

Advances in Neurointensive Care

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Abstract

Purpose: To highlight recent advances in neurological and neurosurgical intensive care. **Data Sources:** A MEDLINE search was conducted from January 1980 to August 2000. Keywords included intensive care, head injury, subarachnoid haemorrhage, status epilepticus, myasthenic crisis, Guillain-Barre syndrome and stroke. All articles in English were considered for review. Additional articles were identified from the references of the retrieved articles and cross-referencing selected articles. **Data Extraction:** All clinical studies, review articles and abstracts were reviewed. **Data Synthesis:** Rapid advances in neurological and neurosurgical intensive care in the last decade have led to the development of specialised neurointensive care units with joint ventures between neurology and neurosurgery. Work in these units have contributed immensely to our understanding of the pathophysiology and management of acute brain injury. The principles of intensive care management include amelioration or reversal of brain injury and preservation of normal neural tissue. Treatment algorithms are possible with the aid of intense clinical and neurophysiologic monitoring. Ongoing clinical and basic science research may provide new treatment options for the intensivist in the acute phase of brain injury. **Conclusion:** Specialised neurointensive care units provide the best environment for the patient with acute brain injury. Outcome is frequently enhanced with clinicians skilled towards dealing with the whole spectrum of neurologic insults.

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Introduction

Neurointensive care has come into being in the past decade as a recognised subspecialty. Pioneering neuro-intensivists in the United States, such as Allan Ropper and Dan Hanley, have led in demonstrating the specialised expertise that neurointensivists offer to critically ill patients. The American Academy of Neurology has also established, for a decade now, the Section in Critical Care and Emergency Neurology. Neurointensive care is also a designated subsection in the journal *Critical Care Medicine*.

Outside the United States, much of neurointensive care management remains a collaborative effort between neurologists, neurosurgeons and general intensivists or anesthesiologists working in mixed intensive care units (ICUs). Indeed, the basic requisites of an effective ICU remain unchanged under any subspecialty label, and neurointensive care is no exception. Neurointensive care, thus, begins with delivery of sound basic intensive care. Outcome, however, can be further enhanced with clinicians oriented and skilled towards dealing

with the spectrum of neurologic pathophysiology, monitoring modalities and effective interventions.¹ Recent literature attests to the favourable impact of intensivists in patient management.²⁻⁵

This paper serves to highlight some recent advances in neurointensive care.

Selective Vulnerability of the Central Nervous System

A major pre-requisite for a good outcome after severe neurologic insult is maintenance of a favourable cerebral oxygen supply-demand relationship and prevention of systemic hypoxia.⁶ After primary injury, the brain is especially susceptible to further hypoxic insults. Factors that increase susceptibility include reduced cerebral blood flow (CBF), impaired pressure autoregulation, impaired cerebral vasodilatation in response to hypoxaemia, abnormal flow-metabolism coupling and impaired vasodilatation in response to acute anaemia.⁷ The pyramidal neurons, in the CA1 region of the hippocampus, are extremely sensitive to injury in both rats, primates and humans.⁸

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The mechanisms by which brain trauma or ischaemia decrease CBF and impair cerebral vascular reactivity are multi-factorial and may be attributed to one of several inter-related mechanisms in the cell death cascade: oxygen free radicals (superoxide anions), excitatory amino-acid receptor-mediated injury and intracellular calcium accumulation.⁹ In addition, apoptosis or programmed cell death has been postulated to explain selective neuronal loss after global or focal ischaemic injury or even head injury.^{10,11}

Current research in neuroprotectants is active at the stage of phase III clinical trials. Promising agents include lubeluzole, cerestat, tirilizad and many others. Our centre is currently involved in several trials of acute stroke therapy as well as a phase III multicentre trial using nimodipine in the treatment of traumatic subarachnoid haemorrhage.

