Article published online: 2022-09-09

Review Article

Delayed Ischemic Neurologic Deficit after Aneurysmal Subarachnoid Hemorrhage

Abstract

Delayed ischemic neurologic deficit (DIND) is the main preventable cause of poor outcomes in aneurysmal subarachnoid hemorrhage (SAH) patients. Of 50% of survivors from a SAH, approximately 30% of patients will present clinical vasospasm (VS). The cornerstone of the DIND management comprises prevention and early identification. Several diagnostic methods have been proposed differing in efficacy, invasiveness, and costs. Serial neurological examination is the most reliable method to detect a new neurological deficit. On the other hand, comatose patients require advanced monitoring methods which identify changes in the microcirculatory environment, brain autoregulation, and spreading depolarization. Multimodality monitoring with continuous electroencephalography, microdialysis, and intracranial pressure monitoring represents altogether the current state-of-art technology for the intensive care of SAH patients. Moreover, advances in genetic biomarkers to predict clinical VS have shown consistent accuracy which may in the near future allow the early prediction of DIND through a simple blood test. Several clinical trials have tested drugs with theoretical effects on DIND prevention or treatment. Nevertheless, nimodipine remains the Holy Grail in the prevention of clinical VS. Among rescue therapies, the endovascular treatment through intra-arterial vasodilator (verapamil or nicardipine) infusion is the most employed method for DIND reversal; however, there is no good quality evidence comparing results of intra-arterial infusion of vasodilators versus balloon angioplasty. Although we have addressed the most refined technology in the management of SAH and DIND, the clinical experience and strict follow-up in neurointensive care will be determinant for favorable long-term outcomes.

Keywords: *Critical care, delayed ischemic deficit, intracranial aneurysms, neurocritical care, subarachnoid hemorrhage, vasospasm*

Vitor Nagai Yamaki, Daniel Dutra Cavalcanti[1], Eberval Gadelha Figueiredo

Department of Neurosurgery, Universidade De Sao Paulo, São Paulo, SP, Brazil, [1]Department of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) has a mortality rate of 50% at initial bleed while roughly half of the survivors will sustain persistent neurological deficit.[1,2] The delayed ischemic neurologic deficit (DIND) affects up to 30%[2-4] of patients with aSAH. Conversely, it is the main preventable cause of poor outcomes in those patients.[1,2] The natural history of DIND is well described in literature, which usually begins approximately between the 4th and 7th day after SAH, being characterized by a new neurological deficit or worsening of a previous one due to large-vessel cerebral vasospasm (VS). Great effort has been made to understand the DIND pathogenesis, besides a large-vessel narrowing mechanism and its ischemic injury. DIND has been also attributed to other mechanisms such as early brain injury, cortical spreading depolarization, microcirculatory thrombosis, loss of cerebral autoregulation, and individual genetic polymorphisms.[2-6]

The digital subtraction angiography (DSA) is the gold standard imaging method to diagnose vessel vasoconstriction which affects 70% of patients with aSAH.[1,7] Nevertheless, only 20% of those will develop DIND.[3,7,8] Clinical surveillance of awake patients is the most reliable tool for early diagnosis of DIND; however, most patients with ruptured aneurysms are unconscious, sedated, and under mechanical ventilation.[3,9] The multicausal etiology of DIND makes its diagnosis and treatment challenging for the intensive care unit (ICU) team. We reviewed new advances in the early diagnosis and treatment of DIND and additionally suggested cost-based approach for management in a developing country.

How to cite this article: Yamaki VN, Cavalcanti DD, Figueiredo EG. Delayed ischemic neurologic deficit after aneurysmal subarachnoid hemorrhage. Asian J Neurosurg 2019;14:641-7.

