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Improving Outcome after Intracerebral Hemorrhage: Maybe It's the Body, Not the Brain

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Intracerebral hemorrhage (ICH) remains a devastating condition with no convincing treatment of proven benefit. Just this past year, two new large clinical trials failed to confirm a benefit of intensive blood-pressure lowering and intraventricular t-PA (1, 2). This adds to the unfortunate growing list of interventions that have tested stroke-specific targets such as early supratentorial hematoma evacuation and hemostatic therapy to reduce hematoma expansion. This was supposed to work; and it has for acute ischemic stroke and aneurysmal subarachnoid hemorrhage. Endovascular embolectomy in patients with reversible focal cerebral ischemia and aneurysm clipping and coiling have fundamentally changed the trajectory and natural history of those stroke subtypes. Interestingly, for ICH, we still believe, and with pretty good reason, that "good care" matters. In fact, limiting care early through a nihilistic approach does lead to worse outcomes. It all makes me wonder if we have been looking in the wrong place. We have been treating ICH like a stroke, when in fact it is a critical illness.

One of the lessons of modern critical care has been that the avoidance of complications and iatrogeny is a treatment itself. The use of low-tidal volume ventilation to limit lung injury in acute respiratory distress patients, glucose control with avoidance of hypoglycemia, and sedation "holidays" to decrease delirium are routinely employed treatments in modern intensive care units. A recent trial of the ABCDEF critical care bundle showed improved outcome (3). Interestingly, none of the letters in ABCDEF stand for targeted treatments focusing on the underlying specific primary disease. They relate to an approach designed to limit delirium, mobilize and wean patients from mechanical ventilation, and engage their families in order to avoid the complications of critical illness broadly defined. So what does this have to do with ICH? One possibility lies in the prevention of infectious complications. It is in this context that the manuscript by Morotti provides a new twist into identifying targets for intervention in improving the outcome of ICH patients (4).

Utilizing a highly characterized cohort of over 2000 ICH patients over 20 years, they tested the hypothesis that diminished white blood cell counts on hospital admission were associated with the occurrence of infectious complications. They found that lymphopenia (defined as an absolute lymphocyte count < 1000/μl) occurred in 27% of the entire cohort and was more common in patients who developed infection, whereas leukopenia,

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neurotropenia, and monocytopenia were not. The association of admission lymphopenia and infectious complications was driven entirely by a higher occurrence of pneumonia in these patients, as urinary tract infections, sepsis, and other infections were not more common. Admission lymphopenia was more common in patients with larger hematomas, older age, presence of intraventricular hemorrhage, infratentorial hematoma location, and lower Glasgow Coma Scale score on admission, all of which are factors known to impact ICH outcome. Because this raised the issue of whether lymphopenia was merely a marker for more severe ICH, the authors adjusted for these factors when assessing the influence of lymphopenia on outcome as indicated by 90-day mortality. In this analysis, lymphopenia was associated with higher mortality. A weakness of the analysis was the lack of adjustment for intubation, which is an obvious risk factor for pneumonia and was more common in patients with admission lymphopenia. However, intubation was not more common in patients with infectious complications in univariate analysis.

These findings add to an emerging ICH literature regarding both alterations in the body's inflammatory response, presumably acutely acquired, and the frequency and impact on outcome of infections. The assumption is that the two are linked, if not causal. In the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, infections occurred in 31% of 800 patients (5). Infected patients had double the mortality of those without infection (16% versus 8%) and a lower likelihood of favorable outcome (score of 2 or better on the modified Rankin Scale [mRS]). In another cohort study, 42% of ICH patients developed infection during hospitalization, with intraventricular hemorrhage, hematoma volume greater than 30 cc, and higher ICH Scores associated with increased infection risk (6). The systemic inflammatory response syndrome (SIRS) occurred in 21% of another group of 249 ICH patients and was predictive of worsened functional outcome (mRS > 3) and poor discharge disposition (7). Another large study of over 500,000 ICH patients from the National Inpatient Sample found that 23% of ICH patients developed nosocomial infections, with the rate actually rising from 18.7% in 2002–2003 to 24.1% in 2010–2011 (8). Not surprisingly, patients with infection had higher risk of death and lower likelihood of discharge home. Finally, in a study of 24,540 ICH patients in California, hospital readmission within 30 days occurred in 14.5%, with the majority related to infection (9). We have a problem. And while we (me too) have been arguing about blood pressure thresholds, whether to give platelets, and the interpretation of the results of STICH (10), our patients have been dying of infection. We have a target for treatment; it just may not have been the one we thought.

In fairness, we are just starting to understand the issue. While lymphopenia was the "lesion" of concern in the study by Morotti, other studies have found different alterations in the immune response in either cell lines or cytokines (11). It would also seem likely that infection was the ultimate mode of death in a set of patients with particularly severe ICH in whom palliative care was appropriately instituted. Just checking blood cultures routinely in ICH patients does not seem to be a high yield strategy (12). And unfortunately, at least in acute ischemic stroke, the prophylactic use of antibiotics has not been shown beneficial (13).

So what do we do now? First, we need to stop treating ICH like a stroke and start treating it like a critical illness. A lesson that we keep learning in neurocritical care is that it is both the body and the brain and we have to take care of both. I am not ready to start prescribing

empiric antibiotics to all my ICH patients. But I am ready to better emphasize in our treatment guidelines and hospital protocols the importance of infection surveillance and "good care" to prevent infection from occurring in the first place. Additionally, we need to support the value of research into mechanisms of immune impairment and infection occurrence in ICH patients as much as we support studies of intervention for the hematoma itself. ICH is a treatable disease, but the treatments may come from unexpected places.

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