For patients who've survived an ischemic stroke, the sense of relief they feel immediately upon recovery is soon tempered by the precarious circumstances they'll now face for the remainder of their lives. The vulnerability to a second and potentially more life-threatening stroke is ever-present. Supportive care for such patients has two main objectives: (1) to minimize injury to potentially ischemic brain tissue and (2) to prevent and treat the many neurologic and medical complications that may occur in the immediate period following stroke.

Many of the medical and neurologic complications to which stroke patients are susceptible may contribute directly (as in the case of cerebral edema) or indirectly (as in the case of infection causing fever) to neuronal injury. There is, therefore, considerable overlap between the goals of protecting neuronal tissue and preventing medical and neurologic complications; this article will offer clinical strategies to succeed at each of these goals.

Strategies for Supportive Care

All stroke patients should receive supportive care. Though there may be a natural inclination to be less aggressive in patients with major stroke, particularly older patients, it should be noted that even in these populations the majority of patients will survive their stroke. The degree of functional recovery, however, may be dramatically impacted by the intensity and appropriateness of supportive care. Typical interventions are discussed below:

Blood pressure management. In healthy individuals, cerebral blood flow is held constant across a wide range of systemic blood pressures. In contrast, the cerebral vasculature in acute stroke patients is unable to adjust to variations in systemic blood pressure, and the relationship between cerebral blood flow and blood pressure becomes linear.[1] This impairment in cerebral autoregulation suggests that lowering systemic blood pressure may decrease cerebral perfusion and increase ischemic brain injury. This theoretical concern is supported by results from a

Keeping Stroke Patients Safe and Secure

Diligent monitoring and swift intervention are needed to prevent long-term complications after acute ischemic stroke.

By Steve Messe, MD and Brett Cucchiara, MD

small randomized trial testing nimodipine as a neuroprotectant agent; in the trial, a correlation between medication-induced blood pressure reduction and worse clinical outcome was seen.[2]

A small randomized controlled trial of candesartan, an angiotensin receptor blocker, in acute stroke did report decreased mortality at 12 months. However, no significant differences in blood pressure were reported.[3] As a general rule, therefore, blood pressure should not be actively lowered in the patient with acute cerebrovascular ischemia. Exceptions include patients who are candidates for or have already received thrombolytic therapy; the risk of intracranial hemorrhage is increased in patients with severe hypertension, patients with evidence of active hypertensive injury to other organs (*e.g.*, myocardial ischemia), and patients with extremely severe hypertension (*i.e.*, greater than 220/120). Decisions about blood pressure management should also take into consideration the patient's baseline blood pressure status.

Table 1 summarizes current recommendations from the American Stroke Association, including recommendations for patients eligible for thrombolytic therapy. In this latter group, the standard protocol for blood pressure management is based on the National Institute of Neurological Disorders and Stroke trial of tPA for acute stroke and should generally be rigidly adhered to.

Beyond avoiding therapies that lower blood pressure, induced hypertension using vasopressive agents has been suggested as a possible therapy for acute stroke. In a cohort of patients with acute hemispheric stroke, vasopressor-induced increases in mean arterial pressure were associated with increases in cerebral perfusion pressure (rising from 72.2+/-2 mm Hg to 97+/-1 mm Hg, $P<0.0001$).[4] Of note, there was also a significant, though modest, increase in ICP (rising from 11.6+/-0.9 mm Hg to 11.8+/-0.9 mm Hg, $P<0.05$).

A small pilot trial of 13 patients treated with vasopressor-

induced hypertension demonstrated increased perfusion and improved outcomes.[5] However, a meta-analysis of 12 small studies concluded that the benefits and risks remain uncertain and thus the use of vasopressors to induce hypertension must be considered experimental until benefit is demonstrated in randomized trials.[6]

In all patients, hypotension should be aggressively treated and the underlying etiology (*i.e.*, myocardial infarction, sepsis) determined and addressed. Initial treatment should include rapid volume replacement with normal saline. If there is no improvement in blood pressure, vasopressive agents should be used.

Volume status. Stroke patients are at a high risk of volume depletion due to decreased oral intake and increased insensible losses. Hypovolemia (based on serum osmolality) has been associated with worse outcome and increased mortality in acute ischemic stroke.[7] Isotonic saline, *i.e.*, "normal" or 0.9%, should be used for volume repletion and maintenance as hypotonic saline has the potential to exacerbate cerebral edema. Dextrose infusions should be avoided as hyperglycemia has been associated with worse outcome following stroke.

