



# **INTRACEREBRAL HEMORRHAGE**

## **ANNOTATED BIBLIOGRAPHY**

**Cristina Gamboa**

University of Illinois at Chicago, College of Medicine  
Medical Candidate, 2010

**Edward P. Sloan, MD, MPH, FACEP**

Department of Emergency Medicine  
University of Illinois at Chicago, College of Medicine

This annotated bibliography is an intended guide on the topic of intracerebral hemorrhage (ICH) and will assist the reader in navigating through information on ICH. Currently available at the FERNE website is a series of lecture material on neurological emergencies including ICH. FERNE supports physicians in continuing their professional education and offers an online ICH CME program. Please visit the following link for further information on the ICH CME program, <http://www.ferne.org/CME/CME.htm>.

## **GENERAL REVIEWS**

**Hsieh PC, Awad IA, Getch CC, Bendok BR, Rosenblatt SS, Batjer HH. Current updates in perioperative management of intracerebral hemorrhage. *Neurol Clin.* 2006;24:745-64.**

Although the title implies this article to be a discussion of ICH management, in reality Hsieh and colleagues give a general review of ICH. Epidemiology, pathophysiology, etiology, and diagnosis of ICH are thoroughly described. ICH is only briefly discussed. Hsieh and colleagues report that ICH burdens approximately 20 in 100,000 people every year. The financial burden of ICH is approximately \$125,000 per ICH patient per year resulting in an overall annual cost of \$6 billion for ICH patients in the United States. A younger demographic is affected by hemorrhagic strokes compared to ischemic strokes. The typical hemorrhagic stroke patient is ten years younger than the ischemic stroke patient. Most ICH bleeds are subcortical and over 50% of spontaneous intracerebral hemorrhages occur in the basal ganglia. Populations at greatest risk include men, the elderly and African American, Asian, and Hispanic communities. The properties of cerebral blood vessels change with age making the elderly at greater risk of an intracerebral hemorrhage.

**Manno EM, Atkinson JL, Fulgham JR, Wijdicks EF. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. *Mayo Clin Proc.* 2005;80:420-433.**

This article is a general review of ICH from the Symposium of Cerebrovascular Diseases. It describes the epidemiology, pathophysiology, specific management of ICH, and new treatment strategies for secondary complications such as edema and tissue necrosis caused by neurotoxin release. The most frequent causes of spontaneous ICH include chronic hypertension, age-related cerebral amyloid angiopathy, anticoagulant therapy, antiplatelet therapy, and drug use. Chronic hypertension is believed to be the most significant risk factor for ICH and is responsible for approximately three-fourths of ICH cases. Hematoma expansion is most frequently associated with secondary damage in ICH patients. However, cerebral edema is increasingly linked to neurological deterioration

resulting from ICH. Manno and colleagues reinstated noncontrast CT imaging as the primary diagnostic tool in ICH patients and described MRI as useful for dating hemorrhages and identifying small vascular lesions possibly missed by CT scans. Clinical presentation, initial evaluation, and management with medical and surgical therapy are also reviewed. This paper concluded with reiterating the most reported common predictors of outcome in ICH patients which include GCS score at presentation, hematoma size, and presence and volume of IVH.

**Badjatia N, Rosand J. Intracerebral hemorrhage. *Neurologist*. 2005;11:311-24.**

This article is a general review of intracerebral hemorrhage and highlights the course and management of this disease. The risks factors, pathophysiology, variables with prognostic significance, management and treatment with both medical and surgical intervention are all considered.

**Fewel ME, Thompson BG, Jr., Hoff JT. Spontaneous intracerebral hemorrhage: a review. *Neurosurg Focus*. 2003;15:E1.**

This article is another general review and describes spontaneous ICH according to its epidemiology, causes, clinical features, diagnostic factors, pathophysiology, and treatment both medical and surgical. Also illustrated are randomized trials of surgical and medical management and nonrandomized surgical studies.

## **EPIDEMIOLOGY**

**Jordan LC, Hillis AE. Hemorrhagic stroke in children. *Pediatr Neurol*. 2007;36(2):73-80.**

In the general population, hemorrhagic strokes account for 15-20% of all strokes. However, a greater burden is exhibited in children with hemorrhagic strokes being approximately 50% of all strokes. The aim of Jordan and colleagues was to review the evaluation process, treatment, etiology, and neurologic outcome of hemorrhagic stroke in

children. Potential therapies, such as the use of rFVIIa, and direction for future research were included in this review. Much of the recommended management is based on findings in adult research and additional work is needed in childhood hemorrhagic stroke.

**Shen JJ, Washington EL. Disparities in outcomes among patients with stroke associated with insurance status.**

In this study, Shen and colleagues researched discharge data from intracerebral hemorrhage and acute ischemic stroke patients from the 2007 National Inpatient Sample to reveal insurance-related disparities among stroke patients. Insurance status was categorized as Medicaid, uninsured, privately insured including HMO/prepaid health plans, Medicare, and other insurance companies. Degree of disparity was determined in relation to neurological impairment and mortality. Overall, uninsured patients had a higher level of neurological impairment, a longer average length of stay (LOS) in the hospital, and a higher risk of mortality. Uninsured ICH patients had an increased risk of mortality, of almost 25% greater, than that of privately insured ICH patients. The disparities among stroke patients revealed in this study should encourage the creation of policy aimed at promoting access to care, both outpatient and preventative, for uninsured patients.

