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CHAPTER 2

Recent Advances in the Management of Spontaneous Intracerebral Hemorrhage

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ABSTRACT

Spontaneous intracerebral hemorrhage (SICH) is the second most common cause of stroke worldwide. It is particularly common in Asians with mortality and morbidity rates higher than that of ischemic stroke. Although a devastating illness, therapeutic approaches have not paralleled advancements in ischemic stroke. The widespread nihilism has been nullified by the recent publication of quality randomized trials which have renewed optimism in managing the illness. Diagnostic advancements like the identification of iodine sign on spectral imaging have added new tools in the armamentarium of neurologists for predicting hematoma expansion. The recent boom in machine learning and artificial intelligence (AI) has provided new predictive models which are reproducible and eliminate human subjective factors. The year 2023 has reinforced therapeutic evidence by positive results of randomized controlled trials demonstrating benefits of a hyperacute care bundle approach (INTERACT3), early minimally invasive hematoma evacuation (ENRICH), and the use of Andexanet alfa in factor Xa-inhibitor anticoagulation reversal (ANNEXa-I). The current year has also added to the evidence by confirming the effects of early intensive blood pressure lowering (INTERACT4) and decompressive hemicraniectomy in large deep intracerebral hemorrhage (SWITCH). We have reviewed these and other recent developments in the management of SICH. These recent advancements usher a new positive and optimistic era for SICH care.

Keywords: Intracerebral hemorrhage, Recent advances, Hematoma expansion, Care bundles.

INTRODUCTION

Spontaneous intracerebral hemorrhage (SICH) is defined as rupture of cerebral blood vessels resulting in bleeding into the brain parenchyma and/or the ventricles in the absence of trauma or surgery.[1] It is the second most common cause of stroke (10–20% of all strokes) and has a pooled worldwide incidence of 29.9 per 100,000 person-years [95% confidence interval (CI) 26.5–33.3].[2] It is particularly more common in the Asian population.[2,3] The mortality rate is twice that of ischemic stroke and ranges from 40 to 50% in the 1st month.[4] The disability caused by the illness is also high with only 12–39% achieving long-term functional independence.[1] Risk factors include hypertension (HTN), age, alcohol abuse, methamphetamine or cocaine use, and presence of genetic alleles associated with cerebral amyloid angiopathy (CAA).[5] Depending on the cause, intracerebral

hemorrhage (ICH) can be classified as either primary or secondary. Primary ICH accounts for about 75% of the cases and occurs due to rupture of abnormal small vessels damaged by HTN or CAA. The location of primary ICH can be lobar or nonlobar. Amyloid deposition due to CAA in the small to medium sized cortical perforators causes lobar ICH. Nonlobar ICH occurs due to lipohyalinosis of small perforators triggered by HTN. These hemorrhages are deep (often with ventricular extension) and most commonly involve the basal ganglia, thalamus, subcortical white matter, pons, and cerebellum. Secondary ICH is associated with both congenital and acquired conditions such as vascular malformations, malignancy, coagulopathies, anticoagulant and thrombolytic use, cerebral vasculitis, drug abuse, and cerebral venous thrombosis.

Even though ICH remains a major cause of morbidity and mortality, therapeutic approaches to its management over the years have not paralleled the pace of ischemic stroke. With the recent publication of quality randomized trials in the past 2 years, this nihilistic perspective has changed to an optimistic one. This article attempts to provide the reader with an updated perspective on the management of SICH in the context of recent trials.

