Acute intracerebral haemorrhage: diagnosis and management

Iain J McGurgan, Wendy C Ziai, David J Werring, Rustam Al-Shahi Salman, Adrian R Parry-Jones

ABSTRACT
Intracerebral haemorrhage (ICH) accounts for half of the disability-adjusted life years lost due to stroke worldwide. Care pathways for acute stroke result in the rapid identification of ICH, but its acute management can prove challenging because no individual treatment has been shown definitively to improve its outcome. Nonetheless, acute stroke unit care improves outcome after ICH, patients benefit from interventions to prevent complications, acute blood pressure lowering appears safe and might have a modest benefit, and implementing a bundle of high-quality acute care is associated with a greater chance of survival. In this article, we address the important questions that neurologists face in the diagnosis and acute management of ICH, and focus on the supporting evidence and practical delivery for the main acute interventions.

INTRODUCTION
Spontaneous intracerebral haemorrhage (ICH) refers to non-traumatic bleeding in the brain parenchyma and is the deadliest form of stroke. The high 1-month case-fatality rate of ~40% and poor long-term outcome make it a major contributor to global morbidity and mortality. Although ICH accounts for a minority of stroke worldwide (10–30%), it is associated with a greater burden of disability-adjusted life years than ischaemic stroke, given its high incidence in low- and middle-income countries. Despite dramatic drops in ischaemic stroke mortality rates, there has been limited improvement in case fatality from ICH in the last few decades and most survivors are left with severe disability.

ICH is not a single entity; 85% of cases are due to cerebral small vessel disease, predominantly deep perforator arteriopathy (also termed hypertensive arteriopathy or arteriosclerosis) and cerebral amyloid angiopathy, while the remainder results from a macrovascular (e.g., arteriovenous malformation, cavernoma, aneurysm and venous thrombosis) or neoplastic cause. Vascular malformations are the most common cause of ICH in young adults, accounting for up to one-third of cases. The term ‘primary’ ICH is often applied to cases caused by cerebral small vessel disease, but it discourages adequate investigation and accurate classification and is not recommended. Deep haemorrhages account for about two-thirds of cases, occur in the internal capsule, basal ganglia or brainstem, and more likely result from deep perforator arteriopathy. About 5–10% of ICH occurs in the cerebellum. The remainder is lobar haemorrhage located in cortico-subcortical areas, often near or reaching the cerebral convexities, of which ~40% are due to arteriosclerosis alone, ~40% to arteriosclerosis and amyloid angiopathy and the remaining ~20% to amyloid angiopathy alone.

There are no medical treatments for acute ICH that have been definitively proven in primary outcome analyses of randomised clinical trials. Patients with ICH are frequently referred for surgery, but the roles of various surgical methods and timing of surgery remain controversial. In this article, we outline a practical approach to the diagnosis and management of acute ICH.

ACUTE EVALUATION
Time is limited; what information do I need to obtain early on?
The approach to an efficient and focused history and physical examination in suspected acute stroke has been outlined in the first article in this series. It is important to obtain a history of any recent trauma, including from a witness if available, and to assess for any circumstantial evidence, making sure to determine...
How to do it

clinically whether the trauma preceded the haemorrhage or vice versa. Acute ischaemic stroke and ICH cannot be reliably distinguished at the bedside but the diagnosis is made rapidly and easily on imaging, so every effort should be made to minimise delays to the initial CT brain scan. Crucial information specific to the management of ICH must be obtained as early as possible after the CT brain scan; table 1 lists the key questions to ask focused on modifiable predictors of outcome.

The National Institutes of Health Stroke Scale (NIHSS) used for ischaemic stroke is also valuable in ICH, but its utility may be limited by the more frequent occurrence of depressed consciousness in ICH.21 The Glasgow Coma Scale (GCS) score is the most useful initial evaluation because of its similar prognostic value to NIHSS, its simplicity and its incorporation in the ICH score (figure 1 outlines its calculation). However, as in ischaemic stroke, aphasia can reduce the verbal subdomain score, and thus cause underestimation of the GCS.

