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Review Article

Recommendations, Considerations and Options–the Dos and Don'ts of Therapeutic and Prophylactic Strategies in Patients with Subarachnoid Hemorrhage

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Abstract

In this commentary article, we discuss five main aspects of therapeutic and prophylactic strategies in the post-interventional care of patients with subarachnoid hemorrhage: (i) Immediate Cerebrospinal Fluid (CSF) diversion, hematoma clearance and anti-fibrinolytic therapy, (ii) Strict vascular monitoring, vasospasm treatment and prevention of Delayed Cerebral Ischemia (DCI), (iii) Continuous Blood Pressure (BP) monitoring and normalization of BP, (iv) Deep sedation, osmotic therapy and hypothermia for control of Intracranial Pressure (ICP) and (v) Electroencephalography (EEG) monitoring and early and/or prophylactic seizure treatment. Beyond these aspects highlighting the treatment options that are special for the biphasic course of the disease, several other factors contribute to optimal care, which are best applied by standardized treatment bundles. Unless there are individually weighted roles of treatment interventions, of measured parameters and of treated conditions, a comprehensive approach to ensure physiological homeostasis (in terms of circulation and respiration as well as humoral and metabolic balance) remains a basic requirement framing the individualized specific treatment. Continuous monitoring of relevant parameters such as BP, end tidal carbon dioxide, ICP, and EEG if available enables multidisciplinary medical and critical care teams to deliver optimal care.

Keywords: Subarachnoid hemorrhage; Cerebrospinal fluid; Vasospasm; Blood pressure; Intracranial pressure; Seizure.

Introduction

Spontaneous non-traumatic Subarachnoid Hemorrhage (SAH) is a rare form of stroke with an incidence of approximately 9:100,000 in western industrialized nations associated with high morbidity and mortality of up to 40%. This form of SAH mainly affects patients of younger age around the fifth decade of life and nearly 80% of cases are due to cerebral aneurysms (aneurysmal SAH, aSAH) [1]. The primary treatment goal of aSAH is to eliminate the source of bleeding by open surgical or endovascular treatment options [2]. As aSAH is often accompanied by intraventricular and intracerebral blood components, patients are at risk of consecutive occluding hydrocephalus and the development of cerebral edema [3]. Furthermore, a distinctive aSAH feature is the biphasic disease course: after initial neuronal damage within the first 72 hours due to toxic effects of subarachnoid blood, transient global ischemia,

and direct damage to the brain parenchyma, delayed onset of neurological deficits, *i.e.* Delayed Cerebral Ischemias (DCI) occur, especially on days 3 to 14 [4]. Although hospital inpatient mortality rates from aSAH have decreased over recent years, 2 persistently high incidences of medical complications necessitate improved therapies and standardized practice in the post interventional care of patients in order to maintain a comprehensive approach [5]. Out of numerous, sometimes controversially discussed treatment options, we here discuss five main aspects of therapeutic and prophylactic strategies, including the key interventions of CSF drainage, vasospasm therapy and DCI prevention, BP and ICP management, as well as seizure treatment.

Immediate CSF diversion, hematoma clearance and anti-fibrinolytic therapy

Symptomatic acute or chronic hydrocephalus is common after aSAH (15-87%) and associated with worse outcome [2]. Pathophysiologically, Intraventricular Hemorrhage (IVH), but also ependymal and plexus choroideus damage, CSF hypersecretion from the choroid plexus, impaired CSF drainage *via* arachnoid granulations or inflammatory responses may cause a disruption of CSF circulation and consequently induce occluding or malresorptive hydrocephalus [2]. Therapeutic targets of CSF dynamic modulation after aSAH include surgical (CSF diversion via External-Ventricular-Drain (EVD) and/or Lumbar Drain (LD), ventriculoperitoneal drain, ventriculostomy) and pharmacological interventions (intracisternal or intraventricular fibrinolytics) [6,7]. Yet, after surviving the initial hemorrhage, still 9-48% of aSAH patients develop chronic, shunt-dependent hydrocephalus [2].

Surgical interventions are recommended for CSF diversion and to reduce the risk of shunt-dependent hydrocephalus

Recommendations and options

In patients with decreased level of consciousness and/or detected acute hydrocephalus, CSF diversion (and ICP measurement) should be applied immediately, 2 and in case of occluding hydrocephalus, primarily EVD placement should be initiated [2]. So far, no clear protocols for EVD management (*i.e.* optimal drainage and weaning strategies) have been developed. Intermittent drainage implies to maintain the EVD closed by default, and to drain CSF when ICP reaches a set threshold, or when patients become symptomatic. Recently, a systematic review and meta-analysis found lower incidences of EVD-related infections (RR=0.20, 95% CI 0.05–0.72) and EVD-blockages (RR=0.45, 95% CI 0.27–0.74) with intermittent, compared to continuous CSF drainage [8]. Rapid wean is defined as EVD closure within 48h of starting a weaning trial without reopening, unless evidence of increased ICP, clinical worsening, CSF leakage or progressive hydrocephalus [9]. In contrast, gradual EVD wean involves to leave the drain open and to raise it gradually over several days [9]. In a prospective multicenter study, Chung et al. suggested lower rates of permanent shunt-dependency and drain complications, as well as decreased lengths of ICU stay in patients with rapid, compared to gradual wean [9]. Although no clear recommendations have been established so far, guidelines emphasise the importance of implementing standardized care bundles in patients who require EVD treatment [2].

After restoration of ventricular communication, lumbar CSF drainage (LD) should be considered [2]. In 210 aSAH patients (WFNS Grade 1-3), LUMAS, a single-center prospective RCT first suggested that LD improves early clinical outcome, yet failed to show long-term outcome benefits [10]. Recently, the EARLYDRAIN trial demonstrated that prophylactic LD decreases rates of secondary infarction (absolute risk difference, −0.11; 95%CI, −0.22-0) and unfavorable outcome at 6 months (absolute risk difference, −0.12; 95%CI, −0.23-−0.01) in all grades of aSAH [11]. Furthermore, with mean CSF drainage rates of 5ml/h during the first 8 days, LD (with/without EVD) was associated with lower ICPs compared to EVD alone [11]. As unfavorable outcome after aSAH has clearly been linked to duration and magnitude of ICP elevation, these findings support the use of LD in addition to standard of care [11].

