subjects received PCCs, recombinant factor VIIa (rFVIIa), and FEIBA in various doses. The rFVIIa and FEIBA corrected the thrombin lag time in the setting of dabigatran, but with thromboembolic events at increasing doses. After 2 weeks, the study participants received rivaroxaban. PCCs were strongly able to reverse the rivaroxaban, but FEIBA was also somewhat effective. Another randomized double-blind placebo-controlled crossover trial of 12 healthy subjects studying rivaroxaban reversal demonstrated that PCCs normalized PT and endogenous thrombin potential immediately after administration in the setting of rivaroxaban. PCCs did not reverse aPTT, endogenous thrombin potential lag time, thrombin time, or ecarin clotting time (ECT) in the setting of dabigatran use.¹³⁴ These data should be viewed with caution, given that the trial was performed only in nonhemorrhagic settings in a very small number of healthy individuals.¹³⁵ In vitro testing has shown that 4-factor PCCs are appropriate for the reversal of factor Xa inhibitors, given that these drugs are protein-bound and cannot be removed with hemodialysis.^{136,137} At this time, there are very little data to suggest the best reversal strategies of NOACs.

Recombinant Factor VIIa

Currently, rFVIIa is still under investigation as a hemostatic agent in ICH. However, at this time, it is unclear which patients, if any, will benefit from the administration of rFVIIa. Phase 2b and phase 3 randomized trials of rFVIIa given within 4 hours of symptoms showed a statistically significant reduction in hematoma expansion without improvement in clinical outcome in patients who are not anticoagulated.^{138,139} The safety profile of rFVIIa is concerning, especially in patients with known vascular risk factors, as patients who received rFVIIa compared to placebo experienced a 20% increase in ischemic strokes and myocardial infarctions.¹⁴⁰ Two trials are

currently in progress to randomize only spot-sign-positive patients to receive rFVIIa versus placebo. These trials are the STOP-IT Study (Spot Sign for Predicting and Treating ICH Growth) and the SPOT-LIGHT trial (Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy).

There are no studies to determine the efficacy of rFVIIa for the reversal of NOACs in patients who are actively bleeding. However, early animal and basic research suggests that rFVIIa could be beneficial at reversing some, but not all, of the NOACs. In mice receiving dabigatran, rFVIIa was ineffective at preventing excess hematoma expansion after an induced ICH.¹⁴¹ In rabbits receiving rivaroxaban, rFVIIa was able to decrease ear bleeding times, aPTT, and TEG[®] clotting times.¹⁴² In rats receiving edoxaban, rFVIIa shortened PT prolongation, showing that rFVIIa may, potentially, be a reversal agent for edoxaban.¹⁴³ These studies are all very preliminary, but demonstrate that rFVIIa needs to be studied further as a reversal strategy for the NOACs. Although further trials may better delineate which patients should receive rFVIIa, currently there is not enough evidence to recommend administering rFVIIa for ICH to any patients at this time.

Tranexamic Acid

The use of tranexamic acid (TXA) has been widely adopted in the trauma literature, most notably since positive results of the CRASH -2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage), a randomized double-blind placebo-controlled trial comparing TXA to placebo in trauma; however, it is unknown whether it will benefit ICH patients.¹⁴⁴ In particular, it may be of interest to determine whether or not patients who are anticoagulated might benefit from TXA.¹⁴⁵ In traumatic brain injury, pooled results from 2 randomized controlled trials demonstrated statistically significant reduction of progression, but did not demonstrate a significant clinical outcome difference. Further evidence will be necessary to determine whether TXA may be beneficial in patients with ICH.¹⁴⁵

Management Of Elevated Intracranial Pressure

Patients with ICH in the setting of anticoagulation are at a high risk for increasing or elevated ICP. Management of ICP in ICH has been largely extrapolated from traumatic brain injury literature. There is evidence to suggest that ICP > 20 mm Hg is associated with increased morbidity and mortality in ICH.¹⁴⁶ As long as there are no concerns for spinal cord injuries, the patient's head of the bed should be elevated to 30° to 45° as a simple measure to decrease ICP.²⁹ In comatose patients with clinical or radiographic signs of elevated ICP, hyperosmolar therapy may be appropriate for use. Either mannitol or hypertonic saline

(3% or 23.4%) may be used in the setting of presumed elevated ICP; however, 23.4% boluses are recommended in the acute treatment of elevated ICP.¹⁴⁷ It is important to note that 23.4% saline may only be given via a central line. Patients may have elevated ICP secondary to intraventricular blood and developing hydrocephalus, as well. When patients are anticoagulated, it is crucial to reverse anticoagulation so that an emergent extraventricular drain can be placed as soon as possible to divert cerebrospinal fluid for treatment of acute hydrocephalus.