What baseline tests should I perform?
For all the complexity and uncertainty in ICH management, the initial diagnosis of acute blood in the brain substance is straightforward. Non-contrast brain CT (figure 2) is rapid, highly sensitive and specific for all forms of ICH, and widely available, so is considered the reference standard for ICH diagnosis.21 26 27

The CT scan should be assessed for ICH location, brain changes consistent with small vessel disease (atrophy, leukoaraiosis (figure 2) and lacunes), the presence and degree of mass effect or midline shift, hydrocephalus, intraventricular extension and the size of the haematoma. Haematoma volume independently predicts haematoma expansion and early mortality11 28 and can be estimated rapidly and accurately on CT with the ABC/2 formula, as shown in figure 1. A blood-fluid level is highly specific for coagulopathy or the use of anticoagulants and should prompt a search for these factors if not already established.29 MR is as sensitive as CT in the hyperacute diagnosis of ICH26 30 but it rarely provides more information in the acute stage; the longer scan duration and delays obtaining MR for often critically ill patients make CT a preferred choice.

Blood tests including coagulation studies, glucose, cardiac-specific troponin and a toxicology screen should be performed. Point-of-care INR testing should be implemented to avoid delays in anticoagulation reversal for patients taking warfarin.31 ECG abnormalities are common, but concomitant myocardial injury should not be overlooked.12

Do I need to request further imaging?
Early diagnosis of macrovascular causes of ICH allows timely starting of specific treatment and refines the prognosis. The decision whether to pursue further imaging has often been made based on assumptions guided

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Important information to obtain as soon as possible after ICH to guide prognostication and management</th>
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<tbody>
<tr>
<td>Is the patient taking anticoagulation or antiplatelet medications?</td>
<td>Anticoagulant and antiplatelet use are independent predictors of haematoma expansion11 and death.12</td>
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<td>Further details of antithrombotic treatment: what agent, what dose and when was the most recent dose (or the most recent International Normalised Ratio(INR) for warfarin)?</td>
<td>This is relevant to establish if anticoagulation reversal is needed, and if so, the type and dose of reversal agent to be used.</td>
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<td>What was the time of onset of symptoms?</td>
<td>This is obviously crucial to determine in all stroke presentations, but is relevant in ICH as the time from symptom onset to baseline imaging relates inversely to the risk of haematoma expansion11 and determines whether to pursue acute blood pressure lowering. Most expansion occurs in the first few hours after ICH.11 It is also important to establish whether the imaging appearances are consistent with the time of onset; a haematoma may appear isodense with brain tissue as early as five days after the onset, so the diagnosis may be missed if CT imaging is delayed.</td>
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<tr>
<td>Is the patient’s blood pressure elevated (systolic blood pressure &gt;150 mm Hg)?</td>
<td>Blood pressure is frequently very high in the acute phase.14 Elevated systolic blood pressure is associated with further neurological deterioration and mortality15 16 and early treatment may be beneficial, although there is much uncertainty about this.</td>
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<td>Has ICH been distinguished from haemorrhagic transformation of ischaemic stroke?</td>
<td>ICH cannot always be definitely distinguished from haemorrhagic transformation of infarction on imaging.15 Features suggesting haemorrhagic transformation include a patchy rather than uniform appearance of the haematoma, hypodensity surrounding the haematoma that may reach the cortex in a wedge shape, and evidence of an occluded vessel visible in the same arterial territory.</td>
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<td>Are there imaging or clinical signs of intraventricular extension of haemorrhage and hydrocephalus?</td>
<td>Intraventricular extension of haematoma and raised intracranial pressure (ICP) from hydrocephalus each predict higher mortality and poor functional outcome18 and require urgent consideration for surgical management (external ventricular drain insertion).</td>
</tr>
<tr>
<td>Are there imaging or clinical signs of mass effect and increased ICP?</td>
<td>Blood pressure targets may require revision if there are signs of elevated ICP, and hyperosmolar agents and ICP management may be indicated.19 20</td>
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ICH, intracerebral haemorrhage.
by patient risk factors, but these are not a reliable way to exclude a potential macrovascular cause in all cases, and clinical practice varies widely.\textsuperscript{33}