DIAGNOSTIC ADVANCEMENTS IN THE CURRENT ERA

Predicting Hematoma Expansion in Intracerebral Hemorrhage

Hematoma expansion (HE) is an independent predictor of poor prognosis after an ICH and occurs in up to one-third of cases.[6] Although it has been described heterogeneously across studies, the most accepted definition across studies is an absolute increase in the volume by 6–12.5 mL and/or more than one-third of the initial volume in follow-up CT scans.[7] Numerous studies have identified specific CT, CT angiography (CTA), and MRI findings which are associated with HE and include the spot sign, leakage sign, spot-tail sign, iodine sign, island sign, satellite sign, blend sign, swirl sign, black hole sign, fluid-blood level, and MRI spot sign.[6,8-17] These signs are summarized in the **Table 1**.[18,19] Among these, the iodine sign on spectral imaging, subarachnoid extension (SAHE), and the MRI spot sign are recently described entities.

TABLE 1: Imaging signs of hematoma expansion with the description and their sensitivity, specificity, PPV, and NPV in predicting it.

Imaging	Sign	Description	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CTA	Spot sign[8]	Enhanced focus in the hematoma-contrast extravasation (site of vessel rupture)	91 (62–100)	89 (72–96)	77 (50–92)	96 (81–99)
	Leakage sign[9]	Increase in CT Hounsfield value within a specific region of interest (>10%)	93.3 (75.7–98.8)	88.9 (81.5–91.2)	—	—
	Spot tail sign[10]	Presence of intrahematoma striate artery on CTA	—	—	—	—

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Imaging	Sign	Description	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CTA-gemstone spectral imaging (GSI)	Iodine sign[11]	Hematoma with enhancing foci on GSI + Internal focus iodine concentration of >7.82 (100 µg/mL)	91.5	79.5	82.7	89.7
NCCT	Island Sign[12]	≥3 small hematomas scattered from the main hematoma or ≥4 small hematomas with only some scattered from the main hematoma	44.7	98.2	92.7	77.7
	Satellite sign[13]	Small hematoma completely separated from the main hematoma of diameter ≤10 mm with a distance between main and small hematoma ranging from 1 to 20 mm	—	—	—	—
	Blend sign[14]	A low-density region within a region of high density within the hematoma (difference 18 HU between the two regions and low-density region not completely surrounded by high density region)	39.3	95.5	82.7	74.1
	Swirl sign[15]	Areas of hypoattenuation/isoattenuation as compared to the brain parenchyma on axial/coronal planes	--	--	--	--
	Black-hole sign[18]	Low-density area completely surrounded by high-density hematoma and a difference of at least 28 HU between them	31.9	94.1	73.3	73.2
	Fluid-blood level[6]	Horizontal interface between hypodense bloody serum and hyperdense fluid (most often seen in anticoagulant induced bleeds)	—	—	—	—
	Subarachnoid extension[19]	Predictor of lobar HE	83 (71–92)	56 (45–67)	57 (45–67)	83 (70–91)

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Imaging	Sign	Description	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MRI	Spot sign[17]	Spot like/serpiginous high signal >1.5 mm in one dimension located within the margins of the hematoma without any connections to any external blood vessel	90 (74–98)	47 (37–58)	94 (83–99)	35 (25–46)

(CTA: CT angiography; GSI: gemstone spectral imaging; HE: hematoma expansion; HU: hounsfield units; NCCT: noncontrast computed tomography; NPV: negative predictive value; PPV: positive predictive value)

These subjective signs have been the basis of development of scores for HE which help in risk stratification and triaging patients for a more aggressive management. The BAT, BRAIN, PREDICT-A/B, and the Brouwers 9-point score have been described which predict HE with reasonable accuracy. The salient features of each of these scores have been summarized in the **Table 2**.[20-24]

Recent Artificial Intelligence Boom and Usage in Predicting Hematoma Expansion

The advent of artificial intelligence (AI) and deep machine learning (ML) has led to better mining and integration of medical imaging information (radiomics) with clinical information (clinicomics).[25] These systems are reproducible and eliminate the human subjective factors in interpretation. Different ML models have been studied which include the k-nearest neighbors (KNN), support vector machines (SVMs), random forests, and XGBoost which have been developed using different programming languages (Python and its libraries).[26-29] Baseline clinical characteristics, ICH volume, CT and CTA imaging markers, location of the ICH, and the systolic blood pressure (SBP) have served as inputs in these algorithms with the HE as the output. In a systematic review involving 34 ML studies on HE, radiomics combined with clinical data predicted HE better than models using radiomic features or clinical features alone with a C-index of 0.79 (validation cohort) for the combined model and 0.73 (validation cohort) and 0.70 (validation cohort) in the radiomic and clinical models, respectively.[28]