**Girot M, Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F et al. Predictors of outcome in patients with cerebral venous thrombosis and intracerebral hemorrhage. Stroke. 2007;38:337-42.**

This is a unique study in the field of ICH that researches the outcomes in cerebral venous thrombosis (CVT) patients with ICH. Patients with both early and delayed intracerebral hemorrhages (624 and 36, respectively) were evaluated in this prospective multinational observational study. CVT patients with early ICH were shown to be older and more likely to have a severe clinical presentation and a worse 6-month outcome than those without ICH. Predictors of death or dependency in early ICH CVT patients included older age, male gender, having a thrombosis of the deep cerebral venous system or of the right lateral sinus and having a motor deficit. The authors suggest CVT patients with early ICH be closely monitored given their high risk of death or dependency.

**Zahuranec DB, Brown DL, Lisabeth LD et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68(20):1651-1657.**

Aggressive treatment in ICH patients is typically limited in cases where we do not resuscitate (DNR) and similar orders exist. Researchers of this study examined short- and long-term mortality of ICH in patients with limited care instruction to determine if there is indeed excess mortality in this population than what is predicted at time of admission. Patients were designated as 'early C-DNR' and 'no early C-DNR' in which C-DNR signified they had one of three limited care instructions for the first 24 hrs: DNR orders, withdrawal of care or deferral of other life-sustaining interventions. Analysis revealed a significant association of short- and long-term mortality with 'early C-DNR' even after adjustment for age, gender, ethnicity, initial GCS, ICH volume, IVH, and infratentorial hemorrhage. Physicians should be mindful that although aggressive treatment in severe ICH cases is associated with functional impairment, in which case denying aggressive treatment is suitable, there is evidence of favorable outcome that could positively affect severe ICH patients, including those with limited care instruction.

**Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S et al. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke*. 2007;38(5):1641-1644.**

This study agrees with current scales that predict ICH mortality, such as the ICH score, but sought to design a grading scale (ICH-GS) that predicts the outcome of ICH patients according to evaluation at time of hospital arrival. Included in the ICH-GS was a different selection of cutoff values and point assignments to predictors of ICH. Compared to ICH score, ICH-GS predicted more variance for in-hospital mortality, 30-day mortality, and good functional outcome at 30-days; had higher sensitivity to in-hospital and 30-day mortality; and higher accuracy for predicting mortality and good functional outcome.

**Sturgeon JD, Folsom AR. Trends in hospitalization rate, hospital case fatality, and mortality rate of stroke by subtype in Minneapolis-St. Paul, 1980-2002.**

**Neuroepidemiology. 2007;28:39-45.**

This study by Sturgeon and Folsom examined hospitalization trends for stroke patients in the Minneapolis-St. Paul area. Reported was an upward trend of ICH-related hospitalizations in both men and women over a twelve year period (1980 to 2002). The ICH hospitalization rate per 100,000 showed approximately a 30% increase from 1980 to 2002 in both men and women (36.5 to 46.7 per 100,000 and 26.2 to 34.1 per 100,000, respectively). This increase in hospitalization is described as minimal but nonetheless there was an increase and it would be valuable to do similar analyses at other hospitals. Although the case fatality of ICH decreased by 32% over the twelve-year period, ICH patients presented the highest in-hospital care fatality rate compared to ischemic and subarachnoid hemorrhage patients. Furthermore, even while decreasing from the 1980's, the ICH mortality rate had the least significant decrease of all stroke subtypes in this study.

**Russell MW, Joshi AV, Neumann PJ, Boulanger L, Menzin J. Predictors of hospital length of stay and cost in patients with intracerebral hemorrhage. Neurology.**

**2006;67:1279-81.**

Hospital length of stay and cost of care for intracerebral hemorrhage patients was investigated by Russell and colleagues. Their analysis of hospital discharge and billing data for over 13,000 patients in a Nationwide Inpatient sample (NIS) estimated the average length of stay (LOS) for all ICH patients to be 7.7 days at an average cost of \$15,256. In addition, average LOS and cost were estimated to be higher for ICH patients discharged alive (9.6 days and \$17,442, respectively). The lifetime cost of an ICH patient is approximated at \$125,000 and inpatient costs can range from \$10,200 to \$21,600. The cost of this disease on society becomes greater for each day an ICH patient is hospitalized. It costs an estimated \$1,569 for each additional day spent in the hospital. The following are predictors of increased LOS and greater associated cost for ICH patients: urban location and teaching status of the hospital, large hospital size, and high ICH caseload. In addition, LOS was on average 40% greater for African-Americans, Hispanics and Asians compared to White. Being mindful of these predictors will allow hospitals to

better prepare for the demographic they serve and possibly further investigate how other patient characteristics affect LOS and cost.

**Koennecke HC. Cerebral microbleeds on MRI: prevalence, associations, and potential clinical implications. *Neurology*. 2006;66:165-71.**

In this article, Koennecke reviews the literature on cerebral microbleeds (CMB) and reports the prevalence, associated factors and potential clinical implications of CMB. The prevalence of CMB is greater in ICH patients compared to their healthy counterpart and CMB and ICH have been suggested to share similar etiological basis. The analysis of existing data on CMB reveals a greater incidence of cerebral microbleeds (CMB) in Asian patients. This particular finding agrees with the greater incidence of ICH in the Asian population reported in other studies.

