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RESEARCH AGENDA

The research agenda for trauma critical care

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Abstract

In this research agenda on the acute and critical care management of trauma patients, we concentrate on the major factors leading to death, namely haemorrhage and traumatic brain injury (TBI). In haemostasis biology, the results of randomised controlled trials have led to the therapeutic focus moving away from the augmentation of coagulation factors (such as recombinant factor VIIa) and towards fibrinogen supplementation and administration of antifibrinolytics such as tranexamic acid. Novel diagnostic techniques need to be evaluated to determine whether an individualised precision approach is superior to current empirical practice. The timing and efficacy of platelet transfusions remain in question, while new blood products need to be developed and evaluated, including whole blood variants, lyophilised products and novel red cell storage modalities. The current cornerstones of TBI management are intracranial pressure control, maintenance of cerebral perfusion pressure and avoidance of secondary insults (such as hypotension, hypoxaemia, hyperglycaemia and pyrexia). Therapeutic hypothermia and decompressive craniectomy are controversial therapies. Further research into these strategies should focus on identifying which subgroups of patients may benefit from these interventions. Prediction of the long-term outcome early after TBI remains challenging. Early magnetic resonance imaging has recently been evaluated for predicting the long-term outcome in mild and severe TBI. Novel biomarkers may also help in outcome prediction and may predict chronic neurological symptoms. For trauma in general, rehabilitation is complex and multidimensional, and the optimal timing for commencement of rehabilitation needs investigation. We propose priority areas for clinical trials in the next 10 years.

Keywords: Haemorrhage, Trauma, Shock, Traumatic brain injury, Coagulopathy, Intracranial hypertension

Introduction

Major injury is the leading cause of death in patients under 35 years of age. Head injury is the first cause of severe disability, whereas haemorrhage remains the leading preventable cause of death. The epidemiology is changing; injuries in the elderly are increasing in high-income countries, whereas the burden of severe trauma from road traffic is increasing in low- and middle-income countries.

The care for trauma patients has changed dramatically in the past decade. Research progress in trauma care has improved recently with increased understanding of the acute response to injury and the development of clinical trial networks. To develop this research agenda for the future, we gathered an international group of experts to produce an expert consensus for the two principal causes of death and disability, haemorrhage and traumatic brain injury (TBI). These experts gave their individual

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responses and these were then collated into a coherent approach to future trauma care. We have structured the agenda along the pathway of clinical priorities, considering haemorrhage first, then imaging and immediate management of traumatic brain injury, followed by aspects of general and neurocritical care.

This article aims to describe recent improvements as well as controversies in the care of trauma and TBI patients. Considering the low level of evidence of many procedures or treatments for the care of trauma patients with or without TBI, we have highlighted the results of currently available randomised controlled trials (RCTs). We provide a glossary of abbreviations in supplemental Table 1 (eTable 1).

What is the current standard of care for delivering the best possible trauma critical care?

Statements are supported by RCTs [24], observational and interventional (non RCT) studies [1, 2, 7, 8, 10–13, 15, 18], reviews [6, 9, 14, 16, 17, 19, 21, 23] and/or international recommendations [3–5, 20–22].

Trauma system developments and organization (Fig. 1) are crucial aspects of care to avoid suboptimal treatment, which is a major cause of preventable deaths within the first hours after trauma.

Overall application of the principles of damage control resuscitation (DCR) including damage control surgery (DCS) to bleeding trauma patients has resulted in substantial improvements in mortality over the past decade [1, 2], associated with improvements in critical care complications and critical care resource utilisation. Contemporary evidence-based guidelines for trauma care have recently been produced or updated [3–5]. Figure 2 gives an overview of the standard of care for trauma patients.

Prehospital care

Contemporary trauma care starts in the immediate post-injury period and considers prehospital and inhospital care as a continuum. Suboptimal care in the prehospital phase may alter outcome in the subsequent disease course, and prehospital practitioners as well as major trauma centres have considerably contributed to the recent and ongoing improvements in outcomes [6]. There are different actors that are crucially involved in the prehospital care (e.g. basic response services, mobile medical

