Critical Care Management of the Acute Ischemic Stroke Patient

Care of a patient with AIS is comprehensive and requires a team approach. Clinicians must be able to control and influence a multitude of physiologic parameters in order to assure optimal outcome.

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Management of the acute ischemic stroke (AIS) patient has changed tremendously over the past 20 years. With the advent of various methods of reperfusion therapy, surgical intervention and evolving neuro-protective strategies, AIS patients are increasingly cared for in critical care units. It has been understood for years that AIS is a neurological emergency, requiring immediate attention and care in the emergency department (ED). Today, the AIS patient (as with the patient with acute coronary syndrome) is often viewed as being "critically ill" and therefore management is undertaken in a setting where continuous neurological, hemodynamic and respiratory monitoring is possible—namely, the intensive care unit (ICU).

In a continuum, there are two facets to critical care management of a patient with AIS: a) neurological critical care (NCC) and b) medical critical care. This article will focus on NCC aspects with some allusion to medical critical care of the patient with AIS. To that end, the emphasis will be upon managing the AIS patient in the ICU, beyond the care received in the ED or the neuro-interventional laboratory. The NCC of the AIS patient involves two general aspects: 1) reperfusion and neuro-protection and 2) management of complications.

Reperfusion and Neuro-protection: Post-thrombolysis Care

Reperfusion via cerebrovascular thrombolysis in the setting of AIS is accomplished via various methods: intravenous (IV) rtPA, intra-arterial (IA) rtPA, mechanical embolectomy, or a combination of these therapies (referred to as "bridging therapy"). However, the general concept of care beyond intervention remains the same, regardless of the method of thrombolysis.

The two fundamental aspects of care for these patients are neurological and hemodynamic monitoring. While in the ICU, neurological monitoring is typically accomplished by frequent bedside assessments or "neuro-checks," starting immediately after arrival to the unit. Obtaining a baseline neurological status is paramount, as it will serve as a reference to which any neurological deterioration is detected. In the sta-

ble post-thrombolysis patient, hourly assessments are performed for the first 24 hours, as recommended by the American Stroke Association (ASA) *Guidelines for Early Management of Adults with Ischemic Stroke*.[1] The unstable patients, such as those with hemodynamic or neurological fluctuations, may require monitoring beyond 24 hours. This decision ultimately depends upon how soon the patient could be discharged from the ICU (and subsequently, the frequency of neuromonitoring is reduced).

Neurological deterioration in the post-thrombolytic patient requires prompt attention and intervention. Immediate neurological examination and comparison to the baseline, followed by a non-contrasted CT scan of the head are the first steps in investigating potential causes. Causes of neurological decline in post-thrombolysis patients are several. However, the single most important cause mandating frequent neurological assessment in the setting of reperfusion therapy (with possible administration of IV or IA rtPA) is hemorrhagic transformation (HT) of the infarct or frank intraparenchymal hematoma (IPH). Historically, the rate of HT leading to neurological deterioration in post-IV rtPA patients has been estimated at about 6.7 percent, although this rate has declined over the years with increasing experience with this medication.[2] Risk factors for HT after IV rtPA include large area of infarction, increasing age, hyperglycemia, uncontrolled hypertension, congestive heart failure and prior treatment with aspirin.[3] Management of this complication will be discussed later in the article.

Strict monitoring and management of blood pressure (BP) is essential in patients who have undergone thrombolytic therapy. The ASA guidelines recommend hourly BP monitoring for the first 24 hours with a goal systolic (SBP) of less than 180 mmHg and diastolic less than 105 mmHg.[1] Persistent (more than 15 minutes) BP above these values requires more frequent monitoring and implementation of continuous infusion of IV antihypertensive medications. Although the ASA recommends against insertion of intra-arterial pressure catheters in the first 24 hours post IV rtPA, select patients with severely uncontrolled BP requiring continuous monitoring may benefit from this procedure, if performed by an experienced clinician.

Continuous or very frequent BP monitoring allows continuous infusion of IV anti-hypertensives such as nicardipine, esmolol or labetolol, while sodium nitroprusside is reserved for elevated BP that is refractory to these medications. Caution should be taken as to avoid excessive lowering of BP, which may lead to hypoperfusion (especially if there is only partial arterial recanalization after thrombolysis) and neurological worsening. Further considerations in hemodynamic monitoring and management are discussed in the next section.