DIAGRAM for Predicting Macrovascular Cause

Although in most cases, a NCCT is often enough in identifying the etiology in primary ICH (due to microvascular disease) with typical lobar and nonlobar locations as described above, certain features increase the likelihood of finding a macrovascular cause like vascular malformations. In the DIAGRAM (DIagnostic AngioGRAphy to find vascular Malformations) study, young age, lobar or posterior fossa location of ICH, and absence of small vessel disease (SVD) were associated with a significant probability of finding a macrovascular cause.[30] The usefulness is highlighted in the European Stroke Organization (ESO) 2023 expert consensus statement on use of acute care bundle in ICH which recommended the use of tools like the DIAGRAM score to identify selected patients who need further imaging like CT angiography for identifying a macrovascular cause.[31]

TABLE 2: HE prediction scores using clinical and/or radiologic data.

Score	Range	Cut-off points (risk of HE)	C-statistic/sensitivity/specificity
Brouwers score*[20]	0–9	0 (5.7%); 1–3 (12.4%); 4–9 (36.4%)	0.77 (validation cohort)
PREDICT-A$[21]	0–23	0–2 (7.1%); 15–23 (70%)	For cut off = 2; sensitivity—0.96 (0.9–0.99), specificity—0.25 (0.2–0.32)
PREDICT-B#[21]	0–28	0–5 (5.6%); 21–28 (73.3%)	For cut off = 5; sensitivity—0.97 (0.91–0.99), specificity–0.25 (0.19–0.32)
BAT[22]	0–5	0–2 (11%); 3–5 (50.8%)	2 validation cohorts—0.65 (0.61–0.68) and 0.70 (0.64–0.77)/sensitivity—50% (at score 3)/specificity—89% (at score 3)
BRAIN[23]	0–24	24 (85.8%)	C-statistic = 0.73 (INTERACT2 cohort)
Fu score@[24]	0–10	Cut-off = 3 (AUROC-0.937)	Sensitivity (at cut-off = 3)—97.8%, specificity (at cut-off = 3)—92.7%

*_Brouwers score_—Warfarin usage (2 points), time to NCCT (≤6 hours—2 points), CTA spot sign (present—3 points), baseline ICH volume (0–2 points).

$_PREDICT-A_ components—GCS (0–4 points), hours to NCCT (0–5 points), Warfarin use (0–4 points), CTA spot sign number (0–8 points).

#_PREDICT-B_ components—NIHSS (0–7 points); hours to NCCT (0–5 points), Warfarin use (0–7 points), CTA spot sign number (0–9 points).

@_Fu score_—Intracerebral hemorrhage baseline volume (0–1 point), time to initial NCCT ≤ 3 hours (2 points), Island sign (6 points), and black hole sign (1 point).

[AUROC: area under the receiver operating characteristic curve; BAT: B—blend sign (1 point), A—any hypodensity (2 points), T—time from onset to NCCT < 2.5 hours (2 points); BRAIN: B—baseline intracerebral hemorrhage volume (0–7 points), R—recurrent intracerebral hemorrhage (4 points), A—anticoagulation use (6 points), I—intraventricular extension (0–2 points), N—number of hours to baseline NCCT (0–5 points); HE: hematoma expansion; NCCT: noncontrast computed tomography]

RECENT ADVANCES IN TREATMENT OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Treat to Target in Intracerebral Hemorrhage: Stopping the "Avalanche"