Address for correspondence:
Dr. Vitor Nagai Yamaki, Rua Arruda Alvim, 49 – Apt153, Zip Code: 054100-20, São Paulo, SP, Brazil.
E-mail: vitoryamaki@gmail.com

Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_15_19

Quick Response Code:

Concepts

The DIND has been labeled in the medical literature to differentiate from VS identified on imaging examinations. DIND was defined as focal (hemiparesis, aphasia, hemianopia, or neglect) or global (two points decrease on Glasgow Coma Scale) neurological impairment lasting for at least 1 h and/or cerebral infarction. However,

- It may not be apparent immediately after aneurysm occlusion
- It may be attributable to ischemia
- Other potential causes of clinical deterioration must be rigorously excluded (hydrocephalus, seizure, rebleeding, and hyponatremia).[10]

The cerebral VS is defined based on different diagnostic tools. The transcranial Doppler (TCD) criteria for VS include mean arterial velocity exceeding 120 cm/s in the middle cerebral artery, whereas velocities >180 cm/s have higher positive predictive value. On contrast-based imaging, a decrease in luminal diameter of >50% is usually considered a severe VS.[11] The DSA is currently the gold standard; however, the computed tomography angiography (CTA) has shown good sensitivity and specificity in recent studies and might be employed as a first-line screening tool.[7]

Cerebral infarction is the presence of hypodensity in the brain area detected on CT or magnetic resonance scan within 6 weeks after aSAH. However, it may not:

- Present on imaging scan between 24 and 48 h after early aneurysm occlusion
- Be attributable to other causes such as aneurysm clipping or endovascular treatment
- Represent a nonischemic lucency related to a ventricular catheter, intraparenchymal hematoma, or brain retraction injury.[10]

Clinical Presentation

Clinical examination of awake patients is the most suitable method to detect DIND.[1,9] A new neurological deficit or decrease in the level of consciousness might represent DIND which may improve or progress to cerebral infarction. However, it is important to state that clinical deterioration might only be attributable to DIND, after exclusion of some differentials, such as hyponatremia, hypotension, hypoglycemia, infections, and others[12] [Figure 1].

On comatose patients, on the other hand, the early diagnosis of DIND depends on multimodality monitoring and clinical experience of the ICU team.[6,13] The prevalence of DIND is underestimated in this population which are at higher risk of unfavorable outcomes. It is estimated that 40%–70% of patients with ruptured aneurysms present with high-grade neurological outcome scales (World Federation of Neurosurgical Societies scale [WFNS]).[2] Loss of consciousness at the onset of SAH is an important marker of early brain injury and good predictor for death and poor neurologic outcome at 12 months.[14] It is usually related with poorer clinical grade and severe findings on CT scan (more blood in the subarachnoid space, inside the ventricles, and diffuse cerebral edema).[14]

Challenge of Early Diagnosis: Intensive Care Unit Monitoring

The early identification of DIND at ICUs depends in most cases of diagnostic tools which should be available in these units. We divided those methods into three categories based on its application: (1) screening examinations, (2) continuous monitoring tests, and (3) molecular and genetic biomarkers.

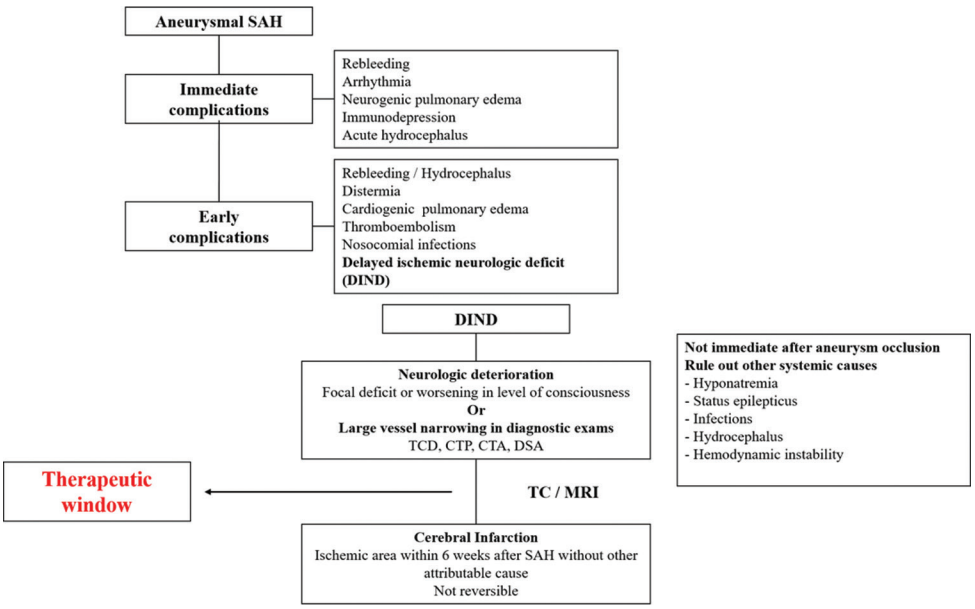

Figure 1: Diagnostic flow chart for delayed ischemia after subarachnoid hemorrhage

Screening examinations

The screening examinations should be performed routinely independently of clinical suspicion. Although these results may not always indicate DIND, it might guide preventive measures to prevent its installation.