Reperfusion Strategies in the Non-thrombolysed AIS Patient

For a patient who arrives outside of the window for thrombolysis or has undergone an unsuccessful attempt to recanalize the occluded artery, the goal of management is to prevent infarct expansion and provide adequate blood flow to the presumed ischemic penumbra. This is achieved by assuring that the patient's volume status and BP are optimized to maintain collateral perfusion to the ischemic penumbra. Providing adequate volume to the patient is paramount, and dehydration and hypovolemia must be avoided at all costs. The patient is typically fluid resuscitated with isotonic crystalloid solution (0.9% saline) to achieve euvolemia and perhaps being mildly volume-expanded. This status is maintained for the duration of the patient's admission to the ICU. Some clinicians also use various formulations of colloids (protein- or non-protein-based) to accomplish volume expansion. Albumin 5% solution is most often used as a colloid volume expander, although the frequency and duration of treatment with this preparation are unclear. It must be stressed that, at least looking at trauma patients, the superiority of colloids over crystalloids as volume expanders has not been established.[4] Invasive monitoring of volume status via central venous catheters (central venous pressure monitoring) are reserved for patients who are at risk of development of volume overload and congestive heart failure (CHF) due to aggressive attempts in fluid resuscitation.

Because of disrupted cerebrovascular autoregulation, patients with AIS typically present with elevated

BP.[5] This is a physiologic response to cerebral ischemia and must not be interpreted as a pathologic or malignant phenomenon. Hence, aggressive attempts to suppress this auto-hypertension must be avoided. Over-zealous treatment of BP may result in neurological deterioration due to hypoperfusion of the ischemic penumbra and expansion of the infarct core. There is no set value for BP maintenance in patients with AIS who have not undergone thrombolysis. BP parameters are set with an aim to sustain stable neurological status or treat worsening due to cerebral blood flow failure. In patients with large artery steno-occlusion, there are sometimes fluctuations of neurological status due to intermittent flow failure. In this scenario, BP is titrated to symptomatic improvement and elimination of clinical fluctuations. Rapid infusion of crystalloid or colloid solutions may be beneficial as the initial step. BP augmentation using vasopressors such as dopamine, phenylephrine or norepinephrine may sometimes be necessary to achieve symptomatic improvement, although how long this "hypertensive therapy" is maintained remains controversial. Once the patient's neurological status has been stable for at least 24 hours, an attempt to slowly wean off the vasopressor may be undertaken. Close and frequent neurological assessments and continuous BP monitoring via an intra-arterial pressure catheter (A-line) during the weaning process (as well as during the augmentation process) is essential.

Some vascular neurologists advocate flat head position (HOB flat) as a way of increasing or optimizing cerebral blood flow (CBF). Although transcranial Doppler (TCD) studies have shown some increase in flow velocities in AIS patients whose heads are kept in a flat position, factors such as patient discomfort due to musculoskeletal pain, orthopnea due to CHF and risk of aspiration may limit the utility of this maneuver.[6]

Fever is not uncommon in AIS patients and is clearly associated with infarct expansion.[7] It is thought that fever evokes a mismatch in supply and demand by increasing cerebral metabolic rate for oxygen (CMRO2). When this increase in brain metabolism is not responded to by a corresponding increase in perfusion (due to arterial steno-occlusion), expansion of the infarct ensues. Fever should be treated aggressively by using oral or rectal acetaminophen with or without cooling blankets. Some centers utilize intravascular temperature catheters connected to a calibrated, closed-system heat-exchange apparatus.