Rupture of a blood vessel inside the brain parenchyma triggers a "hemorrhagic avalanche" which causes the surrounding potentially abnormal microvessels to tear increasing the hematoma volume.[32] The initial goal of treatment should be to prevent the rupture of these microvessels and stop the avalanche. Publication of a series of randomized trials which will be discussed subsequently has provided quality Level-1 evidence for targeted interventions in the hyperacute phase (<6 hours of onset).[33] We propose a novel acronym "R-ICH" for hyperacute targets in SICH. RICH stands for *R*educe *I*njury (brain parenchyma), *C*lot burden (surgical removal), and *H*ematoma expansion.

Once the RICH targets have been achieved, postacute and long-term goals can be set. These are the two *"R"s*—recurrence prevention and rehabilitation.

RICH Goals: Care Bundles

Although care bundles are known to improve outcomes in ischemic stroke, they had not been tested in a randomized fashion in ICH.[34] Single interventions like blood

pressure (BP) reduction (INTERACT2 and ATACH-2), hematoma evacuation, blood sugar, and temperature control had been tested with mixed results.[33] Combining them into a care bundle was tested in a randomized trial (INTERACT3).[35] In this international stepped wedge cluster randomized trial involving 7,036 patients of ICH presenting within 6 hours of onset, implementation of a care bundle comprising warfarin-related anticoagulation reversal (target INR < 1.5) within 1 hour, early intensive SBP control (target <140 mm Hg), care pathway for neurosurgery referral, glycemic (target in nondiabetics = 6.1–7.8 mmol/L and diabetics = 7.8–10.0 mmol/L) and temperature control (body temperature target ≤37.5°C) was associated with a lower likelihood of a poor outcome at 6 months in the care bundle group (OR 0.86; 95% CI 0.76–0.97; $p = 0.015$). The major hindrance in translating this evidence to practice is the challenges in implementation due to differential availability of resources across centers and skill mix as was seen in this study.[36] The core components of the care bundle along with the current recommended ESO and American Stroke Association/American Heart Association (ASA/AHA) guidelines are summarized in the **Table 3**.

TABLE 3: Core components of acute ICH care/care bundle with targets as per ESO/ASA/AHA guidelines.[31,37]

Intervention	Whom to treat	Door to target time	Drugs and therapeutic targets
Reversal of anticoagulation	Patients on VKA with INR ≥1.3	<30 minutes	PCC (25–50 U/kg) and vitamin K (5–10 mg)
	On apixaban or rivaroxaban and last dose taken ≤18 h		Andexanet alfa 400 mg @30 mg/min f/b 4 mg/min for 120 minutes
	On dabigatran		Idarucizumab 5 g (if available) or PCC
Intensive BP lowering	Mild-to-moderate ICHs with presenting SBP = 150–220 mm Hg	Start within 2 hours and reach target in 1 hour	Target SBP: 130–150 mm Hg; <130 mm Hg harmful
	Large ICHs with SBP > 150 mm Hg		Role of intensive SBP reduction unclear
Surgical evacuation of hematoma ± External ventricular drainage	Urgent neurosurgery consult in cases of: • GCS ≤13 • Supratentorial ICH with volume ≥ 20 mL • Posterior fossa ICH • Obstruction of 3rd and 4th ventricles	As soon as patient arrives	• MIS ± thrombolytic for GCS—5–12 and supratentorial ICH with volume ≥ 20 mL • Large IVH with hydrocephalus—EVD > medical management • GCS >3 + ICH volume < 30 mL + IVH requiring EVD→ EVD + thrombolytic • Large deep supratentorial ICHs—decompressive craniotomy • Deteriorating supratentorial ICH—craniotomy and hematoma evacuation* • Posterior fossa ICH—suboccipital decompression

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Intervention	Whom to treat	Door to target time	Drugs and therapeutic targets
Glycemic control	Nondiabetics blood glucose > 7.8 mmol/L	Maintain for 7 days	Avoid hypoglycemia
	Diabetics: Blood glucose > 10 mmol/L		
Control of body temperature	Body temperature ≥37.5°C	Normothermia in < 1 hour	Temperature monitoring q4 h for 7 days and any antipyretic can be used—tablet paracetamol

*Mortality benefit.

