Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes. ICH continues to impart a considerable degree of morbidity and mortality, with 30-day mortality ranging from 44% to 50%. ICH remains a devastating disease, and current treatment options lag far behind those for ischemic stroke.

There are no approved therapies, which improve outcome, and treatment remains mainly supportive. Despite the lack of available acute treatment options for ICH, the past decade of clinical and preclinical research has identified important concepts in its pathophysiology and how this information might be used in developing treatment. Recent clinical trials in ICH have identified important considerations in patient selection, which have informed current and future trials evaluating treatment for ICH, and preclinical work in ICH has identified new treatment targets.

**Targets for Treatment**

An understanding of the pathophysiology of the disease provides a starting point for identification of treatment targets. The pathophysiology of ICH begins with the predisposition of developing the disease, including genetics and risk factors that conspire to generate the initial hemorrhage. Once present, ICH causes both primary and secondary injury. The primary insult is attributable to disruption of adjacent tissue and mass effect. Secondary injury occurs with development of edema, free radical formation, inflammation, and direct cellular toxicity attributable to the deposited hematoma and subsequent degradation by-products. Each of these phases of disease provides a potential treatment target as shown in the Figure. The multiple steps along the path of disease also underscore the fact that successful treatment for ICH will most likely be multifaceted with different treatments at different time points.

A complete discussion of treatment targets for ICH is beyond the scope of this brief summary and has been reported recently. Ongoing clinical trials in ICH are outlined in the Table. This summary will highlight clinical trials evaluating primary and secondary injury in ICH as well as specific treatments targeting subgroups of ICH patients.

**Target: Primary Injury**

**Hematoma Expansion**

The majority of the initial neurological deficit is attributable to the hematoma. More than one third of patients with ICH have hematoma expansion (HE) within the first 24 hours, and this expansion is associated with neurological deterioration. Although early HE and its associated neurologically worsening have been clearly demonstrated, the risk factors associated with HE have not been well defined. Efforts focused on identification of patients who will develop HE with clinical, radiographic, or molecular markers represent promising acute treatment targets. There are currently 2 different ways to address HE with medical therapy: aggressive blood pressure reduction and hemostatic therapy.

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) and the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trials demonstrated that rapid blood pressure reduction in the setting of ICH was safe and feasible. Moreover, in INTERACT, the relative risk of HE ≥33% or ≥12.5 mL was 36% lower (95% confidence interval, 0%–59%; P = 0.05) in the intensive group than in the guideline group, strongly suggesting that aggressive blood pressure control can limit HE. Based on the results of these 2 trials, INTERACT II and ATACH-II are currently ongoing and designed to address the clinical efficacy of aggressive blood pressure reduction in patients with ICH.

Hemostatic therapy with recombinant factor VIIa has been shown to limit HE radiographically; however, this finding did not translate to improved clinical outcome. Clinical trial experience with recombinant factor VIIa highlights the importance of patient selection. Because one third of the patients with ICH are expected to develop HE, including all...
patients with ICH in a clinical trial targeting expansion may dilute the treatment effect of recombinant factor VIIa. In addition, patients who may not have HE and, thus, would not be expected to benefit from hemostatic therapy are also at risk of thromboembolic complication of treatment, further reducing any measurable benefit of treatment. The challenges of clinical trials evaluating hemostatic agents include the well-known time limitation for treatment and identification of patients who are most likely to have HE. At this time, the most promising way to identify the subgroup of patients most likely to have HE is with a radiographic marker, the spot sign. The spot sign refers to an area of contrast extravasation within the hematoma seen on computed tomography angiography.\textsuperscript{17} The spot sign has recently been prospectively validated as a predictor of HE in the Prediction of hematoma growth and outcome in patients with ICH using the CT-angiography spot sign (PREDICT) study.\textsuperscript{18} There are currently 2 ongoing clinical trials using the spot sign to identify patients at highest risk of HE and, thus, most likely to benefit from hemostatic therapy: The Spot Sign for Predicting and Treating ICH Growth (STOP-IT) study\textsuperscript{19} and the “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) study.\textsuperscript{20}

### Table. Ongoing Clinical Trials in Intracerebral Hemorrhage (From Clinicaltrials.gov)

<table>
<thead>
<tr>
<th>Treatment Target</th>
<th>Mechanism</th>
<th>Study</th>
<th>NLM Identifier</th>
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<td>Hematoma expansion</td>
<td>Aggressive blood pressure control</td>
<td>Antihypertensive Treatment in Acute Cerebral Hemorrhage-II (ATACH-II)</td>
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<td>The Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 2)</td>
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<tr>
<td>Hemostatic therapy</td>
<td>The Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT)</td>
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<td>NCT00810888</td>
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<td>“Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT)</td>
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<td>NCT01359202</td>
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<td>Secondary injury</td>
<td>Surgical treatment</td>
<td>Lobar hemorrhage</td>
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<td>Surgical treatment</td>
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<td>Coagulopathy-related ICH</td>
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<td>Intraventricular hemorrhage</td>
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<td>Platelet dysfunction</td>
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<td>Safety of Pioglitazone for Hematoma Resolution In Intracerebral Hemorrhage (SHRINC)</td>
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<td>High-Dose Deferoxamine in Intracerebral Hemorrhage (HI-DEF)</td>
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<td></td>
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<td>Pilot Study of Hypothermia for Intracerebral Hemorrhage in Croatia</td>
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<td></td>
<td>Albumin for Intracerebral Hemorrhage Intervention (ACHIEVE)</td>
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### Target: Secondary Injury