Considerations

Meningitis and ventriculitis are frequent and severe complications of CSF drainage (4-17 infection days per 1,000 EVD days),12 and a strong independent predictor of unfavorable outcome and long-term neurological dysfunction after aSAH [12]. A comprehensive systematic review and meta-analysis found that bolted and antibiotic-coated catheters were superior to tunneled/uncoated catheters (P<0.001), and antibiotic- *vs*. silver-impregnated catheters (P<0.001) in preventing infections [13]. Furthermore, best-practice recommendations include to remove catheters as soon as clinically possible, preferably in less than 5 days [13].

Although microsurgical fenestration of the lamina terminalis had been investigated in terms of facilitating CSF dynamics, a meta-analysis of almost 2,000 aSAH patients revealed no differences in rates of shunt-dependent hydrocephalus (10% in the fenestrated cohort vs 14% in the non-fenestrated cohort) [14]. Therefore, routine fenestration of the lamina terminalis is not recommended by international guidelines [2].

Intraventricular fibrinolytics for hematoma clearance may be considered while intravenous anti-fibrinolytic therapy has no proven effect to prevent re-bleeding.

Recommendations and options

Especially in patients with occluding hydrocephalus due to IVH components, installation of fibrinolytic agents (IVF) may be considered. Although the study was primarily negative,

a prespecified secondary analysis of the CLEAR-III trial demonstrated benefits of IVF in terms of mortality [15]. Moreover, exploratory analyses of CLEAR-III suggest positive effects on functional outcome, however, effects on long-term functional outcome have not been found [15]. Recently, a systematic review and meta-analysis further identified IVF to promote hematoma clearance, reduce rates of catheter occlusion, decrease mortality and improve functional outcome [13]. Overall, IVF complication rates appear low and high dosage of alteplase (4mg/12h) had favourable effects compared to low-dosage of alteplase (1mg/8h), despite absence of dose-related adverse events [13].

Considerations

Current evidence indicates that routine use of antifibrinolytic therapy does not reduce rates of re-bleeding, or improve functional outcome [2]. After conflicting results from older studies, recommendations derive from the ULTRA trial-the largest RCT that evaluated ultraearly and short-term therapy with tranexamic-acid after aSAH [16] Between 2013 and 2019, the authors found similar rates of good clinical outcome (mRS 0-3; 60 *vs* 64%), and of re-bleeding (10 vs 14%) between patients treated with antifibrinolytic medication (within a median of 185 minutes after disease onset, n=480) compared to patients who did not receive tranexamic-acid (n=475) [16].

Strict vascular monitoring, vasospasm treatment and DCI prevention

Neurological deterioration following the acute phase commonly occurs 3 to 14 days after aSAH onset and cerebral infarction due to DCI increases morbidity in patients surviving the initial hemorrhage [17]. With an OR of 3.7 (95% CI 1.9–6.9), cerebral infarction due to DCI represents one of the strongest predictors of in-hospital mortality [17,18]. Pathophysiologically, DCIs are attributed to cerebral vasospasm among other causes (e.g. impaired autoregulation, microthrombosis, cortical spreading ischemia) [19]. In total, 70% of aSAH patients have detectable vasospasm and approximately 30% develop delayed neurological deterioration and focal deficits that may progress to infarction [2,7].

Various diagnostic procedures are available to detect cerebral vasospasms.

Recommendations and options

Especially in high-grade aSAH patients, different methods for monitoring and detection of arterial narrowing may be applied in order to predict DCI [2].With a sensitivity of 90%, non-invasive transcranial Doppler ultrasonography (TCD) monitoring is considered reasonable, and TCD evidence of vasospasm was found to be highly predictive of DCI [2]. Yet, clinical value may be limited by patient anatomy (temporal bone window) and physiological measures such as heart rate and BP [2]. With a similarly high sensitivity, CT-Angiography (macroscopic vasospasm) and CT-Perfusion (alterations to the microcirculation) can be useful in patients with suspected vasospasm [2]. Continuous measure of cerebral function using cEEG may complement other techniques. Although further validation and automatization is needed, detection of a decrease in alpha-power variability, a decrease in alpha-to-delta power ratio, and other patterns have been suggested to predict DCI [2]. So far, there is insufficient evidence that invasive multimodal neuromonitoring relevantly affects long-term clinical outcome [2]. Yet, monitoring of brain tissue oxygenation, lactate-to-pyruvate ratio, and glutamate may also be considered to predict DCI [2].

Considerations

Despite advantages of TCD as a noninvasive, safe and easy to perform bedside neuromonitoring technique, the predictive value for vasospasms and DCI detection is rather low (57%) limiting accuracy and applicability of this technique [20]. Therefore, the combination with other neuromonitoring modalities such as EEG and CTP may be considered to improve DCI prediction, especially in the setting when neurological examination is limited due to clinical severity and/or decreased level of consciousness [21,22].

The continuous administration of nimodipine and other neuroprotective agents is generally recommended.

Recommendations and options

Already 40 years ago, Allen, et al. demonstrated that administration of the dihydropyridine calcium channel blocker nimodipine is beneficial in preventing DCI and improving functional outcome after aSAH [23]. Since then, several trials and meta-analyses confirmed this finding, and early enteral administration of nimodipine (6 x 60mg per day) still represents the only recommended on-label prophylactic therapy [2]. Even in the setting of nimodipine-induced hypotension, consistent administration is recommended, as a therapy disruption has been associated with higher DCI incidences [24] Although enteral administration should be preferred, intravenous therapy seems similarly effective [25].