(EVD: external ventricular drain; GCS: Glasgow Coma Scale; ICH: intracerebral hemorrhage; INR: international normalized ratio; IVH: intraventricular hemorrhage; MIS: minimally invasive surgery; PCC: prothrombin complex concentrate; SBP: systolic blood pressure; VKA: vitamin K antagonists)

Time is Brain in ICH Too!

In May 2024, the INTERACT4 was published which randomly assigned 2,404 acute stroke patients (both ischemic and hemorrhagic) with a motor deficit and elevated SBP (≥150 mm Hg), within 2 hours after the onset of symptoms assessed in the ambulance, to receive immediate treatment to lower the SBP (target range = 130–140 mm Hg; intervention group) or usual BP control.[38] Although there was no difference in functional outcomes between the two groups, the intervention group was associated with decreased odds of poor functional outcome among patients with ICH (common odds ratio 0.75; 95% CI 0.60–0.92). These novel findings underscore the benefits of rapid BP control (<2 hours) in ICH patients and provide evidence for reconfiguring current systems of care for a time intensive urgency toward BP reduction.[33]

ANTICOAGULATION REVERSAL: RECENT ADVANCES

- *The increasing use of direct oral anticoagulants (DOACs) and challenges in ICH treatment*: In a recent Italian population-based stroke registry study, although the incidence of oral anticoagulation related ICH remained stable over a decade, the incidence of DOAC-related ICH overtook that related to vitamin K antagonists (VKA) in 2020 (incidence rate ratio 4.71; 95% CI 1.22–33.54; $p = 0.022$).[39] Similar Indian studies are needed to substantiate this claim. The ease-of-use of DOACs makes them preferable to VKAs. However, unlike rapid reversal agents and ability to monitor for overdose for VKAs (INCH trial), DOAC antidotes have not been previously tested in a randomized fashion.[40] In a prospective cohort study (RE-VERSE AD) evaluating a specific agent to reverse the anticoagulant effects of dabigatran involving 90 patients, idarucizumab normalized test results (dilute thrombin time or ecarin clotting time) in 88–98% of the patients, an effect that was evident within minutes at a dose of 5 g intravenously.[41] Whether these results translate to improved functional outcomes in dabigatran-induced ICH patients remains unexplored. Idarucizumab has recently been introduced in India, but the high costs preclude its widespread use.[42]

- *Tranexamic acid and novel oral anticoagulant induced ICH (NOAC-ICH)*: The efficacy of the antifibrinolytic drug tranexamic acid was tested in a randomized trial (TICH-NOAC) involving 63 patients (32 in IV tranexamic acid arm and 31 in the placebo arm) of NOAC-ICH within 48 hours of NOAC intake and 12 hours of onset of symptoms. The primary outcome of HE was not significantly different between the two arms (aOR 0.63; 95% CI 0.22–1.82; $p = 0.40$).[43] Although the trial did not reach its intended sample size of 109 patients which precludes any firm conclusions, it was the first randomized trial for hemostatic treatments in NOAC-ICH.
- *ANNEXing andexanet alfa into the armamentarium*: Factor Xa inhibitors (FXaI) present a different challenge and have been treated with prothrombin complex concentrates mainly based on observational data.[44] However, the introduction of andexanet alfa, a recombinant modified factor Xa antidote which acts as a decoy and sequesters factor Xa inhibitors, resulted in a targeted therapy for FXaI-ICH. In an individual patient level meta-analysis of the ANNEXa-4 and the TICH-NOAC studies, treatment with andexanet alfa was independently associated with decreased odds of HE (aOR 0.33; 95% CI 0.13–0.80; $p = 0.015$) compared to a nonspecific treatment strategy.[45]

