Updates on aneurysmal subarachnoid hemorrhage: is there anything really new?

Atualizações em hemorragia subaracnóidea aneurismática: há algo realmente novo?

Thire Baggio Machado MARAZZI[1], Pedro Vitale MENDES[2]

ABSTRACT

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is a severe disease, with systemic involvement and complex diagnosis and treatment. Since the current guidelines were published by the AHA/ASA, Neurocritical Care Society and the European Stroke Organization in 2012-2013,there has been an evolution in the comprehension of SAH-associated brain injury and its multiple underlying mechanisms. As a result, several clinical and translational trials were developed or are underway. **Objective:** The aim of this article is to review some updates in the diagnosis and treatment of neurological complications of SAH. **Methods:** A review of PubMed (May, 2010 to February, 2022) was performed. Data was summarized. **Results:** Content of five meta-analyses, nine review articles and 23 new clinical trials, including pilots, were summarized. **Conclusions:** Advances in the comprehension of pathophysiology and improvements in critical care have been reflected in the reduction of mortality in SAH. However, despite the number of publications, the only treatments shown to be effective in adequate, well-controlled clinical trials are nimodipine and repair of the ruptured aneurysm. Thus, doubts about the optimal management of SAH still persist.

Keywords: Subarachnoid Hemorrhage; Aneurysm; Vasospasm, Intracranial.

RESUMO

Antecedentes: Hemorragia subaracnóide aneurismática (HSAa) é uma doença grave, com envolvimento sistêmico, complexo diagnóstico e tratamento. Desde a publicação dos atuais protocolos de conduta pela AHA/ASA, Neurocritical Care Society e European Stroke Organization de 2012-2013, houve evolução na compreensão da lesão cerebral associada à HSA e seus múltiplos mecanismos subjacentes. Como resultado, muitos trabalhos clínicos e translacionais foram desenvolvidos ou estão em andamento. **Objetivos:** O objetivo deste artigo é revisar algumas das atualizações no diagnóstico e tratamento de complicações neurológicas de HSA. **Métodos:** Revisão de Pubmed (Maio de 2010 a Fevereiro de 2022) foi realizada. Dados foram sintetizados. **Resultados:** O conteúdo de 5 metanálises, 9 artigos de revisão e 23 novos estudos clínicos, incluindo pilotos, foram sumarizados. **Conclusões:** Avanços na compreensão da fisiopatologia e melhorias no cuidado crítico têm se refletido na redução da mortalidade em HSA. Entretanto, apesar do volume de publicações, os únicos tratamentos que se mostraram efetivos com testes clínicos bem controlados são o uso de nimodipino e o tratamento dos aneurisma rotos. Assim, dúvidas acerca do manejo ideal em HSA ainda persistem.

Palavras-chave: Hemorragia Subaracnóidea; Aneurisma;Vasoespasmo Intracraniano.

GENERAL CONSIDERATIONS

Aneurysmatic Subarachnoid Hemorrhage (aSAH) is a complex disease and a relevant health problem. In terms of epidemiology, concepts should be highlighted: incidence varies greatly among countries. It is estimated at 2-16 per 100,000 per annum worldwide[1], while Finland is the country with the highest incidence, with 22.7 per 100,000 per annum[2]. Furthermore, aSAH affects a relatively young population, with a peak of around 50 years-old[3], causing higher mortality (about 50% at the time of aneurysmal rupture and with 30-day mortality up to 45%) and extensive long-term morbidity (a third of survivors require full care, and a third are not able to return to work)[4]. And lastly, it is estimated that the global aSAH case-fatality rate has decreased by 17% to 50% in the last 30 years as a result of improving diagnostic accuracy, surgical techniques, critical care support, cardiovascular risk prevention measures and adherence to guideline recommendations[5].

International guidelines are periodically updated with recommendations on screening, diagnosis, treatment and a

[1]Universidade de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil.

[2]Universidade de São Paulo, Departamento de Emergências Clínicas, São Paulo SP, Brazil.

TBMM ⓘ http://orcid.org/0000-0002-2613-490X; PVM ⓘ http://orcid.org/0000-0002-2613-490X; 0000-0002-6062-9105

Correspondence: Thire Baggio Machado Marazzi; Email: thire.marazzi@fm.usp.br.

comprehensive pathophysiological review. However, the last publication was by the AHA/ASA, Neurocritical Care Society, and the European Stroke Organization dated 2012-2013[3,6,7]. This article was developed by summarizing some recent studies (five meta-analyses, nine review articles and 23 clinical trials) and their results as to diagnosis and treatment of aSAH neurological complications.