Considerations

Several RCTs assessed the relevance of statin therapy in aSAH patients [2]. Although treatment with statins significantly decreased the occurrence of vasospasm, no benefits on DCI, outcome and mortality have been observed, 26 consequently, routine use is not recommended [2].

Despite suggested neuroprotective effects, intravenous magnesium sulphate is not recommended routinely after aSAH. Among other studies, the MASH-2 RCT found no benefit in terms of cerebral infarction, outcome, or mortality [27].

Rescue strategies should be considered when vasospasms occur.

Recommendations and options

If clinical deterioration occurs, which can be determined using the NIHSS or GCS (defined as difference of at least 2 points), or with the help of specific prediction tools such as the VASOGRADE, sever vasospasms may be present [28,29]. Especially if neurological examination is unreliable, *i.e.* in patients with decreased level of consciousness, neuromonitoring techniques, e.g. TCD (most studies focus on the middle cerebral artery definition of vasospasms: velocity ≥ 120 cm/s or Lindegaard ratio ≥ 3) or continuous EEG monitoring (cEEG, with abnormalities decreased alpha power variability or late-appearing epileptiform abnormalities) should be applied.20,30 If clinical deterioration does not resolve by induction of euvolemia or BP elevation, additional neuroimaging (CTA and CTP) and rescue strategies should be considered [2,31]. Endovascular options like intra-arterial application of nimodipine and milrinone have been suggested to be beneficial in order to target the proximal and distal vasculature [32]. Intermittent infusion *via* a cervical catheter should be preferred over continuous infusion regarding efficacy and complications (e.g. hypotension and elevated ICP) [33]. Both intra-arterial applicable agents have been suggested to improve angiographic and long-term functional outcomes [34,35]. Yet, besides mostly retrospective case series and single-center cohorts, no high-quality randomized trials have been undertaken to compare different agents, and future studies are needed to evaluate functional outcome und risk stratification [2,34]. Besides that, angioplasty with compliant and noncompliant balloons has been used as a mechanical option to treat vasospasm in the proximal vessels and existing data suggests enhanced angiographic responses compared to intra-arterial application of vasodilators [36]. Furthermore, a combination of angioplasty and *i.e.* medication may result in longer durability of angiographic responses [2]. Poor angiographic responses during angioplasty may be due to ongoing and recurrent vasospasms and DCI. Furthermore, the risk of vessel rupture during angioplasty with consecutive high mortality should be considered.37 Overall, only limited data exists comparing mechanical and medicamentous therapeutic options [36].

Considerations

Due to the increased risk of organ failure (especially pulmonary edema and congestive heart failure), "triple-H therapy" including hemodynamic augmentation methods in form of hypervolemia, hemodilution, and hypertension is no longer recommended [38]. Not only hyper-, but also hypovolemia have been associated with worse outcome after aSAH, so that several studies recommended maintenance of euvolemia. Yet, no clear protocols and approaches (crystalloid infusions, vasopressor therapy) have been tested in RCTs [38]. Finally, because of the risk of gray matter changes and neurotoxicity intra-arterial papaverine should be avoided as a rescue strategy in refractory vasospasms [39].

Continuous BP monitoring, and normalization of BP

Compared to other forms of hemorrhagic stroke and intracranial bleeding, BP management seems to be more complex in SAH patients [7,40]. The acute phase of aSAH is often complicated by elevated BP, in terms of ongoing and recurrent hemorrhage, death and disability [40]. On the other hand, lowering BP reduces Cerebral Perfusion Pressure (CPP) and may increase the risk of DCI due to elevated ICP [40].

Continuous blood pressure monitoring is recommended.

Recommendations and options

Similar to other cerebrovascular diseases, autoregulation has been demonstrated to be impaired in aSAH patients [2,41]. Furthermore, elevated BP variability was found to be associated with DCI and worse outcome [2,41]. Therefore, continuous or highly frequent BP measurement is recommended, in order to minimize BP variability, 2 and closely respond to excessive changes in BP [2,41].

Considerations

Blood pressure monitoring should be part of standard intensive care unit bundles to be able to detect and react to corresponding BP fluctuations [2].

Hypertension should be treated immediately.

Recommendations and options

Approximate normalization of BP, *i.e.* treatment of hypertension within the acute phase of the disease seems justified to reduce the risk of ongoing and recurrent hemorrhage, *i.e.* hematoma progression [40]. Although available evidence in aSAH is insufficient to recommend specific BP goals, international guidelines advice that high BP should be treated [40]. Current recommendations for acute BP reduction derive from the two ICH RCTs INTERACT2 and ATACH2 [42,43]. In acute aSAH, systolic-BP<160mmHg (with CPP >70mmHg and MAP 60-100mmHg) may be a reasonable therapeutic goal [2,41] treatment may be started with nimodipine and analgesia, 40 but more importantly, agents to lower BP should be well tolerated, easy to titrate and effective to achieve and maintain BP targets without excessive variability [40]. The recently published INTERACT3 trial also emphasises the benefits of prompt blood pressure reduction in patients with ICH in order to improve chances of survival without major disability [44]. Yet, it is important to mention that not only early intensive BP lowering but also simultaneous administration of specific care bundles including treatment of hyperglycemia, fever and rapid reversal of abnormal anticoagulation are needed to improve outcome [44].

Considerations

So far, no controlled trials were able to demonstrate advantages of induced hypertension to effectively target DCI [40,45]. Although the trial was terminated after recruitment of only 41 patients, the HIMALAIA RCT suggested an adjusted risk-ratio for poor outcome of 1.0 (95% CI, 0.6-1.8), and a risk-ratio for serious adverse events of 2.1 (95% CI, 0.9-5.0) with induced hypertension [45]. Yet, since most aSAH patients develop some degree of vasospasm, 41 permissive arterial hypertension may be beneficial after the source of bleeding is secured [40]. Therefore, aggressive BP management should be avoided in the post interventional phase and loosened BP targets in patients with vasospasm seem reasonable [40].

