

DELAYED CEREBRAL ISCHEMIA FOLLOWING AN ANEURYSMAL SUBARACHNOID HEMORRHAGE: THE SWORD OF DAMOCLES

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is an acute, life-threatening condition that manifests with severe headache (“thunderclap”), loss of consciousness, nausea, and vomiting. It arises as a consequence of a sudden release of blood into the subarachnoid space following a ruptured cerebral aneurysm. In the first 24-72 hours after an ictus, brain damage is the consequence of increased intracranial pressure and transient global ischemia (1). The diagnosis is often made in a prehospital setting and confirmed by a computed tomography (CT) scan or a lumbar puncture. Once the diagnosis is confirmed, the patient is prepared for surgical clipping or endovascular coiling of the ruptured aneurysm.

Obliteration of the aneurysm prevents rebleeding, which is an important risk factor for poor outcome. Is aneurysm obliteration sufficient to ensure a favorable outcome? Although securing the aneurysm prevents rebleeding, extravasated and degraded blood products may contribute to vascular dysfunction, oxidative stress, and neuronal injury, thereby promoting secondary brain injury (2). These reactions lead to the development of delayed cerebral ischemia (DCI), which is one of the main factors of aSAH outcome in patients (3).

Pathophysiology

Following aSAH, blood enters the subarachnoid space, where erythrocytes gradually undergo lysis and release hemoglobin into the cerebrospinal fluid (CSF) (4). Free hemoglobin is initially present primarily as oxyhemoglobin, but it can oxidize to methemoglobin and subsequently release heme (4,5). These hemoglobin degradation products play an important role in the development of cerebral vasospasm (CV) and DCI. Oxyhemoglobin can scavenge nitric oxide (NO), an important vasodilator, thereby contributing to cerebral vasoconstriction and the development of CV (5,6). At the same time, hemoglobin and heme can promote the generation of reactive oxygen species (ROS), leading to oxidative stress and damage to neurons, endothelial cells, lipids, and proteins (4,7).

Heme is subsequently metabolized, primarily through the action of heme oxygenase-1 (HO-1), producing biliverdin, which is further converted to bilirubin, as well as free iron and carbon monoxide. Free iron is particularly important because it can participate in redox reactions that generate highly reactive oxygen species, further enhancing oxidative stress and neuronal injury (8). In addition, heme can activate inflammatory pathways, including microglial and macrophage responses, thereby contributing to neuroinflammation. Bilirubin and its oxidation products may also contribute to oxidative injury and cerebral vasoconstriction (9). Thus, the degradation of erythrocytes and hemoglobin after aSAH results in the accumulation of several biologically active and potentially toxic compounds,

including oxyhemoglobin, methemoglobin, heme, bilirubin, and free iron. Together, these products contribute to oxidative stress, inflammation, endothelial dysfunction, cerebral vasoconstriction, and ultimately secondary brain injury following aSAH and DCI (10).

Clinical presentation of DCI

DCI is one of the most insidious complications of aSAH. DCI is not only a consequence of CV, but also neuroinflammation and endothelial dysfunction (1). DCI is a major complication of aSAH, typically occurring between days 3 and 14 after the initial hemorrhage, typically peaking around 7-10 days (11). However, it may occur later, even several weeks after the initial hemorrhage (12). This persistent threat of secondary brain injury can be regarded as a “sword of Damocles” hanging over the patient, emphasizing the need for continuous monitoring and early detection.

DCI presents as a new focal neurological deterioration that cannot be explained by other causes such as hydrocephalus, seizures, infection, metabolic disturbances, or the effects of sedative medication, or as a decrease of at least 2 points on the Glasgow Coma Scale (GCS), which should last for at least 1 hour and is not apparent immediately after aneurysm occlusion (1). The clinical manifestations depend on the affected vascular territory and may include new focal neurological deficits such as hemiparesis, facial weakness, sensory disturbances, or aphasia. Patients may also develop a decline in the level of consciousness, ranging from mild confusion and disorientation to somnolence, stupor, or coma. Cognitive and behavioral changes, including impaired attention, slowed responses, and altered behavior, may also occur.