UP-TO-DATE IN DIAGNOSIS

In approximately 70% of patients with aSAH the clinical manifestation was a sudden headache. In order to help clinicians with diagnostic decisions in the emergency department the Ottawa SAH rules were developed. A cohort comprising 2131 patients with a headache peaking within an hour and no neurologic deficits was analyzed[8]. Ottawa SAH rules (Box 1) considered patients high-risk if one or more variables were present from some clinical and epidemiological criterias[8]. This tool, in practice, has reduced the total number of lumbar punctures[9] in low-risk patients. The sensitivity was 100% (95% CI, 97.2%-100.0%) and specificity was 15.3% (95% CI, 13.8%-16.9%)[8].

IMAGING

The imaging method recommended and most used for the diagnosis of SAH is the non contrast head Computed Tomography (CT). It is an easy-to-perform test with high sensitivity (93% to 100%) in the first six hours of symptoms[9]. The sensitivity of this method progressively reduces in the days following the ictus, when other modalities, such as cranial Magnetic Resonance Imaging (MRI), become more sensitive.

MRI is an imaging method that can be used from the hyperacute to the chronic phase[10], requiring an adequate choice of sequence for analysis. More than two days after the ictus, the most used sequence is gradient recalled echo (GRE), reported in some studies with a sensitivity of 94% (95% for CT)[10]. Meanwhile, in subacute and chronic phases (4-15 days), the most sensitive sequences are susceptibility-weighted imaging (SWI) and fluid attenuated inversion recovery (FLAIR), sensitivities: 100% for FLAIR, 50% for CT, 30% for GRE[10].

Generally, physicians prefer CT because of availability, lower costs and time and simpler MRI image acquisition in critically ill patients. However, MRI images provide a superior assessment of brain parenchyma and can be useful to predict unfavorable outcomes. De Marchis et al.[11], even established that for every 10ml of DWI or FLAIR lesion volume, there was an outcome loss similar to 1 addition in Hunt Hess grade [OR 2.01 (95% (CI) 1.10–3.68; p=0.02)]. Other studies using functional outcomes by Rankin scale, cognitive test and Glasgow Outcome Scale have been described in a recent review[10].

For the etiological diagnosis of SAH and programming an aneurysmal surgical approach, digital subtraction catheter angiography (DSA) with 3-dimensional reconstructions remains the gold standard. However, it remains an invasive and risky

method. Alternatives are CT angiography (CTA), with a pooled sensitivity of 97% and specificity of 91%[12], and magnetic resonance angiography (MRA). In meta-analysis[12], MRA and CTA showed the same sensitivity as contrast-enhanced MR angiography (CEMRA) or Time-of-Flight MR angiography (TOF) technique. Nevertheless, some considerations must be made: MRA has higher rates of false-positives and false-negatives (especially lesions <3 mm and located at the skull base and middle cerebral artery)[12] and MRA has low accuracy in aneurysm neck size determination[13]. New techniques have been developed to reduce coil artifacts and increase the already high sensitivity to residual aneurysm screening. One such technique was the sequence non-contrast enhanced zero echo time (zTE)[14].

In recent years, MRI vessel wall assessment techniques have been studied to predict expansion and aneurysmal rupture, and to localize each high-risk in patients with multiple aneurysms[15]. Both qualitative and quantitative, automatic or semi-automatic methods of evaluating wall enhancement have been published, all with good predictive ability and good reproducibility[15,16]. There are still few studies showing a pathophysiological and radiological correlation associated with increased local vessel wall enhancement.

UP-TO-DATES IN COMPREHENSIVE PATHOPHYSIOLOGY

SAH-associated brain injury (SAHBI) is still not completely understood despite medical advances made over the past three decades.

Previously, the SAHBI was didactically divided into early and delayed phases[9]. All studies focused on preventing and treating the most severe complications of each one. Management of unruptured aneurysms, reduction of risk factors, timing and surgical treatment techniques, treatment of rebleeding and

hydrocephalus were the focus of early brain injury (EBI) trials. Meanwhile, in the delayed phase, prevention and treatment of vasospasm (VSP) were used in order to reduce delayed cerebral ischemia (DCI).

As bench studies identified inflammatory mechanisms as precursors of DCI, some translational trials began to be developed. However, although the results demonstrated a reduction in large arteries VSP occurrence, there was no difference in functional outcome, e.g. clinical trials using the endothelin-1 (ET-1) receptor antagonist clazosentan[17]. These results motivated a shift in the focus of investigation from aSAH severe complications to the underlying mechanisms and the cascade triggered at the time of aneurysmal rupture and consequently downstream.