Deep sedation, osmotic therapy, and hypothermia for ICP control

In aSAH patients, ICP elevation may be due to hydrocephalus, ischemia, intracerebral or subdural hemorrhage components, electrolyte imbalance, or a generalized cerebral edema. It is well known that elevation of ICP may induce local but also global cerebral ischemia and consequently increases the risk of poor outcome.2,7 Therefore, international guidelines recommend ICP target values <23mmHg, especially in patients with untreated aneurysm, and maintenance of CPP (60-90mmHg) [46]. Basic measures of ICP management include elevated head positioning as well as adequate sedation with regard to treatment of pain and agitation. Irrespective of the underlying disease, an increase in body-core temperature enhances cerebral metabolism, with augmented cerebral blood-flow and -volume. If compensatory mechanisms are exhausted, ICP may raise [47]. As fever (infectious and noninfectious) is the most common complication during the clinical course of aSAH, an increased risk of poor outcome for each day that a patient has fever (OR 1.4) has been described.48 Therefore, temperature management to control fever after aSAH is recommended to lower ICP [2]. Furthermore, several studies demonstrated that hyperosmotic agents may be used to manage ICP and brain relaxation [49,50].

Analgosedation may be used to support ICP control.

Recommendations and options

Although general anesthesia limits clinical evaluability of patients, analgesia and mechanical ventilation are recommended for ICP control in comatose patients and/or patients with depleted effect of CSF drainage [2]. Usual sedative medication comprises propofol and benzodiazepines. The analgesic component could be covered by opioids or ketamine. Specific pharmacological approaches have so far not been evaluated in RCTs, yet data from literature reviews suggest that bolus administration should be avoided [51]. Furthermore, the implementation of standardized ICU care bundle in patients who require anesthesia for >24h is recommended [2].

Considerations

Despite effects on ICP-control, no benefits of barbiturate therapy have been described in terms of death or disability [52]. In contrast, especially long-term barbiturate therapy has been associated with significant side effects (e.g. pneumonia) and poor outcome [52]. Therefore, long-term barbiturate therapy should be avoided. Propofol as well as inhalative anesthesia agents could have both beneficial and adverse effects [53]. The propofol infusion syndrome, a rather rare complication, is associated with increased morbidity and high mortality, limiting applicability of this drug. Therefore, the use of propofol is not recommended for a duration >7 days and doses >4mg/kg [54].

Osmotic therapy may be used to support ICP control while hypothermia is not generally recommended.

Recommendation and options

It has been demonstrated that administration of osmotic agents (i.e. mannitol and hypertonic saline) potently lowers ICP [50,55,56]. Therefore, short-term administration (over a few minutes) for the treatment of ICP crisis can be recommended; effects develop after a few minutes and last up to two hours [49]. Hypertonic saline increases blood sodium (target values: 155-160mmol/l), and bolus applications as well as continuous infusion may be considered. While most studies, e.g. a prospective study by Huang, et al. found no evidence to recommend one therapy over the other, 55 hypertonic saline (3%) was slightly more effective than mannitol (20%) in terms of lowering ICP, and was still partially effective in "mannitol failures" in a meta-analysis [50].

Considerations

While the use of osmotic agents is justified for prophylactic or therapeutic use in brain swelling, important side effects have to be taken into account. Due to its diuretic effects, mannitol (target osmolarity 330 mOsmol/l) can cause hypovolemia and hypotension. Furthermore, renal elimination may induce metabolic acidosis and renal damage, why daily dosages of 6 x 250mg should not be exceeded.2,57 Although mild hypothermia (32-36°C) has been suggested to lower ICP in different diseases with cerebral injury, there is only limited data on hypothermia application for ICP-control after aSAH [58,59]. As most studies reported high complication rates (e.g. infections, electrolyte disturbances, heart failure, arterial hypotension, arrhythmias, and coagulation disorders), hypothermia should only be considered in individual cases with pharmacologically refractory ICP elevation [58,59].

EEG monitoring, and early and/or prophylactic seizure treatment

Epileptic seizures are common complications of aSAH, affecting up to 26% of patients [2]. Based on seizure occurrence during the

disease course, guidelines distinguish between onset-seizures (at the time of hemorrhage), early (during the first week), and late seizures (after week 1) [2].

Continuous EEG monitoring is recommended in every SAH patient for seizure monitoring.

Recommendations and options

Recent technical advances have made cEEG monitoring feasible, allowing for real-time detection of adverse events [60]. Although available studies on cEEG are very heterogeneous, a systematic literature review found improved detection and increased numbers of subclinical seizures by cEEG [60]. Therefore, current guidelines consider cEEG monitoring reasonable, especially in patients with decreased level of consciousness, fluctuating neurological deficits, or characteristics that have been associated with elevated seizure incidence, *i.e.* high-grade SAH, middle cerebral artery aneurysm and ICH [2].

Considerations

Although benefits of cEEG monitoring have been suggested, 2,60 and the use of quantitative software programs allow for timely interpretation of compressed raw data, 61 insufficient evidence exists whether more aggressive treatment based on these recordings leads to improved clinical outcome [60]. Overall, a full EEG montage should be preferred over a EEG bispectral index monitoring (BIS EEG) and data should be interpreted by experienced neuro-critical care physicians [60].

Seizures should be treated while prophylactic ASM is not recommended.

Recommendations and options

Onset seizures have clearly been associated with poor outcome after aSAH. Especially to prevent non-convulsive status or re-bleeding of unsecured aneurysms, Anti-Seizure Medication (ASM) should be administered upon presentation [2]. As there are no RCTs on duration of ASM use in patients with onset seizures, guidelines recommend treatment for ≤7 days to decrease long-term medication side effects [2]. Although administration of prophylactic ASM has in the past been a standard protocol, recent guidelines recommend against routine peri-interventional ASM use in ruptured aneurysms [2]. Yet, specific patient groups are at high seizure risk after aSAH, *i.e.* patients with higher aneurysm grade, lower Glasgow Coma Scale score at presentation, higher extent of subarachnoid blood on CT, younger age, those with middle cerebral artery aneurysms, and coexisting ICH [62]. In order to minimize medical complications, current guidelines therefore consider short term prophylactic ASM use appropriate within this specific patient group [2].