Importantly, CV and DCI are not synonymous (13). CV refers to narrowing of the cerebral arteries, usually detected by angiography or suggested by increased blood-flow velocities on transcranial Doppler (TCD), whereas DCI is a clinical syndrome resulting from impaired cerebral perfusion and ischemia. Therefore, significant vasospasm may be present without clinical DCI, while DCI can occasionally occur without prominent angiographic vasospasm.

Risk Factors for DCI

Several factors that increase the risk of DCI have been identified. The most important predictors are the severity of the initial hemorrhage, reflected by a poor neurological grade on admission, and the amount of subarachnoid blood, particularly a high modified Fisher grade (14,15). Intraventricular hemorrhage is also associated with an increased risk of DCI (14). Other potential risk factors for DCI include cerebral vasospasm, hydrocephalus, older age, and systemic disturbances such as hyperglycemia, while early cerebral hypoperfusion and loss of consciousness at ictus have also been investigated as potential predictors (16). Although CV is strongly associated with DCI, DCI can occur even in the absence of significant angiographic vasospasm. Overall, patients presenting with a poor clinical grade, extensive subarachnoid blood, and intraventricular hemorrhage are considered to be at particularly high risk of developing DCI (15,17).

Diagnosis and Assessment of DCI

DCI is associated with poor clinical outcomes and reduced quality of life. Differentiating CV and DCI is essential because CV will not always lead to DCI, and up to 50% of patients with DCI have

no angiographic evidence of vasospasm (13). At first, DCI is diagnosed clinically, but also with TCD, computed tomography angiography (CTA), and computed tomography perfusion (CTP) (11). Digital subtraction angiography (DSA) is the gold-standard imaging modality for visualization of the cerebral vasculature. However, given its invasive nature, it is generally reserved for cases requiring detailed vascular assessment or potential endovascular treatment (18).

When clinically feasible, frequent standardized neurological examinations remain the most important modality for DCI monitoring. New focal neurological deficits, a decline in the level of consciousness, or unexplained neurological deterioration should raise suspicion for DCI (11,19).

The differential diagnosis is particularly important because neurological deterioration after aSAH can result from numerous causes, including rebleeding, hydrocephalus, seizures or non-convulsive status epilepticus, infection, metabolic abnormalities, medication effects, cerebral edema, and intracranial hypertension. Therefore, DCI should generally be considered a diagnosis of exclusion in a patient with new neurological deterioration (19).

In patients with poor-grade aSAH or limited neurological examination, multimodal assessment becomes particularly valuable (11,19). TCD can be used to monitor trends in cerebral blood flow velocities and to identify developing vasospasm. However, increased flow velocity indicates vascular narrowing rather than necessarily clinically significant cerebral ischemia. Consequently, TCD findings should be interpreted in conjunction with the neurological examination and other diagnostic modalities.

CTA can demonstrate large-vessel vasospasm, whereas CTP can provide additional information regarding cerebral blood flow (CBF), cerebral blood volume, mean transit time, and areas of potentially threatened tissue. These techniques may be particularly useful in patients in whom clinical examination is unreliable (19,20).

Continuous electroencephalography (cEEG) monitoring may also contribute to the evaluation of patients with unexplained changes in consciousness by detecting non-convulsive seizures and other patterns associated with cerebral dysfunction (11). Near-infrared spectroscopy (NIRS) is a non-invasive, bedside method for monitoring brain tissue oxygen saturation and an indirect measure of CBF. NIRS has potential for early detection of DCI in patients with poor-grade aSAH (21). Invasive brain tissue oxygenation monitoring (PbO₂) is considered the gold standard for measurement of brain tissue oxygen concentration (22). A level <20mmHg PbO₂ suggests focal cerebral hypoxia, and a level <15 mmHg requires immediate intervention to improve cerebral tissue oxygenation (11). Microdialysis of the brain is an invasive technique for continuous bedside monitoring of extracellular concentrations of lactate, pyruvate, lactate/pyruvate ratio, glutamate, glucose, and glycerol in brain tissue (23). It is used for the detection of ischemia and anaerobic metabolism. The most reliable markers for the prediction of ischemia are glutamate and lactate, as their values peak 24h before clinical ischemia. The microdialysis catheter should be placed in the area at risk for DCI (11).