The current concept of pathophysiology of SAHBI is multiphasic, complex and multifactorial, with a cascade of events that are all interrelated and that permeate all stages of the disease[9,18,19]. Considered aSAH phases are a continuum in which all events contribute to outcome.

Some supracited underlying mechanisms already studied were neuroinflammation, microthrombosis, cortical spreading depolarizations, disrupted integrity of the blood-brain barrier, microvascular dysfunction, sympathoadrenal activation and endothelial cell dysfunction. Many reviews on advances in each of these mechanisms and their promising fields of investigation have been published recently[18–20].

UP-TO-DATE IN NEUROLOGICAL MANAGEMENT

aSAH is a disease with severe neurological and systemic manifestations. Below are detailed some therapeutic and monitoring strategies for only neurological complications.

REBLEEDING

At least ten randomized studies between 1982 and 2012 evaluated the use of oral or intravenous antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid) for SAH early rebleeding prevention[21]. The results showed a reduced risk of rebleeding by about 35%, but no improvement in clinical outcomes. In addition, an increase in DCI was observed. Due to these two independent effects, current international guidelines differ in their recommendations about the use of antifibrinolytic drugs. To clarify this doubt, "Ultra-early Tranexamic Acid After SAH" (ULTRA) was developed and published in 2021[22]. Four hundred and eighty patients received ultra-early (at diagnosis) short-term tranexamic acid treatment (bolus 1g plus 1g each 8h, maximum doses 4g). No improvement in clinical outcome at six months was shown. Therefore, there is no evidence for current use.

TIMING AND TREATMENT FOR ANEURYSM REPAIR

Guidelines suggest repairing the aneurysm "as early as feasible"(3), but it was still unclear whether ultra-early treatment (<24h) improves outcomes compared with early treatment (24-72h). Discordant results have been published in retrospective studies and the three largest[23–25] were reviewed in meta-analysis[26]. Patients treated within 24 hours showed poor functional (OR 1.46 [0.47-2.9]) and mortality (OR 1.80 [0.88-3.67]) outcomes, when compared with those treated between 24 and 72 hours. This data should be critically evaluated: one (the largest sample) showed poor outcomes in treatment within 24 hours and all are retrospective, some non-randomized, most treated with coil. Thus, more studies are needed.

EARLY BRAIN INJURY

Intravenous glibenclamide, a SUR1 inhibitor glyburide, has been shown to be safe and effective in reducing cerebral edema in patients with large cerebral infarct in pilot studies[27]. Some studies are underway with the use of the drug in patients with aSAH, including the Brazilian GASH trial[28]. Therefore, at the moment, there is no evidence to support its use.

DCI PREVENTION

Strategies

Although prophylactic hypertension and hypervolemia are not recommended under current guidelines[3,6,7], there are a few randomized controlled trials comparing the volume and pressure management strategies. Recently, a German group performed Randomized Controlled Trial (RCT)[29] with 108 patients comparing goal-directed hemodynamic therapy (GDHT) versus standard therapy. Transpulmonary thermodilution monitoring was used to calculate global end-diastolic index, cardiac index and extravascular lung water index. According to an institutional goal protocol, fluids and vasoactive drugs could be used and titulated in accordance with clinical response or the occurrence of side effects. The results showed that GDHT reduced the rate of DCI (odds ratio: 0.324; 95% CI 0.11−0.86; p = 0.021), with a better functional outcome (GOS=5) three months after discharge, although it did not change the mortality rate when compared with the control group.

Pharmacological therapies

Many pharmacological therapies have been tested for the prevention of EBI and DCI. However, most publication designs are retrospective studies or pilot trials. We summarize some of them and two RCTs in Table 1.

RCT findings

Previously, the guidelines already included results from RCTs with the use of the magnesium sulfate (MASH II)[30]

and endothelin-1 (ET-1) receptor antagonist clazosentan (CONSCIOUS 1 and 2)[17] claiming no clinical benefit. After publication of the current guidelines, no new RCTs showed discordant results of MASH II over intravenous magnesium use. Recently, the use of clazosentanhas become a subject of study: the REACT trial is being developed with different clazosentan doses and it is proposed to identify the subgroups of patients who would benefit (ClinicalTrials.gov Identifier: NCT03585270) from prevention of neurologic worsening by DCI.