**Zahuranec DB, Brown DL, Lisabeth LD, Gonzales NR, Longwell PJ, Eden SV et al. Differences in intracerebral hemorrhage between Mexican Americans and non-Hispanic whites. *Neurology*. 2006;66:30-34.**

As part of the Brain Attack Surveillance in Corpus Christi (BASIC) project, ICH patients were identified and characteristics were analyzed by race. The comparison of ICH in Mexican Americans and Non-Hispanic Whites (NHW) was of particular interest to Zahuranec and colleagues. According to this study, ICH occurs at a greater rate in Mexican-Americans compared to NHWs. Characteristics of intracerebral hemorrhages were different between the two groups with a significant difference in location and size of intracerebral hemorrhages in Mexican-American patients—hemorrhages were described as smaller and nonlobar. Also discovered in this study was lower prevalence of coronary heart disease and higher prevalence of diabetes in Mexican American ICH patients compared to NHW ICH patients.

**Castellanos M, Leira R, Tejada J, Gil-Peralta A, Davalos A, Castillo J. Predictors of good outcome in medium to large spontaneous supratentorial intracerebral haemorrhages. J Neurol Neurosurg Psychiatry. 2005;76:691-95.**

Patients with medium to large ICHs (greater than 20 ml) were studied in effort to reveal potential predictors of good outcome. Many studies focus on mortality and predictors of poor outcomes whereas this study intentionally concentrated on prognostic factors for good outcomes in ICH patients. According to an analysis of patient demographics, a history of hypertension was not linked to patients with good outcomes. Patients with a good outcome, in 85% of the cases, were associated with a low severity of neurological deficits, assessed by CSS, together with a cortical location of bleeding and low fibrinogen levels.

**Kidwell CS, Saver JL, Carneado J, Sayre J, Starkman S, Duckwiler G et al. Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis. Stroke. 2002;33:717-24.**

This study investigated the occurrence of hemorrhagic transformation (HT) in patients receiving intra-arterial (IA) thrombolytic therapy. Of the 89 patients treated with IA thrombolytic therapy, over a third (39%) presented with hemorrhagic transformation. Less than 10% of patients had major symptomatic HT but an upward trend was associated with symptomatic HT and warfarin use ( $P=0.09$ ). Analysis revealed NIHSS score, platelet count, time of recanalization, and glucose level as leading predictors of any hemorrhage (Kidwell 2002).

**Ayala C, Croft JB, Greenlund KJ, Keenan NL, Donehoo RS, Malarcher AM et al. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995-1998. Stroke. 2002;33:1197-201.**

This three-year analysis of national mortality data for intracerebral stroke patients by Ayala and colleagues revealed a greater incidence of ICH-related deaths in persons of African American, Alaska Natives, Asian Pacific Islander (API), and Hispanic ethnic groups. Also revealed was a very high proportion of ICH-related deaths among all stroke deaths in API

adults. According to gender, case fatality rates for hemorrhagic strokes and ischemic strokes were equal in both men and women. However, overall stroke mortality is greater in men whereas, women are more likely to receive care in a nursing home for physical impairment following stroke.

**Hemphill JC, III, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-97.**

Hemphill and colleagues developed a risk stratification scale (the ICH score) for ICH patients in effort to create a standard clinical grading scale analogous to those that exist for other stroke subtypes. An assessment tool, such as the ICH score, will allow for accurate assessment by ICH caregivers not trained in stroke neurology. Researchers of this study agree that GCS score, hemorrhage volume and intraventricular extension are independent predictors of ICH. Uniquely emphasized in this designed 6-point scale is age as an independent predictor of outcome. At the time, other studies had not emphasized age but Hemphill and colleagues stated age-related factors may determine plan of treatment and believe outcome of ICH patients should not be a consequence of age. The characteristic of each predictor was given a value and total ICH score equals the sum of all values. ICH Score values range from 0 to 5 with 5 translating to the highest risk of mortality. Predictors were weighted according to their association with outcome—GCS score has the strongest association and was therefore the most weighted predictor. The ICH Score was proven to be a strong predictor of 30-day mortality and is a useful clinical grading scale for ICH.

## **PATHOPHYSIOLOGY**

**Broderick JP, Diringer MN, Hill MD et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke*. 2007;38(3):1072-1075.**

In effort to evaluate a recent randomized study on rFVIIa and determine the potential factors related to hematoma growth, Broderick and colleagues studied the relationship

between 5 different measures of hemorrhage volume change. Volume change was analyzed according to differences detected between baseline and 24-hour CT scans. This analysis revealed the use of rFVIIa to limit the hematoma growth in ICH patients. Potential factors related to ICH growth were also indicated and most interestingly, a relationship between baseline blood pressure and hematoma growth was not shown.

**Labovitz DL, Boden-Albala B, Hauser WA, Sacco RL. Lacunar infarct or deep intracerebral hemorrhage: who gets which? The Northern Manhattan Study. *Neurology*. 2007;68(8):606-608.**

Comparison of lacunar infarct (LAC) and deep intracerebral hemorrhages revealed distinguishing characteristics between the two. Hypocholesteremia is associated with DICH and hypercholesteremia with LAC. Specifically low cholesterol is risk factor of hypertensive ICH. Other differences between LAC and DICH, although not all significant, include a greater association of diabetes and older age to LAC and alcohol use, smoking and male gender to DICH.

