Intracerebral hemorrhage: update and future directions

Hemorragia intracerebral: atualização e direções futuras

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ABSTRACT
Intracerebral hemorrhage (ICH), defined as bleeding into the brain parenchyma, is a significant public health issue. Although it accounts for only 10 to 15% of strokes, it is associated with the highest morbidity and mortality rates. Despite advances in the field of stroke and neurocritical care, the principles of acute management have fundamentally remained the same over many years. The main treatment strategies include aggressive blood pressure control, early hemostasis, reversal of coagulopathies, clot evacuation through open surgical or minimally invasive surgical techniques, and the management of raised intracranial pressure.

Keywords: Cerebral Hemorrhage; Stroke; Critical Care.

SEARCH STRATEGY
A PubMed search for articles published up to June 2019 was performed using the terms “intracerebral hemorrhage” [Title] and (“spontaneous” [Title/Abstract]), which turned out 1,102 articles. Additionally, the reference lists of the most recent guidelines on the management of spontaneous intracerebral hemorrhage were searched. Articles with at least one abstract in English or Portuguese were included.

BACKGROUND
Intracerebral hemorrhage (ICH) is defined as bleeding into the brain parenchyma that may extend into the ventricles and, less frequently, the subarachnoid and subdural spaces. It accounts for 10 to 15% of all causes of stroke and is associated with the highest mortality rates (around 35% at 7 days and 59% at 1 year). The annual incidence of 10 to 30 per 100,000 inhabitants has remained stable in the last three decades. Although there was a 50% decrease
in the incidence of ICH in patients below 60 years of age, an there was an 80% increase in patients above 74 years of age. Advances in the field of stroke and neurocritical care have reduced mortality within 30 days — after ICH in the past years, although early case-mortality rates (within 48 hours) have not improved.

Spontaneous (non-traumatic) ICH can be primary or secondary. Primary ICH represents 78 to 88% of cases and originates from spontaneous rupture of small vessels, usually from chronic hypertension and cerebral amyloid angiopathy (CAA). Secondary ICH results from ruptured vascular abnormalities such as arteriovenous malformations (AVM), cavernomas, and aneurysms. According to location, hematomas can be classified as deep (37%), lobar (49%), infratentorial (9%) or of undetermined location (5%). Treatment strategies include blood pressure control, reversal of coagulopathy and neurosurgery in selected cases.

ETIOPATHOLOGY

The main risk factors for ICH are hypertension, anticoagulation use, heavy alcohol consumption, family history of ICH, personal history of ischemic stroke, low educational levels, and APOE ε2 or ε4 genotype. Alternatively, reduced prevalence of ICH was found in patients with a history of hypercholesterolemia or moderate alcohol consumption (less than two glasses a day). Hypercholesterolemia has been described in many studies as a protective factor, although statin use has not been related to a higher ICH risk and can even reduce it.

Primary intracerebral hemorrhage

The main primary etiologies leading to vasculopathy and cerebral hemorrhage are hypertension and CAA. Chronic hypertension induces lipohyalinosis of small perforating arteries, leading to deep hemorrhages that frequently extend to the ventricles. In 1868, Charcot and Bouchard attributed intracerebral bleeding to the rupture of dilated arteriolar wall (microaneurysms). These morphological entities were posteriorly identified as subadventitious hemorrhages or extravascular thrombi consequences of endothelial damage from the hematoma. The main topographies of hypertensive ICH are in the territories of the small ‘penetrating’ arteries originating off the stems of the main cerebral arteries (the putamen, thalamus, pons, and cerebellum).

Amyloid angiopathy is the most common etiology in patients over 70 years of age with lobar ICH. Progressive deposition of beta-amyloid peptide on the wall of leptomeningeal and cortical vessels reduces their complacency, leading to a spectrum of hemorrhagic manifestations including cerebral microbleeds (CMB), cortical superficial siderosis (cSS), and intracerebral hemorrhage. The main characteristics of CAA are the presence of lobar, cortical or cortical-subcortical hemorrhage, CMB, and cSS in patients above 55 years of age (Figure 1). The Boston criteria were proposed in 1995 and modified in 2010 to estimate the chance of CAA in patients with ICH (Table 1).