Among the newly-published RCTs, two were more prominent: the use of oral simvastatin (STASH trial)[31] and intrathecal use of nimodipine (NEWTON2 trial)[32], both lacking favorable results in clinical outcome.

Therefore, unfortunately, no additional drug therapy has been suggested in high-quality studies.

Therapies remain controversial

The use of intraventricular fibrinolytic therapy had already been evaluated in meta-analyses in 2004[33]showing benefits in reducing DCI and morbidity. However, the quality of the nine studies included, with only one randomized, was considered low or moderate. Despite the limitations, the ASH treatment Japanese guideline[34] incorporated the therapy into its recommendations. We found two subsequent published studies (Table 1), only one with a primary functional outcome[35,36]. In this study, the intraventricular fibrinolytic therapy had no benefits[36].

Emerging therapies

Cilostazol, a selective phosphodiesterase-3 inhibitor with vasodilating and antiplatelet action, has been shown to be a promising and safe enteral drug.

A meta-analysis published in 2018[37] evaluated the use of Cilostazol in four RCTs and a prospective cohort, in a total of 543 patients. The result was decreased risk of symptomatic vasospasm (0.31, 95% CI 0.20 to 0.48; P < 0.001), cerebral infarction (0.32, 95% CI 0.20 to 0.52; P < 0.001) and poor outcome (0.40, 95% CI 0.25 to 0.62; P < 0.001). No serious adverse effects were related with a dose of 100mg oral BID for 2 weeks. These studies however, included only those from the Japanese population. Most trials must be performed with another population.

Another promising therapy is continuous infusion unfractionated heparin, the use of which was associated with a reduction in rescue therapy necessity in severe vasospasm and DCI incidence, and improved cognitive outcomes[38,39]. In these, the dose used was started at 8 U/kg/h 12 hours after surgery, progressing in 36 hours to 10 U/kg/h (Maryland Protocol). The pathophysiological explanation is complex, as heparin has broad effects: antifibrinolytic and anti-inflammatory effects, reduction of free radicals, interaction with hemoglobin-free complex and activation endothelial.

An RCT is underway for large-scale evaluation of effects and safety: Randomizing Aneurysmal Subarachnoid Heparin Heparin Assay (ASTROH)[40].

Table1. Clinical trials of delayed cerebral ischemia therapeutics.

Study	Study type	Agent	Biological Background	Result
STASH (Simvastatin in Aneurysmal Subarachnoid Hemorrhage)31	RCT	Simvastatin 40 mg/d orally for 21 days	Complex and multiple mechanism. Success phase II trials with others statins	No differences for long-term or short-term outcome
NEWTON2 (Study of EG-1962 Compared to Standard of Care Oral Nimodipine in Adults With Aneurysmal Subarachnoid Hemorrhage)32	RCT	Microparticle formulation of 600mg nimodipine. Application intratecal	Oral nimodipine improves clinical outcome, no reduction radiologic VSP	Trial stopped early due to high rate of vasospasm and DCI
Intraventricular Tissue Plasminogen Activator in Subarachnoid Hemorrhage Patients: A Prospective, Randomized, Placebo Controlled Pilot Trial35	Pilot trial Phase II	Dose 2 mg 12/12h intraventricular tissue plasminogen activator (TPA)	Amount of intracranial hemorrhage directly associated with worse clinical outcome.	TPA as a potent clot clearance accelerator. No clinical outcome assessment
Prospective, randomized, open-label phase II trial on concomitant intraventricular fibrinolysis and low-frequency rotation after severe subarachnoid hemorrhage36	Prospective randomized Phase II	5 mg of rt-PA was diluted in 2 mL of NaCl and given as an intraventricular bolus every 12 hours	Amount of intracranial hemorrhage directly associated with worse clinical outcome.	No reduction of delayed cerebral ischemia or poor functional outcome
Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment39	Controlled retrospectively	Low-dose intravenous heparin infusion:8 U/kg/hr progressing over 36 hours to 10 U/kg/hr	Microthrombotic mechanisms in intracranial vasculature shown to be associated with DCI in bench study	Reduction in the occurrence of DCI and vasospasm in the intervention group. No increase in bleeding.

RCT: Randomized Clinical Trial; DCI: Delayed Cerebral Ischemia; VSP: vasospam.