**Jauch EC, Lindsay CJ, Adeoye O, Khoury J, Barsan W, Broderick J et al. Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. *Stroke*. 2006;37:2061-65.**

Controlling and preventing hematoma growth in ICH patients is universally a focus of ICH management. Researcher of this articles investigated hemodynamic parameters on vessel wall stress to determine their relationship to hematoma volume. Results did not reveal hemodynamic parameters to impact hematoma growth and therefore, hemodynamic parameters are an unlikely target for reducing early hematoma growth.

**Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-81.**

Of particular interest in this study was hematoma growth and its association to increase risk of mortality or poor functional outcome. Davis and colleagues conducted a meta-

analysis of ICH patients and found hematoma growth to be an independent indicator of both mortality and functional outcome after ICH. Increase risk of mortality was significantly associated with percentage of hematoma growth, initial ICH volume, GCS score and IVH. The likelihood of death increased by 5% for every 10% increase in hematoma size. The same increase in hematoma size also predicts a worsening condition, which is 16% more likely to occur for every 10% increase in hematoma size.

**Zia E, Pessah-Rasmussen H, Khan FA, Norrving B, Janzon L, Berglund G et al. Risk factors for primary intracerebral hemorrhage: a population-based nested case-control study. *Cerebrovasc Dis.* 2006;21:18-25.**

According to Zia and colleagues associated risk factors of intracerebral hemorrhage are high systolic blood pressure, diabetes, high triglycerides, short stature and psychiatric morbidity. Nonlobar primary intracerebral hemorrhages showed a greater association to diabetes and psychiatric morbidity, whereas lobar hemorrhages were more closely associated to smoking. High systolic blood pressure had no bias to a specific location and was associated to both lobar and nonlobar hemorrhages.

**Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol.* 2006;5:53-63.**

Xi and colleagues describe the mechanisms of brain injury associated with intracerebral hemorrhage. Causes of bleeding, pathological changes, secondary injury mechanisms, modifiers of injury, and therapeutic targets are considered in this review.

**Fountas KN, Kapsalaki EZ, Parish DC, Smith B, Smisson HF, Johnston KW et al. Intraventricular administration of rt-PA in patients with intraventricular hemorrhage. *South Med J.* 2005;98:767-73.**

Red blood cell (RBC) lysis related to intracerebral hemorrhages is proven to contribute to brain edema in ICH patients. The mechanism and cause of brain edema is of interest to researchers because this secondary condition causes neurological deterioration in ICH patients. This study used an animal model of 87 rats to investigate the effects of lysed

RBCs on cerebral blood flow (CBF) and blood-brain barrier (BBB) integrity. Lysed or packed RBCs were injected into the parenchyma of the right caudate nucleus and the following were measured at their respective times: brain water and sodium contents at 24 hours; CBF at 2 hours, 24 hours and 72 hours; BBB disruption at 24 hours or 72 hours; and BBB integrity at 24 hour and 72 hours. Result revealed no ischemic cerebral blood flow with brain edema. However, blood-brain barrier permeability increased with conditions of both lysed and packed RBCs suggesting that RBC components contribute to edema formation.

**Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology. 2004;63:461-67.**

Predictors of early neurological deterioration (END) in ICH patients with supratentorial hemorrhages were examined in this study by Leira and colleagues. Early neurological deterioration occurred in close to a quarter of patients (22.9%). Independent predictors of END in this study were high body temperature, neutrophil count, and plasma fibrinogen and patients exhibiting END were eight times more likely to have a poor outcome (Leira 2004).

**Schellinger PD, Fiebach JB, Hoffmann K, Becker K, Orakcioglu B, Kollmar R et al. Stroke MRI in intracerebral hemorrhage: is there a perihemorrhagic penumbra? Stroke. 2003;34:1674-79.**

Researchers of this study set out to investigate the possibility of perihemorrhagic ischemia as a surrogate indicator to identify ICH patients who may benefit from surgical intervention. Magnetic resonance imaging was performed on 32 patients with hyperacute ICH determining a mean hematoma size of  $16.9 \pm 17.2$  ml for both men and women. No significant overall perihemorrhagic apparent diffuse coefficient (ADC) was detected and data does not suggest an associated perihemorrhagic and ischemic penumbra in hyperacute ICH patients.

**Quinones-Hinojosa A, Gulati M, Singh V, Lawton MT. Spontaneous intracerebral hemorrhage due to coagulation disorders. Neurosurg Focus. 2003;15:E3.**

This review by Quinones-Hinojosa and colleagues examined spontaneous ICH due to coagulation disorders. A detailed description of hemostasis physiology and the pathophysiology of spontaneous ICH due to coagulation disorders are given in this review. Most notably is a reported small associated risk linked to bleeding disorders (both congenital and acquired disorders of hemostasis) and intracerebral hemorrhages.

**Gebel JM, Jr., Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S et al. Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke. 2002;33:2636-41.**

Perihematomal edema was measured in 142 patients to investigate if edema volume is a predictor of functional outcome or mortality in hyperacute spontaneous ICH (SICH) patients. Researchers of this study suspected edema volume to be a predictor of poor functional outcome and indeed found a significant correlation between edema and 12-week functional outcome in hyperacute SICH patients without intraventricular extension.