Considerations

Besides clear, RCT-proven benefits, ASM after aSAH may induce serious adverse effects such as arterial hypotension, organ toxicity, prolonged ventilator support, and overtreatment may potentially harm patients [60]. Phenytoin for seizure prevention has been associated with increased morbidity and mortality [2]. Amongst other studies, a systematic review of literature found phenytoin-induced fever, deranged liver function, thrombocytopenia, rash, and Stevens-Johnson syndrome in over 20% of treated patients, 62 so that current guidelines state that the side-effect profile of phenytoin outweighs seizure prophylaxis and therapy benefits of this drug [2]. When comparing different durations of prophylactic antiepileptic medication after aSAH, a systematic review and meta-analysis with a total of 959 patients found that long-term exposure to prophylactic ASM (>3 days) was associated with poor clinical outcomes (OR 1.55; 95% CI 1.01–2.39; p=0.045) compared to short-term use [63]. Therefore, prophylactic treatment for >7 days in the management of delayed seizure risk is not recommended [2] (Table 1).

Therapeutic and prophylactic strategies in SAH patients	
Immediate CSF diversion, hematoma clearance, and anti-fibrinolytic therapy	
Recommendations & options	**Considerations**
• Immediate CSF diversion in patients with disturbed vigilance and/or detected acute hydrocephalus (CoR 1, LoE B-NR) • Intraventricular installation of fibrinolytic agents • Lumbar CSF drainage after restoration of ventricular communication permanent CSF diversion (CoR 1, LoE B-NR)	• Routine use of intravenous anti-fibrinolytic therapy (no benefits) (CoR 3: no benefit, LoE A) • High rates of shunt infections (bolted and antibiotic-coated catheters should be preferred, catheters should be removed as soon as clinically possible) • Microsurgical fenestration of the lamina terminalis (no effects on rates of shunt-dependent hydrocephalus) (CoR 3: no benefit, LoE C-LD)
Strict vascular monitoring, vasospasm treatment, and DCI prevention	
Recommendations & options	Considerations
• Vasospasm monitoring (transcranial doppler ultrasound, CT-Angiography, CT-Perfusion) (CoR 2a, LoE B-NR) • early enteral administration of nimodipine (CoR 1, LoE A) • Balloon angioplasty, i.a. nimodipine and milrinone ("rescue" strategies") (CoR 2b, LoE B-NR)	• Induction of hypervolemia/"triple-H therapy" (increased risk of organ failure) (CoR 3: Harm, LoE B-R) • Routine use of statins (no benefits) (CoR 3: No benefit, LoE A) • Routine use of i.v. magnesium sulphate (no benefits) (CoR 3: No benefit, LoE A)
Continuous BP monitoring, and normalization of BP	
Recommendations & options	**Considerations**
• Continuous/high frequent BP measurement (CoR 1, LoE C-EO) • Treatment of hypertension within the acute phase of the disease	• Aggressive BP management in the post interventional phase (permissive arterial hypertension may be beneficial in patients with vasospasm) (CoR 2b, LoE B-NR)
Deep sedation, osmotic therapy, and hypothermia for ICP control	
Recommendations & options	**Considerations**
• Analgesia and mechanical ventilation in comatose patients and/or patients with depleted effect of CSF drainage	• Long-term barbiturate therapy (side effects), propofol >7 days and doses >4 mg/kg (propofol infusion syndrome)
• Hyperosmotic agents (mannitol and/or hypertonic saline) (CoR 2a, LoE B-R)	• Hypothermia (high complication rates) (CoR 2b, LoE C-LD)
EEG monitoring, and early and/or prophylactic seizure treatment	
Recommendations & options	**Considerations**
• Continuous EEG monitoring (CoR 2a, LoE B-NR)	• Phenytoin (increased morbidity and mortality) (CoR 3: harm, LoE B-NR)
• ASM treatment of onset seizures upon presentation for ≤ 7 days (CoR 2a, LoE B-NR)	• Long-term exposure to prophylactic ASM (poor clinical outcome) (CoR 3: no benefit, LoE B-NR)
• Short term prophylactic ASM use in patients with high seizure risk (CoR 2b, LoE B-NR)	
*Level of Evidence (LoE) and Class of Recommendation (CoR) according to AHA-guidelines	