Biomarkers for DCI Prediction

The development of molecular biology has discovered reliable CSF biomarkers, including micro ribonucleic acid (miRNA), messenger RNA (mRNA), fibrin degradation product (FDP), soluble re-

ceptors, calcium-binding protein (CBP), and high-mobility group box one protein (HMGB1) (11). Serum matrix metalloproteinase-9 (MMP-9), von Willebrand factor (vWF), and vascular endothelial growth factor (VEGF) are increased in patients at risk of DCI (24). Elevated NSE and S100 β levels in CSF and serum have been associated with the development of DCI following aSAH, suggesting their potential utility as predictive biomarkers (25). Cell-free hemoglobin CSF may also serve as a promising biomarker for the prediction of DCI (26).

Prevention of DCI

The risk of DCI is highest during the first two weeks after aSAH. Patients with a greater amount of subarachnoid blood, particularly those with high modified Fisher grades, and patients presenting with poor neurological status are at increased risk (14,15). Management, therefore, consists of prevention, intensive neurological and physiological monitoring, early recognition of cerebral hypoperfusion, and treatment aimed at restoring adequate cerebral perfusion when DCI develops.

Nimodipine

The most important pharmacological intervention for the prevention of DCI is enteral nimodipine (11,19). Nimodipine is a dihydropyridine calcium-channel blocker that has demonstrated a beneficial effect on neurological outcome after aSAH (1). Importantly, its benefit is not adequately explained simply by its effect on angiographic vasospasm, suggesting that neuroprotective and microcirculatory mechanisms may also contribute (27).

The standard regimen is 60 mg administered enterally every 4 hours, generally continued for 21 days after hemorrhage. Hypotension is the principal dose-limiting adverse effect. If systemic hypotension develops, treatment should be individualized, with adjustment of the dosing interval or temporary interruption when necessary rather than exposing the patient to clinically significant hypotension. Current guidelines consider early enteral nimodipine a fundamental component of aSAH management because it reduces the risk of DCI and is associated with improved functional outcomes (19).

It is important to distinguish nimodipine from other calcium-channel blockers. Other calcium-channel blockers have not demonstrated comparable evidence for improving functional outcomes and should not be considered equivalent substitutes (11).

Intrathecal administration of nimodipine and nicardipine has been investigated in several studies. Sustained-release formulations delivered via implants placed at the time of aneurysm clipping have shown promising results (28,29). Intravenous milrinone, a phosphodiesterase-3 inhibitor, was effective in the treatment of DCI (more than two-thirds of cases), but hypotension and tachycardia are side effects of its use (30). As the volume of subarachnoid blood clot is a predictor of DCI, instilling tissue plasmin activator (tPA)/urokinase into the cisterns and ventricles showed a risk reduction of significant DCI (31). Thrombolytics can be instilled into the ventricular or lumbar CSF drainage system.

Maintenance of Euvolemia

Optimization of intravascular volume is another central component of DCI prevention (11). Hypovolemia should be actively avoided because a reduction in circulating volume may compromise cerebral perfusion in the setting of impaired autoregulation. However, prophylactic hypervolemia is not rec-

ommended (19). The historical “triple-H” strategy - hypertension, hypervolemia, and hemodilution - has largely been abandoned because routine hypervolemia does not provide a proven neurological benefit and may cause substantial systemic complications, including pulmonary edema, cardiac strain, electrolyte abnormalities, and increased need for mechanical ventilation (11,19). Crystalloids, such as normal saline (0.9% NaCl), are commonly used for initial volume replacement. Hypertonic saline (3% NaCl) is considered for the reduction of cerebral edema and symptomatic hyponatremia. The use of colloids is controversial due to concerns about increased risk of cerebral edema (11,19).