General Principles in the Management of NICU Patients

Appropriate cardiopulmonary stabilisation of the acute neurologic critically ill patient is the corner stone of initial management in the neurointensive care unit (NICU). The clinical impact of hypoxia or hypotension on outcome was clearly demonstrated in the Traumatic Coma Data Bank (TCDB) study. Both factors were associated with a worse outcome, with the influence of hypotension being greater than that of hypoxia (Table I).¹²

With few exceptions, haemodynamic management of NICU patients should have, as immediate and over-riding considerations, normovolaemia, normotension and iso-osmolality [exceptions include patients at risk for normal perfusion pressure breakthrough bleeding (induced hypotension and cerebral metabolic rate suppression) and cerebro-vasospasm (hypertensive-hypervolaemic-haemodilution therapy)]. 'Traditional' therapeutics of mild dehydration, and precipitous blood pressure reduction of acute stroke patients may instead be detrimental to adequate cerebral oxygen delivery.¹³ Recently the successful use of 3% or 23.4% hypertonic sodium chloride in the acute control of intracranial pressure (ICP) confirms its efficacy but does not address concerns with long-term effects of the sodium load.¹⁴

Acute neuroendocrine management in the NICU include, in particular, management of polyuria with its differential diagnoses of diabetes insipidus, osmotic diuresis, or post-resuscitation fluid mobilisation. Hyponatraemia may occur secondary to the syndrome of inappropriate antidiuretic hormone secretion or the cerebral salt-wasting syndrome. Both hypoglycaemia and hyperglycaemia should be scrupulously avoided.

Hyperthermia and seizures should be treated aggressively as they impose increased cerebral metabolic demands on neurologic patients who may already have borderline or impaired cerebral blood supply. Surveillance and early

TABLE I: OUTCOME BY SECONDARY INSULT AT TIME OF ARRIVAL AT TRAUMATIC COMA DATA BANK HOSPITAL EMERGENCY DEPARTMENT¹²

Secondary insults	Outcome				
	No. of patients (n)	Percentage of total	Good or moderate	Severe or vegetative	Dead
Total cases	699	100	42.9	20.5	36.6
Neither	456	65.2	51.1	21.9	27.0
Hypoxia	130	18.6	29.2	20.8	50.0
Hypotension	165	23.5	19.4	15.8	64.8
Both	52	7.4	5.8	19.2	75.0

detection of infection is important as sepsis is a leading cause of death in the neurologic critically ill patient. Meticulous skin care, frequent turning and suctioning and chest physiotherapy are needed to prevent decubitus ulceration, atelectasis, infection and neuropraxia. As acute brain injury is associated with a hypermetabolic state, early and adequate nutrition is required and had been shown to increase survival, shorten ICU length of stay, and reduce infections in patient groups such as the head injured.¹⁵ Zinc microsupplementation has been shown to more rapidly improve Glasgow Coma Scale scores in patients with brain injury.¹⁶ Specific disease conditions will now be highlighted.

Severe Head Injury (SHI)

Organised neurotrauma systems, based on a continuum of monitored care and aggressive surgical or medical intervention, are critical to survival with good outcome.¹⁷ Our standardised head injury treatment protocol for SHI has yielded results comparable with other recently reported series (Table II).¹⁸⁻²¹ Two important paradigms in the current treatment of SHI are (i) determine and maintain an adequate cerebral perfusion pressure (CPP) with ICP control,¹⁹ and (ii) understand and monitor the time-course and characteristics of CBF and metabolism changes after SHI, in order to sustain aerobic metabolism and prevent secondary brain insults.^{22,23} Current recommendations regarding management of SHI have been clearly spelled out by the Brain Trauma Foundation, the European Brain Injury Consortium and the Society of British Neurological Surgeons. There are three standards established in the management of SHI:

- 1) in the absence of increased ICP, hyperventilation should be avoided,
- 2) the use of steroids is not recommended, and
- 3) prophylactic use of anticonvulsant is not recommended for prevention of late post-traumatic seizures.