Neuro-protective Considerations in AIS

Over the past few decades, numerous pharmacologic approaches have been evaluated to assess the potential for some agents to provide "neuro-protection." These clinical experiments have been largely based upon prior success with animal models. Various agents ranging from citicoline and NXY-059 to rapid infusion of magnesium have been assessed without conclusive evidence that they have an impact on neurological or functional outcome.[8-10]

The most intriguing and widely investigated intervention aiming to provide neuro-protection in AIS patients is induced hypothermia (IH). The fascination with the use of IH in AIS was probably inspired by the success of this intervention in patients with global anoxic encephalopathy due to cardiac arrest.[11] Although IH has not proven to provide definitive neuro-protection when long-term outcomes are assessed, it may have an impact on mortality in AIS patients with large cerebral infarcts.[12] The seemingly successful impact on mortality in these patients is perhaps due to its effect in lowering cerebral metabolism, thus preventing compressive injury or elevated intracranial pressure (ICP) resulting from progressive cerebral edema (CE).[13]

Several methods are used to provide IH. The simplest pathway is via the use of cooling blankets, ice bags, cold (4°C) IV saline and gastric lavage using chilled free water. Sophisticated devices equipped with pads with circulating fluid or intravenous catheters connected to closed-system cooling apparatus are utilized by some centers.

How soon IH is started and how long it should be sustained is unknown. This is partly due to the heterogeneous course and behavior of the infarct. To achieve the maximal benefit, it is reasonable to assume that, when the goal is neuro-protection, IH should be initiated as soon as possible. However, the time window for implementation of this procedure is

unclear. If the purpose of IH is to prevent progression of regional CE, it should be continued until there is imaging confirmation of stability of CE. Complex AIS cases with significant CE may need invasive ICP monitoring. Based on pooled data from traumatic brain injury studies, IH can be used as an adjunct method to control and prevent elevations in ICP.[14]

It is worth emphasizing that in conscious AIS patients (unlike post-arrest patients who are usually comatose), IH—whether done via surface or invasive mode—can be quite uncomfortable, and other methods for control of CE should be considered. Additionally, IH can have several complications, including arrhythmia (most commonly bradycardia), electrolyte imbalance, shivering and susceptibility to infections.[13]

Complications of Acute Ischemic Stroke: Infarct Expansion

Potential causes for infarct expansion were previously discussed. To reiterate, any situation that causes perfusion failure could lead to expansion of the infarct core. This may include hypotension due to volume depletion or aggressive use of antihypertensive medications vis-à-vis a persistent arterial occlusion. Another potential cause of perfusion failure is arterial re-occlusion post IV rtPA which occurs at a frequency of approximately 34 percent.[15] Management of infarct expansion is largely preventative. Should neurological deterioration occur, the goal of therapy is maintenance of the ischemic penumbra via strategies that were previously discussed—that is, to make sure that collateral circulation to ischemic penumbra is preserved. Little could be done once the infarct has expanded. Completion of an infarct is clinically evident when reperfusion efforts (enhancing volume and pressure) fail to reverse the acute neurological change. Ultimately, a completed infarct can be visualized and confirmed on magnetic resonance imaging (MRI) diffusion weighted (DWI) sequence.

Hemorrhagic Transformation and Intraparenchymal Hematoma

Although all efforts should be focused to prevent this potential complication of AIS, the magnitude of aggressiveness in treatment of HT/IPH depends upon how relevant the associated neurological worsening is. A small hemorrhagic blush within the infracted area without a change in clinical symptoms is managed conservatively, although heparin and antiplatelet formulations are sometimes held briefly to assure that the blush does not progress into an IPH. The status of HT can be followed clinically and via serial CT scans.

Collective statistics from studies using various forms of thrombolytics have shown that symptomatic HT occurs at a frequency ranging between zero and seven percent.[16] The first step is management of symptomatic HT/IPH is discontinuation of antithrombotics. If heparin has been used, its reversal using protamine sulfate is imperative. The dose is 1mg IV per every 100 units of heparin, reducing the dose by 0.25mg/100 units for every hour elapsed from the time that heparin infusion was stopped. The medication must be given slowly (over 10 minutes) to avoid systemic hypotension.