Rescue therapies

In the treatment of established DCI, some rescue therapies are recommended. In this context however, no treatment was supported by a high-quality clinical trial and the impact of complications remains unmeasured. All recommendations were based on observational, retrospective, uncontrolled case series or institutional protocols.
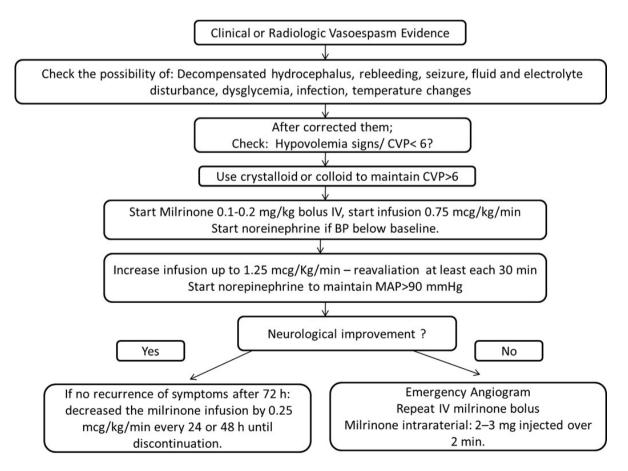
Induction of arterial hypertension is the first treatment recommended by many guidelines in this scenario[3,6,7]. In 2018, the RCT[41] compared functional outcome by Rankin scale among patients with and without induction of arterial hypertension three hours after onset of clinical symptoms. Hypertension was performed with norepinephrine or fluids, and was progressively increased until clinical improvement or MAP > 130 mmHg or SBP > 230, while the control maintained MAP around 80.

The study was paused with 41 participants due to slow recruitment and adverse effects. The adjusted risk ratio for poor outcome was 1.0 (95% confidence interval, 0.6–1.8) and the risk ratio for serious adverse events 2.1 (95% confidence interval, 0.9–5.0) was reported.

Endovascular treatments with arterial balloon and intra-arterial vasodilator infusions, commonly used after hypertension induction due to favorable results in retrospective studies and case series, are not yet supported by RCT results. Venkatraman[42] separated 55 studies using different doses and types (fasudil, nimodipine, nicardipine,papaverine verapamil) of intra-arterial vasodilators. The control group included patients without endovascular treatment or arterial balloon. Despite differences in outcome results with each vasodilator, all robustly reduced the severity of vasospasm but without neurological response. This study did not include milrinone as a vasodilator.

Milrinone is a selective inhibitor of the phosphodiesterase III isoenzyme with a vasodilatador and inotropic effect, which has been used as a rescue therapy after failure of induced hypertension in some specialized services in the world[4,43], although it is not cited in current guidelines. Milrinone can be used as a continuous intravenous infusion (IV), intra-arterial (IA) bolus, or a combination of both (IVIA). Studies evaluating therapeutic modalities do not show differences in safety and outcome between intravenous or associated therapy[44]. In 2016, a meta-analysis found 24 studies using milrinone IV, IA, IVIA, all with low quality of evidence[45]. Unfortunately, the only RCT was discontinued in 2017 due to lack of suitable subjects[46].

Specifically, the intravenous milrinone infusion protocol (initiation dose, continuous infusion dose, velocity of increment and withdrawal and treatment time) is based on service experiences, the most widespread being the Montreal Protocol (Figure 1)[43]. There is still a lack of studies that evaluate the

Algorithm adaptation of milrinone using Montreal Protocol. CVC: Central Venous Pressure; BP: Blood Pressure; MAP: Median Arterial Pressure.
Figure 1. Adaptation of Montreal Protocol.

comparison of safety and benefit between intravenous infusion protocols from different institutions.

Recently, a retrospective study[47] with 40 patients showed benefits without side effects with high doses of IV milrinone. In this study, 18 patients received boluses of up to 8mg IV with continuous infusion of up to 2.75 mcg/kg/min (maximum cumulative daily 230mg).

Other inotropic therapies have been shown to be effective in reversing vasospasm. In a few comparative studies[48,49], the benefit of using dobutamine outweighs that of milrinone in refractory patients. The risks and precautions are the same with both drugs: hypotension is the main complication and the use of a cardiac output monitor is the main additional care.

For both drugs, high quality studies are needed.

OTHER FREQUENT NEUROLOGICAL COMPLICATIONS

Despite the prevalence of seizures in SAH, no randomized clinical trials with new antiepileptic drugs for primary or secondary prophylaxis have been published.

In conclusion, advances in the comprehension of pathophysiology and improvements in critical care have been reflected in the reduction of mortality in SAH. However, despite the number of publications, the only treatments shown to be effective in adequate, well-controlled clinical trials are nimodipine and repair of the ruptured aneurysm. Thus, doubts about the optimal management of SAH still persist.