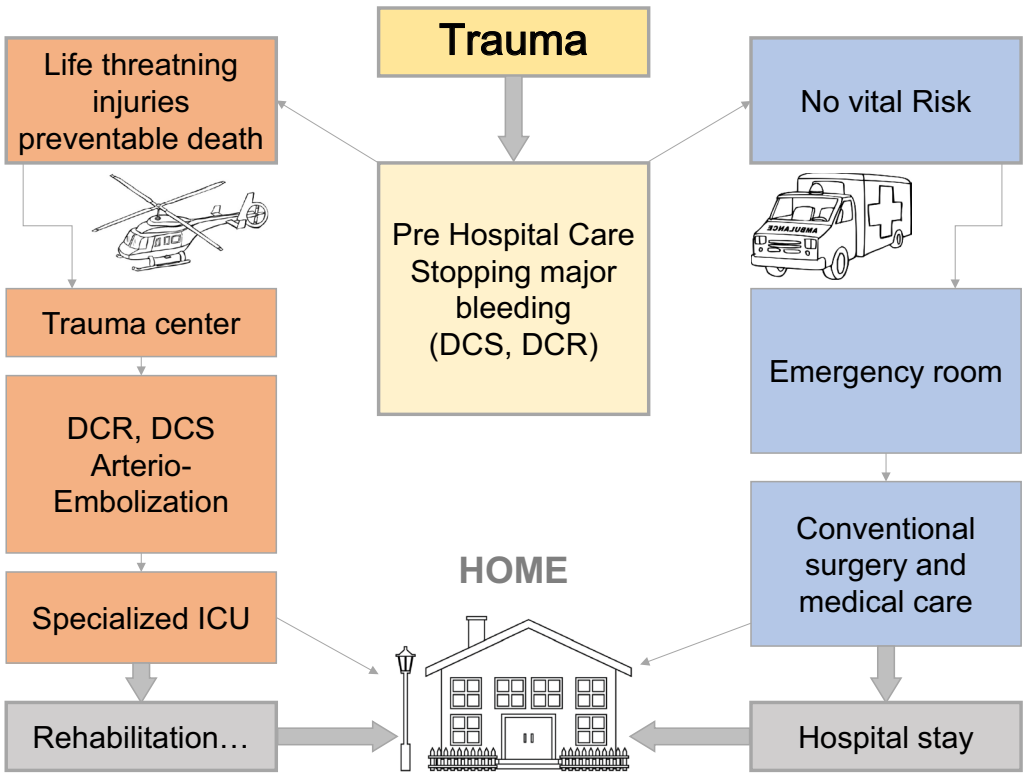

Fig. 1 Current trauma system and organization in Western Europe. A trauma system is a chain of sequential specific procedures to provide quality response from the scene to the appropriate hospital. A central coordination with ongoing quality controls is warranted. Doing so will provide a network of trauma centres that can be mobilized in case of multicasualty events. *DCR* damage control resuscitation, *DCS* damage control surgery

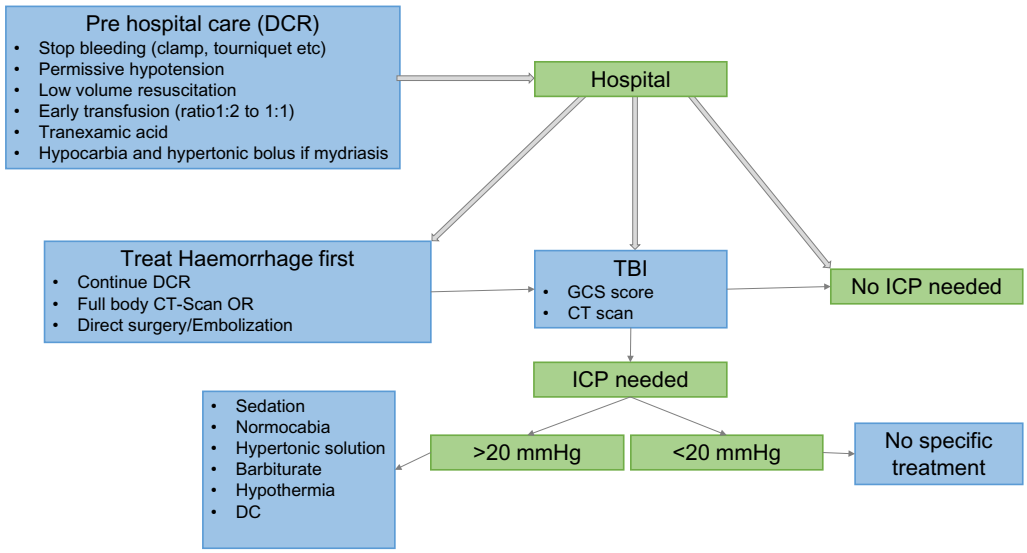

Fig. 2 Standard of care of severe trauma patients. DCR is a systematic approach involving haemostatic resuscitation permissive hypotension (when appropriate) and damage control surgery (DCS). DCS prioritizes short-term physiological recovery (abbreviated operations) over anatomical reconstruction; definitive operations are deferred. The aim of this global strategy is a rapid transfer to ICU for correction of acidosis, hypothermia and coagulopathy.*TBI* traumatic brain injury, *DCR* damage control resuscitation, *DCS* damage control surgery

teams, helicopter emergency medical services and dispatching teams). Together, they form an essential bridge to definitive care and prehospital care must be optimized while minimising prehospital times.

Principles of contemporary management of trauma patients: DCR strategy

Achieving early haemorrhage control is a multifaceted process that includes an expert-led team-based approach to the initial assessment of the patient, permissive hypotension, early use of restricted volume replacement strategy, for transfusion, plasma-to-RBC ratio of at least 1:2 as needed, early use of tranexamic acid.