Positioning in bed. In patients with middle cerebral artery occlusion, upright posture can decrease cerebral blood flow and increase oxygen extraction in the affected hemisphere. Conversely, positioning patients flat in bed can improve cerebral blood flow. In patients with acute middle cerebral artery stroke, lowering the head of the bed from 30 degrees to 15 degrees increased middle cerebral artery mean flow velocity measured by transcranial Doppler by 12 percent (p=0.001), and by an additional eight percent when lowered from 15 degrees to 0 degrees (p=0.05).[8] Importantly, there was no change in blood pressure or heart rate with these changes in head position. Based on these data, it seems reasonable to maintain acute stroke patients in the flat position until neurologically stable.

There are no data to suggest a definitive time period; however, a common practice is to maintain the flat position for the initial 24 hours after presentation. If neurologic status worsens on position change, the patient should be returned to the flat position, and measures should be taken to improve cerebral perfusion and maintain collateral blood flow. In patients with increased intracranial pressure due to swelling from large hemispheric stroke, elevating the head of the bed may improve venous drainage and reduce ICP, but this may come at the cost of reduced cerebral perfusion pressure. There are few data to guide decision making in this difficult situation. In patients who cannot tolerate lying flat in bed due to orthopnea or other medical conditions, the head of the bed should be kept at the lowest level tolerated by the patient. Finally, frequent changes in body position (regardless of head position) are indicated to minimize the risk of pressure sores.

Glycemic control. Considerable evidence supports a link between hyperglycemia and poor outcome after stroke. Compared with normoglycemic patients, acute stroke patients who present with hyperglycemia have larger infarct volume, poorer functional outcome, and a higher likelihood of hemorrhage if treated with thrombolysis.[9-11] Hyperglycemic patients also have reduced salvage of at-risk brain tissue within the ischemic penumbra.[12] Data in critically ill patients without stroke suggest a benefit to intensive glucose control. In a large randomized trial of patients admitted to a surgical intensive care unit, strict normalization of serum glucose with an insulin drip reduced multiorgan failure, sepsis, and overall mortality.[13] Mortality reduction has also been shown in a similar trial of patients with myocardial infarction.[14]

Although there are at present no data proving a benefit of glucose lowering specifically in stroke patients, a pilot trial has demonstrated that aggressive glycemic control utilizing a continuous insulin, potassium, and glucose infusion is feasible and safe.[15] A larger randomized trial is currently ongoing. At present, strict glucose control using frequent finger-stick glucose checks and aggressive sliding scale insulin are reasonable, regardless of whether the patient has a known history of diabetes. Use of a more intensive glucose lowering regimen, although rational, must await further clinical trial data.

Hypoglycemia is a well-known stroke mimic and may present with focal neurologic symptoms. Prolonged hypoglycemia may also directly injure neurons. Thus, serum glucose should be checked immediately on presentation and hypoglycemia urgently treated with a dextrose infusion.

Temperature control. Fever is common in acute stroke patients, with as many as 25 percent generating a temperature of 38.0°C or more within the first 48 hours of admission.[16] Increased core temperature in acute stroke may increase neuronal metabolic demands, neurotransmitter release, and free-radical production within the ischemic penumbra.

Body temperature in acute stroke patients has been correlated with initial stroke severity, infarct size, mortality, and functional outcome in survivors. For each 1°C increase in body temperature, the risk of death or severe disability more than doubles.[17] Therapeutic hypothermia has been shown to improve neurologic outcome in cardiac arrest.[18] However, there are important differences between resuscitated cardiac arrest and stroke (*e.g.*, global versus focal brain insult, complete reperfusion versus incomplete or no reperfusion) that limit extrapolation of these trials. Numerous trials of induced hypothermia in stroke are underway. However, until data from these trials demonstrate a benefit of hypothermia, normothermia (temperature above 35.5°C and below 37.5°C) should be the goal. Lastly, fever in a stroke patient should be aggressively treated with antipyretics and possibly ice packs or other cooling devices, concurrent with a thorough search for an infectious source.