Removal of the hematoma before red blood cell lysis and release of toxic material may limit the deleterious effect on otherwise salvageable brain parenchyma. Thus, it is intuitive that rapid resolution of the hematoma and edema would be associated with more rapid functional recovery. Treatment options to reduce the production of blood degradation products include surgical hematoma evacuation. Unfortunately, surgical trials of hematoma evacuation have not demonstrated a difference in mortality or outcome between patients randomized to surgical evacuation compared with medical management.\textsuperscript{21,22} Ultra-early hematoma evacuation (within 4 hours) has been associated with rebleeding complication,\textsuperscript{23} suggesting that timing of surgery should be a consideration in future trials. The International Surgical Treatment of ICH (STICH) study demonstrated a signal of efficacy in a subgroup of patients, namely, those with hematomas extending <1 cm from the cortical surface, and a Glasgow Coma Scale of 9 to 12 showed a trend toward a favorable outcome in patients who were randomized to surgery within 96 hours compared with medical management. This information has informed a follow-up trial,
Surgical Trial in Lobar ICH (STICH-II), which will evaluate whether early surgical evacuation of the hematoma in patients with spontaneous lobar ICH will improve outcome compared with conservative treatment. In addition, less invasive surgical techniques with and without the use of thrombolytic for hematoma evacuation have demonstrated impressive radiographic reduction in hematoma volume. These newer techniques are currently under investigation to determine clinical efficacy.

Another method to reduce toxic blood degradation products is pharmacological enhancement of hematoma resolution and iron chelation. Preclinical work demonstrates that the peroxisome proliferator–activated receptor γ agonists promote hematoma resolution, decrease neuronal damage, and improve functional recovery. The Safety of Pioglitazone for Hematoma Resolution In Intracerebral Hemorrhage (SHRINC) trial is a randomized phase 2 dose-escalation safety study evaluating the safety of the peroxisome proliferator–activated receptor γ agonist, pioglitazone, in patients with ICH.

Based on the results from the recently completed Dose Finding and Safety Study of Deferoxamine in Patients with ICH (DFO in ICH) Study, a dose of 62 mg/kg per day of deferoxamine in patients with ICH was found to be well tolerated and not associated with an increase in serious adverse effects. The follow-up HI-DEF study will evaluate whether treatment with this dose of deferoxamine is of sufficient promise to improve outcome before pursuing a larger clinical trial to examine its effectiveness as a treatment for ICH. It is probably not realistic to expect that these types of pharmacological treatments would have a very large clinical effect, but may complement the more acute treatments, when one is found to improve clinical outcomes.

Target: Specific Subgroups

Two subgroups of patients tend to have worse outcomes: those with intraventricular hemorrhage (IVH) and those with coagulopathy-related ICH. Effective treatment for these 2 groups has the potential to have dramatic impact on morbidity and mortality in these patients. The IVH Thrombolysis Trial demonstrated an acceptable safety profile of intraventricular recombinant tissue plasminogen activator and a more rapid rate of clot resolution than placebo-treated patients with a trend toward better clinical outcome at 30 days. The Clot Lysis: Evaluating Accelerated Resolution of IVH Phase III (CLEAR III) trial is evaluating the clinical efficacy of intraventricular recombinant tissue plasminogen activator in clearing IVH in this group of patients. The International Normalized Ratio (INR) Normalization in Coumadin Associated ICH (INCH) trial is evaluating prothrombin complex and fresh-frozen plasma in normalization of the international normalized ratio as well as the safety profile of each treatment. This patient population will become more complex as we start to see ICH in the setting of the newer anticoagulants which, as of now, have no reversal therapy for their anticoagulant effect.

Conclusion

Despite the elusive nature of a successful treatment for ICH, current progress in developing treatment remains encouraging with more targets for potential therapy as the pathophysiology of the disease is better understood. Solid preclinical data should drive the translational studies; however, radiographic and biological markers and information from completed clinical trials provide an opportunity to improve patient selection for future clinical research.

Well-known potential treatments, such as aggressive blood pressure control, surgical therapy, and enhanced drainage of IVH, are now in the clinical efficacy stage of evaluation; refinement of surgical technique and pharmacological agents with neuroprotective potential are in phase 2 evaluation. New targets under evaluation include genetic, radiographic and biochemical markers as well as more efficient clinical trial design and patient selection. Rehabilitation strategies remain untapped.

The complexity of this disease suggests that successful treatment for ICH will be multifaceted with acute treatment limiting HE and mass effect supplemented by neuroprotective and rehabilitation strategies. The ideal treatment strategy will be one that is practical and applicable for both specialized stroke centers and community hospitals.

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