The ANNEXa-I further strengthened evidence in favor of andexanet alfa. In this randomized trial involving 452 patients for efficacy analysis, the primary endpoint of hemostatic efficacy occurred in 67% of patients receiving andexanet and in 53.1% patients receiving usual care (adjusted difference = 13.4 percentage points; 95% CI 4.6–22.2; $p = 0.003$).[46] There was, however, an associated increase in thrombotic events including ischemic stroke (thrombotic events in 10.3% of patients in the andexanet arm as compared to 5.6% usual care arm; difference = 4.6 percentage points; 95% CI 0.1–9.2; $p = 0.048$); ischemic stroke occurred in 6.5% versus 1.5% patients, respectively. The trial was not powered to show a difference in mortality or functional outcomes, the question which still remains unanswered.

ADVANCES IN SURGICAL MANAGEMENT OF INTRACEREBRAL HEMORRHAGE

The choice of patients for surgical treatment, the most appropriate technique, and the optimal timing of intervention have been a matter of debate for years.[47] This is primarily due to randomized trials failing to demonstrate any benefit of hematoma evacuation on death and functional outcome compared to conservative care.

In supratentorial ICH patients with a hematoma volume >10 mL and significant neurological deficit, the benefits of craniotomy compared to conservative management remain uncertain.[37] Both the STICH I and STICH II failed to demonstrate any improvement in functional outcomes with craniotomy.[48,49] Limited data, however, suggests that craniotomy for hematoma evacuation may be considered in deteriorating patients as a lifesaving measure primarily due to the STICH II identifying a trend toward decreased mortality with surgery, despite a crossover rate of 21% from conservative arm to surgery of which 74% were attributable to deterioration.[49]

In the recent years, there has been interest in minimally invasive surgery (MIS) for hematoma evacuation in supratentorial ICHs using endoscopic or stereotactic aspiration mainly due to its propensity to reduce hematoma volume, perihematomal edema, and less destruction of brain tissue as compared to conventional craniotomy.[37] However, this enthusiasm had not translated

into trial results until the ENRICH results.[50] In the MISTIE-III (Third Minimally Invasive Surgery with Thrombolysis in Intracerebral Hemorrhage Evacuation) trial involving 499 patients (255 in the MISTIE arm and 251 in the usual medical care arm-modified intention to treat), no overall benefit was seen in the primary outcome of functional recovery in the MIS group with local application of alteplase for hematoma aspiration within 6–72 hours after onset (adjusted risk difference = 4%; 95% CI 4–12; $p = 0.33$).[51]

The ENRICH trial looked at whether early MIS resulted in better functional outcomes compared to medical management.[50] In this study involving 300 patients (150 in surgical arm and 150 in medical arm) of lobar (69.3%) or anterior basal ganglia (30.7%) ICH with a hematoma volume of 30–80 mL within 24 hours after the time last known to be well, MIS resulted in better functional outcomes at 180 days which was primarily due to intervention for lobar ICHs. Although this trial supported MIS surgery for lobar supratentorial ICHs, it left several questions unanswered over the optimal technique and patient selection for early surgery. Further ongoing trials like the NESICH (NCT05539859), MIND (NCT03342664), EVACUATE (NCT04434807), DIST (NCT05460793), and EMINENT-ICH (NCT05681988) will provide better answers to the optimal timing, technique, and the right patient for MIS.[33,52]

TIME TO SWITCH TO DECOMPRESSIVE CRANIECTOMY FOR LARGE DEEP SUPRATENTORIAL INTRACEREBRAL HEMORRHAGES?