Recommended guidelines include:

- 1) avoidance of hypotension and hypoxia,
- 2) ICP monitoring of patients who had GCS of 3 to 8 after resuscitation and abnormal computed tomographic (CT)

TABLE II: OUTCOME OF SEVERE HEAD INJURY IN NEUROTRAUMA CENTRES

	Tan Tock Seng ¹⁸ 1998	Cruz ²⁰ 1998	Rosner ¹⁹ 1995	TCDB ²¹ 1991
Number of patients	48	178	158	746
Glasgow Outcome Score (%)				
4 to 5	60.4	74	59	25.2
3	10.4	14	9	28
2	14.6	3	2	14
1	14.6	9	29	32.5

TCDB: Traumatic Coma Data Bank

Glasgow Outcome Score 4 to 5: good outcome/moderate disability; 3: severe disability; 2: persistent vegetative state; 1: death

scan,

- 3) treatment of ICP above 20 to 25 mmHg,
- 4) use of mannitol for the control of raised ICP,
- 5) high dose barbiturate therapy in haemodynamically stable salvageable SHI patients with ICP refractory to maximal medical and surgical interventions, and
- 6) replacement of 140% of resting metabolism expenditure in non-paralysed patients and 100% resting metabolism expenditure in paralysed patients using enteral or parenteral formulas containing at least 15% of calories as protein by the seventh day after injury.

Experimental multi-modality cortical probes, measuring pressure, temperature, pH, and cortical PO₂, with the potential for microdialysis analysis are being studied. Chan et al²⁴ described the technique of combining transcranial doppler with jugular venous oxygen saturation (SjvO₂) monitoring to determine the optimal CPP at the inflection point where the autoregulatory plateau in the CPP-CBF is reached. Although the study's grouped data has since served as targeted values for existing guidelines, increasingly CPP and ICP targets should be determined for individual patients.²⁵ Continuous or close monitoring of SjvO₂ is aimed at guiding treatment regimes to achieve a favourable global brain O₂ supply-demand with normal SjvO₂ values.²⁰ While oligoemic SjvO₂ has clearly been shown to be harmful,²⁶ Gopinath et al²⁷ have recently shown that hyperaemic SjvO₂ values are also associated with poor outcome. Whether the latter study reflects irreversibly impaired brain cellular function or is an indictment of the consequence of focal ischaemia from inappropriately aggressive SjvO₂-directed 'optimised' hyperventilation is unclear. When medical management to treat raised intracranial hypertension fails, aggressive surgical interventions such as decompressive bifrontal craniectomy have yielded promising results.²⁸ The poor outcome of patients with loss of CO₂ and pressure vasoreactivity (cerebrovasomotor paralysis) has also prompted the use of prostaglandin inhibitors such as indomethacin and a new concept by the Lund group known as brain volume reduction therapy. The latter is a

combination of lowering systolic blood pressure, moderate barbiturate-induced metabolic suppression, di-hydro-ergotamine induced pre-capillary arteriolar vasoconstriction and hyperoncotic fluid therapy to reduce vasogenic edema.^{29,30} Recently published data suggest that it is highly effective in controlling raised ICP and reducing mortality in what has previously been a very high mortality subset of SHI patients.²⁹ More controversial is whether this technique should be extended to all head injured patients, even in those without loss of vasoreactivity.³⁰ Other cerebro-protective techniques such as induced moderate hypothermia³¹ and calcium channel³² antagonists have shown promise in smaller trials. A National Institute of Neurological Disorders and Stroke (NINDS) phase III trial for moderate hypothermia in SHI has, however, been halted, and conclusions regarding the efficacy of this therapy remains unclear. Results of a worldwide trial on the use of nimodipine in traumatic subarachnoid haemorrhage are eagerly awaited.