Seizure Prophylaxis And Management

The 2010 AHA guidelines did not recommend that prophylactic antiseizure drugs be given to patients with ICH, and this remained unchanged in the 2015 guidelines.^{11,28} The actual incidence of seizures in ICH is unknown, but has been described as being between 1.7% in some populations to 17% in patients with cortical/supratentorial ICH.^{148,149} Patients who have clinical or electrographic seizures on electroencephalography should receive an antiepileptic drug, according to both guidelines.^{11,28} Thus, if patients with ICH in the ED appear to be seizing, they should be treated. The likelihood of seizures is highest nearer to the onset of the ICH.^{148,149} Phenytoin has been demonstrated to be harmful as a prophylactic medication in patients with ICH. Two separate studies have demonstrated a worsened outcome in patients who were given prophylactic antiepileptic drugs in ICH.^{149,150} In 2009, a prospective cohort of patients taking phenytoin demonstrated worse outcome after ICH; levetiracetam did not have a similarly detrimental effect.¹⁵⁰ Another prospective study of 295 patients with ICH demonstrated antiepileptic drug use led to a poorer outcome in ICH, even when other factors associated with outcome were taken into account.¹⁴⁹ Given the strength of evidence available, emergency clinicians should not prescribe prophylactic antiepileptic drugs to patients with ICH.

Surgery

Based on 2 multicenter randomized controlled trials (STICH I and STICH II [Surgical Trial in Intracerebral Hemorrhage]), patients with supratentorial ICH are, overall, unlikely to benefit from surgery. In 2005, STICH I randomized 1033 patients to surgery or conservative treatment. At 6 months, 26% of surgical patients (compared to 24% of medically managed patients) had a good outcome ($P = .414$).¹⁵¹ STICH II randomized 601 patients to surgery or medical management. At 6 months, 59% of patients who were randomized to the early surgery group had a poor outcome compared to 62% of patients in the medical management group ($P = .367$).¹⁵² Thus, the available evidence does not support routine surgical evacuation of ICH. However, concerns about the high crossover from conservative to surgical management

in STICH II may have obscured a potential treatment effect of surgery over conservative medical management. Thus, neurosurgeons may occasionally elect to decompress or evacuate ICH patients, depending on the clinical scenario.

In contrast to the case with supratentorial ICH, posterior fossa ICH often benefits from decompression. Small-volume masses or hemorrhage are dangerous in the posterior fossa due to the proximity of the brainstem and due to fourth ventricular compression, which could lead to obstructive hydrocephalus. Although there are no randomized controlled trials comparing decompression to conservative management in the setting of cerebellar hemorrhage, there are case series that describe its utility.

Posterior fossa decompression was first described in a large case series in the literature in 1984 by Da Pian et al.¹⁵³ They concluded from 155 cerebellar hematomas and 50 brainstem hematomas that certain patients with posterior fossa ICH benefit from decompressive surgery. In their case series, patients with fourth ventricular shift, hydrocephalus, and patients with intraventricular blood may benefit from decompression in cerebellar ICH.¹⁵³ In 1995, van Loon et al described 49 patients, of whom 17 were managed nonoperatively, 30 underwent a ventricular drain, and 6 had a hematoma evacuation. They concluded from this series that patients who had compressed cisterns should undergo hematoma evacuation, as other therapies are unlikely to be adequate.¹⁵⁴ It is believed that a clinical trial determining the utility of decompression in posterior fossa is unlikely to take place, given that there is no clinical equipoise regarding the subject.²⁸ The 2015 AHA guidelines have a Class I, Level of Evidence B recommendation for surgery in patients with cerebellar hemorrhage who are actively deteriorating, have brainstem compression, or have hydrocephalus secondary to ventricular obstruction.²⁸ Emergency clinicians need to be acutely aware of this indication for surgical intervention in the setting of ICH so that they may rapidly notify their neurosurgery consultants. Minimally invasive surgery may be a trajectory for newer therapies for ICH. Endoscopic or stereotactic placement of a catheter is performed, often in conjunction with tPA to evacuate ICH.