Secondary intracerebral hemorrhage

An important and increasing cause of secondary ICH is anticoagulation, which significantly increases the risk of intracranial hemorrhage, hematoma expansion, and hemorrhage; MRI: magnetic resonance imaging. CT: computed tomography; ICH: intracerebral hemorrhage; CMB: cerebral microbleed; cSS: cortical superficial siderosis.

Table 1. Modified Boston criteria for the diagnosis of amyloid angiopathy in patients with intracerebral hemorrhage.

| Modified Boston criteria | Definite CAA |
|--------------------------|-------------|
| Full postmortem examination demonstrating: | • Lobar, cortical or cortical-subcortical hemorrhage |
| • Severe CAA with vasculopathy |
| • Absence of other diagnostic lesion |

| Probable CAA with supporting pathology | Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating: |
|----------------------------------------|---------------------------------------------|
| • Lobar, cortical or cortical-subcortical hemorrhage (including ICH, CMB or cSS) |
| • Some degree of CAA in specimen |
| • Absence of other diagnostic lesion |

| Probable CAA | Clinical data and MRI or CT demonstrating: |
|--------------|---------------------------------------------|
| • Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical or cortical-subcortical regions (cerebellar hemorrhage allowed) or single lobar, cortical or cortical-subcortical hemorrhage and cSS (focal or disseminated) |
| • Age ≥ 55 years |
| • Absence of other cause of hemorrhage* |

| Possible CAA | Clinical data and MRI or CT demonstrating: |
|--------------|---------------------------------------------|
| • Single lobar, cortical or cortical-subcortical ICH, CMB, or cSS (focal or disseminated) |
| • Age ≥ 55 years |
| • Absence of other cause of hemorrhage* |

CAA: cerebral amyloid angiopathy; CMB: cerebral microbleed; cSS: cortical superficial siderosis; CT: computed tomography; ICH: intracerebral hemorrhage; MRI: magnetic resonance imaging.

*Other causes of hemorrhage (differential diagnosis of lobar hemorrhages): antecedent head trauma, hemorrhagic transformation of an ischemic stroke, arteriovenous malformation, hemorrhagic tumor, warfarin therapy with international normalizing ratio >3, and vasculitis.
mortality. Warfarin use may increase the risk of ICH in 2 to 5 fold, depending on the intensity of anticoagulation. Congenital or acquired coagulation factor deficiencies, thrombocytopenic disorders, and lymphoproliferative disorders are less frequent etiologies.

Structural lesions are potentially treatable causes of ICH and should be searched for with vascular imaging studies, such as computerized tomographic angiography (CTA). Up to 10% of brain aneurysms can result in intraparenchymal bleeding. Arteriovenous malformations, angiomatous cavernomas, and tumors may also be involved in ICH development. Other conditions include brain neoplasms or metastasis, cerebral venous thrombosis, and reversible cerebral vasoconstriction syndromes.

**SMASH-U classification**

A tool for etiological classification published in 2012 entitled SMASH-U, classifies ICH according to its different etiologies: structural lesions, related to medications, amyloid angiopathy, systemic diseases, hypertension, and undetermined (Table 2).[

**DIAGNOSIS**

Patients with ICH are usually admitted to the hospital with sudden onset of focal neurological deficits, severe acute headaches, nausea, vomiting, seizures, decreased level of consciousness, and high blood pressures. Brain imaging is essential for diagnostic confirmation and differentiation from ischemic stroke. Both non-contrasted head CT and MRI are highly sensitive for the detection of acute bleeding, although MRI (gradient-eco and susceptibility sequences) is more sensitive in detecting prior hemorrhage. Hematoma volume can be estimated using the ABC/2 method (A, maximal hematoma diameter on axial imaging; B, maximal hematoma diameter perpendicular to A; and C, number of axial slices with the hematoma multiplied by the slice thickness [slices with <25% of hematoma volume are ignored, slices with 25 to 75% of hematoma volume count as 0.5, and those with >75% of hematoma volume count as 1]) (Figure 2).