Symptomatic HT/IPH resulting from IV thrombolysis may require immediate neurosurgical attention for possible evacuation. Surgical intervention by this time is largely performed as a “life-sparing” endeavor. Medical management includes administration of cryoprecipitate at a dose of 1 unit per 5kg of body weight and transfusion of platelets (6 to 8 units). Cryoprecipitate contains factor VIII which corrects the systemic fibrinolytic state created by IV rtPA. The mortality of symptomatic HT/IPH resulting from thrombolytics is unfortunately high and mirrors that of spontaneous (primary) intracerebral hemorrhage (40–80 percent).[17]

Cerebral Edema and Elevated Intracranial Pressure

CE and elevated ICP are devastating sequelae of AIS, carrying a mortality approaching 80 percent.[18] CE onsets within 48 hours of the infarct and peaks on days 3 to 5. Ultra-early as well as delayed CE (occurring up to 14 days after the initial infarct), leading to rapid mass effect (ME) are also possible. The edema associated with AIS is cytotoxic, microscopically characterized by swelling of neuronal tissue. Biochemically, cytotoxic CE is caused by failure of the

Na+/K+/ATPase pump (disruption of the energy-driven trans-membrane gradient) and clinically manifested by a decline in neurological status. ME and compression of brain structures such as thalamus, brainstem or contralateral hemisphere (midline shift) may cause deterioration in mental status, with or without worsening focal deficits. The severity and rate of this decline has a direct relationship with cerebral compliance—that is, how much additional volume the cranial vault is able to accommodate without a significant rise in ICP. Theoretically, atrophic brains are more compliant, although the course of the infarct and the associated CE could be quite unpredictable. Regional edema and ME cause the initial deterioration in neurological status and later on, depending on the size of the infarct and the extent of swelling, elevation of ICP becomes an issue. Therefore, timely identification and management of CE is imperative in order to prevent life-threatening rise in ICP.

Management of CE associated with AIS is both preventative and therapeutic. Fever must be aggressively treated and hyperglycemia and administration of hypotonic crystalloids must be avoided. Hypertonic saline (HS) at a concentration of 3% may be administrated continuously to prevent progression of edema. Some practitioners administer HS "prophylactically" when they visualize a large infarct on brain imaging and anticipate development of significant edema. However, the benefit of this practice remains to be delineated. The dosage or rate of administration of HS is also unknown, but as a rule of thumb, the HS drip is titrated to achieve a goal serum Na+ of 145 to 155 mEq/L.[19] The infusion is continued until the patient is neurologically stable and brain imaging shows stability of the edema. It is then slowly tapered off allowing passive correction of "therapeutic" hypernatremia over hours to days. The use of IV corticosteroids in treating CE associated with AIS is controversial.

Large infarcts with significant CE have the propensity to raise ICP leading to displacement of brain matter from one compartment to another. This migration, which is called herniation, occurs in an effort to equalize pressure in face of a inter-compartmental pressure gradient. Depending on the location of the lesion, herniation may be transtentorial (uncal), transfalcine, tonsillar, or central (caudal displacement of diencephalon). Clinical manifestations of transtentorial herniation are mental status decline, a change in respiratory pattern, unilaterally dilated ad non-reactive pupil due to oculo-motor palsy and ipsilateral hemparesis. Failure to promptly respond to these signs could result in rapid deterioration and death.

The goal for therapy is to keep ICP below 20 mmHg, although there is no absolute value at which the patient runs the risk of cerebral herniation. The initial step in management of elevated ICP is to place the patient's head at 30 degrees. This maneuver facilitates venous outflow of blood, thereby reducing the total volume contained within the cranium. The next step is hyperventilation in an effort to reduce arterial blood content of the vault. This is achieved by vasoconstriction caused by respiratory alkalosis. The goal is to maintain blood PCO2 of 26-30 mmHg.[20] This is only a temporary measure and is meant simply to "buy time" until a more effective intervention takes place. Although variable from one individual to another, the effects hyperventilation in reducing ICP will eventually wear off as the alkalosis is buffered by intrinsic mechanisms. Prolonged hyperventilation is not recommended as it can compromise CBP, precipitating ischemia. Osmolar diuresis using boluses of 20% IV mannitol or HS is also effective in reducing ICP. The dose for IV mannitol is 0.25 to 1.5g/kg as needed providing that serum osmolarity remains below 315-320 mOsm/L.[21] At this juncture, it is reasonable to obtain continuous ICP monitoring using an intraparenchymal fibroptic probe inserted through a cranial bolt. This will allow more appropriate scheduling of treatment with osmolar agents, preventing over-usage of these medications.