(a) *Triage* As many haemorrhagic deaths occur within the first 2–4 h after injury, identification of the bleeding patient and directing investigations and interventions only to those that will affect outcome are of paramount importance [7, 8].
(b) *Temporary haemorrhage control* Use of temporary haemostatic measures, and DCR that is tailored to the patient's physiologic status. In recent years, the importance of temporary haemorrhage control has been emphasised including the use of pelvic binders and the use of tourniquets for compressible haemorrhage [9].
(c) *Massive transfusion* Early administration of blood products in a balanced ratio which is close to reconstituted whole blood has become the standard of care [4] despite the lack of clear evidence.
(d) *Permissive hypotension* Permissive hypotension has become the accepted approach to management of blood pressure when patients are actively bleeding [4]. Permissive hypotension reduces haemorrhage from bleeding sites and supports a resuscitation regimen that avoids dilution. The overall outcome improvements seen with its incorporation into DCR practice are compelling [10] even if, in the initial phase following trauma with severe TBI, hypotension should be avoided [4]. The approach also excludes the use of vasopressors in hypovolemic trauma patients.
(e) *Avoiding fluids and dilutional coagulopathy* The DCR approach aims to maintain the haemostatic competence of blood throughout the bleeding process. Practice has moved to eliminating crystalloid (and artificial colloid) infusions and to replace volume with a balanced transfusion of red cells and plasma [3–5]. In addition, the physiologic milieu to support coagulation must be maintained throughout; for example, in a retrospective study, hypocalcaemia was suggested to alter outcome [11]. Standard of care therefore includes having a major haemorrhage protocol that is activated early and consistently delivers this balanced transfusion regimen to the bleeding trauma patient until haemorrhage control is achieved [12, 13].
(f) *Treating established coagulopathy* Trauma patients develop a mixed coagulopathy with several different endogenous and resuscitation-induced components

[14, 15]. Empiric tranexamic acid to treat fibrinolysis in these patients is now considered a standard of care [4].

(g) *Definitive haemorrhage control* After transfer to the trauma centre, if the patient's haemodynamics are stable, the patient will undergo CT scan; otherwise surgery or arterial embolization will be performed for fast and definitive haemorrhage control. As DCR has protected the body's haemostatic potential, overall the need for DCS has also decreased and definitive surgery can be utilized more often [16]. Interventional radiology techniques for haemorrhage control have also become part of the damage control surgery armamentarium [17].

Although DCR has led to a reduction in the severity and complexity of organ failure and sepsis [18], trauma remains a significant cause of mortality, morbidity and consumes significant healthcare resources [19].

Principles of contemporary TBI management

The recently revised guidelines (2016) aimed to summarize the evidence available for neuromonitoring and treatment strategies [20]. Adhering to the principles of these guidelines has been associated with improvements in outcomes [21]. In severe TBI patients, most clinical decisions will be driven by clinical exam, neuroradiology and neuromonitoring (principally of intracranial pressure—ICP) [22]. The main causes of elevated ICP and the three different stages of treatment for TBI are presented in Fig. 3a, b, respectively.

(a) *Rapid detection and treatment of intracranial injury with CT scan* Widespread CT scan with explicit guidelines for early imaging have improved the accuracy and timeliness of diagnosis.

(b) *Centralization to specialist neurosurgical and neurocritical care centres* Rapid access to a specialist centre for early, definitive, neurosurgical opinion, neurosurgery and neurocritical care as required.

(c) *Avoid secondary insults* Early and aggressive management of hypoxia and hypotension which are associated with worse outcomes [23]. Improvements seen in neurocritical care in the last decade have been principally attributed to standardization of care to prevent and minimise secondary injury.

(d) *Maintenance of cerebral perfusion* ICP and cerebral perfusion pressure (CPP) monitoring is recommended in all patients who are at risk of elevated ICP based on clinical and/or imaging features to reduce mortality [20, 22]. Controlling ICP and CPP within a target range, commonly ICP less than 20 mmHg and CPP 60–70 mmHg. The interventions (see Fig. 3b) used for reaching these goals include sedation, CSF withdrawal, and hyperosmotic infusions to reduce brain oedema. "Second-tier therapies" such as hyperventilation, and high dose sedatives, are reserved only for patients with refractory high ICP as these interventions are not without risk; decompressive craniectomy (life-saving therapy) is considered when other options have failed [24].

What have been the major recent advances and remaining areas of uncertainty in management and treatment?

Statements are supported by RCTs [27, 31–35, 40, 42–45, 51–53], observational and interventional (non RCT) studies [26, 28, 30, 38, 47–50, 54, 56, 58–63], reviews [29, 36, 37, 39, 46, 55, 57] and/or international recommendations [25, 41].

The epidemiology of when, why or how trauma patients die is yet to be fully described. Some patients recover rapidly without sequelae, whereas others have a prolonged clinical course complicated by repeated infections, leaving them with life-long health impairments. Understanding how early interventions relate to mortality and outcomes other than early death will require large coordinated research studies to identify the detail and to define the research questions for the future. Also, general patterns of care applied to other populations of ICU patients (protective ventilation, corticosteroids, etc.) have been recently evaluated in the setting of trauma patients. The principal advances in the field that are described in this section (Table 1) were based, mainly, on RCTs (Table 2).