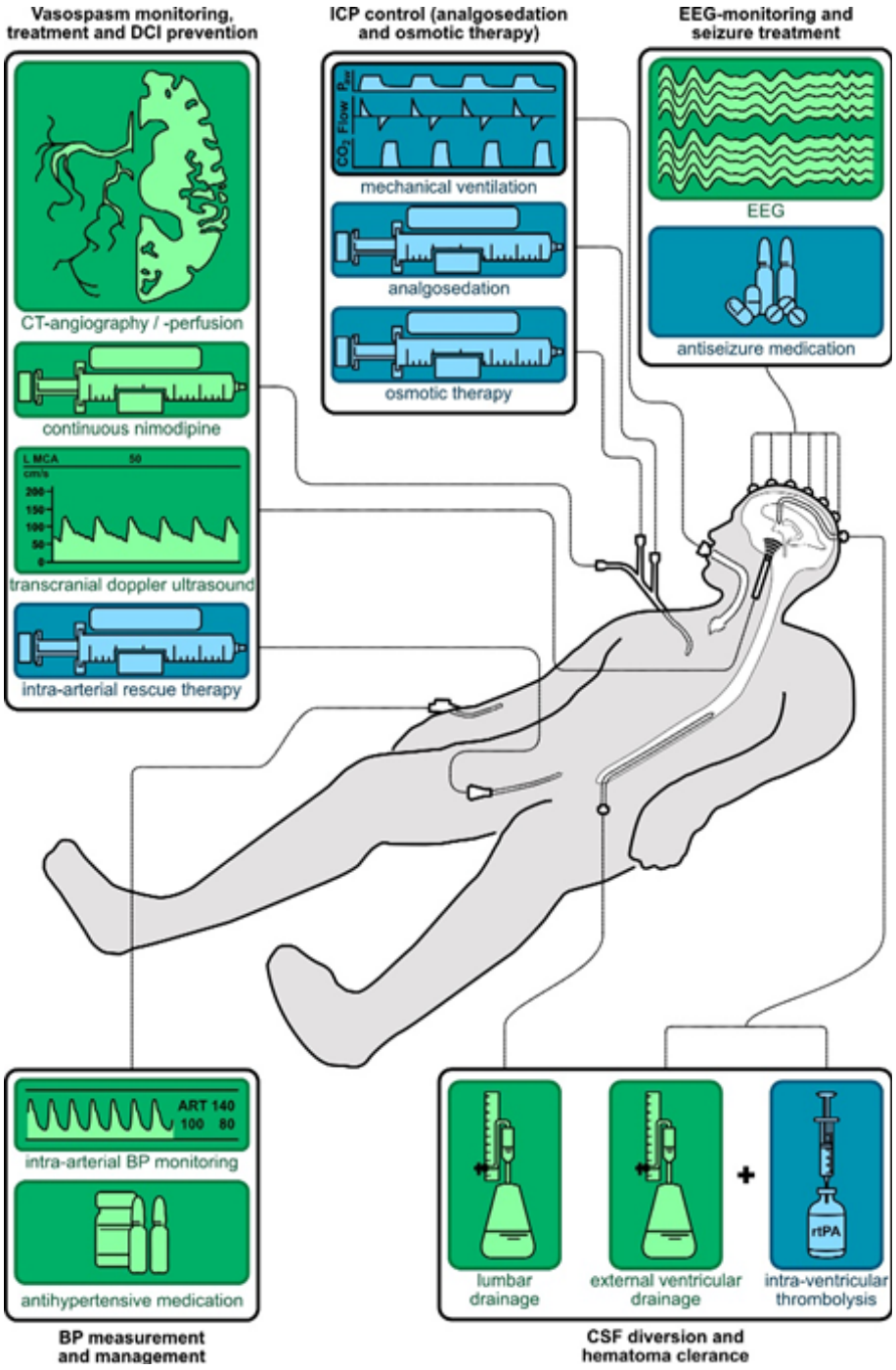

Figure 1: Schematic illustration of recommendations and options in the post-interventional care of aSAH patients. Colors distinguish between recommendations (green) and options (blue) in the post-interventional care of aSAH patients. DCI: delayed cerebral ischemia. CT: Computed Tomography. ICP: Intracranial Pressure. EEG: Electroencephalography. BP: Blood Pressure. CSF: Cerebrospinal Fluid.

Conclusion

This commentary article summarizes recommendations and options for post-interventional aSAH treatment strategies, proven effective according to current guidelines and available literature. Furthermore, it serves to highlight considerations of ineffective or even potentially harmful interventions. The article does not cover all possible and recommended topics, yet focuses on treatment options that are special for the biphasic disease course of aSAH.

While invasive key interventions e.g. EVD are often unavoidable, individualized specific treatment measures are recommended to address the pathophysiological consequences of aSAH. The overall picture of an optimal patient treatment comprises a circulatory, respiratory and humoral balance - best described as physiological homeostasis. Within the frame of physiological homeostasis, circulation should maintain adequate brain perfusion. Normal hemodynamic ranges and the absence of extreme excursions are basic. Finally, appropriate oxygenation and decarboxylation frame the treatment as a standard measure.

In general, there are only few RCTs on therapeutic strategies in aSAH, e.g. there is limited studies evaluating anesthetic management, BP goals, and pharmacological approaches to support ICP-control. In order to avoid hematoma progression within the early disease phase, SAH guidelines even adapted recommendations from intra-cerebral-hemorrhage trials. In contrast, strategies for DCI prevention have been studied extensively. While there is consensus on nimodipine use, only few intra-arterial rescue options seem reasonable, and several standard protocols have been completely abandoned, e.g. triple-H-therapy and routine use of ASM. Finally, some new strategies have been suggested for standard practice recently, e.g. early lumbar-drain and intraventricular fibrinolysis, and technical advances have made neuromonitoring feasible.

Overall, it should be emphasized that "an expert multidisciplinary medical and critical care management is of paramount importance in this complex field".

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Glossary:

aSAH, Aneurysmatic SAH

ASM, Anti-Seizure Medication

BP, Blood Pressure

CPP, Cerebral Perfusion Pressure

CSF, Cerebrospinal Fluid

DCI, Delayed Cerebral Ischemia

EEG, Electroencephalography

EVD, External-Ventricular-Drain

ICP, Intracranial Pressure

IVF, Intraventricular Fibrinolysis

IVH, Intraventricular Hemorrhage

LD, Lumbar CSF Drainage

MAP, Mean Arterial Pressure

SAH, Subarachnoid Hemorrhage

TCD, Transcranial Doppler Ultrasonography

References

1. Lawton MT, Vates GE (2017) Subarachnoid Hemorrhage. N Engl J Med 377: 257-266.
2. Hoh BL, Ko NU, Amin-Hanjani S, et al. (2023) 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke 54: e314-e370.
3. Claassen J, Park S (2022). Spontaneous subarachnoid haemorrhage. Lancet 400: 846-862.
4. Macdonald RL, Schweizer TA (2017) Spontaneous subarachnoid haemorrhage. The Lancet 389: 655-666.
5. Kurtz P, Taccone FS, Bozza FA, et al. (2021) Systemic Severity and Organ Dysfunction in Subarachnoid Hemorrhage: A Large Retrospective Multicenter Cohort Study. Neurocrit Care 35: 56-61.
6. Fang Y, Huang L, Wang X, et al. (2022) A new perspective on cerebrospinal fluid dynamics after subarachnoid hemorrhage: From normal physiology to pathophysiological changes. J Cereb Blood Flow Metab 42: 543-558.
7. Treggiari MM, Rabinstein AA, Busl KM, et al. (2023) Guidelines for the Neurocritical Care Management of Aneurysmal Subarachnoid Hemorrhage. Neurocritical care 39: 1-28.
8. Palasz J, D'Antona L, Farrell S, Elborady MA, Watkins LD, et al. (2022) External ventricular drain management in subarachnoid haemorrhage: A systematic review and meta-analysis. Neurosurg Rev 45: 365-73.
9. Chung DY, Thompson BB, Kumar MA, et al. (2022) Association of External Ventricular Drain Wean Strategy with Shunt Placement and Length of Stay in Subarachnoid Hemorrhage: A Prospective Multicenter Study. Neurocritical care 36: 536-545.