**Castillo J, Davalos A, Alvarez-Sabin J, Pumar JM, Leira R, Silva Y et al. Molecular signatures of brain injury after intracerebral hemorrhage. Neurology. 2002;58:624-29.**

In this study, markers of cellular death in tissue surrounding the hemorrhage site in ICH patients were investigated in 124 patients admitted within 24 hours of hemorrhage onset. Glutamate, cytokines and adhesion molecules were measured in blood samples taken from participants after admission. Poor clinical outcomes and increased volume of the residual cavity after ICH were associated with high concentrations of blood glutamate measured within the first 24 hours. Excitotoxicity and inflammation are suggested to have an important role in causing secondary brain injury after hemorrhage onset. Furthermore, magnitude of inflammatory response was independently related to size of peripheral hypodensity. Results for this study can be useful in developing a strategy aimed at preventing secondary brain damage in ICH patients.

**Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000;343:1826-32.**

This study investigated phenylpropanolamine and the associated risk of hemorrhagic stroke. According to this national study, including 702 patients from 43 U.S. hospitals and 1376 control subjects, phenylpropanolamine, particularly in appetite-suppressors, is a risk factor for intracerebral hemorrhages in women.

**Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28: 1-5.**

The main goal of this study was to determine the situation in which early hematoma growth occurs and whether growth is related to neurological deterioration. It was a prospective observation study examining ICH patients within 3 hours of onset. The findings of this study are significant in ICH research and are frequently cited by other researchers in this field. It was discovered that over a third of volume growth occurs in the first hour of bleeding in ICH patients, with subsequent bleeding more abundant in the hours to follow. Furthermore, early neurological deterioration was associated with hemorrhagic growth occurring in the first 3-4 hours of hemorrhage onset. It is a misconception that bleeding ceases within minutes of onset and it is important to consider the duration of initial bleeding for intervention.

**Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24:987-93.**

Analysis of ICH medical records in the Greater Cincinnati area revealed intracerebral hemorrhage volume, intraventricular hemorrhage volume, GCS score and operative removal of hematoma to be significant predictors of 30-day mortality. Hemorrhage volume in intracerebral hemorrhage patients is the best predictor of 30-day mortality. Greater volume in both types of hemorrhages and lower GCS scores predict increased mortality. Lethal volumes predicting mortality vary according to hemorrhage location. According to

Broderick and colleagues, pontine hemorrhages greater than 5 cm<sup>3</sup> and cerebellar hemorrhages greater than 30 cm<sup>3</sup> may be considered the most lethal with all patients dying within 30-days.

## **CLINICAL PRESENTATION & DIAGNOSIS**

**Zimmerman RD, Maldjian JA, Brun NC, Horvath B, Skolnick BE. Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by CT scan. AJNR Am J Neuroradiol. 2006;27:666-70.**

Zimmerman and colleagues conducted a board approved multicenter clinical trial to evaluate intra- and inter-reader variability in the measurement of hematoma volume by using CT scans. A masked reading method was utilized in this trial. Results of this study revealed minimal variability in interpreting ICH and IVH volumes on CT scans of trial participants.

**Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke. 2004;35:1364-67.**

This retrospective study by Ohwaki and colleagues, assessed 76 patients with hypertensive ICH and presented data suggesting a significant positive relationship between maximum systolic BP and hematoma growth. Hematoma enlargement was reported more often in patients with a SP greater than 160 mmHg.

**Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA. 2004;292:1823-30.**

The intention of this prospective, multicenter study was to compare the accuracy of MRI and CT scans in detecting acute ICH. It was concluded that MRIs are possibly as accurate as CT scans for detecting acute hemorrhages. MRIs are regarded as more accurate in

detecting chronic ICHs. In addition, this particular study found primary intraparenchymal hematomas of ICH to be on average 21 ml.

**Bhattathiri PS, Gregson B, Prasad KS, Mitchell P, Soh C, Mitra D et al. Reliability assessment of computerized tomography scanning measurements in intracerebral hematoma. Neurosurg Focus. 2003;15:E6.**

Bhattathiri and colleagues set out to assess the reliability of CT scanning measurements obtained in ICH patients. The value of CT scans in diagnosing ICH is well recognized in medicine and a demonstration of large inter- and intraobserver agreement of CT scan evaluation by Bhattathiri and colleagues confirms its usefulness.

**Hua Y, Schallert T, Keep RF, Wu J, Hoff JT, Xi G. Behavioral tests after intracerebral hemorrhage in the rat. Stroke. 2002;33:2478-84.**

A rat-model, designed to mimic intracerebral hemorrhages, was used to study neurological deterioration and edema formation. Behavioral deficits, as a result of ICH, have been studied in other rat-models but unique to this study was direct injection of blood into the brain parenchyma to study the effects of blood even in the absence of direct vascular rupture. Sensorimotor tests were performed on the rats to examine neurological deficits and recovery of function following ICH. According to the results, blood in the brain parenchyma does cause alterations in brain functioning. It is suggested that behavioral tests, similar to those used in this study, can be used to assess the degree of damage, process of recovery and residual impairment in ICH patients. In addition, researchers of this study investigated the use of thrombin inhibitors as preventative therapy for edema. Edema prevention is important because the neurological damage resulting from edema may be more profound than that of hematoma volume. Formation of thrombin, a component of the coagulation cascade, occurs immediately following a hemorrhagic stroke and is a contributing factor of neurological deterioration in ICH. Degree of damage is dependent on thrombin concentration and it is expected that a clot of 100  $\mu$ l can produce approximately 30 U of thrombin. Thrombin inhibitors proved to significantly improve neurological deficits in this rat model and possibly the reduction of edema by thrombin inhibitors is beneficial for ICH patients.