ACKNOWLEDGEMENTS

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009 Apr 1;8(4):P355-69. https://doi.org/10.1016/S1474-4422(09)70025-0

2. Ingall T, Asplund K, Mähönen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000 May 1;31(5):1054-61. https://doi.org/10.1161/01.STR.31.5.1054

3. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012 May 3;43(6):1711-37. https://doi.org/10.1161/STR.0b013e3182587839

4. Rouanet C, Silva GS. Aneurysmal subarachnoid hemorrhage: current concepts and updates. Arq Neuropsiquiatr. 2019 Nov;77(11):806-14. https://doi.org/10.1590/0004-282X20190112

5. Lovelock CE, Rinkel GJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. Neurology. 2010 May 11;74(19):1494-501. https://doi.org/10.1212/WNL.0b013e3181dd42b3

6. Diringer MN, Bleck TP, Hemphill JC 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011 Sep;15(2):211-40. https://doi.org/10.1007/s12028-011-9605-9

7. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G; European Stroke Organization. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35(2):93-112. https://doi.org/10.1159/000346087

8. Perry JJ, Stiell IG, Sivilotti MLA, Bullard MJ, Hohl CM, Sutherland J, et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. JAMA. 2013 Sep 25;310(12):1248-55. https://doi.org/10.1001/jama.2013.278018

9. Chou SH-Y. Subarachnoid hemorrhage. Continuum (Minneap Minn). 2021 Oct 1;27(5):1201–45. https://doi.org/10.1212/CON.0000000000001052

10. Nelson SE, Sair HI, Stevens RD. Magnetic resonance imaging in aneurysmal subarachnoid hemorrhage: current evidence and future directions. Neurocrit Care. 2018 Oct 1;29(2):241-52. https://doi.org/10.1007/s12028-018-0534-8

11. De Marchis GM, Filippi CG, Guo X, Pugin D, Gaffney CD, Dangayach NS, et al. Brain injury visible on early MRI after subarachnoid hemorrhage might predict neurological impairment and functional outcome. Neurocrit Care. 2015 Feb;22(1):74-81. https://doi.org/10.1007/s12028-014-0008-6

12. Sailer AMH, Wagemans BAJM, Nelemans PJ, de Graaf R, van Zwam WH. Diagnosing intracranial aneurysms with MR angiography: systematic review and meta-analysis. Stroke. 2014 Jan;45(1):119-26. https://doi.org/10.1161/STROKEAHA.113.003133

13. Neifert SN, Chapman EK, Martini ML, Shuman WH, Schupper AJ, Oermann EK, et al. Aneurysmal Subarachnoid Hemorrhage: the Last Decade. Transl Stroke Res. 2021 Jun;12(3):428-46. https://doi.org/10.1007/s12975-020-00867-0

14. Shang S, Ye J, Luo X, Qu J, Zhen Y, Wu J. Follow-up assessment of coiled intracranial aneurysms using zTE MRA as compared with TOF MRA: a preliminary image quality study. Eur Radiol. 2017 Oct;27(10):4271–80. https://doi.org/10.1007/s00330-017-4794-z

15. Fu Q, Wang Y, Zhang Y, Zhang Y, Guo X, Xu H, et al. Qualitative and quantitative wall enhancement on magnetic resonance imaging is associated with symptoms of unruptured intracranial aneurysms. Stroke. 2021 Jan;52(1):213-22. https://doi.org/10.1161/STROKEAHA.120.029685

16. Raghuram A, Varon A, Roa JA, Ishii D, Lu Y, Raghavan ML, et al. Semiautomated 3D mapping of aneurysmal wall enhancement with 7T-MRI. Sci Rep. 2021 Sep 15;11(1):18344. https://doi.org/10.1038/s41598-021-97727-0

17. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011 Jul 1;10(7):P618-25. https://doi.org/10.1016/S1474-4422(11)70108-9

18. Osgood ML. Aneurysmal subarachnoid hemorrhage: review of the pathophysiology and management strategies. Curr Neurol Neurosci Rep. 2021 Jul 26;21(9):50. https://doi.org/10.1007/s11910-021-01136-9

19. Geraghty JR, Davis JL, Testai FD. Neuroinflammation and Microvascular Dysfunction After Experimental Subarachnoid Hemorrhage: Emerging Components of Early Brain Injury Related

to Outcome. Neurocrit Care. 2019 Oct;31(2):373-89. https://doi.org/10.1007/s12028-019-00710-x