Table 1. Guidelines for Treatment of Elevated Blood Pressure in Ischemic Stroke

Not Eligible for Thrombolysis

Blood Pressure (mm Hg)	Treatment
Systolic 220 or lower OR Diastolic 120 or lower	Observe unless there is other end-organ involvement (eg, aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy)
Systolic > 220 OR Diastolic 121 to 140	Goal is a 10% to 15% reduction in blood pressure using: • Labetalol 10 to 20mg IV over 1 to 2 minutes (may repeat or double every 10 minutes; max dose is 300mg) OR • Sodium nitroprusside IV infusion starting at 5mg/hour (titrate by 2.5/hour every 5 min. to max of 15mg/hour)
Diastolic > 140	Goal is a 10% to 15% reduction in blood pressure using: • Nitroprusside IV infusion starting at 0.5 µg/kg/min (requires continuous blood pressure monitoring)

Eligible for Thrombolysis

Blood Pressure (mm Hg)	Treatment
Pretreatment	
Systolic > 185 OR Diastolic > 110	• Labetalol 10 to 20mg intravenously over 1 to 2 minutes (may repeat once) OR • Nitropaste 1 to 2 inches. If blood pressure does not consistently remain below 185/110, do not administer tPA.
After Treatment Started	Monitor BP every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours
Diastolic > 140	Sodium nitroprusside IV infusion starting at 0.5 µg/kg/min (requires continuous blood pressure monitoring)
Systolic > 230 OR Diastolic 121 to 140	• Labetalol 10mg intravenous over 1 to 2 minutes (may repeat or double dose every 10 minutes to a maximum dose of 300 mg or start a drip at 2 to 8mg/minute) OR • Nicardipine IV infusion starting at 5mg/hour (titrate by 2.5/hour every 5 minutes to max of 15mg/hour) OR • If blood pressure is not controlled, consider nitroprusside
Systolic 180 to 230 OR Diastolic 105 to 120	Labetalol 10mg intravenously over 1 to 2 minutes (may repeat or double dose every 10 minutes to a maximum dose of 300mg or start a drip at 2 to 8mg/minute)

Adapted from: Adams HP Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update a scientific statement from the stroke council of the American Heart Association/American Stroke Association. Stroke 2005;36:916-23.

Oxygenation. One of the more intuitive priorities in the care of the acute stroke patient is the maintenance of adequate tissue oxygenation. However, given that many stroke patients do not have significant lung disease or respiratory compromise, it is not clear that all patients require supplemental oxygen. A quasi-randomized study found no benefit of supplemental oxygen given to stroke patients.[19] A randomized trial of high flow oxygen via face mask in patients with ischemic penumbra present on MRI diffusion and perfusion imaging reported reduced diffusion volume at four hours and improved National Institutes of Stroke Scales at one week, but there were no significant differences at three months.[20]

Current American Stroke Association recommendations call for supplemental oxygen to be given as needed to maintain an oxygen saturation of more than 95 percent by pulse oximetry or blood gas. There is no convincing evidence to suggest benefit from hyperbaric oxygen in stroke, with the exception of stroke due to arterial air embolism.

Prevention and Management of Medical Complications

Medical complications such as pneumonia, sepsis, pulmonary embolism and myocardial infarction account for approximately half of the fatalities in the early period following stroke.[21]

Cardiovascular events. Stroke is frequently complicated by cardiac events such as myocardial infarction and arrhythmia. All patients who are admitted with acute stroke should have an ECG to identify active or prior cardiac ischemia and to assess cardiac rhythm. If available, continuous cardiac telemetry is a useful means of identifying intermittent arrhythmias, such as atrial fibrillation, that may have important diagnostic implications in the stroke patient.

Monitoring Stroke Patients

It is important to be aware that ECG changes are seen frequently in acute stroke and may occasionally be the result of central nervous system injury and the corresponding hyperadrenergic state. Commonly seen electrocardiographic changes include ST segment depression, QT prolongation, inverted T waves, and prominent U waves.

Cardiac enzymes should be obtained if ischemia is suspected, but again, they must be carefully interpreted. A consecutive series of 160 acute stroke patients (of which 140 were ischemic) found elevated troponin levels in 10 (six percent). Troponin levels rapidly normalized, and chest pain, Q-waves, and focal akinesis were rare, implying that modestly elevated troponin levels in stroke patients are primarily neurogenic in origin.[22] In cases of confirmed myocardial infarction following stroke, decisions about double antiplatelet therapy, anticoagulation, glycoprotein IIb and IIIa inhibitors, and invasive procedures must take into account the extent and acuity of the cerebral infarction to estimate the excess risk of intracranial hemorrhage or other complications associated with these therapies.