The MISTIE II trial (Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator for ICH Evacuation Trial II) compared volume on CT in patients with hematoma evacuation compared to medical management, and demonstrated a significant reduction in perihematomal edema volume in the surgical arm compared to the medical arm.¹⁵⁵ The MISTIE III trial, which is ongoing at this time, compares minimally invasive hematoma evacuation with medical management, with the endpoint of functional outcome at 180 days. Intrathecal rtPA is also being studied as an option to improve outcomes in patients with intraventricular hemorrhage as a method to

hasten resolution of intraventricular hemorrhage. The CLEAR III trial (Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage) is an ongoing double-blind placebo-controlled study comparing intrathecal rtPA to saline.¹⁵⁶

Do Not Resuscitate Orders

Do Not Resuscitate (DNR) and Comfort Care orders have become the leading proximate cause of death in ICH, leading to concerns about a “self-fulfilling prophecy,” whereby the impression of clinicians of a likely poor outcome results in limitation of care and subsequent death.¹⁵⁷ However, on a case-by-case basis, with input from the patient's family, neurology, neurosurgery, or radiology regarding prognosis and treatment options, some patients should be made DNR while in the ED. For example, elderly patients with large ICHs may be appropriate for early DNR or withdrawal of care.

The ICH score is often used clinically to defend decisions related to limitations of care.¹⁵⁸ A recent prospective observational cohort study of 109 patients with a mean hematoma volume of 39 cc found that patients who did not have a new DNR order placed during the first 5 days after ICH had a lower 30-day mortality than would otherwise be predicted by their ICH score. Based on the ICH score alone, this cohort of patients would have had a 50% mortality; however, the cohort had an observed mortality that was much lower, at 20.2%. Of note, a significant number (21.5%) of these patients still had a modified Rankin Scale score of 5 or were severely disabled.¹⁵⁹ Nonetheless, the study is enlightening in that it suggests judicious use/interpretation of the ICH score for prognostic purposes.¹⁶⁰ The ICH score is shown in **Table 6** (see page 12).

Controversies And Cutting Edge

Novel Prehospital Computed Tomography Scanners

New mobile stroke units have recently been described in the literature. One such stroke unit, the mobile stroke team unit of Cleveland, has deployed an ambulance that has a registered nurse, paramedic, emergency medical technician, and a CT technologist. A stroke physician evaluates the patient and a neuroradiologist reads the images obtained in a noncontrast head CT. Point-of-care laboratory work is performed, and patients are able to receive tPA for ischemic stroke prior to hospital arrival. Likewise, patients with ICH may also be treated. Thus far, the mobile stroke unit has treated 1 prehospital anticoagulant-associated ICH with 4-factor PCC. The patient's INR was initially 2.2, and was found to be 1.1, 106 minutes later.¹⁶¹ Although prehospital anticoagulation reversal is likely a long way off in most areas of the country, this method of ischemic and hemorrhagic stroke treatment is promising. PCCs are

more ideal in the prehospital scenario as well, given that they are able to be stored at room temperature, unlike FFP, which requires refrigeration.¹⁰⁵

Optic Nerve Sheath Diameter In Intracerebral Hemorrhage

Elevated ICP may be detectable with the use of optic nerve sheath diameter (ONSD) on ultrasound. Numerous studies have demonstrated the reliability of this method in ruling out elevated ICP in trauma.¹⁶² ONSD is performed by measuring 3 mm behind the eye over closed eyelids, as depicted in **Figure 6**.¹⁶³ A study of 61 patients demonstrated that emergency physicians were able to accurately measure ONSD when compared to CT. In this study, the intraclass correlation coefficient was 0.9.^{164,165} The ONSD has

Figure 6. Optic Nerve Sheath (Outlined In White)



Image courtesy of Natalie Kreitzer, MD.

a 100% sensitivity and specificity at 5.7 mm for high ICP, which was defined as > 20 mm Hg for more than 30 minutes.¹⁶⁴ This may be a useful method to detect elevated ICP in the setting of ICH.