Imaging and clinical data, such as the absence of hypertension and atypical location, may help identify patients with possible structural etiologies that require further investigation and vascular imaging. MRI findings indicating secondary etiologies include the presence of flow-voids in arteriovenous malformations, lobar microbleeds in CAA and contrast enhancement in tumors or inflammatory etiologies. If the first MRI is normal in suspected cases, a follow-up imaging within four to six weeks is required.

**Table 2.** Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined etiologic classification of intracerebral hemorrhage.

| Etiologic classification SMASH-U | Description |
|---------------------------------|-------------|
| S - Structural lesion           | Image or pathology confirming structural vascular malformation diagnosed on the site of ICH |
| M - Medication                  | Warfarin use with INR greater than or equal to 2, direct oral anticoagulants within 3 days, therapeutic IV heparin, or systemic thrombolysis |
| A - Amyloid angiopathy          | Lobar, cortical or subcortical hemorrhage and age ≥ 55 years |
| S - Systemic disease/other      | Systemic disease or other ICH etiology except from anticoagulation, hypertension or amyloid angiopathy |
| H - Hypertension                | Deep or infratentorial hemorrhage or pre-ICH hypertension, defined as: a) Most recent pre-ICH blood pressure ≥ 160×100 mmHg b) Mention of elevated blood pressure prior to ICH by patient, relative or medical records, with left ventricular hypertrophy as a biomarker of hypertension c) Any use of blood pressure medication prior to ICH |
| U - Undetermined                | None of the above |

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**Figure 2.** Hematoma volume estimation. (A) Non-contrasted computed tomography axial slice with maximal hematoma area with green lines indicating the maximum diameter (A line) measuring 3.21 cm and its maximum perpendicular diameter (B line) measuring 2.26 cm. (B) Axial slice 10 mm cranial to A shows hematoma area of 75–100% of the reference slice. (C) Axial slice 10 mm caudal to A shows hematoma area of 25–75% of the reference slice. (D) Axial slice 20 mm caudal to A shows hematoma area below 25% of the reference slice. Thus, the estimated hematoma volume is 2.26×3.21×(1.0+0.5+0.0)/2=5.44 mL.
Vascular imaging such as CTA, MR-angiography and digital subtraction angiography can assist in etiological definition. Imaging findings indicating vascular abnormalities include the presence of subarachnoid hemorrhage, dilated vessels, perihematoma calcifications, hyperintensity within venous sinus or cortical veins, unusual hematoma shape, unusual location, and disproportionally large peri-hematoma edema.

**Hematoma expansion**

Hematoma expansion is frequently seen on follow-up imaging. Patients presenting early symptom onset and receiving anticoagulated are at higher risk for hematoma expansion. The presence of expansion is associated with a worse prognosis, thus preventing it is one of the treatment goals. Several tools have been proposed to predict hematoma expansion, including the BRAIN algorithm (Table 3), the HEP and BAT scores, and image markers such as “spot sign”, “leakage sign”, “island sign”, “blend sign”, “black hole sign”, and “satellite sign”. The “spot sign” is detected through CTA and is characterized by a spot of contrast enhancement inside the hematoma. The “leakage sign” is more sensitive than the spot sign and the image is acquired 5 minutes after CTA (late phase). Images from both arterial and late phases are evaluated and an increase in more than 10% of Hounsfield units between images determines a positive “leakage sign”. The “island sign”, “blend sign”, “black hole sign”, and “satellite sign” are seen in the non-contrasted head-CT. The “island sign” is defined as scattered small hematomas apart from the main hematoma and the “blend sign” is defined as blending of a relatively hypoattenuating area with adjacent hyperattenuating region within a hematoma. The “black hole sign” is defined as a relatively hypoattenuating area (black hole) encapsulated within the hyperattenuating hematoma and the “satellite sign” is defined as small (maximal diameter <10 mm) hemorrhage close to but completely isolated from the main hemorrhage in at least a single slice.