Current management instead emphasizes goal-directed euvolemia, usually achieved with isotonic crystalloid solutions and individualized assessment of fluid balance, urine output, hemodynamic parameters, and, when appropriate, dynamic measures of fluid responsiveness.

Treatment of Symptomatic DCI

When DCI is suspected or diagnosed, the first step is to identify and correct potentially reversible systemic factors that can worsen cerebral perfusion. These include hypovolemia, hypotension, hypoxemia, anemia, fever, hyperglycemia or hypoglycemia, electrolyte abnormalities, and increased intracranial pressure (19). Once the ruptured aneurysm has been definitively secured by surgical clipping or endovascular treatment, hemodynamic augmentation with induced hypertension can be considered in patients with symptomatic DCI (11).

Induced Hypertension

The physiological rationale for induced hypertension is to increase cerebral perfusion pressure (CPP) and CBF in regions where autoregulation is impaired and distal resistance is increased due to vasoconstriction or microvascular dysfunction (32). Generally, higher mean arterial pressure (MAP) targets during DCI are 80-100mmHg or even higher in some cases (11). Continuous monitoring of CPP can help guide blood pressure management (33).

Vasopressor therapy, most commonly with norepinephrine, may be used to increase mean arterial pressure in a controlled manner (11). The response should be assessed primarily through neurological improvement and, when available, through multimodal measures of cerebral perfusion and oxygenation (22,23).

Importantly, induced hypertension should be considered a treatment for symptomatic DCI rather than a prophylactic intervention. Routine prophylactic elevation of blood pressure in clinically stable patients has not demonstrated sufficient benefit and may expose patients to complications such as myocardial ischemia, arrhythmias, pulmonary edema, and other forms of end-organ injury (19). The blood-pressure target should therefore be individualized rather than universally defined. A reasonable clinical approach is to increase blood pressure progressively while monitoring the patient's neurological response, cardiac function, intracranial pressure, and systemic tolerance (33). In patients with a secured aneurysm, this strategy may improve perfusion to ischemic yet viable cerebral tissue.

Endovascular Treatment

Patients with severe neurological deterioration attributable to cerebral vasospasm who fail to respond adequately to medical management may require endovascular rescue therapy (33). This approach

should generally be considered in specialized neurointerventional centers. Two principal endovascular strategies are used: balloon angioplasty and intra-arterial vasodilator therapy.

-Balloon Angioplasty

Balloon angioplasty is particularly effective for severe focal vasospasm involving accessible proximal intracranial arteries (34). Mechanical dilation of the constricted arterial segment can produce rapid and substantial improvement in vessel caliber and cerebral blood flow.

Its major limitation is anatomical: distal and diffuse vasospasm may not be amenable to balloon treatment. In addition, angioplasty carries procedure-related risks, including arterial dissection, perforation, thromboembolism, and vessel rupture. Consequently, it is generally reserved for severe vasospasm in appropriately selected patients (11,34).

-Intra-arterial Vasodilators

Intra-arterial administration of vasodilating agents can be used when vasospasm is diffuse, distal, or not suitable for balloon angioplasty (19,34). Agents such as intra-arterial nimodipine, verapamil, and milrinone can produce transient relaxation of cerebral arterial smooth muscle and improve angiographic cerebral blood flow (11). A major limitation is that the effect may be temporary, requiring repeated treatment. Systemic hypotension can also occur, particularly with some vasodilating agents. Monitoring treatment response involves neurological examination and imaging studies (TCD, CTA, CTP, DSA) (11,19,35).

Endovascular therapy should therefore be viewed as a rescue treatment for severe or refractory DCI, rather than a routine prophylactic intervention (19,33).

Therapeutic Options with Limited Evidence

A number of therapeutic strategies have been investigated for the prevention or treatment of DCI, but current evidence does not support their routine use.