Other steps in reducing ICP are pharmacological-induced coma using agents such as pentobarbital. The regimen varies among centers, but the common goal is to titrate pentobarbital infusion to bring ICP below 20 mmHg. Some centers also use bedside electroencephalographic (EEG) monitoring with a goal of achieving "burst suppression." However, adjunct use of bedside EEG when the actual goal is to achieve normal ICP using pentobarbital infusion is controversial. The use of IH in reducing ICP was discussed ear-

lier. To re-emphasize, pooled data have shown that IH could reduce the mortality of large hemispheric AIS from 80 percent to 44 percent.[12]

It is sometimes impossible to reduce or prevent edema progression with medical therapy alone, even if the above measures are followed meticulously. The final step in management of refractory intracranial hypertension is decompressive hemicraniectomy with duroplasty (DHD), a procedure usually performed in patients with massive or "malignant" hemispheric infarcts. DHD allows outward expansion of the edematous brain tissue, preventing compression of central brain structures from ME or herniation. If done early (<48 hours), DHD has been shown to cut mortality by 30 percent with a number needed to treat (NNT) of two and appears to be associated with improved outcome.[22,23] Although specific criteria for performing this procedure vary from case to case and from one center to another, crude paradigm utilized by most institutions are: 1) age less than 60 years (based on evidence from European trials), 2) procedure to be done within 24-48 hours of presentation and 3) infarct involving the non-dominant hemisphere for language.[24] Performance of DHD in the language dominant hemisphere is currently subject to debate.

Principles of Medical Critical Care in the AIS Patient

As with any patient cared for in the ICU, patients with AIS have medical needs and may have medical complications. Because of high incidence of acute coronary syndrome (ACS) and arrhythmia in patients with AIS, cardiac rhythm monitoring is very important. Fortunately, it is a routine part of the general ICU monitoring policies and procedures. Patients with evidence of ACS or myocardial infarction (MI) should be treated accordingly. It is recommended that patients with AIS be provided with supplemental oxygen (O_2) at all times. Hypoxia can have a detrimental effect on the infarct causing it to expand. Although it is necessary to keep oxygen saturation (SpO_2) above or equal to 92 percent in these patients, data supporting the use of supplemental O_2 in patients without evidence of hypoxia is scarce. It is reasonable however to supply AIS patients (even those with no signs of hypoxia) with O_2 in order to prevent impending hypoxia due to airway obstruction. Some experts also believe in maximizing oxygen delivery to the ischemic tissue through increasing blood oxygen tension (pO_2) by means of continuous supplementation of O_2, regardless of patients SpO_2 personal communication. Patients with active or impending airway compromise will obviously require endotracheal intubation (EI) and mechanical ventilatory support. Approximately six percent of AIS patients will need EI and mechanical ventilation.[25] EI should be performed as quickly and efficiently as possible to avoid a prolonged period of hypoxia during the procedure. Ventilator settings should be optimized to assure adequate oxygenation. This is sometimes measured by calculating the ratio of pO_2 to FiO_2 (P/F ratio). A P/F ratio of 400 or greater is reasonable.

Metabolic demands of patients with AIS are usually altered as a result of acute illness. Hypoglycemia and hyperglycemia must be avoided at all costs, as both states have the potential to aggravate ischemic brain tissue and perpetuate neuronal death. Concentrations of electrolytes especially potassium and magnesium should be kept within normal parameters. These electrolytes are necessary for optimal neuronal function. Magnesium is an N-methyl D-aspartate (NMDA) receptor antagonist and may have a role in suppression of glutamate-driven excito-toxicity, a complex biochemical phenomenon responsible for continued neuronal death beyond the initial ictus.[26] Because ICU patients are in a relatively high catabolic state, their metabolic demands must be met by providing effective nutritional support. Enteric feedings should be initiated as soon as possible. If oral intake is not feasible due to dysphagia, delivery of liquid formulation via a naso-gastric, naso-duodenal or naso-jejunal tube is acceptable. The use of dextrose-containing crystalloids is not congruent to nutritional support and may be potentially harmful, particularly if there is associated hyperglycemia.