Chest radiography is useful to assess heart size and identify pulmonary edema, which should prompt evaluation and management of congestive heart failure. In patients with significant heart failure, efforts to increase cerebral perfusion with intravenous fluids and cessation of antihypertensive agents may have the opposite effect due to worsening of cardiac output. In these cases, optimization of cardiac output is a reasonable primary goal.

Deep vein thrombosis and pulmonary embolism. Venous thromboembolism is a common and potentially devastating complication of stroke. It has been estimated that pulmonary embolism accounts for up to 25 percent of fatalities following stroke.[23] Risk factors for deep vein thrombosis include advanced age, lower extremity paralysis and atrial fibrillation. Subcutaneously administered heparin or low-molecular weight heparin have been shown to reduce the risk of deep vein thrombosis.[24] There is also evidence that elastic compression stockings, aspirin and sequential compression devices can reduce the risk of deep vein thrombosis, and this effect may be additive with antithrombotic medication.[23,25]

All stroke patients should receive some form of prophylaxis against deep vein thrombosis or pulmonary embolism. In patients suspected of harboring DVT, lower extremity ultrasound is indicated. Serum D-dimer is probably a less useful alternative, given the high pre-test probability of deep vein thrombosis or pulmonary embolism in stroke patients. Patients with established deep vein thrombosis or pulmonary embolism should generally be treated with anticoagulant therapy. If anticoagulant therapy is contraindicated, consideration should be given to placement of an inferior vena cava filter, though the long term effects of this intervention are controversial.

Infection. Infection is commonplace in the acute stroke patient. Pneumonia and urinary tract infections occur most frequently, each affecting about 10 percent of acute stroke patients.[21] Less frequent infectious processes include cellulitis and sepsis. Acutely ill patients, particularly the elderly, may not immediately generate fever and may instead present with unstable vital signs, decreasing oxygenation, or a change in neurologic exam. A high index of suspicion for infection must be maintained and a rapid evaluation of possible sources initiated when appropriate. Close attention should be paid to urinary catheters and intravenous and central lines. Empiric antibiotics are appropriate in cases where infection is strongly suspected, pending the results of diagnostic tests. Aggressive treatment of fever is indicated, as described previously.

Malnutrition and aspiration. Poor nutritional status at hospital admission is associated with worse outcome following stroke due to increased risk of infection, gastrointestinal bleeding, and bed sores.[26] Further, acquired malnutrition following a stroke is also associated with a worse prognosis. Swallowing dysfunction is common in acute stroke patients and is associated with a high risk of inadequate nutritional intake and aspiration. Swallowing evaluation should be performed in all patients with dysarthria, aphasia, or facial, buccal, or lingual weakness. Inability to swallow safely should precipitate early placement of a nasogastric tube in order to assure gastrointestinal access for nutrition and medications. If swallowing difficulties persist greater than one to two, weeks a percutaneous gastrostomy tube should be considered.

Airway compromise. Patients with brainstem stroke or a decreased level of arousal due to large hemispheric stroke have an increased risk of airway compromise secondary to loss of protective reflexes or oropharyngeal weakness.[27] Patients who are unable to protect their airway should undergo endotracheal intubation, with the recognition that those who require intubation have a poor prognosis, with a mortality rate of over 60 percent.[28]

Activity level. Rapid mobilization after the acute period may reduce the risk of pneumonia, deep vein thrombosis, pulmonary embolism, and pressure sores. Shorter time to mobilization and rehabilitation training has been associated with a greater odds of discharge to home (as opposed to a nursing home or death) at six weeks.[29] As soon as a patient has become neurologically stable, physical therapy should be initiated.

Prevention And Management Of Neurologic Complications

Neurologic complications following acute stroke include cerebral edema, recurrent stroke, intracranial hemorrhage, and seizures. Frequent neurologic examinations, followed by repeat neuroimaging if a significant change is noted, may allow rapid identification and treatment of these complications.

Cerebral edema. Patients with large hemispheric or cerebellar infarction are at highest risk of developing clinically significant cerebral edema. Edema typically peaks between three and five days after stroke onset. Clinical-pathologic correlates include decreased level of consciousness from compression of thalamic and midbrain reticular activating system; enlargement of the ipsilateral pupil from oculomotor nerve compression, ipsilateral lower extremity weakness, or hyperreflexia from subfalcine herniation with compression of the previously unaffected anterior cerebral artery; and ipsilateral upper and lower extremity weakness or hyperreflexia due to Kernohan notch phenomenon. Acute hydrocephalus from occlusion of cerebrospinal fluid drainage pathways may be seen with large cerebellar infarctions.