DCR and haemostasis management

DCR

In the prehospital arena, there is new focus on how the injured can be kept alive and physiology maintained until haemorrhage control and definitive intervention can be achieved, especially when prehospital times may be long. This paradigm is captured in the military concept of 'prolonged field care' and aims to mitigate the consequences of severe haemorrhage, ischaemia and coagulopathy before they become irreversible. For that purpose, a strategy of remote DCR is applied. Surgical options involve traction for closed extremity injuries, extremity tourniquets, stabilization of pelvis with specific devices, gauze packing etc., whereas conventional DCR is applied [9].

The dramatic shift in the principles and conduct of DCR has been based on, and subsequently led to, the overturning of many previously deeply held tenets of trauma management. The list is very long but includes a move away from such basic principles as 'Airway, Breathing, Circulation' (to place control of rapid exsanguination first); and away from resuscitation to normal blood

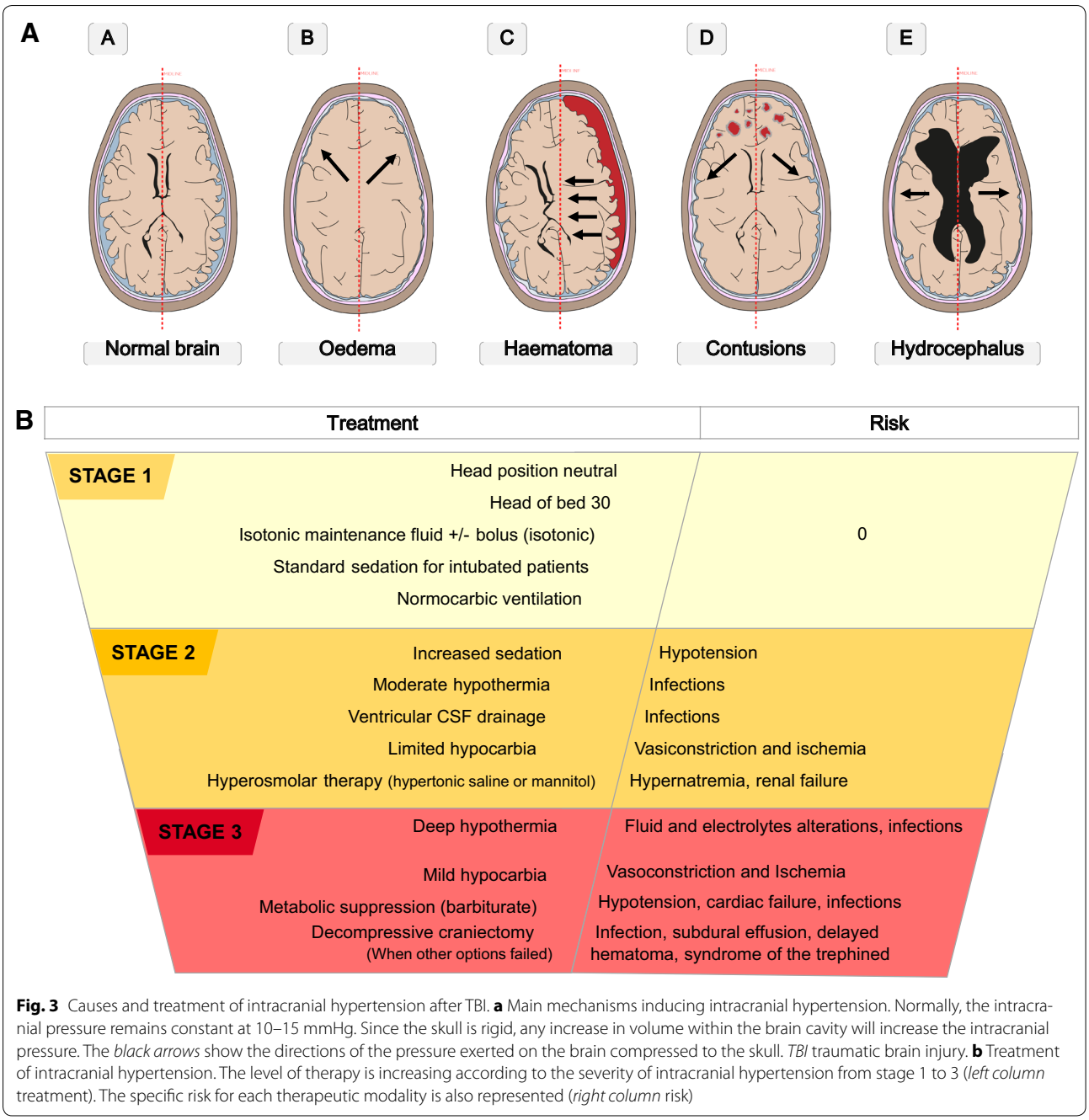

Fig. 3 Causes and treatment of intracranial hypertension after TBI. **a** Main mechanisms inducing intracranial hypertension. Normally, the intracranial pressure remains constant at 10–15 mmHg. Since the skull is rigid, any increase in volume within the brain cavity will increase the intracranial pressure. The *black arrows* show the directions of the pressure exerted on the brain compressed to the skull. *TBI* traumatic brain injury. **b** Treatment of intracranial hypertension. The level of therapy is increasing according to the severity of intracranial hypertension from stage 1 to 3 (*left column* treatment). The specific risk for each therapeutic modality is also represented (*right column* risk)

pressure with crystalloid or colloid solutions to major haemorrhage protocols focusing on protection of haemostasis and balanced blood transfusion.