Until 2024, it was unknown if decompressive craniectomy led to improved clinical outcomes in severe deep ICHs. The SWITCH was a multicenter, open label assessor blinded randomized trial involving 197 patients (96 in decompressive craniectomy plus usual care and 101 in usual care) which suggested that decompressive craniectomy plus usual care might be superior to usual care alone in patients with large deep supratentorial ICHs (adjusted risk difference –13%; 95% CI –26 to 0).[53] Further large trials are needed to substantiate these results.

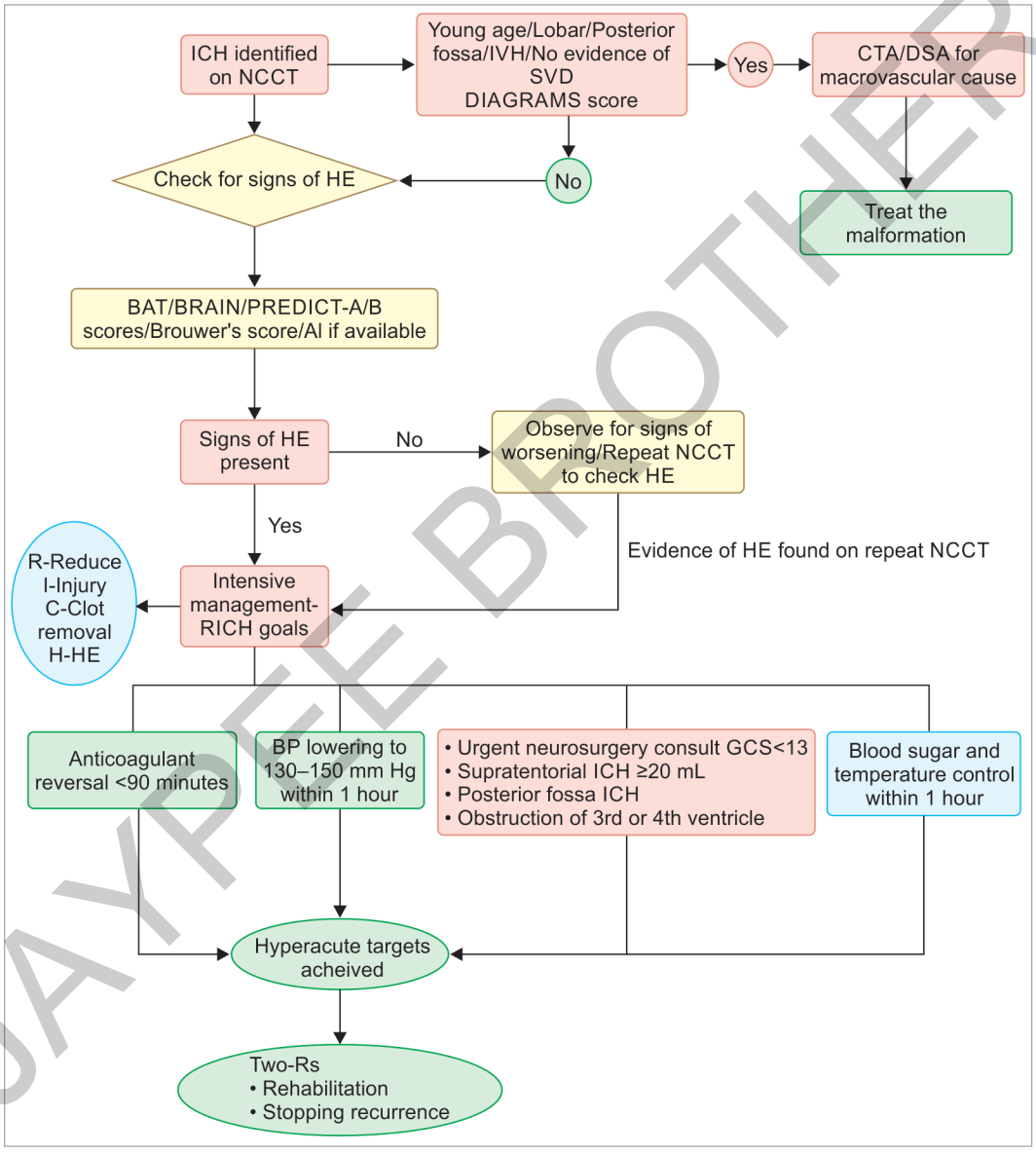
POST-INTRACEREBRAL HEMORRHAGES CARE

Enhancing post ICH recovery is an area of active research. Most rehabilitative strategies have focused on gross motor recovery neglecting the sensory and the cognitive aspects of the deficit. Recently, numerous lower limb exoskeletons have been developed for assisting or augmenting with walking. Some of them are stationary and are used mainly for gait retraining after trauma. Others are mobile and support the entire body weight or provide an assistive force while walking. In a randomized trial of exoskeleton-based physical therapy (ExStRA) involving 36 patients with a median of 39 days post stroke (both ischemic and hemorrhagic stroke included), no significant improvement in walking independence (functional ambulation category) was found as compared to standard care.[54] The development of Robotics has led to development of Robotic mobile exoskeletons for gait training of stroke survivors.

The timing of rehabilitation is also a matter of debate with studies suggesting that very early and intensive rehabilitation can impair functional recovery.[55] The AHA/ASA 2022 guideline recommends that rehabilitation should be started 24–48 hours after stroke onset. In addition, it recommended against intense and frequent mobilization within 24 hours. In remote areas, there has been increasing enthusiasm in the field of telerehabilitation with randomized trials demonstrating low-to-

moderate evidence that they are noninferior to in-person care.[56,57]

Depression is also common following ICH and may occur in up to 20% of patients. The benefits of treatment must be balanced by the increased risk of secondary events with selective serotonin reuptake inhibitors. Three recent randomized trials (FOCUS, AFFINITY, and EFFECTS) tried to harness the pleiotropic effects of fluoxetine enrolling both ischemic