Management of patients with cerebral edema and increased ICP from ischemic stroke is empiric, with limited data to support any particular strategy. In general, invasive ICP monitoring does not appear to be of great utility.[30] Raising head position to 30 degrees or greater may increase venous drainage and decrease ICP but may decrease cerebral perfusion. Hyperventilation can rapidly reduce ICP, but the effect is short-lived (on the order of hours) and, therefore, of limited utility in the absence of definitive therapy to lower ICP.

Osmotic agents such as mannitol, glycerol and hypertonic saline, which have a longer duration of effect than hyperventilation, may be used to "buy time" until edema begins to subside spontaneously. A common strategy is to give a bolus of mannitol 1.0g/kg, followed by 0.25 to 0.5g/kg every four to six hours for several days or until clinical or radiographic evidence of decreased edema is present. There are no convincing data that these agents improve outcome. Steroids have been shown to be ineffective in ischemic stroke and may increase the rate of infectious complications.[31]

In patients with large hemispheric stroke, hemicraniectomy appears to decrease mortality compared to historical controls and may possibly result in improved functional outcome.[32] Optimal patient selection and timing of this intervention remains undetermined, and its efficacy remains to be established in a randomized trial. In patients with large cerebellar infarcts with decreasing mental status secondary to brainstem compression and hydrocephalus, there is general agreement that suboccipital craniectomy or ventriculostomy is indicated.[33]

Recurrent stroke. Combined analysis of over 40,000 patients in the International Stroke Trial and Chinese Acute Stroke Trial shows that aspirin (160 to 325mg) given within 48 hours of stroke onset reduces the rate of recurrent ischemic stroke from 2.3 to 1.6 percent ($p < 0.000001$) over two to four weeks. There was a small increase in the rate of intracerebral hemorrhage (0.8 vs 1.0 percent, $p=0.07$), but this did not negate the benefit from early aspirin.[34] In contrast, unfractionated heparin and low

molecular weight heparins have not shown overall benefit in reducing recurrent stroke, partly because of an increased risk of intracranial and other hemorrhagic complications.[35] These findings apply to patients in atrial fibrillation at the time of stroke as well. In patients who receive thrombolytic therapy, aspirin should be avoided during the first 24 hours.

Intracranial hemorrhage. Patients with acute ischemic stroke are at significant risk of intracranial hemorrhage, especially if treated with anticoagulant or thrombolytic therapy. Small asymptomatic hemorrhages may not require any change in therapy. More significant and symptomatic intracranial hemorrhage mandates cessation of anti-thrombotic therapy and reversal of anticoagulation, if applicable. Patients who have received thrombolytic therapy should be treated with cryoprecipitate and platelet transfusion, as per the NINDS rt-PA Stroke Study protocol. A large randomized trial found that surgical evacuation does not improve outcome in unselected patients with primary intracerebral hemorrhage.[36] Nevertheless, a neurosurgical consultation should be obtained and it is reasonable to consider emergency surgical evacuation in patients with large (>3cm) cerebellar hemorrhages, or those with large, superficial hemorrhages causing substantial mass effect, with rapidly deteriorating condition.

Seizures. Seizures in the acute ischemic stroke setting have been reported in one to six percent of patients.[37] Early seizure occurrence has been associated with stroke location (particularly with regard to cortical involvement), size, severity and hemorrhage.[38] It remains controversial as to whether anticonvulsants should be initiated in all patients with early seizure as the potential for seizure prophylaxis should be weighed against factors such as age, disability, and risk of adverse effects. For most patients, with seizure in the setting of acute stroke, it is reasonable to consider initiating anticonvulsant therapy and continuing it for at least 12 months before weaning if they remain seizure free. There is no evidence to support prophylactic use of anticonvulsants in patients with ischemic stroke who have not had seizures.

Conclusion

The period immediately following an acute stroke is a time of significant risk. Meticulous attention to the care of the stroke patient during this time can prevent further neurologic injury and minimize common complications, optimizing the chance of functional recovery. **PN**

Adapted from MedLink® Neurology (www.medlink.com) with permission.