The role of permissive hypotension needs further study, especially in relation to its role in patients with concomitant TBI for which hypotension should be avoided [4], when there are prolonged transport times and in the context of modern non-crystalloid-based resuscitation [25].

Innovation in the field of novel devices for temporary and definitive bleeding control is progressing rapidly. Evaluation of device efficacy is required although this can

Table 1 Recent major advances in management

Early fibrinogen supplementation and closer monitoring of fibrinogen levels decrease the risk of massive transfusion during severe haemorrhage
Early administration of plasma, platelets and red blood cells in a 1:1:1 ratio may help achieve haemostasis in trauma patients with major bleeding
Tranexamic acid reduces the risk of death in bleeding trauma patients
Decompressive craniectomy for treating refractory intracranial hypertension reduces mortality despite uncertainties regarding neurological outcome
Monitoring the cumulative burden of ICP per patient could be a predictor of mortality at 6 months
Strategies incorporating brain tissue oxygenation ($PbtO_2$) together with standard ICP and CPP management may improve outcomes
Lung care including specific empirical antibiotic treatment of pneumonia and bundles (protective mechanical ventilation, prompt extubation readiness) may improve outcome of TBI patients

be challenging as new generations of devices are continuously being developed. This includes the role of resuscitative balloon occlusion of the aorta, and whether it can replace emergency thoracotomy in some trauma cases [9]. Developing organ protective approaches should also focus on methods to reduce endothelial dysfunction which may lead to reduced resuscitation requirements, reduced tissue oedema and improved organ function after haemorrhage resuscitation. Further developments will include how coronary perfusion can be maintained and the heart protected from the effects of ischaemia and reperfusion, such as with deep hypothermia or early ventricular assist devices.

Haemostasis management

In haemostasis biology, the importance of early loss of fibrinogen is leading to research into the potential for early fibrinogen supplementation and closer monitoring of fibrinogen levels during haemorrhage [26]. The monocentre RETIC RCT, published this year, suggests a role for early fibrinogen use in severe multiple trauma patients [27]. The recent multicentre randomised PROPPR study showed that plasma or platelets in a 1:1:1 vs a 1:1:2 ratio with red blood cells decreased the early mortality rate compared to lower doses of these products [28]. The potential to personalise the approach to coagulopathy management has led to renewed interest in thromboelastometry as a point-of-care test to diagnose and guide management in a therapeutically relevant time frame [29]. These research areas have already led to translational studies and are beginning to be investigated in clinical trials large enough to determine clinical efficacy.

The mechanisms of coagulopathy are now seen to involve a complex interplay between dysregulated coagulation, fibrinolysis and endothelial dysfunction [30]. Results of RCTs have led to therapeutic focus moving away from the augmentation of coagulation factors (e.g. via compounds such as recombinant factor VIIa—CONTROL) [31] and towards a new focus on fibrinogen supplementation (e.g. CRYOSTAT) [32] and antifibrinolytics such as tranexamic acid (CRASH-2) [33]. In parallel we have recognised the negative effects of dilutional resuscitation and moved to delivering an empiric background resuscitation and plasma-based resuscitation aiming for an equal number of plasma and platelet units for each red cell unit delivered (PROPPR) [34]. Studies are now looking at the possibilities for individualised management of coagulopathy with point-of-care diagnostics [35].

Uncertainties

For trauma-induced coagulopathy, the specific phenotypes and underlying patterns of coagulation with their mechanisms still need to be elucidated [3]. Tranexamic acid is currently delivered empirically to bleeding trauma patients to reduce hyperfibrinolysis (CRASH-2 study, Table 2). It has been suggested that tranexamic acid should only be given in the presence of thromboelastometry evidence of hyperfibrinolysis [36]. However, the thromboelastometry devices used in trauma do not yet have sufficient evidence in terms of which treatment thresholds should be used, and whether precision strategies will lead to better outcomes. A much deeper understanding of the pathophysiology of acute traumatic coagulopathy in the acute response to injury is also required [37]. In the interim, studies comparing empiric therapy with targeted coagulopathy treatment are required, including the role of thromboelastometry and empiric versus guided use of tranexamic acid. Although the evidence for balanced plasma transfusions is unlikely to be improved upon in coming years, the timing and efficacy of platelet transfusions remain in question [34]. Comparison of strategies employing blood component therapy versus those using factor concentrates will also address some of the international controversies in this area [27]. Going forward, new blood products should be evaluated for efficacy, including whole blood variants, cold platelets and red cells, lyophilised plasma and engineered products with greater haemostatic or oxygen-delivering capability.