**Woo D, Broderick JP. Spontaneous intracerebral hemorrhage: epidemiology and clinical presentation. Neurosurg Clin N Am. 2002;13:265-79, v.**

This article focuses on the epidemiology and clinical presentation of ICH patients. The clinical presentation of ICH is described as a smooth, continuous progression of clinical symptoms. Although a sudden onset of symptoms is typically characteristic of subarachnoid hemorrhages, close to a third of ICH patients present with this pattern. The principal cause of ICH is hypertension and particularly targets elderly populations. However in younger adults, vascular malformations are frequently the cause of intracerebral hemorrhages.

## **ANTICOAGULATION-RELATED ICH**

**Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007;68:116-21.**

The increase incidence of anticoagulation-associated ICH (AAICH) is reflected by the increase use of warfarin over the past 10-15 years. This study searched for temporal trends in the incidence of AAICH and a relationship associated with cardioembolic ischemic strokes in greater Cincinnati. Reported was a substantial rise in AAICH cases with approximately a 50% increase in ICH incidences from 1988 to 1999 (16.5 and 24.6 per 100,000, respectively). Authors state atrial fibrillation as the most common reason for warfarin use and warfarin as the primary cause of AAICH. Flaherty and colleagues agree with other researchers that AAICH patients have far worse outcomes than other patient with ICH.

**Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. Stroke. 2006;37:256-62.**

Considered in this review was ICH associated with treatment of oral anticoagulation therapy (OAT). Steiner and colleagues discuss the epidemiology, pathophysiology and current treatment options of OAT-ICH. Outlined in the paper are guidelines for reversing the effect of anticoagulation and a presentation of unresolved issues on treatment. Steiner and colleagues conclude from their review that well-designed clinical trials are needed to identify effective acute treatment for OAT-ICH. OAT is used to treat a common condition in the elderly and given that our population is aging, finding an effective treatment for this disease will prove to be crucial in the years to come.

**Goldstein JN, Thomas SH, Frontiero V, Joseph A, Engel C, Snider R et al. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. Stroke. 2006;37:151-55.**

A recognized plan for intracerebral hemorrhages in patients on anticoagulation therapy is the rapid reversal of anticoagulation. Since bleeding has been reported to be most abundant in hours immediately following onset of hemorrhage, emergency department care is most crucial in these cases. The focus of this study was to examine emergency department intervention on such patients and determine the effectiveness in reversing anticoagulation and improving outcome. Results indicated earlier treatment of anticoagulation increased the likelihood of successful correction in the first 24-hours for warfarin-related ICH. Mortality and morbidity were not reduced with more rapid correction of INR. Authors agree with other experts that therapy with FFP and vitamin K, those used in this study, are not the most efficient at treating warfarin-related ICH given they are too slow. Prothrombin complex concentrate (PCC) or rFVIIa were not available in this study. This particular study and other research on warfarin-related ICH have established a relationship between the degree of anticoagulation and both hematoma growth and mortality. Authors of this study highly suggest institutionalizing a standard practice for immediately correcting coagulation which includes rapid use of warfarin reversal agents in ICH patients.

**Huttner HB, Schellinger PD, Hartmann M, Kohrmann M, Juettler E, Wikner J et al. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke. 2006;37:1465-70.**

Patients receiving oral anticoagulant therapy (OAT) are more susceptible to intracerebral hemorrhages and prompt reversal of anticoagulation is necessary to control hematoma growth. The goal of Huttner and colleagues was to investigate outcome differences when treating OAT-ICH with vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC). The indicator of effective treatment for OAT-ICH was limited hematoma growth, defined by growth less than 33%. In general, PCC administration significantly lowered the incidences of hematoma growth compared to other treatments but not in cases where elevated INR was corrected early. Therefore, PCC therapy lowers the risk of hematoma growth but does not show increased effectiveness over vitamin K and FFP therapies. It is recommended to first treat OAT-ICH patients by rapidly reversing elevated INR.

**Sjöblom L, Hardemark HG, Lindgren A, Norrving B, Fahlen M, Samuelsson M et al. Management and prognostic features of intracerebral hemorrhage during anticoagulant therapy: a Swedish multicenter study. Stroke. 2001;32:2567-74.**

Sjöblom and colleagues agree with other researchers that rapid reversal of anticoagulation is the most immediate step in treating anticoagulation (AC)-related ICH. Their analysis of AC-related ICH data from 10 hospitals in Sweden did not reveal advantage to using of a specific therapy. Early clinical deterioration was also stated as being more severe in AC-related ICH patients compared to spontaneous ICH patients. Concluded was the need for randomized controlled trials of presently used therapies.

**Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke*. 2003;34:224-29.**

**Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE et al. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74-79.**

**Mayer SA. Recombinant activated factor VII for acute intracerebral hemorrhage. *Stroke*. 2007;38(2 Suppl):763-767.**

In 2003, Mayer published an article highlighting the possibility of using ultra-early hemostatic therapy in ICH patients to treat rapid bleeding within the first few hours of hemorrhage onset. Recombinant activated factor VIIa (rFVIIa) was suggested as the most promising candidate for this type of therapy. At the time, evidence lacked to prove ultra-early hemostatic therapy as an effective treatment and Mayer stated the need for more clinical trials to test this treatment approach.