CT angiography (CTA) should be performed acutely in all patients, preferably within 2 days of the non-contrast brain CT,\textsuperscript{34} except those definitely at low risk of having an underlying macrovascular cause (figure 3). Imaging predictors of haematoma expansion on CTA such as the ‘spot sign’ (foci of contrast extravasation within the haematoma) may also add prognostic value.\textsuperscript{11, 35} If CTA is negative for structural vascular abnormalities, MR/MR angiography should be considered as soon as possible as it has additional diagnostic yield.\textsuperscript{34} Digital subtraction angiography is then warranted in patients at high risk of an underlying macrovascular cause after negative CTA (and negative MR, if performed).\textsuperscript{34} There is an appreciable yield of repeat digital subtraction angiography performed a few weeks later, especially in lobar ICH,\textsuperscript{36} so persistence is often required.

Beyond the acute phase, MR (including blood-sensitive sequences to detect cerebral microbleeds and cortical superficial siderosis) provides important additional information about the underlying cerebral small vessel disease.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Upper panel: Calculation of the intracerebral haemorrhage score, a clinical grading scale and a useful communication tool. Predicted 30-day case-fatality rates are derived from the original validation study\textsuperscript{22}; *a subsequent study in which early do-not-resuscitate orders were not placed observed 30\% lower mortality rates.\textsuperscript{23} Lower panel: The use of the ABC/2 calculation (essentially the formula for the volume of an ellipsoid) to rapidly and accurately\textsuperscript{24, 25} estimate the volume of an acute left-sided ganglio-capsular haemorrhage on non-contrast CT brain scan. (Copyright Iain McGurgan).}
\end{figure}
Should I pursue intensive treatment?

The focus for the great majority of patients should be on the full provision of high-quality active treatment and supportive care, at least in the first 24–48 hours. Decisions about instituting a ceiling of care should depend on an assessment of prognosis, but this is difficult to determine acutely. There are multiple dedicated ICH prognostic grading scales, the most widely used being the ICH score, which has acceptable discrimination for functional outcome measured by the modified Rankin score at up to 12 months (figure 1). Such scales should not be used, however, as the sole means to gauge prognosis or guide the withdrawal of supportive treatment.

Like other conditions with high rates of poor outcomes and a perceived lack of effective treatments, ICH is vulnerable to therapeutic nihilism. Early ceilings of care and a focus on comfort measures are more likely to be pursued acutely in ICH than in ischaemic stroke, independent of neurological deterioration and co-morbidities, and are associated with poorer outcome. While timely do-not-resuscitate orders are important considerations in stroke management, these should not influence other aspects of care. In practice, however, do-not-resuscitate orders in ICH often herald less active supportive care, so clinicians should be cautious when considering early do-not-resuscitate orders.

ACUTE MANAGEMENT

How do I approach the management of ICH?

ICH is a neurological emergency. The presence of expanding haematoma and vasogenic oedema inside the fixed volume of the cranial vault can lead to a precipitous increase in intracranial pressure (ICP) and fatal brain herniation syndromes. The principle of ‘time is brain’ also firmly applies to ICH; haematoma expansion occurs very early and independently predicts a poor outcome. The rapid delivery of a care bundle incorporating anticoagulation reversal, intensive blood pressure management and neurosurgery/critical care if required has been associated with a substantial improvement in 30-day case-fatality rates.

The overarching goals of acute management are to stabilise the patient to ensure they survive the initial insult, and to prevent secondary brain injury (figure 4). Patients with ICH may require immediate intensive care unit admission. Otherwise, all patients should be admitted to an acute stroke unit as soon as possible; the benefit is at least as great for patients with ICH as it is for those with ischaemic stroke. The general principles of acute care are the same as those for acute ischaemic stroke, as outlined in the first article in this series. Secondary prevention measures, cerebral small vessel disease and decisions regarding restarting antithrombotic therapy will be addressed in subsequent articles.