ICP management

Neuromonitoring

Invasive ICP monitoring, often as part of a multimodal approach, has identified the cumulative burden of ICP

Table 2 Data on major recent advances in randomised controlled studies

Title	Intervention	Primary outcome	Results	Conclusion
CONTROL (recombinant factor VIIa (rFVIIa) in trauma haemorrhage) [31]	573 of planned 1502 enrolled. 2 groups: standard of care + (1) placebo or (2) rFVIIa	30-day mortality	Terminated early for futility 30-day mortality Blunt: placebo, 10.7%; rFVIIa, 11.0% Penetrating: placebo, 13.2%; rFVIIa, 18.2%	In unselected bleeding trauma patients rFVIIa does not improve outcomes in trauma patients
CRYOSTAT (early high-dose cryoprecipitate for trauma haemorrhage) [32]	Feasibility study. 43 enrolled, 2 groups: (1) standard of care or (2) standard of care + 2 pools of cryoprecipitate	Ability to receive study cryoprecipitate within 90 min of arrival	89% received cryoprecipitate within 90 min Fibrinogen levels higher after 4 RBC units (2.5 vs 1.7 g/dl)	Cryoprecipitate can be given early and normalises Fg levels in trauma. Trend to improved mortality taken forward into CRYOSTAT2 phase III trial
CRASH (tranexamic acid for trauma haemorrhage) [33]	20,211 parents with suspected haemorrhage enrolled to (1) placebo or (2) tranexamic acid	Mortality at 28 days	Reduced 28-day mortality in tranexamic acid group: 14.5% vs 16.0%	Tranexamic acid improves survival in trauma patients with suspected haemorrhage
PROPPR (pragmatic, randomized optimal platelet and plasma ratios in trauma haemorrhage) [34]	680 patients enrolled 2 groups of empiric treatment with blood product ratios of 1:1:1 vs 1:1:2 FFP/platelets/RBCs	24-h and 30-day all-cause mortality	Trends but no significant difference in mortality at 24 h and 30 days. Death due to exsanguination reduced in 1:1:1 group (9.2% vs 14.0%)	Higher dose empiric transfusion of plasma and platelets likely reduces bleeding deaths in trauma patients
BEST-TRIP trial (trial of intracranial pressure monitoring in traumatic brain injury) [40]	324 patients, 2 groups: (1) management based on ICP monitoring. (2) Management based on imaging-clinical examination	Composite outcome of 21 measures of functional and cognitive status	No difference in the primary outcome ($p = 0.49$). 6-month mortality 39% vs 41%; $p = 0.49$	Care focused in ICP monitoring was not superior to care based on clinical examination and imaging
DECRA study (decompressive craniectomy in diffuse intracranial hypertension) [43]	155 patients with refractory ICHT, group 1: DCT; group 2: standard care	GOS-E at 6 months	Lower GOS-E in the DCT group: OR 1.84; 95% CI 1.05–3.24; $p = 0.03$) No difference in mortality	Decreased ICP and length of stay in ICU but poorer outcome in DCT group
RESCUEicp (trial of decompressive craniectomy for traumatic intracranial hypertension) [24]	408 patient with refractory ICHT, group 1: DCT; group 2: standard care	GOS-E at 6 months	Higher rate of vegetative state (8.5% versus 2.1%), lower mortality in DCT group	Poorer neurological outcome despite higher survival rate in DCT group
EUROTHERM trial (hypothermia for intracranial hypertension after traumatic brain injury) [42]	387 patients ICHT despite first-tier therapy, group 1: hypothermia; group 2: standard care	GOS-E at 6 months	Study stopped for safety concerns. Worse outcome in the hypothermia group, OR 1.53 (95% CI 1.02–2.30; $p = 0.04$)	No improvement of neurological outcome with hypothermia

FFP fresh frozen plasma, *RBC* red blood cells, *ICHT* intracranial hypertension, *DCT* decompressive craniectomy, *GOS-E* glasgow outcome scale-extended

per patient (a combination of intensity and time spent over a threshold) as a predictor of mortality at 6 months [38]. Strategies incorporating brain tissue oxygenation ($PbtO_2$) together with standard ICP and CPP management have shown a trend toward improved outcomes. Strong evidence on benefits of multimodal neuromonitoring is, however, still lacking [39]. The BEST-TRIP trial on ICP monitoring [40] showed no difference in outcome when treatment was based on clinical monitoring and standard CT follow-up compared to treatment based on ICP monitoring. The trial, conducted in two middle-income countries, with poor prehospital care and absent rehabilitation, did not prove (or negate) the value of ICP monitoring [41] but rather the efficacy of two protocols focused on therapy of raised ICP, either documented or suspected [41]. For these reasons the findings of the trial are difficult to be extend to the general TBI population [40, 41].