Aneurysmal Subarachnoid Haemorrhage (SAH)

The incidence of spontaneous aneurysmal SAH varies from 6 to 16 per 100,000.³³ In Singapore, an autopsy study yielded 105 deaths due to ruptured cerebral aneurysms among 33,137 deaths over the period 1982 to 1996.³⁴ Sixty-four per cent of cases occurred between ages 31 to 60 years and there was a marginal predilection for females. In the Cooperative Study, the peak incidence of spontaneous SAH occurred in the 50 to 54 years age group with a female to male ratio of 3:2.³⁵

The most feared consequence of aneurysmal SAH is re-bleeding, which has a case fatality rate of approximately 70%.³⁶ The risk of re-bleeding is about 4% in the first 24 hours and between 1% to 2% per day over the subsequent 4 weeks.³⁷ The mainstay of therapy to prevent re-bleeding is surgical clipping of the aneurysm, although lately, coiling of the aneurysm via interventional neuroradiological techniques is becoming more important especially for posterior circulation aneurysms. The optimal timing for aneurysm surgery is still being debated. Early surgery

eliminates the risks of re-bleeding and facilitates treatment of vasospasm. However, a swollen brain and a clot laden subarachnoid space in the acute phase may increase the operative complication rate. Delayed surgery, on the other hand, has been reported to have superior surgical results. Unfortunately in terms of the overall management outcome, the results of delayed surgery were no better due to the complication of re-bleeding occurring while awaiting surgery.³⁸ The International Cooperative Study on the Timing of Aneurysm Surgery failed to show any significant difference in the overall management outcome in relation to timing of aneurysm surgery.³⁹ At present, early clipping is recommended for patients with good neurological condition and accessible aneurysms according to published guidelines.^{36,40}

Endovascular embolisation with Guglielmi detachable coils (GDC) is a promising treatment for cerebral aneurysms. In a Food and Drug Agency (FDA) multicentre clinical trial involving 150 aneurysms, 90% coil packing were achieved in 75% of patients.⁴¹ The periprocedural mortality rate was 2.9% and the permanent stroke rate was 5% in patients with ruptured aneurysms and 9% in patients with unruptured aneurysms. The re-bleeding rate was 3.3% for ruptured and 4.1% for unruptured aneurysms. The results are better than the natural history for ruptured aneurysms. Hence, this option should be offered to patients who are not surgical candidates.

The most common cause of death in SAH is vasospasm. The onset usually occurs 3 to 5 days after the bleed, peaking in severity on days 6 to 8 and resolving by about the tenth day.⁴² In the Cooperative Study, vasospasm accounted for 28% of mortality and 39% of morbidity.³⁹ Triple H therapy (hypervolaemia, haemodilution and induced hypertension) together with nimodipine are currently being used to treat vasospasm. Other pharmacologic measures include intraoperative administration of tissue plasminogen activator and use of tirilazad mesylate, an aminosteroid-free radical scavenger. Intraluminal angioplasty with balloons or papaverine have been reported to reverse vasospasm in many uncontrolled clinical studies.^{43,44} However, its effect on functional outcome has not been fully evaluated and it is associated with a mortality rate of 4%.^{43,44}

At the National Neuroscience Institute, our standard protocol involves early surgery for good grade patients and routine administration of nimodipine. Prior to surgical clipping, the central venous pressure is maintained between 5 to 10 mmHg and the blood pressure maintained within 120 to 160 mmHg. After clipping, the blood pressure is aimed at above 160 mmHg. In patients with symptomatic vasospasm, hypervolaemia with central venous pressure of 8 to 12 mmHg and systolic blood pressure of up to 200

mmHg will be induced to reverse the neurological deficits. Refractory cases are treated with angioplasty. The outcome with this approach is similar to published series in the literature.⁴⁵

Intracerebral Haemorrhage

Intracerebral haemorrhage accounts for a quarter of all strokes in Singapore with a much higher morbidity and mortality compared to ischaemic strokes.⁴⁶ The most common aetiology is hypertension. The four classical sites of hypertensive intracerebral haemorrhages are the putamen/basal ganglia, thalamus, brainstem and cerebellum. Other causes of spontaneous intracerebral haemorrhage include aneurysms, vascular malformations, cerebral amyloid angiopathy, brain tumours, coagulopathy, vasculitides, moya-moya disease and drug abuse.