Potential Antidotes For Novel Oral Anticoagulants

Potential antidotes are on the horizon for NOACs, and would be useful in the setting of NOAC-associated ICH. Andexanet alfa is a modified recombinant form of factor Xa, and binds to factor Xa inhibitors with an affinity similar to that of native factor Xa.¹⁶⁶ Andexanet alfa is currently in phase 3 trials for the reversal of factor Xa inhibitors. Aripazine is in a phase 1 trial, and is being studied as a universal synthetic molecule that can bind to any anticoagulant to reverse its effects. Aripazine currently demonstrates no evidence of procoagulant effects.¹⁶⁷

Disposition And Transport

ICH patients should be admitted to an intensive care unit, ideally a neurological intensive care unit (NICU). Non-NICU admission has been associated with higher mortality than NICU admission. (OR, 3.4; 95% CI, 1.65-7.6).¹⁶⁸ Other factors that contribute to higher in-hospital mortality rate are lower GCS score at presentation, fewer ICH patients admitted to a particular ICU, and smaller ICUs.¹⁶⁸ Patients with ICH should be rapidly transferred to facilities capable of managing ICH if this care is not available at the institution to which the patient initially presents. Emergent air transportation may be necessary, and has been demonstrated to be both safe and effective in the ICH setting.¹⁶⁹

Summary

When patients present to the ED and are diagnosed with ICH, key elements of management and disposition must be performed simultaneously to ensure the best care. In addition to a complete history and physical examination, important actions in the ED include airway control, urgent CT imaging, blood pressure management, frequent reassessment, and initiation of appropriate reversal strategies according to the anticoagulant taken. Consultation, ICU admission, and possible transfer should be initiated as rapidly as possible. Patients on warfarin or factor Xa inhibitors should be promptly treated with factors and/or PCC, while patients on dabigatran should be treated with the recently approved idarucizumab, if available, or urgent dialysis if not. Data are quite limited regarding optimal coagulopathy reversal in the setting of NOACs at this time; however, the emergency clinician must be aware of new developments and become involved in developing local protocols to manage these patients to improve outcome.

Risk Management Pitfalls For Intracerebral Hemorrhage In Anticoagulated Patients

- 1. “I thought that the ICU would take care of this patient’s blood pressure.”**
Blood pressure management should begin in the ED in patients with ICH. It is generally safe to take measures to reduce blood pressure in this setting.
- 2. “I did not want to use PCC to manage reversal of ICH because it was too expensive.”**
Expense is relative to outcomes. In the appropriate patient population (VKA or factor Xa inhibitors), PCC is likely the most effective method to reverse coagulopathy in the setting of ICH. PCCs are ideal in patients who may not tolerate a larger volume of infusion, such as those with congestive heart failure.
- 3. “My patient on dabigatran had an ICH, but I did not put in a dialysis catheter; that is too invasive.”**
Dabigatran is a small molecule, and thus is able to be dialyzed. Idarucizumab has recently been approved as an antidote for dabigatran, but if it is not available, dialysis is a consideration.
- 4. “The patient with the cerebellar hemorrhage became more sleepy prior to transfer, but I assumed the accepting neurosurgeon would be waiting in the ED.”**
Never make assumptions and always provide up-to-date communication with the accepting physician whenever transferring a patient. Patients with cerebellar hemorrhage and declining mental status are candidates for emergent decompressive surgery.
- 5. “My nurses were uncomfortable starting a nicardipine infusion for the patient’s ICH and had never heard of clevidipine, so we continued with labetalol, even though it didn’t seem to be working.”**
Frequently, patients with ICH require continuous infusion of antihypertensives to maintain adequate blood pressure control.
- 6. “My patient with hydrocephalus waited in the ED a very long time for transportation and he deteriorated, but no one let me know.”**
Patients with ICH are at high risk for hydrocephalus, which can be corrected by external ventricular drain placement. They should be rapidly transported to an appropriate facility, and even flown if necessary, as they are at high risk of decompensating.
- 7. “I thought it was a regular headache, so I did not order a head CT.”**
Key factors may be present in the presentation of ICH that will help clue emergency clinicians that a more ominous problem is present. Head CT should be considered in patients with headache, especially in patients who are anticoagulated.
- 8. “I did not transfer the patient because....”**
Patients with ICH have better outcomes when cared for by a team of neuroscience specialists in an ICU. If these resources are unavailable, patients need to be transferred to another facility.
- 9. “The patient did not mention taking warfarin and his INR was normal, so I did not ask about any other agents.”**
More and more patients will be taking NOACs, and emergency clinicians must screen for all anticoagulants once an ICH has been diagnosed. This is especially important when patients present with atrial fibrillation or have another reason that they may require anticoagulation.
- 10. “I thought the elderly patient from the nursing home had severe dementia and the history we received in the report from EMS did not sound concerning for an ICH.”**
Age is an important risk factor for ICH, and a thorough workup should be performed in patients who are confused or have a change in mental status. It is important to note a baseline mental status in patients who present with an altered mental status.