The TCD is a noninvasive diagnostic method that provides evidence of large-vessel narrowing based on measurements of flow velocity of intracranial arteries. The main advantage is the noninvasiveness nature of the test. However, its validity has been contested because its results can be influenced by technical and anatomical factors.[7,8,15] The TCD ultrasonography is highly operator dependent while the distal vasculature might also be influenced by hydrocephalus and elevated intracranial pressure (ICP).[3] Furthermore, cerebral VS identified in the TCD does not always translate into high risk of DIND. Carrera *et al*.[16] published a series with 441 aSAH patients who underwent TCD ultrasonography; 40% of patients with DIND did not reach 120 cm/s on any vessel. The low sensitivity related to the method has been questioned for its use as a screening test for VS and delayed ischemic deficits. Recently, the transient hyperemic response test (THRT) or carotid occlusion test described in 1991, and initially employed to study cerebral autoregulation, has been used to predict the risk of DIND. Approximately 83% of patients with clinical VS presented abnormal THRT.[17]

The DSA is the gold standard imaging method to diagnose cerebral VS. Nevertheless, the invasiveness of the method with its inherent risks, in addition to the use of contrast agents and radiation are the drawbacks related to the test.[7] The CTA is a less invasive method with reliable accuracy compared to classic angiography to detect VS.[7] Indeed, the large-vessel narrowing identified in those imaging examinations does not always translate into neurological deficits. Sensitivity of CTA to identify VS ranges from 75% to 97% in most series; while its sensitivity to detect DIND drops down to 50%.[8,18] The computed tomography perfusion (CTP) is currently the most reliable imaging method to predict DIND since it analyzes the regional perfusion of the narrowed vessels identified in the CTA and DSA.[7,18,19] A recent meta-analysis with 570 patients suggested CTP as a valid diagnostic method for DIND; however, it was not a feasible tool for predicting delayed deficit.[20] Its sensitivity to diagnose DIND is nearly 80% in most series.[18,19] However, is use still needs to be standardized regarding cutoff values and critical time window for evaluation. Takahashi *et al*.[18] submitted patients to CTP within 24 h after the onset of an aSAH. Elevated mean transit times were significantly related to best functional outcomes but did not correlate with incidence VS. They concluded that the use of CTP in the 1st day of SAH might detect early brain injury related to microcirculatory disturbance, high ICP, or transient VS, all critical for favorable clinical outcomes. The risk of radiation exposure of CT examinations on a cost-effectiveness analysis showed that the CTA in addition to CTP is preferred to the TCD with improved outcomes and lower health-care costs. It is recommended that in most stroke centers, the CTA and CTP should be performed together within a critical time window between days 4 and 8.[15]

Continuous monitoring examinations

A better comprehension of the SAH pathogenesis allowed advanced neurophysiological monitoring of cerebral autoregulation, metabolic changes, brain tissue oxygen, and even electrocorticographic activity. Different combinations of these modalities are present in well-equipped stroke units worldwide.

Continuous monitoring demonstrating abnormal cortical electrical activity might represent neuronal hypoperfusion and dysfunction during aSAH.[3,5,6] A real-time feedback from the continuous electroencephalography (cEEG) in patients with ruptured aneurysms has shown depression of fast activity or slowing of rhythms.[5] Recent data suggest that these changes might be an early predictor of DIND occurrence and therefore would permit therapeutic interventions within a window of opportunity.[13] Consistent results supporting cEEG monitoring for aSAH have shown that a decrease in the alpha/delta ratio alone or in combination with a decrease in alpha variability permitted early detection of DIND, several hours prior to clinical deterioration (median time of 7 h) and cerebral infarction (median time of 44 h).[5,6]