Uncertainties

Despite advances in monitoring and care of TBI patients there are several aspects where further research and innovation are necessary. At the bedside, we have limited clinical insight into the pathophysiological processes at play causing increased ICP or reduced perfusion. A CT scan may rule out expanding intracranial masses, but the contribution of processes such as oedema, vasodilatation and blood–brain barrier dysfunction are unknown. We cannot therefore identify a specific patient population or physiology for targeted trials or clinical care of existing or novel therapeutic interventions. Overall, the next generation of diagnostic and monitoring tools should focus on specific mechanisms and targets rather than consequences of treatments alone.

ICP treatment

In neurocritical care, therapeutic hypothermia and decompressive craniectomy have been considered important despite the lack of strong evidence. However, recent RCTs could not confirm the benefit of these strategies (Table 2).

Hypothermia

Hypothermia after TBI should not be considered standard practice. The Eurotherm trial [42] showed worse outcomes in TBI patients with raised ICP treated early with hypothermia. However, it may still have utility after the failure of second-tier therapies to control ICP and further research is required.

Decompressive craniectomy

The DECRA study [43] showed worse outcome in patients treated by decompressive craniectomy (DC) even if, after adjustment for covariates, the differences were not significant. The recently published RESCUEicp trial [24], on the contrary, demonstrated decreased mortality with DC. However, more patients survived in a vegetative or very severely disabled state. The definition of "favourable" outcome in RESCUEicp included the upper stratum of severe disability, which was considered unfavourable in previous studies and in DECRA. The proportion of favourable outcomes according to the classical definition (good recovery or moderate disability) was 27% in the DC group and 26% in the medical group. DECRA studied DC as an early intervention for intracranial hypertension refractory only to first-tier therapies, whereas RESCUEicp studied DC as a last-tier intervention when intracranial hypertension was refractory to tiered escalation of ICP-lowering therapies (i.e. a more usual clinical scenario for this high-risk intervention). RESCUEicp has, therefore, a clinically sound design and patient population, and DC remains an important therapeutic option in case of refractory intracranial hypertension. However, given the potential for poor neurological outcomes [24], use of DC must be contextualised for individual patients.

Uncertainties

Interventions such as therapeutic hypothermia [42] have failed to show improvement in favourable outcomes. Whether these failures testify to a lack of efficacy or may be due to suboptimal design of clinical trials in TBI remains to be clarified. These trials highlight that settings and generalizability should be considered. Research efforts should focus on identifying which (sub)groups of patients may best benefit from a specific approach. In particular, there is uncertainty around what constitutes favourable outcome after TBI. Personal beliefs, ethical concerns and social attitudes all play into a difficult debate, and whether the degree of disability is acceptable will depend on the patient, his or her family, and societal influences.

New therapeutic options for TBI

Specific targets

Recent international RCTs of neuroprotective drugs such as progesterone [44] and erythropoietin [45] early after injury have not produced positive clinical trials despite strong preclinical evidence—continuing two decades of failed pharmacological human trials in TBI. Better preclinical studies modelled on human pathophysiology and alternative clinical trial designs have been already identified as necessary prerequisites for successful future studies. Importantly, we have underevaluated TBI as a cause of chronic, long-lasting brain damage, perhaps months or years after injury [46]. If late phenomena impact quality

Table 3 Clinical studies to be conducted in the field of trauma patients (studies 1–5) and TBI patients (studies 6–10)

1. Prospective cohort study: international prospective study to describe contemporary modes and timing of death in trauma patients, and different patterns and outcomes of multiple organ dysfunction syndromes
2. Prospective cohort experimental medicine study: elucidate the different phenotypes and mechanisms of trauma-induced coagulopathy, their clinical manifestations and how they can be rapidly identified by diagnostic devices. The roles of platelets and the endothelium are large gaps in current knowledge
3. RCT: Study to determine whether a targeted, individualised approach to the management of trauma-induced coagulopathy results in improved outcomes over empiric transfusion-based therapies using balanced or whole-blood resuscitation
4. RCTs: Studies evaluating the role of specific coagulation therapeutics such as fibrinogen and procoagulant concentrates, novel blood-derived therapeutics and bioengineered haemostatic agents
5. Prospective cohort experimental medicine study: human studies of the acute immune response to injury (including leukocyte, platelet and endothelial responses). These should focus on schemes that stratify patients at the earliest possible time points in the care continuum, including the prehospital phase, monitoring modalities and which examine individualised, monitor-guided therapies to improve outcomes
6. CER study. Define patients' profiles from large prospective database to predict efficacy of specific interventions (precision medicine)
7. CER study. Observational cohort with high-quality clinical data for neuroimaging and biological samples for outcome prediction
8. CER study. Defining the need and targets of PBtO2 (PBtO2 targeted) and of ICP therapy (ICP targeted)
9. RCT study. Do prophylactic antibiotics after intubation reduce ventilator-associated pneumonia?
10. RCT study. Do beta-blockers reduce death and disability when administered acutely after brain trauma?

of survival after TBI, different damage mechanisms, with a prolonged time window, may become potential therapeutic targets.