In the acute phase, patients with significant impairment of conscious level may require intubation for airway protection or respiratory insufficiency. Optimal blood pressure control in spontaneous intracerebral haemorrhage remains controversial: too high a pressure may precipitate re-haemorrhage; conversely overzealous reduction of blood pressure may compromise cerebral perfusion.⁴⁷ In practice, we do not intervene if the systolic blood pressure is not more than 180 mmHg. Blood pressure should not be allowed to fall below pre-morbid levels. Underlying coagulopathy should be corrected as soon as possible.

Both hyperosmolar agents such as mannitol and controlled hyperventilation are widely used for short-term control of raised intracranial pressure from sizeable intracerebral haematomas. PCO_2 is targeted between 30 to 35 mmHg. Mannitol 20% (0.25 to 0.5 g/kg every 4 h) is indicated for patients with signs and symptoms of progressively increasing intracranial pressure or clinical deterioration associated with mass effect. Due to its rebound phenomenon, mannitol is recommended for only 5 days. Serum osmolality should be measured twice daily in patients receiving osmotherapy and targeted to 310 mOsm/L or less. Ventricular drainage is indicated in cases complicated by hydrocephalus.

For seizure control, phenytoin is often given IV at 15 mg/kg (<50 mg/min) for loading and maintained at 300 mg on. Dose adjustment is then titrated according to clinical response as well as the serum phenytoin level. There is no evidence to support routine use of prophylactic anticonvulsant although it is often practiced due to fear of re-bleeding after a fit.

The role of surgical evacuation of hypertensive intracerebral haematomas remains controversial. Meta-analysis of three randomised controlled trials of open surgery and one endoscopic evacuation prior to June 1997 indicate a non-significant increase in odds of death and

dependency at 6 months for patients treated surgically.⁴⁸ A recent single centre randomised trial involving 17 cases in the surgical arm and 17 cases in the medical arm showed that the 1-month mortality rate is lower in the surgical compared to the medical arm, but at 6 months the mortality rates in both groups are similar (surgical 17%, medical 24%, $P = 0.75$). The functional outcome was also similar at 6 months (69% poor outcome with medical treatment, 50% poor outcome with surgery, $P = 0.47$).⁴⁹ While awaiting the results of large randomised trials, the relative indications for surgery include cerebellar haematoma >3 cm in diameter and progressive basal ganglionic haematoma in the non-dominant hemisphere of a young patient. Treatment of intracerebral haemorrhage from underlying tumour or vascular malformation depends on the pathology and anatomy of the lesion. Patients with large haematomas with clinical deterioration may require urgent decompression.

Status Epilepticus

Traditionally status epilepticus had been defined as more than 30 minutes of either continuous seizure activity or two or more seizures without recovery of consciousness in between.⁵⁰ In recent years, several authors had suggested shortening the duration of status to more than 5 minutes in order to highlight the urgency of early treatment.^{51,52} This is because status of longer duration is less responsive to anticonvulsants and has a worse prognosis compared to status of shorter duration.⁵³ Precipitating causes must be identified and treated. Neuroimaging should be performed in patients with new onset status and those with focal seizures. Lumbar puncture is required when an infectious aetiology or subarachnoid haemorrhage not seen on CT scan head is suspected. Electroencephalogram (EEG) is helpful in the following circumstances:

- determining whether the patient has a generalised or focal epileptiform abnormality or an underlying metabolic abnormality,
- diagnosis of non-convulsive status, and
- titration to burst suppression.