The invasive ICP monitoring permits to identify the increase in ICP and determination of ideal mean arterial blood pressure parameters and also provides an overall analysis of the brain autoregulation through the pressure reactivity index (PRx).[21] The concept of "optimal CPP" therapy based on PRx values refers to an individualized approach to the SAH patients, especially in the first 48 h after bleeding.[21] However, it is noteworthy that the CPP should be maintained above 70 mmHg, the threshold to initiate metabolic crises and brain tissue hypoxic injury.[2,4,22] Parenchymal brain tissue oxygenation tension (PbtO2) also provides important information regarding brain metabolism. The brain hypoxia is considered an indicator of worse prognosis in SAH and might be used for early diagnosis of silent infarction.[13]

Cerebral microdialysis (CMD) provides important information about cellular metabolism and the interstitial environment of the brain after SAH.[23,24] It has permitted a better understanding of mechanisms underlying early and delayed brain injury. Although several metabolites might be analyzed with this method, a recent consensus about the clinical use of the microdialysis supported strong evidence for the use of glucose and lactate levels, in addition to the lactate/pyruvate ratio (LPR) to identify ischemic injury

and yield an individualized and targeted care intervention. Cutoffs for a pathological environment in SAH patients were determined as follow: CMD-glucose <0.7 mmol/l, CMD-lactate >4 mmol/l, and CMD-LPR >40, which represents a metabolic distress.[23] Recent data support that these changes may predict the occurrence of delayed ischemia by several hours (12–16 h). The best parameters to be analyzed are the CMD-LPR and cerebral metabolic rate-glucose concentrations; however, remote ischemia from the probe location (contralateral) was not predicted.[2,3] Skjøth-Rasmussen *et al*.[25] used that dynamic changes in the microcirculatory environment (LPR and lactate-glycerol ratio peak in addition to peak in glycerol concentration) predicted DIND occurrence with sensitivity of 94%, with a mean warning period of 11 h. Samuelsson *et al*.[26] did also find similar results, with a LPR peak 16 h prior to a subsequent DIND, however, with lower sensitivity (40%). They have attributed those differences as consequences of CMD probe placement, and closer position to the injured tissue results in higher sensitivity to detect the early ischemic pattern of the microcirculation.

Genetic biomarkers

Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variation in human genome, characterized by wrong replacement of a single nucleotide throughout DNA.[27] Most SNPs have no clinical repercussions. SNPs in genes of certain enzymes have been associated with increased risk of determined diseases.[27] Relationship of SNPs in genes of the endothelial nitric oxide synthase (eNOS),[28] haptoglobin,[29] apolipoprotein E,[30] and endothelin[31] with DIND has been described. The eNOS gene's SNP is the most studied in literature; the "*a* allele" of the eNOS intron VNTR polymorphism has been related to the occurrence of DIND in clinical series and meta-analysis.[28] Recently, the endothelin-1 has also been associated with delayed ischemic deficit, and the dominant effect of G allele in the endothelin receptor A G/C SNP showed statistical significance with development of clinical VS in prospective series.[31] Although only available for clinical research and at high cost, we believe that this technology will be widely available in stroke units and a simple blood test may predict which patients are at high risk for DIND.

Treatment

An optimal management of SAH must target an aggressive management of DIND. Advances in the experimental and clinical research have elucidated the mechanisms underlying the pathogenesis of cerebral VS and delayed ischemia. Therefore, a target-based management has been suggested to optimize long-term outcomes.[2] The microvascular spams, microthrombosis, blood–brain barrier disruption, spreading depolarizations, and loss of autoregulation mechanism are the main targets in the current treatment of DIND.

Systemic hemodynamic strategy

The evident mechanisms in the delayed ischemia pathophysiology are the large-vessel narrowing and depletion of regional blood supply. Therefore, therapies such as triple-H prophylaxis to improve local blood delivery and use of vasodilator drugs have been tested to prevent the onset of DIND.[32] Although the use of the triple-H strategy has insufficient evidence, induced hypertension[3,4] is the first-line therapy for the treatment and prevention of VS since it augments cerebral blood flow and cerebral oxygenation and reverts neurological deficits. At institution of this therapy, a saline bolus followed by vasopressor drugs (norepinephrine, phenylephrine, and dopamine) is a safe practice, even in the occasion of a concomitant nontreated unruptured aneurysm.[33] An optimal target for blood pressure should ideally be reached based on ICP monitoring.[21,34] However, studies have demonstrated that systolic blood pressure (SBP) should be kept around 160–180 mmHg but never below 100 mmHg. If clinical improvement is not verified, most centers have adopted a target of 120 mmHg for CPP, 140 for mean arterial blood pressure, and 220 mmHg for SBP.[3] Moreover, it is important to state that pressure control should always be individualized based on the "normal range" for each patient.