10. Al-Tamimi YZ, Bhargava D, Feltbower RG, et al. (2012) Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: A prospective, randomized, controlled trial (LUMAS). Stroke 43: 677-682.

11. Wolf S, Mielke D, Barner C, et al. (2023) Effectiveness of Lumbar Cerebrospinal Fluid Drain Among Patients With Aneurysmal Subarachnoid Hemorrhage: A Randomized Clinical Trial. JAMA neurol 80: 833-842.

12. Ramanan M, Shorr A, Lipman J (2021) Ventriculitis: Infection or Inflammation. Antibiotics (Basel) 10: 1246.

13. Haldrup M, Miscov R, Mohamad N, et al. (2023) Treatment of Intraventricular Hemorrhage with External Ventricular Drainage and Fibrinolysis: A Comprehensive Systematic Review and Meta-Analysis of Complications and Outcome. World Neurosurg 174: 183-196.e6.

14. Komotar RJ, Hahn DK, Kim GH, et al. (2009) Efficacy of lamina terminalis fenestration in reducing shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: A systematic review. Clinical article. J neurosurg 111: 147-54.

15. Hanley DF, Lane K, McBee N, et al. (2017) Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet 389: 603-611.

16. Post R, Germans MR, Tjerkstra MA, et al. (2021) Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. Lancet 397: 112-8.

17. Neifert SN, Chapman EK, Martini ML, et al. (2021) Aneurysmal Subarachnoid Hemorrhage: the Last Decade. Transl Stroke Res 12: 428-446.

18. Stienen MN, Germans M, Burkhardt JK, et al. (2018) Predictors of In-Hospital Death After Aneurysmal Subarachnoid Hemorrhage: Analysis of a Nationwide Database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). Stroke 49: 333-340.

19. Macdonald RL, Schweizer TA (2017) Spontaneous subarachnoid haemorrhage. Lancet 389: 655-66.

20. Kumar G, Shahripour RB, Harrigan MR (2016) Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. J Neurosurg 124: 1257-64.

21. Stienen MN, Visser-Meily JM, Schweizer TA, et al. (2019) Prioritization and Timing of Outcomes and Endpoints After Aneurysmal Subarachnoid Hemorrhage in Clinical Trials and Observational Studies: Proposal of a Multidisciplinary Research Group. Neurocrit Care 30: 102-13.

22. Kunze E, Pham M, Raslan F, et al. (2012) Value of Perfusion CT, Transcranial Doppler Sonography, and Neurological Examination to Detect Delayed Vasospasm after Aneurysmal Subarachnoid Hemorrhage. Radiol Res Pract 2012: 231206.

23. Allen GS, Ahn HS, Preziosi TJ, et al. (1983) Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 308: 619-624.

24. Hernandez-Duran S, Mielke D, Rohde V, Malinova V (2019) Does Nimodipine Interruption due to High Catecholamine Doses Lead to a Greater Incidence of Delayed Cerebral Ischemia in the Setting of Aneurysmal Subarachnoid Hemorrhage? World Neurosurg 132: e834-e40.

25. Geraldini F, De Cassai A, Diana P, et al. (2022) A Comparison between Enteral and Intravenous Nimodipine in Subarachnoid Hemorrhage: A Systematic Review and Network Meta-Analysis. Neurocritical care 36: 1071-1079.

26. Shen J, Huang KY, Zhu Y, et al. (2017) Effect of statin treatment on vasospasm-related morbidity and functional outcome in patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. Journal of neurosurgery 127: 291-301.

27. Dorhout Mees SM, Algra A, Vandertop WP, et al. (2012) Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. Lancet 380: 44-49.

28. de Oliveira Manoel AL, Jaja BN, Germans MR, et al. (2015) The VASOGRADE: A Simple Grading Scale for Prediction of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage. Stroke 46: 1826-1831.

29. Aldakkan A, Mansouri A, Jaja BN, Alotaibi NM, Macdonald RL (2017) Subarachnoid Hemorrhage International Trialists C. Predictors of Delayed Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage with Asymptomatic Angiographic Vasospasm on Admission. World Neurosurg 97: 199-204.

30. Rosenthal ES, Biswal S, Zafar SF, et al. (2018) Continuous electroencephalography predicts delayed cerebral ischemia after subarachnoid hemorrhage: A prospective study of diagnostic accuracy. Ann Neurol 83: 958-69.

31. Wilson CD, Shankar JJ (2014) Diagnosing Vasospasm after Subarachnoid Hemorrhage: CTA and CTP. Can J Neurol Sci 41: 314-379.

32. Maher M, Schweizer TA, Macdonald RL (2020) Treatment of Spontaneous Subarachnoid Hemorrhage: Guidelines and Gaps. Stroke 51: 1326-1332.

33. von der Brelie C, Doukas A, Stopfer A, et al. (2017) Clinical Course and Monitoring Parameters After Continuous Interventional Intra-Arterial Treatment in Patients with Refractory Cerebral Vasospasm. World Neurosurg 100: 504-513.

34. Bernier TD, Schontz MJ, Izzy S, et al. (2021) Treatment of Subarachnoid Hemorrhage-associated Delayed Cerebral Ischemia with Milrinone: A Review and Proposal. J Neurosurg Anesthesiol 33: 195-202.