Statins have demonstrated biological effects that could theoretically be beneficial in vasospasm and endothelial dysfunction; however, routine statin initiation solely for the prevention of DCI is not currently recommended (19).

Similarly, intravenous magnesium supplementation has not demonstrated sufficient improvement in neurological outcome to support routine use as a DCI-prevention strategy (36). Magnesium should nevertheless be corrected when clinically significant hypomagnesemia is present (37).

Clazosentan, papaverine, fasudil, nitric oxide analogues, erythropoietin, sildenafil, and free radical scavengers (nicaraven) are promising therapeutic agents, but further studies are needed to establish their efficacy in DCI treatment (11,34).

Practical Therapeutic Algorithm Proposal

In clinical practice, management of DCI can be conceptualized as a stepwise approach (19,33):

Prevent DCI: administer enteral nimodipine and maintain euvolemia.

- Monitor closely: perform frequent neurological examinations and use TCD, CTA/CTP, cEEG, or other neuromonitoring techniques when clinically indicated.
- Investigate neurological deterioration: exclude rebleeding, hydrocephalus, seizures, infection, metabolic disturbances, hypoxemia, hypotension, and other causes.
- Confirm or strongly suspect DCI: assess cerebral perfusion and the presence of vasospasm using appropriate imaging and physiological monitoring.
- Optimize systemic physiology: correct hypovolemia, hypotension, hypoxemia, fever, electrolyte disturbances, and elevated intracranial pressure.
- Treat symptomatic DCI: after aneurysm securement, consider controlled induced hypertension with vasopressor support.
- Escalate therapy: in severe or refractory cases, consider endovascular balloon angioplasty and/or intra-arterial vasodilator therapy.
- Continue multimodal assessment: evaluate the neurological and physiological response and modify treatment according to the patient's clinical course.

Conclusion

The contemporary management of DCI following aSAH recognizes cerebral ischemia as a multifactorial dynamic process rather than simply a consequence of angiographic vasospasm. Even after aneurysm securing, the brain remains vulnerable to sudden deterioration. Prevention therefore relies on early enteral nimodipine, maintenance of euvolemia, and intensive neurological surveillance, supported by TCD, CTA, CTP, cEEG, and other neuromonitoring modalities when clinical assessment is limited.

Once symptomatic DCI develops, reversible systemic factors should be corrected and, in appropriately selected patients, induced hypertension may augment cerebral perfusion. Severe or refractory vasospasm may require endovascular rescue therapy. Ultimately, management has shifted from prophylactic hypervolemia toward an individualized, physiology-driven strategy focused on preserving viable brain tissue. The critical challenge remains recognizing the narrow window between reversible ischemia and irreversible infarction, when timely intervention may determine the outcome.

References:

1. Dodd WS, Laurent D, Dumont AS, Hasan DM, Jabbour PM, Starke RM, Hosaka K, Polifka AJ, Hoh BL, Chalouhi N. Pathophysiology of delayed cerebral ischemia after subarachnoid hemorrhage: a review. *Journal of American Heart Association* 2021;10:e021845.
2. Flynn L, Andrews P. Advances in the understanding of delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *F1000Res*. 2015;4:1200.