If refractory to induced hypertension and volume resuscitation, another practice for hemodynamic enhancement is through cardiac output augmentation. Dobutamine has been used for refractory VS, with satisfactory rates of reversal neurologic deficits.[35] Milrinone has also been successfully employed due to its inotropic effects.[35] The Montreal Neurological Hospital published a case series with >80 patients with symptomatic VS; 72% presented with good functional outcomes in 1-year follow-up with minimal medical complications such as pulmonary edema, myocardial ischemia, and others.[36] This therapy requires invasive monitoring of cardiac output, targeting a cardiac index >4 L/min/m.[3]

Target drugs

Several drugs have been tested based on a specific target in the pathophysiology cascade of DIND. Statins have been widely tested for VS prevention.[37] Besides its effect on cholesterol production, it has other effects which include an increase in IL-10 and eNOS in addition to a decrease in the oxidative stress, platelet adhesion/aggregation, and activation of matrix metalloproteinases.[22] However, statins failed to improve functional outcomes, to reduce DIND incidence, and to reduce mortality rates in SAH patients.[22,38] The use of erythropoietin for the treatment of VS after SAH aimed to improve brain oxygenation through stimulation in blood cell production. Randomized clinical trials (RCTs) testing these drugs showed not enough evidence of improvements in DIND or clinical outcomes in the follow-up period.[39] An endothelin A receptor antagonist, clazosentan, has also

been tested in the SAH treatment.[31] The CONSCIOUS trials did demonstrate a reduction in angiographic VS. However, it failed to show improvements in clinical outcomes or reduce cerebral infarction.[40] Other drugs, such as aspirin, enoxaparin, magnesium, steroids, and nicardipine, have also been studied without promising results in the clinical setting. Nimodipine, a calcium channel blocker, might be considered the cornerstone for DIND treatment with significant contribution to improvements in SAH outcomes in the past two decades.[1,41] Initially employed as a vasodilator against angiographic VS, the beneficial effect of nimodipine in the SAH acts through a different mechanism that improves functional outcomes, reduces brain infarction, delayed deficits, and death, but interestingly, does not have an effect on angiographic VS.

Endovascular therapy

Patients with nonreversible neurological deficits after induced hypertension and maintenance of euvolemia, as well as normal circulation blood volume, are candidates for rescue therapy through endovascular techniques. There are two endovascular modalities for the treatment of VS: balloon angioplasty and intra-arterial vasodilator injection.[4,42] The transluminal balloon angioplasty is an early described and widely studied technique that consists of a forced mechanical dilation of the narrowed vessel.[43] It is limited to proximal large vessels with 90% success rate and long lasting, especially if performed within 2 h from the onset of neurological deficit.[44] There is only one RCT addressing angioplasty for cerebral VS after SAH. In this study, its prophylactic use did not show benefits. It is noteworthy that procedure-related complications are not negligible, and up to 5% may develop thrombosis, embolism, dissection, and even rupture with fatal consequences.[45]

The intra-arterial vasodilator injection consists of local delivery of vasodilator drugs with advantages of reaching distal vessels and less procedure-related complications compared to the angioplasty. Nevertheless, it presents a short-period effectiveness and may also cause intracranial hypertension due to vasodilation. It is currently the most employed method, and several medications have been tested but none in RCTs. The most commonly used are the calcium channel blockers such as nimodipine, nicardipine, and verapamil. The first is the most used worldwide, except in the United States.[42] All these three agents show satisfactory results in case series; however, good quality RCTs are necessary for better evidence.[3,4] We have addressed both techniques separately, but they might be combined if necessary and may show even better results.[42] In the clinical practice, angioplasty might offer superior results except for distal VS.