Brain to lung interactions

The interactions between the brain and lungs are now better, but still incompletely understood. Treatments including specific empirical antibiotic treatment of pneumonia [47], implementation of treatment bundles including protective mechanical ventilation and prompt extubation readiness have been successfully introduced in clinical practice [48–50], although large RCTs of these treatments have not been conducted. Conflicting results were published in three multicentre randomised studies regarding the use of corticosteroids. Low dose of hydrocortisone may decrease the rate of hospital-acquired pneumonia (HAP) in severe trauma patients, and especially in TBI patients [51, 52]. The MRC CRASH trial randomised 10,008 moderate to severe TBI patients to 48-h infusion of high-dose methylprednisolone or placebo and found an increased mortality in the treatment group [53].

Long-term outcome and rehabilitation

Long-term outcomes and consequences of TBI

Early magnetic resonance imaging (MRI) has been investigated as a prognostic tool, and assessment of white matter injury with quantitative 3-T diffusion tensor imaging improved the prediction of long-term outcome as compared with the current clinical/radiographic assessment [54]. However, uncertainty remains in both its discriminative predictive value and which acute phase lesion patterns correlate with long-term outcome [55]. Novel biomarkers may also help in outcomes prediction, and recent research has shown that tau protein levels may predict chronic neurologic symptoms after TBI [56]. Recently, it was demonstrated that damages caused by TBI affected remote brain networks. Functional MRI showed a functional reorganization of motor networks following TBI [57] and will probably improve our understanding of chronic consequences of TBI [58].

Rehabilitation is a key issue

Early rehabilitation is challenging, and focus on activities of daily life and long-term rehabilitation aims for social reintegration including return to work. Functional rehabilitation constantly improves through better organization and dedicated specialist teams. Also, a better comprehension of the temporal evolution of the pathophysiology of severe trauma patients could be maximized by treating the long-term dysregulation of the neuroendocrine immune interactions. Indeed, there is emerging evidence showing chronic inflammation and ongoing white matter degeneration for many years after severe TBI [59]. Sympathetic hyperactivation also plays a major role and is linked to maladaptive inflammation in trauma with and without TBI. Beta-blockers display specific attenuation of retrieval of emotional episodic memory that may decrease retrieval of traumatic memories in anxiety-related disorders [60, 61].

Uncertainties

Cognitive problems are one of the most important factors in determining people's subjective well-being and their quality of life. This burden affects the daily life of survivors and their families and has large social and economic

costs. Several instruments have been developed for capturing specific aspects, from generic health status to specific cognitive functions [57], but uncertainties remain on how to include them in a global strategy of care. Current controversies in acute rehabilitation include what the optimal timing before starting rehabilitation is (early versus only after return of consciousness), and whether acute rehabilitation should occur within major trauma centres or in rehabilitation centres run by specialized rehabilitation teams.

General conclusion

Finally, in all aspects discussed above, there is almost no evidence with respect to whether the science and management strategies hold true for specific patient groups such as children, the elderly and adults with comorbidities such as obesity and diabetes. The trauma community must develop the research networks and infrastructure to specifically investigate these patient populations.

What do the international group of experts recommend as the top 10 studies/trials to be done in the next 10 years?

The extreme heterogeneity of the trauma population and of the types of injuries is challenging for researchers. The conventional approach to overcome variability is to perform RCTs. However, the majority of RCTs have failed to demonstrate efficacy of the experimental arm, and this explained why numerous recommendations in the setting of trauma patients are not supported by strong evidence. An alternative approach is to perform comparative effectiveness research (CER). The goal of CER is to demonstrate the effects of two or more interventions on outcome. The collaboration of international funding agencies and the international initiatives on trauma and TBI research will generate evidence from large-scale non-randomised studies, and these studies could be as valuable as RCTs. International networks built through international collaboration, coordination of standardized data collection and big-data sharing have been created such as the International Trauma Research Network [62], the Resuscitation Outcome Consortium [63], the International Initiative for Traumatic Brain Injury Research (InTBIR), or the Center-TBI (https://www.center-tbi.eu/project/overview). The top 10 studies to perform in the future would improve outcomes and are presented in Table 3.

Conclusion

In the last decade, outcomes from trauma have improved with standardization of treatment and with the creation of specific research networks and infrastructure. New management paradigms and opportunities for the development of new diagnostic modalities and therapeutic interventions have emerged. However, empiric, one-size-fits-all strategies are unlikely to be optimal and precision approaches to patients need to be explored. The understanding of long-term outcomes and consequences of trauma remains poor and should be better investigated for better prediction, trial design and future care. There needs to be a renewed focus on high-quality experimental/translational medicine to identify new innovative approaches that can be taken forward into well-designed and well-conducted clinical trials. Finally, success of a trauma system is largely determined by the level of public policy support, and unfortunately in many developing countries, a trauma system is non-existent. Helping these countries should be one of the big challenges for the next decades since trauma remains a major cause of mortality and disabilities across the world.

Electronic supplementary material

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