In 2005, Mayer and colleagues conducted a study on the effects of recombinant activated factor VII (rFVIIa) assigning 399 ICH patients to receive placebo (96 patients) or rFVIIa (303 patients). rFVIIa patients were further assigned to take rFVIIa at the following dosages: 40, 80, or 60 µg per kilogram. Significant improvement in clinical outcomes was shown for ICH patients treated with rFVIIa. Improvement in recovery status, measured by the Rankin Scale, and neurologic impairment, measured by the NIHSS, was statistically significant on rFVIIa-treated patients.

In 2007, Mayer released an article stating his continued support for ultra-early hemostatic therapy with the use of rFVIIa. He describes ultra-early hemostatic therapy as an urgent intervention that can stop ongoing bleeding, reduce tissue injury and improve functional outcome when administered early enough. Highlighted in this article were findings from the 2005 rFVIIa ICH trial, mentioned above, which offered evidence that use of rFVIIa may benefit ICH patients by limiting hematoma growth.

**Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringner MN et al.**  
**Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med.**  
**2005;352:777-85.**

This article by Mayer and colleagues published in the New England Journal of Medicine also highlighted the randomized trial on the use of rFVIIa for ICH patients conducted in 2005.

**Brown DL, Morgenstern LB. Stopping the bleeding in intracerebral hemorrhage. N Engl J Med. 2005;352:828-30.**

This short article is a commentary on the article by Mayer et al, titled *Recombinant activated factor VII for acute intracerebral hemorrhage*, which was released in the same journal and issue. The research by Mayer and colleagues released in 2005 was regarded by Brown as important but not clinically directive. Brown believes research on rFVIIa is warranted but thinks there is more benefit to investigating treatment associated with clinical management.

## **CLINICAL MANAGEMENT, TREATMENT & RESEARCH**

**Broderick J, Connolly S, Feldmann E, Hanley D, Kase C et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 Update: A guideline from the American Stroke Council, High Blood Pressure Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38;2001-2023.**

This article is an update to the 1999 AHA Guidelines for Management of Spontaneous Intracerebral Hemorrhage. Recommendations given for ICH patients in this report are organized according to the degree of evidence for each recommendation. Different from the 1999 AHA Guidelines, is the addition of recommendations for the management of ICH related to coagulation and fibrinolysis and slight changes in the recommended therapy for elevated blood pressure.

**Naval NS, Nyquist PA, Carhuapoma JR. Advances in the management of spontaneous intracerebral hemorrhage. *Crit Care Clin.* 2006;22(4):607-617.**

Management of spontaneous ICH is discussed in this article with emphasis on initial stabilization, prevention of hematoma growth, underlying etiology and treatment with new therapeutic approaches such as minimally invasive surgery (MIS).

**Qureshi AI, Harris-Lane P, Kirmani JF, Ahmed S, Jacob M, Zada Y et al. Treatment of acute hypertension in patients with intracerebral hemorrhage using American Heart Association guidelines. *Crit Care Med.* 2006;34:1975-80.**

Blood pressure management of ICH patients was of particular interest to Qureshi and colleagues when they conducted a single-center prospective analysis on spontaneous ICH patients with acute hypertension. Management of acute elevated blood pressure in these patients was carried out according to the 1999 American Heart Association (AHA) guidelines for spontaneous intracerebral hemorrhages. Each received intravenous nicardipine within 24 hours of symptom onset to reduce and maintain mean arterial pressure (MAP) to less than 130 mmHg. The recommended treatment for acute hypertension in ICH patients was well tolerated in 86% of patients. Excessively high rates of neither neurological deterioration nor hematoma expansion occurred in ICH patients receiving nicardipine. Therefore, it was concluded that treatment with antihypertensive medicine is not associated with damaging effects.

**Spengos K, Tsivgoulis G, Zakopoulos N. Blood pressure management in acute stroke: a long-standing debate. *Eur Neurol.* 2006;55:123-35.**

This review article by Spengos and colleagues describes the pros and cons for lowering blood pressure in ICH patients. The con for this therapy is the possibility that further brain injury can result from decreased CPP when blood pressure is aggressively reduced. The pros are centered around eliminating the negative effects of increase acute BP and are based around the following arguments that high BP in acute ICH are associated with subsequent death, associated with cerebral edema and has shown increase risk of hematoma enlargement in patients with ICH.

**Dawson J, Walters M. New and emerging treatments for stroke. Br Med Bull. 2006;77-78:87-102. Epub@2006 Nov 7.:87-102.**

Dawson and Walters created this article in effort to review and discuss evidence-based management of acute strokes including acute ischemic stroke and intracerebral hemorrhages. The necessity of rapid assessment, imaging, monitoring and management of acute strokes are all discussed in this review. Specific to the subject matter of ICH is a section on specific treatment for ICH.

**Segal R, Furmanov A, Umansky F. Spontaneous intracerebral hemorrhage: to operate or not to operate, that's the question. Isr Med Assoc J. 2006;8:815-18.**

Acknowledged in this report are current findings that surgical therapy for management of spontaneous ICH (SICH) produce no overall benefit but believe that signs of rapid deterioration call for surgical intervention. Guidelines for surgical treatment of SICH patients state surgical treatment is obligatory for patients who are deteriorating and who have reasonable outcome potential. Researchers of this study evaluated the criteria, over a two year period, for selecting ICH patients as surgical candidates at their hospital and discovered a successful outcome (measured by postoperative 6 month survival rate) for close to 90% of these patients.