As mentioned before, fever has a harmful effect on the ischemic brain tissue and must be treated rapidly and effectively. Although evidence of infection is absent in many AIS patients who present with fever, proper measures must be taken to provide surveillance against infections. Blood cultures, urinalysis,

and x-ray of the chest are the basic diagnostic tools for this purpose. Initiation of empiric broad-spectrum antibiotics, although viewed by some as being self-fulfilling, may not be a completely inapt approach until basic diagnostic data eliminate evidence of infection. However, the spectrum must be narrowed as soon as possible once the pathogen is identified or discontinued if the results of the tests are negative for an infectious agent. Antibiotics themselves may precipitate fever; a characteristic that calls for their discontinuation in the absence of an infection.[27]

Finally, deep vein thrombosis (DVT) prophylaxis using subcutaneous heparin or low molecular weight heparinoid (LMWH) must be instituted as soon as possible. Patients who have received IV or IA rtPA usually receive these medications 24 hours after thrombolysis. Others should be started as soon as possible; unless there is a contra-indication (heparin induced thrombocytopenia or on-going hemorrhage). Either H2 or proton pump antagonists are used for peptic (stress) ulcer prophylaxis.

Conclusion

Care of a patient with AIS is quite comprehensive and requires a team approach. A subtle change in neurological status can foreshadow a major catastrophe or death. Clinicians who care for patients with AIS must be able to control and influence a multitude of physiologic parameters in order to assure optimal outcome. The vigor of management of AIS in the first 24 to 48 hours is a strong determinant of outcome and subsequent recovery. ■

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1. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007; 38:1655-1711.

2. NINDS rt-PA, Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995; 333: 1581–1587.

3. Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke. 2008; 39: 2249 - 2256.

4. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004; 350: 2247 - 2256.

5. Morfis L, Schwartz RS, Poulos R, Howes LG. Blood pressure changes in acute cerebral infarction and hemorrhage. Stroke. 1997; 28: 1401 - 1405.

6. Wojner-Alexander AW, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. Neurology 2005; 64: 1354 -1357.

7. Azzimondi G, Bassein L, Nonino F, et al. Fever in acute stroke worsens prognosis. A prospective study. Stroke. 1995; 26: 2040 - 2043.

8. Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE; Citicoline Stroke Study Group. A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology. 2001; 57: 1595 - 1602.

9. Lees KR, Zivin JA, Ashwood T, et al; Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators. NXY-059 for acute ischemic stroke. N Engl J Med. 2006; 354: 588 - 600.

10. Muir KW, Lees KR, Ford I, Davis S; Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet. 2004; 363: 439 - 445

11. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. Engl J Med. 2002; 346: 549 - 556.

12. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia the treatment of patients with severe middle cerebral artery infarction. Stroke. 1998; 29: 2461 - 2466.

13. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med. 2009; 37(Suppl): S186 - 202.

14. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet. 2008; 371: 1955 - 1969.

15. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. Neurology. 2002; 59: 862 - 867.

16. Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. Stroke. 2007; 38: 431 - 440.

17. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Circulation. 2007; 116: 391 - 413.

18. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996; 53: 309 - 315.

19. Tyagi R, Donaldson K, Loftus CM, Jallo J. Hypertonic saline: a clinical review. Neurosurg Rev. 2007; 30: 277 - 290.

20. Mayer SA, Chong JY. Critical care management of increased intracranial pressure. J Intensive Care Med. 2008; 17: 55 - 67.

21. Steiner T, Ringleb P, Hacke W. Treatment options for large hemispheric stroke. Neurology. 2001; 57(Suppl 2): S61 - 68.

22. Jüttler E, Schwab S, Schmiedek P, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007; 38: 2518 - 2525.

23. Köhrmann M, Schwab S. Hemicraniectomy for malignant middle cerebral artery infarction. Curr Opin Crit Care. 2009; 15: 125-130.

24. Chen CC, Cho DY, Tsai SC. Outcome of and prognostic factors for decompressive hemicraniectomy in malignant middle cerebral artery infarction. J Clin Neurosci. 2007; 14: 317 -321.

25. Gujjar AR, Deibert E, Manno EM, Duff S, Diringer MN. Mechanical ventilation for ischemic stroke and intracerebral hemorrhage. Neurology. 1998; 51: 447 - 451.

26. Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. Pharmacol Rev. 1999; 51: 7 - 61.

27. Johnson DH, Cunha BA. Drug fever. Infect Dis Clin North Am. 1996; 10: 85 - 91.