FLOWCHART 1: Management algorithm for spontaneous ICH in the current era with emphasis on time bound targets.

(ICH: intracerebral hemorrhage; NCCT: noncontrast computed tomography scan; SVD: small vessel disease; HE: hematoma expansion)

stroke and ICH patients and found that, although the risk of poststroke depression was reduced, the risk of bone fractures and hyponatremia was increased, and no significant improvements in functional outcomes were seen.[58]

EMERGING THERAPEUTIC OPTIONS: NANOPARTICLES

Recently, numerous active pharmaceutical ingredients have been used in ICH mainly in preclinical studies which include desferoxamine, curcumin, and resveratrol.[59] These drugs target ferroptosis and the oxidative stress. The major issue precluding their use has been their toxicity and poor bioavailability. Nanotechnology has allowed us a novel method of drug loading enhancing target bioavailability. Nanomaterials such as polymer, micelles, nanoemulsions, liposomes, and exosomes have been recently tried in ICH and have shown promise. Further developments in nanotechnology might make randomized studies feasible in the coming decade.

CONCLUSION

As seen in this review, there has been an increase in the intensity in managing ICH patients which has been primarily driven by the above-mentioned positive trials. Enlightened by the RICH and double-R approach, we propose a new algorithm for managing ICH in the current era incorporating evidence gained from these studies **(Flowchart 1)**. As we eagerly wait for the results of ongoing trials to further change the ICH landscape, time has come to shift gears to a more intensive "Time is brain" approach. Emerging advancements in diagnostics using AI and therapeutics using nanoparticles are likely to further reduce morbidity and mortality in the coming decade.

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Advances in Stroke

Salient Features

- Advances in intravenous thrombolysis and mechanical thrombectomy
- Cutting-edge imaging techniques in stroke
- Advances in the management of intracerebral hemorrhage
- Underdiagnosed aortic arch atheroma, its diagnosis and management

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