Clinical care

Other concerns in the delayed ischemic deficit are the "extracranial manifestations" related to the pathological process of the whole SAH.[12] The temperature control is critical for SAH patients, normothermia should be kept. There is no evidence to support controlled therapeutic hypothermia with or without the use of barbiturate thus far.[46] Anemia should also be avoided with risk of DIND exacerbation.[47] Either blood transfusion in the ICU or lower hemoglobin level is related to poorer outcomes. Therefore, the cutoff value for blood transfusion is a matter of controversy. The ongoing Aneurysmal SubArachnoid Hemorrhage–Red Blood Cell Transfusion and Outcome[48] will compare a liberal transfusion strategy (≤100 g/L) with a restrictive strategy (≤80 g/L) to provide conclusions regarding this discussion. According to the Neurocritical Care Societies guidelines,[49] it is suggested a cutoff hemoglobin level from 8 to 10 g/dL for blood transfusion in a SAH patient. However, in patients with DIND, a more aggressive strategy should be employed with a transfusion threshold of 9–10 g/dL. Moreover, a strict management of glucose level, in addition to levels of the electrolytes, is determinant for good outcomes.

Optimal Approach to Delayed Ischemic Neurologic Deficit versus Developing Country's Reality

Evidence and knowledge regarding delayed ischemic deficits following SAH are rising fast, and experimental hypothesis is gaining strong evidence to turn out into first-line therapies. However, the ideal management of SAH and DIND prevention is financially demanding practices which are usually not available even in high-volume stroke centers worldwide. Multimodality monitoring with CMD, continuous EEG and ICP monitoring, and wide availability to endovascular therapies might certainly provide the best care for patients with DIND.

In developing countries, the clinical experience should be the Holy Grail of SAH management. In the low-grade patient group, the periodical clinical examination is currently the best and most feasible way to early detect symptomatic VS. For sedated and unconscious patients, screening by repeating imaging examinations (DSA, CTA, and CTP, if available) and TCD is reasonable. From clinical series and RCTs, it is possible to predict high-risk factors for DIND development after SAH. Therefore, for those patients, extra caution should be taken based on the hemodynamic monitoring, electrolytes and glucose levels, sedation, temperature, hemoglobin levels, infectious surveillance, and blood pressure control. The use of oral nimodipine is mandatory. Euvolemia and induced hypertension are also critical. Moreover, it is important a cost-effectiveness decision-making since expensive technologies are not widely available. Crobeddu *et al*.[9] reported a predictive model of patients who have not developed DIND. Older patients (≥68 years old) with good neurological status at admission (WFNS I-III) and favorable Fisher grade scale (1 or 2) were at very low

risk of developing DIND. Based on these findings, an early discharge from the ICU might be safely performed, reducing costs from long-stay hospitalization.