20. Geraghty JR, Testai FD. Delayed cerebral ischemia after subarachnoid hemorrhage: beyond vasospasm and towards a multifactorial pathophysiology. Curr Atherocler Rep. 2017 Oct 23;19(12):50. https://doi.org/10.1007/s11883-017-0690-x

21. Baharoglu MI, Germans MR, Rinkel GJE, Algra A, Vermeulen M, van Gijn J, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2013 Aug 30;2013(8):CD001245. https://doi.org/10.1002/14651858.CD001245.pub2

22. Post R, Germans MR, Tjerkstra MA, Vergouwen MDI, Jellema K, Koot RW, et al. Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. Lancet. 2021 Jan 9;397(10269):112-8. https://doi.org/10.1016/S0140-6736(20)32518-6

23. Qian Z, Peng T, Liu A, Li Y, Jiang C, Yang H, et al. Early timing of endovascular treatment for aneurysmal subarachnoid hemorrhage achieves improved outcomes. Curr Neurovasc Res. 2014 Feb;11(1):16–22. https://doi.org/10.2174/1567202610666131210104606

24. Oudshoorn SC, Rinkel GJE, Molyneux AJ, Kerr RS, Mees SMD, Backes D, et al. Aneurysm treatment <24 versus 24-72 h after subarachnoid hemorrhage. Neurocrit Care. 2014 Aug;21(1):4-13. https://doi.org/10.1007/s12028-014-9969-8

25. Phillips TJ, Dowling RJ, Yan B, Laidlaw JD, Mitchell PJ. Does treatment of ruptured intracranial aneurysms within 24 hours improve clinical outcome? Stroke. 2011 Jun 16;42(7):1936-45. https://doi.org/10.1161/STROKEAHA.110.602888

26. Rawal S, Alcaide-Leon P, Macdonald RL, Rinkel GJE, Victor JC, Krings T, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid haemorrhage: inconsistent results of early treatment within 1 day. J Neurol Neurosurg Psychiatry. 2017 Mar;88(3):241-8. https://doi.org/10.1136/jnnp-2016-314596

27. Sheth KN, Elm JJ, Molyneaux BJ, Hinson H, Beslow LA, Sze GK, et al. Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2016 Oct 1;15(11):P1160-9. https://doi.org/10.1016/S1474-4422(16)30196-X

28. da Costa BBS, Windlin IC, Koterba E, Yamaki VN, Rabelo NN, Solla DJF, et al. Glibenclamide in Aneurysmatic Subarachnoid Hemorrhage (GASH): study protocol for a randomized controlled trial. Trials. 2019 Jul 9;20(1):413. https://doi.org/10.1186/s13063-019-3517-y

29. Anetsberger A, Gempt J, Blobner M, Ringel F, Bogdanski R, Heim M, et al. Impact of goal-directed therapy on delayed ischemia after aneurysmal subarachnoid hemorrhage. Stroke. 2020 Jul 9;51(8):2287-96. https://doi.org/10.1161/STROKEAHA.120.029279

30. Mees SMD, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. Lancet. 2012 Jul 7;380(9836):44-9. https://doi.org/10.1016/S0140-6736(12)60724-7

31. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD; STASH Collaborators. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014 Jul 1;13(7):P666-75. https://doi.org/10.1016/S1474-4422(14)70084-5

32. Macdonald RL, Hänggi D, Ko NU, Darsaut TE, Carlson AP, Wong GK, et al. NEWTON-2 cisternal (nimodipine microparticles to enhance recovery while reducing toxicity after subarachnoid hemorrhage): a phase 2, multicenter, randomized, open-label safety study of intracisternal EG-1962 in aneurysmal subarachnoid hemorrhage. Neurosurgery. 2020 Dec 15;88(1):E13–26. https://doi.org/10.1093/neuros/nyaa430

33. Amin-Hanjani S, Ogilvy CS, Barker FG 2nd. Does intracisternal thrombolysis prevent vasospasm after aneurysmal subarachnoid hemorrhage? A meta-analysis. Neurosurgery. 2004 Feb 1;54(2):326-34. https://doi.org/10.1227/01.neu.0000103488.94855.4f

34. Committee for Guidelines for Management of Aneurysmal Subarachnoid Hemorrhage, Japanese Society on Surgery for Cerebral Stroke. Evidence-based guidelines for the management of aneurysmal subarachnoid hemorrhage english edition. Neurol Med Chir (Tokyo). 2012;52(6):355-429. https://doi.org/10.2176/nmc.52.355