3. Stienen MN, Germans M, Burkhardt J-K, Neidert MC, Fung C, Bervini D, Zumofen D, Rothlisberger M, Marbacher S, Maduri R, et al. Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: analysis of nationwide database (Swiss SOS (Swiss Study on Aneurysmal Subarachnoid Hemorrhage)). *Stroke* 2018;49:333-340.
4. Pan P, Xu L, Zhang H, Liu Y, Lu X, Chen G, Tang H and Wu J. A Review of Hematoma Components Clearance Mechanism After Subarachnoid Hemorrhage. *Front. Neurosci.* 2020;14:685. doi: 10.3389/fnins.2020.00685
5. Hugelshofer M, Buzzi R, Schaer DJ, et al. Cerebrospinal fluid hemoglobin drives subarachnoid hemorrhage-related secondary brain injury. *Nat Commun.* 2021;12(1):3364.
6. Pluta RM. Dysfunction of nitric oxide synthases as a cause and therapeutic target in delayed cerebral vasospasm after SAH. *Acta Neurochir Suppl.* 2008;104:139-147.
7. Dumont AS, Dumont RJ, Chow MM, et al. Cerebral vasospasm after subarachnoid hemorrhage: putative mechanisms and novel approaches. *J Neurosurg.* 2003;98(6):1167-1180.
8. Schallner N, Lieberum JL, Gallo D, et al. Microglia regulate blood clearance in subarachnoid hemorrhage by heme oxygenase-1. *J Clin Invest.* 2015;125(10):4109-4125.
9. Wang J, Doré S. Heme oxygenase-1 exacerbates early brain injury after intracerebral hemorrhage. *Brain.* 2007;130(Pt 6):1643-1652.
10. Saba ES, Lee YY, Kim M, et al. Roles of Heme Oxygenase-1 in Neuroinflammation and Brain Health. *Int J Mol Sci.* 2022;23(11):6217.
11. Thilak S, Brown P, Lawrence E, Gopal S, Mullhi R, Chacko C, Ahmed Z, Chelvarajah R, Pooni J, Veenith T. Delayed cerebral ischaemia after subarachnoid haemorrhage: pathophysiology, diagnosis and neurotherapeutic opportunities. *Discover Medicine* 2025;2:103.
12. Schmidt TP, Weiss M, Hoellig A, et al. Revisiting the timeline of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: toward a temporal risk profile. *Neurocrit Care* 2022;37:735-743.
13. Francoeur CL, Mayer SA. Cerebral vasospasm after subarachnoid hemorrhage. *Critical Care Clinics* 2016;32(1):1-16.
14. Fang YJ, Mei SH, Lu JN, Chen YK, Chai ZH, Dong X, Araujo C, Reis C, Zhang JM, Chen S. New risk score of the early period after spontaneous subarachnoid hemorrhage: For the prediction of delayed cerebral ischemia. *CNS Neurosci Ther.* 2019;25(10):1173-1181.
15. van der Steen WE, Leemans EL, van den Berg R, et al. Radiological scales predicting delayed cerebral ischemia in subarachnoid hemorrhage: systematic review and meta-analysis. *Neuroradiology* 2019;61,247–256.
16. de Rooij NK, Rinkel GJE, Dankbaar JW, Frijns CJM. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. *Stroke.* 2013;44(1):43-54
17. Xiao ZK, Wang B, Liu JH, et al. Risk factors for the development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *World Neurosurgery* 2025;193:427-446.
18. Schirmer CM, Baker A, Bulsara KR, et al. Diagnostic cerebral angiography: a report of the