**Diffusion-weighted imaging abnormalities**

The occurrence of diffusion-weighted imaging (DWI) abnormalities is described in 15 to 46% of patients with ICH, and lesions can be found in perihematomal or remote regions. The presence of DWI lesions in the perihematomal region is associated with higher hematoma volumes, whereas remote lesions are associated with lobar hemorrhages, leukoaraiosis, higher rates of anti-platelet medication, amyloid angiopathy, previous ICH, and atrial fibrillation. Potential embolic sources were described in patients with DWI lesions, such as atrial fibrillation and performance of catheter angiography before MRI. Another possible explanation for this phenomenon is the occurrence of hyperacute and spontaneous hemorrhage following an ischemic stroke of embolic etiology with recanalization.

There is probably a sum of mechanisms influencing the appearance of these ischemic lesions in the setting of acute ICH. Patients with brain hemorrhage usually have a vulnerable microvasculature due to chronic hypertension or amyloid angiopathy, that suffer from an acute state of blood pressure variability, raised intracranial pressure (ICP) and failure in autoregulation, which may culminate in acute cerebral ischemia. Additionally, patients could present with other risk factors for ischemic stroke and even embolic sources causing the ischemia seen on MRI.

**MEDICAL TREATMENT**

ICH is a medical emergency and requires prompt diagnosis and management. Early deterioration occurs in up to a third of patients in the first hours. Initial treatment starts with clinical assessment, airway protection, and hemodynamic stabilization. Further management includes anticoagulation, anti-platelet agents, and surgical evacuation of hematoma. The BRAIN algorithm (Table 3) can help predict hematoma expansion, which is associated with a worse prognosis. Table 3. The BRAIN algorithm for hematoma expansion.

| “BRAIN” score | Milliliters per score: |
|---------------|-----------------------|
| B - Baseline ICH volume | ≤10=0, 10–20=5, >20=7 |
| R - Recurrent ICH | Yes=4 |
| A - Anticoagulation with warfarin at onset | Yes=6 |
| I - Intraventricular extension | No=0, Yes=2 |
| N - Number of hours to baseline computed tomography | ≤1=5, 1–2=4, 2–3=3, 3–4=2, 4–5=1, >5=0 |
| Total | Number of points and risk of expansion: 0–6: 3.4–8.0%, 6–10: 11.3–23.1%, 11–15: 27.2–46.7%, 16–20: 52.1–71.9%, 20–24: 76.0–85.8% |

ICH: intracerebral hemorrhage.

**Figure 3.** Non-contrasted computed tomography imaging of acute intracerebral hemorrhage with expansion signs. Non-contrast computed tomography of acute intracerebral hemorrhage. (A) Cerebellar intracerebral hemorrhage with “blend sign” (white arrows) and “black-hole sign” (yellow arrow). (B) Lobar intracerebral hemorrhage with “satellite sign” (yellow arrow). (C) Deep intracerebral hemorrhage with “island sign” (yellow arrows).
stabilization. Neuroimaging must be performed as soon as possible in order to differentiate ischemic from hemorrhagic stroke and initiate proper treatment. Treatment should preferably be carried out in a tertiary center, with a multidisciplinary team of neurologists, neuroradiologists, neurosurgeons and a neurointensive care unit. Acute treatment includes blood pressure management, coagulopathy reversal, neurosurgical interventions for hematoma evacuation, external ventricular drainage (EVD) and ICP monitoring.