Management of the complications of ICH is a key focus of acute care. Raised ICP can result from the mass effect of the bleed or peri-haematomal oedema or from hydrocephalus. Although there is a lack of evidence to guide its management in ICH, measures used for raised ICP in other settings may help. These include raising the head of the bed to 30° (although without supportive evidence in acute stroke), mild sedation, analgesia and mannitol (or hypertonic saline, depending on cardiac and renal comorbidities). Intensive ICP monitoring is recommended in those with a GCS<9, evidence of herniation or hydrocephalus. Corticosteroids are possibly associated with more harm than benefit when used for lowering ICP in ICH, so should not be used. Early-onset seizures are not uncommon, occurring in one in seven patients, with most occurring at or near the onset. Clinical seizures should be managed with antiseizure medications, but prophylactic treatment should not be offered routinely. Cortical involvement, age younger than 65 years, volume greater than 10 mL and early seizures within 7 days of ICH identify patients at higher risk of subsequent late seizure development.

If the patient takes anticoagulant treatment, how do I reverse it?

Anticoagulation-associated ICH accounts for nearly 20% of all cases. The haemorrhage in this setting is of larger volume, is more likely to exhibit...
haematoma expansion and is associated with higher morbidity and mortality compared with ICH not associated with anticoagulation. Stopping antithrombotic therapy and reversing anticoagulation immediately after the diagnosis of ICH is, therefore, crucial. Although ICH risk associated with the use of direct oral anticoagulants (DOACs) was around half that of warfarin in randomised trials, a previous lack of specific reversal agents for DOACs prompted concerns that DOAC-associated ICH may be associated with poorer outcomes. In fact, the prognosis of ICH associated with DOACs is likely better or at least no worse than that of warfarin, and the availability of approved specific reversal agents for DOACs has improved. Table 2 provides a guide to the reversal of anticoagulation.

Poorer outcomes are also seen for ICH associated with antiplatelet therapy, but platelet transfusions increase rather than decrease morbidity and mortality in this group, and therefore should not be used.

Patients with ICH in the context of coagulation factor deficiencies or thrombocytopenia should undergo replacement, with input from a haematologist. Several trials have assessed the efficacy of coagulation factors more generally in the management of acute ICH but found that the risk of thromboembolic complications outweighed the benefits. A trial of early administration of factor VIIa in an identified subgroup of patients most likely to benefit, however, has been approved (FASTEST, NCT03496883). Antifibrinolytic drugs, on the other hand, have
proven promising. A large trial of intravenous tranexamic acid (TICH-2) showed a significant reduction in haematoma growth and early mortality, but there was no overall benefit for the primary outcome of later functional recovery, and it is thus not recommended as part of current care. A further study focusing on effects on early mortality and targeting earlier treatment is planned, and an ongoing trial is evaluating tranexamic acid in hyperacute presentations of ICH including mobile units (STOP-MSU, NCT03385928). Randomised evidence on associations of tranexamic acid in anticoagulation-associated ICH is lacking, although a trial in DOAC-associated ICH is currently underway (TICH-NOAC, NCT02866838).

**Do I need to lower the patient’s blood pressure, and if so, by how much?**

Observational data suggest that blood pressure is very high in the acute phase after ICH, significantly higher than that after ischaemic stroke. High blood pressure in acute ICH is associated with haematoma expansion and poor clinical outcome. There have been concerns for many years that high blood pressure may be necessary to ensure adequate cerebral perfusion after ICH, and that aggressively treating it may cause harm. Such concerns have been assuaged by evidence that suggests that adequate cerebral blood flow is maintained after acute blood pressure reduction in ICH. However, results of the two largest trials of intensive blood pressure lowering early after ICH have
Table 2: Strategies and rationale for anticoagulation reversal in acute ICH