- SNIS Standards and Guidelines Committee, endorsed by ANZSNR and ESMINT. *J Neurointerv Surg.* 2026 Apr 30. doi:10.1136/jnis-2026-024980.
19. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2023;54(7):e314-e370.
 20. Lolli VE, Guenego A, Sadeghi N, Jodaitis L, Lubicz B, Taccone FS, Gouvea Bogossian E. CT perfusion imaging in aneurysmal subarachnoid hemorrhage. State of the art. *Front Radiol.* 2024;4:1445676.
 21. Park JJ, Kim Y, Chai CL, Jeon JP. Application of Near-Infrared Spectroscopy for the detection of delayed cerebral ischemia in poor-grade subarachnoid hemorrhage. *Neurocrit Care* 2021;35(3):767-774.
 22. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Pickard JD, Menon DK. Monitoring cerebral blood flow and metabolism with microdialysis and tissue oxygenation. *Acta Neurochir Suppl.* 2012;114:123-129.
 23. Stovell MG, Helmy A, Thelin EP, Jalloh I, Hutchinson PJ, Carpenter KLH. An overview of clinical cerebral microdialysis in acute brain injury. *Front Neurol.* 2023;14:1135061.
 24. McGirt MJ, Lynch JR, Blessing R, Warner DS, Friedman AH, Laskowitz DT. Serum von Willebrand factor, matrix metalloproteinase-9, and vascular endothelial growth factor levels predict the onset of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 2002;51(5):1128-1134.
 25. Siman R, Giovannone N, Toraskar N, Frangos S, Stein SC, Levine JM, Kumar MA. Evidence that a panel of neurodegeneration biomarkers predicts vasospasm, infarction, and outcome in aneurysmal subarachnoid hemorrhage. *PLoS One.* 2011;6(12):e28938.
 26. Akeret K, Buzzi RM, Saxenhofer M, et al. The HeMoVal study protocol: a prospective international multicenter cohort study to validate cerebrospinal fluid hemoglobin as a monitoring biomarker for aneurysmal subarachnoid hemorrhage related secondary brain injury. *BMC Neurology* 2022;22:267.
 27. Macdonald RL, Weir B. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Rev Neurol.* 2007;3:256-263.
 28. Hänggi D, Etminan N, Aldrich F, Steiger HJ, Mayer SA, Diringer MN, Hoh BL, Mocco J, Fallick HJ, Macdonald RL; NEWTON Investigators. Randomized, open-label, phase 1/2a study to determine the maximum tolerated dose of intraventricular sustained release nimodipine for subarachnoid hemorrhage (NEWTON). *Stroke.* 2017;48(1):145-151.
 29. Ehtisham A, Taylor S, Bayless L, Samuels OB, Klein MW, Janzen JM. Use of intrathecal nicardipine for aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm. *South Med J.* 2009;102(2):150-153.
 30. Castle-Kirszbaum M, Lai L, Maingard J, Asadi H, Danks RA, Goldschlager T, Chandra RV. Intravenous milrinone for treatment of delayed cerebral ischaemia following subarachnoid haemorrhage: a pooled systematic review. *Neurosurgical Review.* 2021;44(6):3107-3124.
 31. Amin-Hanjani S, Ogilvy CS, Barker FG 2nd, Dumont AS, Kassell NF, Dempsey RJ, Lawton MT, Haines SJ. Does intracisternal thrombolysis prevent vasospasm after aneurysmal subarach-

- noid hemorrhage? A meta-analysis. *Neurosurgery*. 2004;54(2):326-335; discussion 334-335.
32. Carrera E, Schmidt JM, Oddo M, et al. Cerebral autoregulation in subarachnoid hemorrhage. *Front Neurol*. 2021;12:688362.
33. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care* 2016;20(1):277.
34. Daou BJ, Koduri S, Thompson BG, Chaudhary N, Pandey AS. Clinical and experimental aspects of aneurysmal subarachnoid hemorrhage. *CNS Neurosci Ther*. 2019; 25: 1096-1112.
35. Nastasovic T, Lazic I, Ilic R, Milisavljevic F. Delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage- areas at risk. *Neurosurg Rev*. 2024;47(1):284.
36. Dorhout Mees SM, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J, van Oostenbrugge RJ, Al-Shahi Salman R, Lavados PM, Rinkel GJ, van den Bergh WM; MASH-2 Study Group. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet* 2012 Jul 7;380(9836):44-9.
37. Picetti E, Barbanera A, Bernucci C, Bertuccio A, Bilotta F, Boccardi EP, Cafiero T, Caricato A, Castioni CA, Cenzato M, Chiericato A, Citerio G, Gritti P, Lanterna L, Menozzi R, Munari M, Panni P, Rossi S, Stocchetti N, Sturiale C, Zoerle T, Zona G, Rasulo F, Robba C. Early management of patients with aneurysmal subarachnoid hemorrhage in a hospital with neurosurgical/neuroendovascular facilities: a consensus and clinical recommendations of the Italian Society of Anesthesia and Intensive Care (SIAARTI)-part 2. *J Anesth Analg Crit Care* 2022;2(1):21.