Steve Messe, MD is Assistant Professor of Neurology at the Hospital of the University of Pennsylvania, Division of Stroke and Critical Care, in Philadelphia.

Brett Cucchiara, MD is Assistant Professor of Neurology at the Hospital of the University of Pennsylvania, Division of Stroke and Critical Care, in Philadelphia.

1. Novak V, Chowdhary A, Farrar B, et al. Altered cerebral vasoregulation in hypertension and stroke. Neurology 2003;60(10):1657-63.

2. Ahmed N, Nasman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke 2000;31(6):1250-5.

3. Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke 2003;34(7):1699-703.

4. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of induced hypertension on intracranial pressure and flow velocities of the middle cerebral arteries in patients with large hemispheric stroke. Stroke 2002b;33(4):998-1004.

5. Hillis AE, Ulatowski JA, Barker PB, et al. Apilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. Cerebrovasc Dis. 2003;16:236-46.

6. Mistri AK, Thompson GR, Potter JF. Pressor Therapy in Acute Ischemic Stroke. Stroke 2006;37:1565-71.

7. Bhalla A, Sankaralingam S, Dundas R, Swaminathan R, Wolfe CD, Rudd AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. Stroke 2000;31(9):2043-8.

8. Wojner AW, Garami Z, Noser EA, Shaw S, Malkoff M, Alexandrov AV. Heads down: lower head position is better in acute ischemic stroke. [abstract]. Stroke 2003;34(1).

9. Els T, Klisch J, Orszagh M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc Dis 2002;13(2):89-94.

10. Kidwell CS, Saver JL, Carneado J, et al. Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis. Stroke 2002;33(3):717-24.

11. Tanne D, Kasner SE, Demchuk AM, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. Circulation 2002;105(14):1679-85.

12. Parsons MW, Barber PA, Desmond PM, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 2002;52(1):20-8.

13. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345(19):1359-67.

14. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ 1997;314(7093):1512-5.

15. Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). Stroke 1999;30(4):793-9.

16. Grau AJ, Buggle F, Schnitzler P, Spiel M, Lichy C, Hacke W. Fever and infection early after ischemic stroke. J Neurol Sci 1999;171(2):115-20.

17. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996;347(8999):422-5.

18. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

19. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. Stroke 1999;30(10):2033-7.

20. Singhal AB, Benner T, Roccatagliata L, et al. A pilot study of normobaric oxygen therapy in acute ischemic stroke. Stroke 2005;36(4):797-802.

21. Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. Stroke 1998;29(2):447-53.

22. Chalela JA, Ezzeddine MA, Davis LA, et al. Myocardial ischemia in acute stroke patients: a troponin I study. [Abstract]. American Heart Association. 27th AHA International Conference On Stroke and Cerebral Circulation. San Antonio, February 2002.

23. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. Stroke 2001;32(1):262-7.

24. Adams HP Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34(4):1056-83.

25. Kamran SI, Downey D, Ruff RL. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. Neurology 1998;50(6):1683-8.

26. Food Trial Collaboration. Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. Stroke 2003;34(6):1450-6.

27. Krieger D, Hacke W. The intensive care of the stroke patient. 3rd ed. New York: Churchill Livingstone; 1998.

28. Bushnell CD, Phillips-Bute BG, Laskowitz DT, Lynch JR, Chilukuri V, Borel CO. Survival and outcome after endotracheal intubation for acute stroke. Neurology 1999;52(7):1374-81.

29. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? Stroke 1999b;30(5):917-23.

30. Schwab S, Aschoff A, Spranger M, Albert F, Hacke W. The value of intracranial pressure monitoring in acute hemispheric stroke. Neurology 1996;47(2):393-8.

31. Norris JW, Hachinski VC. High dose steroid treatment in cerebral infarction. BMJ 1986;292:21-3.

32. Schwab S, Steiner T, Aschoff A, et al. Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke 1998;29(9):1888-93.

33. Mathew P, Teasdale G, Bannan A, Oluoch-Olunya D. Neurosurgical management of cerebellar haematoma and infarct. J Neurol Neurosurg Psychiatry 1995;59(3):287-92.

34. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke : a combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31(6):1240-9.

35. Coull BM, Williams LS, Goldstein LB, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). Stroke 2002;33(7):1934-42.

36. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet 2005 365(9457):387-97.**

37. Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology 2001;57(2):200-6.

38. Bladin CF, Alexandrov AV, Bellavance A, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57(11):1617-22.