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Reversal strategy</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Warfarin</td>
<td>(1) Stop warfarin immediately and check the INR, but don’t wait for the result to act in life-threatening bleeds.</td>
<td>Prothrombin complex concentrate is superior to fresh frozen plasma in normalising the INR for warfarin-associated ICH.</td>
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<td></td>
<td>(2) Vitamin K 10 mg intravenous infusion (slow-acting), monitor for anaphylaxis.</td>
<td>Vitamin K administration, in addition, may help to prevent a later re-increase in INR.</td>
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<td>(3) Four-factor prothrombin complex concentrate with INR-based dosing.</td>
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<tr>
<td></td>
<td>(4) Repeat INR every 3–6 hours; the optimal target is uncertain, but aim for normalisation of the INR (&lt;1.3).</td>
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<tr>
<td>Dabigatran</td>
<td>(1) Stop dabigatran immediately, check thrombin time, activated partial thromboplastin time.</td>
<td>Idarucizumab, a humanised monoclonal antibody fragment, rapidly and safely reverses dabigatran anticoagulation.</td>
</tr>
<tr>
<td></td>
<td>(2) Consider oral-activated charcoal (50 g) if last intake is &lt;4 hours and safe to administer to the patient.</td>
<td></td>
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<tr>
<td></td>
<td>(3) Idarucizumab 2×2.5 g boluses intravenously if recent ingestion or prolonged laboratory clotting times (not recommended if the thrombin time is within the normal range).</td>
<td></td>
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<tr>
<td>Factor Xa inhibitors</td>
<td>(1) Stop the agent immediately, check prothrombin time, anti-factor Xa activity.</td>
<td>Andexanet alpha, a recombinant inactive factor Xa ‘decoy’, rapidly and effectively reduces anti-factor Xa activity.</td>
</tr>
<tr>
<td>(apixaban, rivaroxaban,</td>
<td>(2) Consider oral-activated charcoal (50 g) if last intake is &lt;4 hours and safe to administer to the patient.</td>
<td></td>
</tr>
<tr>
<td>edoxaban and betrixaban)</td>
<td>(3) Andexanet alpha intravenous bolus and infusion, dosing dependent on the dose and last dose timing of the factor Xa inhibitor.</td>
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</tr>
<tr>
<td></td>
<td>(4) Most centres have protocols prescribing the use of andexanet alpha; prothrombin complex concentrate is still more often used in practice.</td>
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</tr>
<tr>
<td>Heparin</td>
<td>(1) Stop heparin infusion/low-molecular-weight heparin (LMWH) immediately, check activated partial thromboplastin time.</td>
<td>Protamine sulphate fully reverses the effect of unfractionated heparin but only partly neutralises the effect of LMWH; the same dosing strategy can be used, but the longer half-life of LMWH may require cautious repeat infusions.</td>
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<td></td>
<td>(2) Protamine sulphate slow intravenous infusion, 1 mg per 100 units of heparin, if activated partial thromboplastin time is prolonged or heparin was administered within the previous 2 hours.</td>
<td>Further evidence is needed to establish the role of andexanet alpha in the management of LMWH-associated ICH; trials are ongoing.</td>
</tr>
<tr>
<td></td>
<td>(3) Max dose 50 mg, monitor for anaphylaxis.</td>
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ICH, intracerebral haemorrhage.

renewed uncertainty. Meta-analyses of these trials and other smaller studies showed that early intensive blood pressure lowering was safe, but without functional or mortality benefit. In contrast, a linear association between systolic blood pressure achieved in the first 24 hours and functional status was found in a recent individual participant data meta-analysis of the two largest trials, with improvements in functional recovery seen for blood pressure as low as 120–130 mm Hg. These trials excluded patients with large and severe haematomas, however, so caution must be exercised when treating such patients, especially where large reductions in very hypertensive patients might predispose to harm. Table 3 provides some practical advice for blood pressure management in acute ICH, based on existing guidelines. It should be noted that, in light of the uncertainty described above, future research might conclude that there is no benefit from acute intensive blood pressure lowering.