**Nievas MN. Why, when, and how spontaneous intracerebral hematomas should be operated. Med Sci Monit. 2005;11(1):RA24-RA31.**

Neivas supports surgical intervention in ICH patients and emphasize the need to thoroughly evaluate a patient before determining if they are an appropriate candidate for surgery. They acknowledge the poor outcomes associated with surgery in patients who have large hematomas but believe that other predictors such as those associated with 6 month mortality (e.g. GCS, preictal status according to activities of daily living (ADL), and age) need consideration before opting out on surgery. Supported is the necessity of medical treatment in all patients with less severe cases of ICH, specifically those presenting with small-volume hematomas, normal level of consciousness, and minimal focal neurological deterioration. They believe consideration of hematoma evacuation is

important in cases where patients are deteriorating and early surgical intervention produces better outcomes. Poorer outcomes to surgical intervention are believed to be reduced with minimally invasive surgical treatments and appropriate selection of ICH candidates with preoperative evaluation of factors that may exacerbate outcome of the patient.

**Priorities for clinical research in intracerebral hemorrhage: report from a National Institute of Neurological Disorders and Stroke workshop. *Stroke*. 2005;36:e23-e41.**

This special report is a product of the 2003 National Institute of Neurological Disorders and Stroke (NINDS) workshop. The goal of this workshop was to develop a consensus for ICH research priorities. The authors of this report are NINDS ICH workshop participants and the collaboration of participants resulted in this document which addresses research priorities in the following areas: current state of ICH research, basic science, imaging, medical, surgical and clinical methodology.

**Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387-97.**

STICH trial was an international, multicenter, parallel-group study investigating the benefits of early surgical therapy. It randomized 1073 patients from 83 centers and 27 countries to either an early surgery therapy or conservative treatment group. Early surgical treatment was a combination of neurosurgery to evacuate the hematoma within 24hrs of randomization and best medical treatment. Conservative treatment was defined as best medical treatment only with evacuation considered in cases where neurological deterioration was an issue. Patients randomized to the early surgery group in the STICH trial did not show a significant improvement in outcome when compared to the conservative treatment group. In addition, poorer outcomes to surgical intervention are associated with initial GCS scores of eight or below. According to a cost analysis of treatment for UK patients in the STICH trial, there may be financial benefit to early surgical intervention but findings lacked significant value and much be analyzed further. In the

STICH trial, surgical intervention did improve the outcome in some patients but only when hematoma size was 1cm or less from the cortical surface. It is suggested that craniotomies are more beneficial and produce better outcomes for ICH patients with superficial hematomas versus those with deep hematomas. However, more research and clinical trials are needed to determine significant benefit of surgical intervention for these patients. The continued lack of significant support for surgical intervention has fueled the question of whether there is actual benefit to surgery in ICH patients. The statistically insignificant results of the STICH trial continue to raise the question of urgency for inclusion of surgical therapy in policy relating to ICH patients. Mendelow and colleagues raised the question of whether ICH patients are a demographic that would honestly benefit from policy instructing surgery intervention.

**Tsivgoulis G, Vemmos KN, Zakopoulos N, Spengos K, Manios E, Sofia V et al.**  
**Association of blunted nocturnal blood pressure dip with intracerebral hemorrhage.**  
**Blood Press Monit. 2005;10:189-95.**

Tsivgoulis and colleagues researched nondipping patterns of nocturnal blood pressure which were previously only linked to ischemic cerebrovascular disease, but are now being associated with ICH. Investigation of abnormal circadian BP rhythms in ICH patients revealed an inverse relationship between nocturnal systolic blood pressure dipping and risk of intracerebral hemorrhage. Dipping patterns have been distinctly linked to stroke subgroups, such that intracranial hemorrhages are associated with reverse dippers and ischemic strokes with extreme dippers. Few studies have been conducted to examine the pathological role of abnormal circadian BP tendencies and more research is needed.

**Pouratian N, Kassell NF, Dumont AS. Update on management of intracerebral hemorrhage. Neurosurg Focus. 2003;15:E2.**

The aim of this article is to review current management practices of ICH. Management of ICH includes either medical or surgical treatment. Authors of this article subdivide surgical treatment due to the belief that differences among surgical treatment are blurred when all surgical techniques are grouped into one. Treatment options for ICH are discussed through a unique emphasis on randomized trials as they investigate different surgical

treatments used in ICH management. Also included is a short discussion of hemostatic therapy honoring that surgical intervention lacks proven benefit for ICH patients.

**Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. Crit Care Med. 2001;29:635-40.**

Specialized intensive care units are suspected to provide higher quality care being that they are able to focus on special needs and are staffed by caregivers who are trained on a specific disease process. Higher GCS score, younger age, access to full-time intensivist, large number of ICH patients, more ICU beds, and neuro ICU admission were discovered to be independent predictors of low hospital mortality. Furthermore, ICH patients admitted to a neuro ICU showed lower mortality compared those admitted to a general ICU. These implications are important when considering critical care services for emergent cases like ICH.

**Broderick JP, Adams HP, Jr., Barsan W, Feinberg W, Feldmann E, Grotta J et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 1999;30:905-15.**

The guidelines outlined in this article are for the management of spontaneous intracerebral hemorrhage and include recommendations for the diagnosis of ICH, treatment of acute ICH, surgical treatment of ICH and prevention of ICH.