35. Durrant JC, Hinson HE (2015) Rescue therapy for refractory vasospasm after subarachnoid hemorrhage. Curr Neurol Neurosci Rep 15: 521.

36. Hosmann A, Rauscher S, Wang WT, et al. (2018) Intra-Arterial Papaverine-Hydrochloride and Transluminal Balloon Angioplasty for Neurointerventional Management of Delayed-Onset Post-Aneurysmal Subarachnoid Hemorrhage Vasospasm. World Neurosurg 119: e301-e312.

37. Schacht H, Kuchler J, Boppel T, et al. (2020) Transluminal balloon angioplasty for cerebral vasospasm after spontaneous subarachnoid hemorrhage: A single-center experience. Clin Neurol Neurosurg 188: 105590.

38. Anetsberger A, Gempt J, Blobner M, et al. (2020) Impact of Goal-Directed Therapy on Delayed Ischemia After Aneurysmal Subarachnoid Hemorrhage: Randomized Controlled Trial. Stroke 51: 2287-2296.

39. Smith WS, Dowd CF, Johnston SC, et al. (2004) Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 35: 2518-2522.

40. Minhas JS, Moullaali TJ, Rinkel GJE, Anderson CS (2022) Blood Pressure Management after Intracerebral and Subarachnoid Hemorrhage: The Knowns and Known Unknowns. Stroke 53: 1065-1073.

41. Hawkes MA, Anderson CS, Rabinstein AA (2022) Blood Pressure Variability after Cerebrovascular Events: A Possible New Therapeutic Target: A Narrative Review. Neurology 99: 150-60.

42. Anderson CS, Heeley E, Huang Y, et al. (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 368: 2355-65.

43. Qureshi AI, Palesch YY, Barsan WG, et al. (2016) Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. N Engl J Med 375: 1033-43.

44. Ma L, Hu X, Song L, et al. (2023) The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): An international, stepped wedge cluster randomised controlled trial. Lancet 402: 27-40.

45. Gathier CS, van den Bergh WM, van der Jagt M, et al. (2018) Induced Hypertension for Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage: A Randomized Clinical Trial. Stroke 49: 76-83.

46. Cossu G, Messerer M, Stocchetti N, Levivier M, Daniel RT, et al. (2016) Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: A systematic review. Minerva Anestesiol

47. Birg T, Ortolano F, Wiegers EJA, et al. (2021) Brain Temperature Influences Intracranial Pressure and Cerebral Perfusion Pressure After Traumatic Brain Injury: A CENTER-TBI Study. Neurocritical care 35: 651-661.

48. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. (2001) Fever in subarachnoid hemorrhage: Relationship to vasospasm and outcome. Neurology 56: 1299-1304.

49. Mohney N, Alkhatib O, Koch S, O'Phelan K, Merenda A (2020) What is the Role of Hyperosmolar Therapy in Hemispheric Stroke Patients? Neurocritical care 32: 609-619.

50. Mortazavi MM, Romeo AK, Deep A, et al. (2012) Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. J neurosurg 116: 210-221.

51. Le Roux P (2022) Neuro-ICU: Monitoring and Management of Intracranial Pressure. A Practical Review. In: Rodríguez CN, Baracchini C, Mejia-Mantilla JH, et al., eds. Neurosonology in Critical Care: Monitoring the Neurological Impact of the Critical Pathology. Cham: Springer International Publishing; 2022: 15-46.

52. Roberts I, Sydenham E (2012) Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev 12: CD000033.

53. Sharma D (2021) Perioperative Management of Aneurysmal Subarachnoid Hemorrhage: A Narrative Review: Erratum. Anesthesiology 134: 672.

54. Kam PC, Cardone D (2007) Propofol infusion syndrome. Anaesthesia 62: 690-701.

55. Huang XC, Yang LL (2015) [Comparison clinical efficacy of 3% hypertonic saline solution with 20% mannitol in treatment of intracranial hypertension in patients with aneurysmal subarachnoid hemorrhage]. Zhejiang Da Xue Xue Bao Yi Xue Ban 44: 389-395.

56. Wagner I, Hauer EM, Staykov D, et al. (2011) Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. Stroke 42: 1540-1545.

57. Pasarikovski CR, Alotaibi NM, Al-Mufti F, Macdonald RL (2017) Hypertonic Saline for Increased Intracranial Pressure after Aneurysmal Subarachnoid Hemorrhage: A Systematic Review. World Neurosurg 105: 1-6.

58. Gasser S, Khan N, Yonekawa Y, Imhof HG, Keller E (2003) Long-term hypothermia in patients with severe brain edema after poor-grade subarachnoid hemorrhage: feasibility and intensive care complications. J Neurosurg Anesthesiol 15: 240-8.

59. Seule MA, Muroi C, Mink S, Yonekawa Y, Keller E (2009) Therapeutic hypothermia in patients with aneurysmal subarachnoid hemorrhage, refractory intracranial hypertension, or cerebral vasospasm. Neurosurgery 64: 86-92.

60. Kondziella D, Friberg CK, Wellwood I, Reiffurth C, Fabricius M, et al. (2015) Continuous EEG monitoring in aneurysmal subarachnoid hemorrhage: a systematic review. Neurocrit Care 22: 450-461.

61. Gollwitzer S, Muller TM, Hopfengartner R, et al. (2019) Quantitative EEG After Subarachnoid Hemorrhage Predicts Long-Term Functional Outcome. J Clin Neurophysiol 36: 25-31.

62. Raper DM, Starke RM, Komotar RJ, Allan R, Connolly ES Jr (2013) Seizures after aneurysmal subarachnoid hemorrhage: A systematic review of outcomes. World Neurosurg 79: 682-690.

63. Chen Y, Xia F, Cai C, et al. (2021) Duration and choices of prophylactic anticonvulsants in subarachnoid hemorrhage: a systematic review and meta-analysis. Neurosurg Rev 44: 2459-2467.