Case Conclusions

Your first patient, the 78-year-old man with congestive heart failure and a right parietal lobe bleed, had an emergent need for rapid reversal of his INR, even with the risks associated with his mechanical heart valve. You administered 50 units/kg of 4-factor PCC to limit the amount of volume he was given, decreased his blood pressure to a goal SBP of 140 mm Hg, and transferred him to the NICU.

Your second patient, the 65-year-old woman on dabigatran with a thalamic ICH and intraventricular extension also required rapid reversal of her coagulopathy. Since she had taken her dabigatran just a few hours prior to her arrival, you presumed that she was therapeutically anticoagulated. You successfully prevented hematoma expansion by giving her idarucizumab, 5 grams.

The third patient with the cerebellar ICH constituted a neurosurgical emergency. He also required reversal with 50 units/kg of 4-factor PCC as well as posterior decompression. Even though he likely had elevated intracranial pressures, you knew he should not be hyperventilated unless he was definitively en route to the operating room. He also benefited from a dose of mannitol (1.5-2 g/kg), although hypertonic saline (30 mL of 23.4% saline) could also have been used if a central line had been placed.

Time- And Cost-Effective Strategies

- In patients diagnosed with ICH, it may be time- and (potentially) cost-effective to fly them to another facility. Although the costs of rapid transportation are high, the clinical outcome may hinge on rapid transport.
- Head CT should be performed as soon as possible once ICH is suspected. The longer patients go without a diagnosis, the higher the risk of deterioration.
- Management and disposition should occur rapidly and simultaneously. Even if an entire history is unknown, arrangements for transportation should be made to a facility that frequently cares for patients with ICH.
- A coagulation panel and complete blood count should be ordered in all patients with ICH. Even though NOACs may not be detected by routine laboratory testing, make sure patients do not have thrombocytopenia or an elevated INR that may require reversal.
- If at all possible, DNR status should not be made while the patient is in the ED. Although ICH has high morbidity and mortality, there is evidence to suggest that DNR status tends to a poorer prognosis, and likely does not save time.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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- All of the following are risk factors for ICH EXCEPT:**
 - Age
 - Prior seizure history
 - Warfarin use
 - Hypertension
- All of the following measures should be done in suspected elevated intracranial pressure EXCEPT:**
 - Elevate head of bed
 - Increase respiratory rate to target $PCO_2 < 30$
 - Hyperosmotic therapy
 - Treat pain
- What imaging should be ordered in patients with suspected ICH?**
 - Noncontrast head CT
 - Magnetic resonance imaging
 - Magnetic resonance angiography
 - CT angiography
- In a patient taking a VKA, when should correction of INR take place?**
 - Within first 12 hours
 - Within first 24 hours
 - Within first 4 hours
 - Immediately after diagnosis of ICH

5. In a patient with an ICH who has congestive heart failure, atrial fibrillation, and warfarin use, what should be used to reverse coagulopathy?
 - a. PCC only
 - b. PCC and vitamin K
 - c. FFP
 - d. rFVIIa

6. In a patient taking dabigatran for atrial fibrillation found to have an ICH, what should be done to reverse coagulopathy if idarucizumab is not available?
 - a. PCC
 - b. FFP
 - c. Vitamin K
 - d. Dialysis

7. In a patient on rivaroxaban with ICH, what should be done to reverse coagulopathy?
 - a. PCC
 - b. FFP
 - c. Vitamin K
 - d. Dialysis

8. Which antiepileptic drug should be given to all patients found to have an ICH?
 - a. Lamictal
 - b. Phenytoin
 - c. Valproic acid
 - d. None

9. Which location of ICH is most amenable to neurosurgical intervention?
 - a. Frontal lobe
 - b. Basal ganglia
 - c. Cerebellum
 - d. Pons

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