An important principle of management is early and

aggressive treatment with anticonvulsants. The pharmacokinetic properties of important drugs are outlined in Table III. Benzodiazepines are recommended as first-line treatment.⁵⁴ Intravenous diazepam acts rapidly but has a short duration of action whereas lorazepam is better than diazepam due to its longer half-life.⁵⁵ Phenytoin is commonly given after treatment with benzodiazepines. Its main side effects are hypotension and cardiac arrhythmias. Hypotension is due to propylene glycol which is used as a solvent and may be averted with fosphenytoin.⁵⁶ The latter is a water-soluble disodium phosphate ester of phenytoin that is rapidly converted in the body to phenytoin by circulating phosphatases. It is bioequivalent to phenytoin and may be administered at a rate three times that of phenytoin as it is not formulated with propylene glycol. Therapeutic free (unbound) and total plasma phenytoin concentrations are consistently attained after intravenous loading doses. In the status epilepticus study, this occurred within 10 to 20 minutes of the start of infusion.⁵⁷ In addition, phlebitis occurred significantly less often in patients treated with fosphenytoin compared to those treated with phenytoin. Patients with refractory seizures are treated with barbiturates. At the National Neuroscience Institute, we prefer to use phenobarbitone as it has a long half-life (50 to 120 hours). In addition, phenobarbitone has a much greater intrinsic anticonvulsant action than the other barbiturates (including thiopentone and pentobarbitone) at equal central nervous system depressant levels.⁵⁸ This is attributed to its preferential concentration in active epileptiform cortical regions and specific physico-chemical membrane-stabilising action. Tolerance to its sedative and respiratory depressant effects occur but not to its anticonvulsant effect. This is due to the aryl drug moiety which conveys potent anticonvulsant properties at doses below values that depress the brainstem reticular formation and consciousness. Patients treated with barbiturate coma for refractory seizures have a high mortality.⁵⁹⁻⁶⁹ At our institute, the mortality rate is 21%.⁶⁹

Intravenous epilim (sodium valproate) is another anticonvulsant which had been used to treat status epilepticus.⁷⁰⁻⁷³ Its success rate in terminating status within

TABLE III: PHARMACOKINETIC PROPERTIES OF DRUGS USED TO TREAT STATUS EPILEPTICUS

	Diazepam	Lorazepam	Midazolam	Phenytoin	Phenobarbitone	Valproate
Loading dose	0.25 mg/kg	0.1 mg/kg	0.2 mg/kg	20 mg/kg	20 mg/kg	15 mg/kg
Rate	<5 mg/min	<2 mg/min	<4 mg/min	<50 mg/min	<100 mg/min	3 mg/kg/min
Elimination half-life	30 h	14 h	1.5-3.5 h	24 h	50-120 h	8-12 h
Time to stop status	½-2 min	3-5 min	1-2.5 min	15-30 min	20-30 min	<20 min
Duration of action	15 min	4-14 h	Varies*	24 h	>48 h	8-12 h
Time to enter brain	10 sec	2-3 min	2 min	1 min	20 min	10 min
Time to reach peak brain conc	8 min	23 min	30 min	15-30 min	30 min	30 min

* midazolam accumulates with continuous infusion

30 minutes ranged from 80% to 83%. It is administered as an intravenous bolus dose 15 mg/kg over 5 minutes followed 30 minutes later by a continuous infusion of 1 mg/kg/h. It is contraindicated in liver dysfunction and thrombocytopenia. Its main side effects are hepatitis, hyperammonaemia, coma, haematologic (quantitative and qualitative platelet defects), tremor and weight gain. These are more common when serum levels are >150 mg/L. Rare cases of haemorrhagic pancreatitis had been reported. It does not cause significant cardiovascular or haemodynamic side effects.

Alternative anticonvulsants for treating refractory status epilepticus include chlormethiazole,^{58,74} high-dose midazolam⁷⁵⁻⁷⁷ and lorazepam,^{77,78} propofol^{79,80} and other agents such as lidocaine, paraldehyde, and general anaesthesia with isoflurane.⁸⁰ Further studies are needed to compare their relative safety and efficacy.