Conclusions

Advances in the prevention, early diagnosis, and treatment of DNID have increasingly contributed to improvements in functional outcomes following SAH. Nimodipine remains as the cornerstone for DIND prevention. Neurological examination is suitable for good grade patients, while for those sedated or comatose patients, multimodality monitoring is the most accurate method. Induced hypertension with maintenance of euvolemia is the first-line therapy, and for refractory clinical VS, endovasscular therapy is the best alternative. Although several technological advances in the SAH management have arisen, the current state-of-art method for optimal quality care is clinical experience and strict follow-up in the neuro-ICU. Several variables must be controlled in those critical patients that will certainly imply in satisfactory outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. 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;43:1711-37.
2. Budohoski KP, Guilfoyle M, Helmy A, Huuskonen T, Czosnyka M, Kirollos R, *et al.* The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2014;85:1343-53.
3. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. Crit Care 2016;20:277.
4. Durrant JC, Hinson HE. Rescue therapy for refractory vasospasm after subarachnoid hemorrhage. Curr Neurol Neurosci Rep 2015;15:521.
5. Rots ML, van Putten MJ, Hoedemaekers CW, Horn J. Continuous EEG monitoring for early detection of delayed cerebral ischemia in subarachnoid hemorrhage: A pilot study. Neurocrit Care 2016;24:207-16.
6. Foreman B, Albers D, Schmidt JM, Falo CM, Velasquez A, Connolly ES, *et al.* Intracortical electrophysiological correlates of blood flow after severe SAH: A multimodality monitoring study. J Cereb Blood Flow Metab 2018;38:506-17.
7. Wilson CD, Shankar JJ. Diagnosing vasospasm after subarachnoid hemorrhage: CTA and CTP. Can J Neurol Sci 2014;41:314-9.
8. Cremers CH, Vos PC, van der Schaaf IC, Velthuis BK, Vergouwen MD, Rinkel GJ, *et al.* CT perfusion during delayed cerebral ischemia after subarachnoid hemorrhage: Distinction between reversible ischemia and ischemia progressing to infarction. Neuroradiology 2015;57:897-902.
9. Crobeddu E, Mittal MK, Dupont S, Wijdicks EF, Lanzino G, Rabinstein AA. Predicting the lack of development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Stroke 2012;43:697-701.
10. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, *et al.* Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: Proposal of a multidisciplinary research group. Stroke 2010;41:2391-5.
11. Washington CW, Zipfel GJ; Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Detection and monitoring of vasospasm and delayed cerebral ischemia: A review and assessment of the literature. Neurocrit Care 2011;15:312-7.
12. Hall A, O'Kane R. The extracranial consequences of subarachnoid hemorrhage. World Neurosurg 2018;109:381-92.
13. Helbok R, Madineni RC, Schmidt MJ, Kurtz P, Fernandez L, Ko SB, *et al.* Intracerebral monitoring of silent infarcts after subarachnoid hemorrhage. Neurocrit Care 2011;14:162-7.
14. Suwatcharangkoon S, Meyers E, Falo C, Schmidt JM, Agarwal S, Claassen J, *et al.* Loss of consciousness at onset of subarachnoid hemorrhage as an important marker of early brain injury. JAMA Neurol 2016;73:28-35.
15. Ivanidze J, Charalel RA, Shuryak I, Brenner D, Pandya A, Kallas ON, *et al.* Effects of radiation exposure on the cost-effectiveness of CT angiography and perfusion imaging in aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol 2017;38:462-8.
16. Carrera E, Schmidt JM, Oddo M, Fernandez L, Claassen J, Seder D, *et al.* Transcranial doppler for predicting delayed cerebral ischemia after subarachnoid hemorrhage. Neurosurgery 2009;65:316-23.
17. Al-Jehani H, Angle M, Marcoux J, Teitelbaum J. Early abnormal transient hyperemic response test can predict delayed ischemic neurologic deficit in subarachnoid hemorrhage. Crit Ultrasound J 2018;10:1.
18. Takahashi Y, Sasahara A, Yamazaki K, Inazuka M, Kasuya H. Disturbance of CT perfusion within 24 h after onset is associated with WFNS grade but not development of DCI in patients with aneurysmal SAH. Acta Neurochir (Wien) 2017;159:2319-24.
19. Dankbaar JW, de Rooij NK, Smit EJ, Velthuis BK, Frijns CJ, Rinkel GJ, *et al.* Changes in cerebral perfusion around the time of delayed cerebral ischemia in subarachnoid hemorrhage patients. Cerebrovasc Dis 2011;32:133-40.
20. Cremers CH, van der Schaaf IC, Wensink E, Greving JP, Rinkel GJ, Velthuis BK, *et al.* CT perfusion and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. J Cereb Blood Flow Metab 2014;34:200-7.
21. Schmidt JM, Ko SB, Helbok R, Kurtz P, Stuart RM, Presciutti M, *et al.* Cerebral perfusion pressure thresholds for brain tissue hypoxia and metabolic crisis after poor-grade subarachnoid hemorrhage. Stroke 2011;42:1351-6.
22. Brathwaite S, Macdonald RL. Current management of delayed cerebral ischemia: Update from results of recent clinical trials. Transl Stroke Res 2014;5:207-26.
23. Hutchinson PJ, Jalloh I, Helmy A, Carpenter KL, Rostami E, Bellander BM, *et al.* Consensus statement from the 2014 international microdialysis forum. Intensive Care Med 2015;41:1517-28.
24. Carteron L, Bouzat P, Oddo M. Cerebral microdialysis monitoring