35. Kramer AH, Roberts DJ, Holodinsky J, Todd S, Hill MD, Zygun DA, et al. Intraventricular tissue plasminogen activator in subarachnoid hemorrhage patients: a prospective, randomized, placebo-controlled pilot trial. Neurocrit Care. 2014 Oct;21(2):275-84. https://doi.org/10.1007/s12028-014-9965-z

36. Etminan N, Beseoglu K, Eicker SO, Turowski B, Steiger H-J, Hänggi D. Prospective, randomized, open-label phase II trial on concomitant intraventricular fibrinolysis and low-frequency rotation after severe subarachnoid hemorrhage. Stroke. 2013 Aug 1;44(8):2162-8. https://doi.org/10.1161/STROKEAHA.113.001790

37. Saber H, Desai A, Palla M, Mohamed W, Seraji-Bozorgzad N, Ibrahim M. Efficacy of cilostazol in prevention of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a meta-analysis. J Stroke Cerebrovasc Dis. 2018 Nov 1;27(11):P2979-85. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.06.027

38. James RF, Khattar NK, Aljuboori ZS, Page PS, Shao EY, Carter LM, et al. Continuous infusion of low-dose unfractionated heparin after aneurysmal subarachnoid hemorrhage: a preliminary study of cognitive outcomes. J Neurosurg. 2018 May 11;130(5):1460-7. https://doi.org/10.3171/2017.11.JNS17894

39. Simard JM, Aldrich EF, Schreibman D, James RF, Polifka A, Beaty N. Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment. J Neurosurg. 2013 Dec;119(6):1611-9. https://doi.org/10.3171/2013.8.JNS1337

40. Neurocritical Care Society 14th Annual Meeting. Neurocrit Care. 2016 Sep;25(1 Suppl 1):1–310. https://doi.org/10.1007/s12028-016-0301-7

41. Gathier CS, van den Bergh WM, van der Jagt M, Verweij BH, Dankbaar JW, Müller MC, et al. Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a randomized clinical trial. Stroke. 2017 Nov 20;49(1):76-83. https://doi.org/10.1161/STROKEAHA.117.017956

42. Venkatraman A, Khawaja AM, Gupta S, Hardas S, Deveikis JP, Harrigan MR, et al. Intra-arterial vasodilators for vasospasm following aneurysmal subarachnoid hemorrhage: a meta-analysis. J Neurointerv Surg. 2018 Apr;10(4):380-7. https://doi.org/10.1136/neurintsurg-2017-013128

43. Lannes M, Teitelbaum J, del Pilar Cortés M, Cardoso M, Angle M. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: the Montreal Neurological Hospital protocol. Neurocrit Care. 2012 Jun;16(3):354-62. https://doi.org/10.1007/s12028-012-9701-5

44. Crespy T, Heintzelmann M, Chiron C, Vinclair M, Tahon F, Francony G, et al. Which Protocol for Milrinone to Treat Cerebral Vasospasm Associated With Subarachnoid Hemorrhage? J Neurosurg Anesthesiol. 2019 Jul;31(3):323-9. https://doi.org/10.1097/ANA.0000000000000527

45. Lannes M, Zeiler F, Guichon C, Teitelbaum J. The use of milrinone in patients with delayed cerebral ischemia following subarachnoid hemorrhage: a systematic review. Can J Neurol Sci. 2017 Mar;44(2):152-60. https://doi.org/10.1017/cjn.2016.316

46. Shapiro S. Milrinone in addition to hyperdynamic therapy in the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. Clin Trial. 2018 May 3; NCT 02712788.

47. Alamri AS, Alturki A, Badawy M, Letourneau J, Lannes M, Angle M, et al. Abstract TMP101: safety and outcome of high doses iv milirinone in subarachnoid hemorrhage with refractory vasospasm. Stroke. 2016 Feb 16;47(1 Suppl 1):ATMP101. https://doi.org/10.1161/str.47.suppl_1.tmp101

48. Naidech A, Du Y, Kreiter KT, Parra A, Fitzsimmons B-F, Lavine SD, et al. Dobutamine versus milrinone after subarachnoid hemorrhage. Neurosurgery. 2005 Jan 1;56(1):21-7. https://doi.org/10.1227/01.NEU.0000144780.97392.D7

49. Mutoh TM, Kobayashi S, Kazumata K, Ishikawa T, Suzuki A. Dobutamine versus mirlinone for intensive hyperdynamic therapy to relieve focal cerebral ischemia caused by vasospasm after subarachnoid hemorrhage. Circulation. 2011 Jan 1;124(21).