Which patients should I refer for neurosurgery?
The rationale for clot removal surgery is to reduce direct and secondary brain injury (figure 4). The location of ICH has a large bearing on decision-making. Neurosurgical intervention is generally recommended for infratentorial bleeding despite a lack of randomised evidence, given the high risk of brainstem compression and herniation syndromes in the confined space of the posterior fossa. Clinical guidelines recommend posterior fossa decompressive evacuation for cerebellar ICH>3 cm in diameter, or for smaller haematomas associated with brainstem compression or hydrocephalus from ventricular obstruction. This recommendation is based on observational evidence that haematoma evacuation is associated with decreased mortality, but there is no evidence for improvements in functional outcome. Management of hydrocephalus by external ventricular drainage alone is not recommended in this setting and may be harmful, especially if the basal cisterns are compressed. The lack of clinical equipoise probably precludes the design of any future randomised trials to address the question of surgical vs conservative management. Equipoise exists in bounds, however, where supratentorial haemorrhage is concerned.
randomised controlled trials have addressed surgical evacuation of supratentorial ICH, with all of the larger trials and meta-analyses returning neutral results on the primary outcomes. As a result, best medical management is usually pursued, but trials were complicated by high crossover rates, and there appear to be subgroups of patients who might benefit from surgical intervention. Patients with a GCS at presentation of 10–13, that is, not at either extreme of arousal, those with large ICH and those with superficial bleeds may experience improved outcomes.

Multiple surgical techniques have been investigated for different indications; table 4 provides a summary of the evidence for each. Developments in minimally invasive surgery for patients with supratentorial ICH are promising. The only large trial of catheter evacuation followed by irrigation with alteplase (MISTIE III) found no clear benefit but noted that the procedure was safe. There was, however, evidence of functional improvement in patients meeting the surgical goal of reducing haematoma size to <15 mL. The ongoing ENRICH trial (NCT02880878) is investigating a novel minimally invasive technique involving a small-directed craniotomy and image-guided trans-sulcal evacuation and is one of several currently enrolling trials, some with an earlier time window for surgery (Dutch ICH Surgery Trial, NCT03608423; MIND, NCT03342664; INVEST, NCT02654015).

Optimal timing of surgical intervention remains controversial due to the risk of re-bleeding, although reducing haematoma volume early may reduce secondary brain injury and could improve outcome.
FUTURE DIRECTIONS
The management of ICH has not paralleled the dramatic advances in acute ischaemic stroke therapeutics driven by many large randomised controlled trials. Clinical trials in ICH face unique challenges; a less common and more severe on average condition with poorly understood pathophysiology results in a sizeable proportion of patients being ineligible. Aspiring to recruit every ICH survivor to at least one trial is the only way to resolve uncertainties and improve outcome. Fortunately, we have much about which to be optimistic. There are currently over 60 active (or soon-to-be recruiting) ICH trials, many focused on the possible interventions of haemostatic agents and surgical techniques, where much uncertainty persists.

CONCLUSION
ICH has the worst outcomes of all stroke subtypes, but increased research interest in recent years has led to significant advances in its diagnosis and management. The focus of existing treatment is the prevention of haematoma expansion, and progress in supportive care, blood pressure control and anticoagulation reversal has been rewarded with improved outcome. The role of neurosurgery is still unclear but the field is rapidly evolving, with minimally invasive techniques showing promise in selected groups, even in the context of neutral trials so far.

Key points
► Intracerebral haemorrhage is a medical emergency; its rapid diagnosis, investigation and treatment should prevent further brain injury and improve outcome.
► Although 30-day case fatality is ~40%, full supportive care should be considered for at least the first 24–48 hours, as prognostication can be difficult.
► Hyper-acute interventions such as anticoagulation reversal, blood pressure lowering and neurosurgery may improve recovery, but many uncertainties remain.
► Clinical trials based on pathophysiological knowledge and embedded in routine clinical practice are the main hope for its better management.

FURTHER READING

Correction notice This article has been corrected since it appeared Online First. Text has been corrected from thrombocytopenia to thrombocytopenia

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