**Blood pressure management**

Intensive blood pressure management is thought to reduce hematoma expansion and improve functional outcomes. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) study showed that patients with aggressive blood pressure management with systolic blood pressures (SBP) at a target of 140 mmHg or less had lower hematoma growth. The INTERACT2 study included 2,800 patients with acute ICH. Although it did not reach statistical significance on its primary outcome, defined as moderately severe disability or less in 90 days, an ordinal analysis of modified Rankin scores showed improved functional outcomes with intensive blood pressure lowering. Systolic blood pressure reduction to levels close to 140 mmHg was safe and did not increase the risk of perihematomal ischemia. Because of this study, the current American Heart Association guidelines for the management of ICH suggests lowering systolic blood pressure to 140 mmHg or less.

In June 2016, the Anti-hypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) study was published, comparing standard (SBP of 140–179 mmHg) to intensive (110–139 mmHg) blood pressure management. The study was interrupted due to futility after the inclusion of 1,000 patients. At first glance, ATACH-II results seem conflicting with INTERACT2, since the “intensive” treatment was not superior to the “standard” one, but rather was associated with higher complication rates (especially kidney impairment). However, it was observed that the “standard” group maintained a mean SBP of about 140 mmHg, while the “intensive” group had a mean SBP of about 120 mmHg. The final conclusion was that “very intensive” blood pressure reduction with SBP levels below 120 mmHg does not offer additional benefits when compared to “intensive” treatment with SBP levels around 140 mmHg.

**Reversal of coagulopathy**

Coagulation disorders are a common cause of intracerebral hemorrhage and should be promptly treated. Reversal of anticoagulation in patients receiving vitamin K antagonists (warfarin) is achieved through intravenous vitamin K administration (10 mg), followed by fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC). PCC is preferable in comparison to FFP due to its faster action and greater effectiveness. The INR target should be of 1.4 or less and its measurement should be repeated shortly after PCC administration. If the values are still above 1.4, FFP may be administered for greater INR reduction.

For patients with ICH using factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) or thrombin inhibitors (dabigatran), treatment options include PCC, FEIBA or FVIIa. Activated charcoal may be used if ingestion occurred within 2 hours. For direct reversal of dabigatran, idarucizumab 5 g IV in 2 doses or hemodialysis can be performed. Andexanet, a reversal agent for factor Xa inhibitors, was recently approved by the Food and Drug Administration (FDA). In patients anticoagulated with unfractionated heparin (UFH), IV infusion must be immediately discontinued and protamine sulfate should be administered (1 mg for every 100 U of heparin given in the last 2–3 hours) at a maximum dosage of 50 mg. In case partial thromboplastin time (PTTt) remains

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**Adapted from Prabhakaran, et al. Stroke. 2012**

*Figure 4. Possible mechanisms leading to ischemia in intracerebral hemorrhage.*
elevated, protamine can be readministered at a dose of 0.5 mg for every 100 units of UFH. Low molecular weight heparin can be reversed with protamine sulfate or recombinant factor VII. PCC and FFP are not recommended in these cases. Platelet transfusion in patients using antiplatelet agents was proven ineffective and even harmful. Hemostatic medications in ICH patients without coagulopathy have been proven ineffective. Factor VII and tranexamic acid did not improve survival or functional outcome after ICH.

**Intensive care**

Pneumatic compression is indicated for deep venous thrombosis prevention until the documentation of bleeding cessation, when low molecular weight heparin (LMWH) or UFH can be initiated in prophylactic doses. Glycemic and temperature control are crucial, and dysglycemia and hyperthermia should be avoided. Anti-seizure medication is solely indicated in the presence of seizure activity and continuous electroencephalogram (EEG) is recommended in patients with decreased level of consciousness not fully explained by the extent or location of the brain lesion.