to improve individualized neurointensive care therapy: An update of recent clinical data. Front Neurol 2017;8:601.
25. Skjøth-Rasmussen J, Schulz M, Kristensen SR, Bjerre P. Delayed neurological deficits detected by an ischemic pattern in the extracellular cerebral metabolites in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 2004;100:8-15.
26. Samuelsson C, Hillered L, Enblad P, Ronne-Engström E. Microdialysis patterns in subarachnoid hemorrhage patients with focus on ischemic events and brain interstitial glutamine levels. Acta Neurochir (Wien) 2009;151:437-46.
27. Cargill M, Altshuler D, Ireland J, Sklar P, Ardlie K, Patil N, *et al.* Characterization of single-nucleotide polymorphisms in coding regions of human genes. Nat Genet 1999;22:231-8.
28. Paschoal EH, Yamaki VN, Teixeira RK, Paschoal Junior FM, Jong-A-Liem GS, Teixeira MJ, *et al.* Relationship between endothelial nitric oxide synthase (eNOS) and natural history of intracranial aneurysms: Meta-analysis. Neurosurg Rev 2018;41:87-94.
29. Gaastra B, Glazier J, Bulters D, Galea I. Haptoglobin genotype and outcome after subarachnoid haemorrhage: New insights from a meta-analysis. Oxid Med Cell Longev 2017;2017:6747940.
30. Wu HT, Ruan J, Zhang XD, Xia HJ, Jiang Y, Sun XC. Association of promoter polymorphism of apolipoprotein E gene with cerebral vasospasm after spontaneous SAH. Brain Res 2010;1362:112-6.
31. Griessenauer CJ, Starke RM, Foreman PM, Hendrix P, Harrigan MR, Fisher WS, *et al.* Associations between endothelin polymorphisms and aneurysmal subarachnoid hemorrhage, clinical vasospasm, delayed cerebral ischemia, and functional outcome. J Neurosurg 2018;128:1311-7.
32. Treggiari MM, Walder B, Suter PM, Romand JA. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. J Neurosurg 2003;98:978-84.
33. Reynolds MR, Buckley RT, Indrakanti SS, Turkmani AH, Oh G, Crobeddu E, *et al.* The safety of vasopressor-induced hypertension in subarachnoid hemorrhage patients with coexisting unruptured, unprotected intracranial aneurysms. J Neurosurg 2015;123:862-71.
34. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, Pickard JD. Clinical relevance of cerebral autoregulation following subarachnoid haemorrhage. Nat Rev Neurol 2013;9:152-63.
35. Naidech A, Du Y, Kreiter KT, Parra A, Fitzsimmons BF, Lavine SD, *et al.* Dobutamine versus milrinone after subarachnoid hemorrhage. Neurosurgery 2005;56:21-6l discussion 26-7.
36. 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;44:152-60.
37. 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;13:666-75.
38. Liu H, Xu X. Effect of simvastatin in patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. Am J Emerg Med 2017;35:1940-5.
39. Springborg JB, Møller C, Gideon P, Jørgensen OS, Juhler M, Olsen NV. Erythropoietin in patients with aneurysmal subarachnoid haemorrhage: A double blind randomised clinical trial. Acta Neurochir (Wien) 2007;149:1089-101.
40. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, *et al.* Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. Stroke 2012;43:1463-9.
41. Barker FG 2nd, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: A metaanalysis. J Neurosurg 1996;84:405-14.
42. Hollingworth M, Chen PR, Goddard AJ, Coulthard A, Söderman M, Bulsara KR. Results of an international survey on the investigation and endovascular management of cerebral vasospasm and delayed cerebral ischemia. World Neurosurg 2015;83:1120-60.
43. Eskridge JM, McAuliffe W, Song JK, Deliganis AV, Newell DW, Lewis DH, *et al.* Balloon angioplasty for the treatment of vasospasm: Results of first 50 cases. Neurosurgery 1998;42:510-6.
44. Polin RS, Coenen VA, Hansen CA, Shin P, Baskaya MK, Nanda A, *et al.* Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2000;92:284-90.
45. Zwienenberg-Lee M, Hartman J, Rudisill N, Madden LK, Smith K, Eskridge J, *et al.* Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with fisher grade III subarachnoid hemorrhage: Results of a phase II multicenter, randomized, clinical trial. Stroke 2008;39:1759-65.
46. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, Kreiter KT. Fever after subarachnoid hemorrhage: Risk factors and impact on outcome. Neurology 2007;68:1013-9.
47. Kurtz P, Schmidt JM, Claassen J, Carrera E, Fernandez L, Helbok R, *et al.* Anemia is associated with metabolic distress and brain tissue hypoxia after subarachnoid hemorrhage. Neurocrit Care 2010;13:10-6.
48. English SW, Fergusson D, Chassé M, Turgeon AF, Lauzier F, Griesdale D, *et al.* Aneurysmal subArachnoid hemorrhage-red blood cell transfusion and outcome (SAHaRA): A pilot randomised controlled trial protocol. BMJ Open 2016;6:e012623.
49. Diringer MN, Bleck TP, Claude Hemphill J 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;15:211-40.