**SURGICAL TREATMENT**

Patients evolving with hydrocephalus should receive an EVD with ICP monitoring, especially if there is impaired consciousness. Cerebral perfusion pressure must be kept at 60–70 mmHg. Although studies have suggested the safety of intraventricular alteplase in patients with intraventricular hemorrhage, treatment efficacy is uncertain. Patients with cerebellar hemorrhage and progressive neurological decline, brainstem compression or hydrocephalus should undergo hematoma evacuation. Decompressive craniectomy with or without hematoma evacuation should be considered in comatose patients, in large hematomas with midline shifts or refractory elevated ICP. Hematoma evacuation through minimally invasive surgery, endoscopic aspiration or early evacuation do not have proven efficacy. The MISTIE III study prospectively evaluated minimally invasive surgery with thrombolysis for hematoma evacuation in patients with ICH volumes ≥30 mL. Although the primary outcome (modified Rankin scores of 0–3 at 1 year) was negative, the subgroup of patients with residual hematoma of ≤15 mL or reduction of ≥70% had better functional outcomes and survival rates. A summary of treatment approaches with management algorithm is depicted in Figure 5.

**PROGNOSIS**

Baseline prognostic scoring systems are helpful in defining mortality risks. The most commonly used score worldwide is the ICH score (Table 4). This scale

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**Figure 5. Acute intracerebral hemorrhage treatment algorithm**

EVD: external ventricular drainage; FFP: fresh frozen plasma; ICH: intracerebral hemorrhage; ICU: intensive care unit; ICP: intracranial pressure; INR: international normalized ratio; IV: intravenous; LMWH: low molecular weight heparin; PCC: prothrombin complex concentrate; SBP: systolic blood pressure; UFH: unfractionated heparin.
Table 4. Intracerebral hemorrhage scale and prognosis.

| ICH scale and prognosis | 3–4 | 5–12 | 13–15 | ≥30 mL | <30 mL | Yes | No | Yes | No |
|-------------------------|-----|------|-------|--------|-------|-----|----|-----|----|
| Glasgow Coma Scale      | 2   | 1    | 0     | 1      | 0     |     |    |     |    |
| Hematoma volume         |     |      |       |        |       |     |    |     |    |
| ≥30 mL                  |     |      |       |        |       |     |    |     |    |
| <30 mL                  |     |      |       |        |       |     |    |     |    |
| Intraventricular bleed  |     |      |       |        |       | 1   |    |     |    |
| No                      |     |      |       |        |       | 0   |    |     |    |
| Intratenorial origin    |     |      |       |        |       |     |    |     |    |
| Yes                     |     |      |       |        |       |     |    |     |    |
| No                      |     |      |       |        |       |     |    |     |    |
| Age                     |     |      |       |        |       |     |    |     |    |
| ≥80 years               |     |      |       |        |       |     |    |     |    |
| <80 years               |     |      |       |        |       |     |    |     |    |
| Total                   |     |      |       |        |       |     |    |     |    |
| 0                       |     |      |       |        |       |     |    |     |    |
| 1                       |     |      |       |        |       |     |    |     |    |
| 2                       |     |      |       |        |       |     |    |     |    |
| 3                       |     |      |       |        |       |     |    |     |    |
| 4                       |     |      |       |        |       |     |    |     |    |
| 5 and 6                 |     |      |       |        |       |     |    |     |    |

ICH: intracerebral hemorrhage.

stratifies 30-day mortality risk and varies from 0 to 654. In the original study, mortality in patients scored 0 was 0%, while patients with scores 4 or higher have mortality rates of almost 100% in the first 30 days54. Since the publication of the ICH score in 2001, other mortality prediction scales have been developed. As an important limitation for these scales, patients who had withdrawal of care in the first days of admission were included in the analysis. Caregivers should be cautious when defining prognosis in ICH in order to avoid engaging a self-fulfilling prophecy. Consequently, waiting at least 24 hours before deciding to withdraw care is recommended8,55.

FINAL REMARKS

Intracerebral hemorrhage is a life-threatening acute neurological disorder requiring emergent treatment. Neuroimaging is imperative for diagnosis, etiological classification, prediction of hematoma growth, and prognosis. Although frequently detected, the mechanisms and clinical significance of acute DWI imaging are still uncertain. Treatment mainstays include blood pressure reduction and coagulopathy reversal, which should be promptly initiated. Surgical treatment with EVD insertion, hematoma evacuation or decompressive craniectomy is often necessary. The role of minimally invasive surgery is still uncertain, although recent studies have shown promising results.

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