The prognosis of status epilepticus depends on the underlying aetiology, duration of status, associated systemic abnormalities, age of patient and type of treatment. All are important, but duration and aetiology are key determinants of outcome.^{52,80}

Myasthenic Crisis

Myasthenic crisis is defined as an acute weakness of the respiratory and bulbar muscles which require ventilatory assistance. It may or may not be associated with generalised muscle weakness.⁸¹ The prognosis of crisis has improved since the 1940s with significant reduction in mortality and improved outcome.⁸² This is due to technological and medical advances over the last few decades: namely, the use of positive-pressure (instead of negative-pressure) and volume-controlled ventilation, endotracheal tubes that could be used for weeks instead of days, improvements in bronchial toilet and management of pneumonia. Improved ICU care played a pivotal role in overall management. Concomitantly, the introduction of immunosuppressive

agents led to a further reduction in morbidity and mortality.⁸²

The most important step during treatment of crisis is early intubation and mechanical ventilation.^{80,83} The decision to intubate is made on the basis of clinical evaluation and ventilatory parameters. The ventilatory parameters for intubation are: vital capacity <15 mL/kg and negative inspiratory pressure ≤ 25 cmH₂O. One should not delay intubation if the patient has marginal respiratory compensation—the respiratory failure in myasthenic crisis does not improve quickly and patients progressively get worse due to fatigue and mucus plugging. Hypoxia and hypercarbia are late manifestations of neuromuscular failure. Once intubated, assist control or intermittent mandatory ventilation is the ventilator mode of choice to allow complete rest and prevent fatigue. Weaning is carried out after 48 hours of ventilatory support. Extubation is performed if the vital capacity is >15 mL/kg, negative inspiratory pressure >25 cmH₂O and tidal volume >5 mL/kg. Respiratory management is an important arm in the treatment of crisis. The main principles of ventilator management and bronchial toilet are outlined in Table IV.

Specific treatment in myasthenic crisis requires either plasmapheresis (PE) or intravenous immunoglobulin (IVIG) administration.⁸⁴ When these are given early in crisis, they may spare patients ICU admission. A retrospective study suggests that PE is superior to IVIG.⁸⁵ Further prospective studies to compare these two therapies are required. Improvement with PE correlates roughly with reduction in antibody titre, but even patients with antibody-negative myasthenia gravis may improve with PE.^{86,87} Since IVIG or PE provides only temporary relief, immunosuppressive treatment with steroids should be started at the same time. Pulse methyl-prednisolone was shown to be beneficial for some patients in crisis in one study.⁸⁸ It appeared to produce less initial worsening and more rapid improvement in severe myasthenic patients than conventional doses of prednisone.

TABLE IV: RESPIRATORY MANAGEMENT IN MYASTHENIC CRISIS

Intervention	No atelectasis	Atelectasis	Pneumonia
Sighs*	Nil	2-4 sighs an hour	4-8 sighs an hour
PEEP	5 cmH ₂ O	5-10 cmH ₂ O	5-10 cmH ₂ O
Regular suction**	every 3-4 hours	every 2-4 hours	every 1-4 hours
Chest physiotherapy***	Nil	every 4-6 hours	every 4-6 hours
Turning in bed	every 2 hours	every 2 hours	every 2 hours
Antibiotics	Nil	Nil	Yes

PEEP: positive-end expiratory pressure

* Sighs are instituted at 150% of the tidal volume and can be delivered at 15-30 min intervals. Maximum number should not exceed 2 consecutive sighs every 15 minutes.

** Frequency of suctioning depends on amount of secretions. Glycopyrrrolate can be used if secretions are copious. Suctioning is routinely performed after chest physiotherapy.

*** Frequency depends on amount of secretions and severity of underlying condition.

Guillain-Barre Syndrome

Guillain-Barre syndrome (GBS) is one of the most frequent causes of acute generalised paralysis and respiratory failure.

The main issues in intensive care management include respiratory support, management of autonomic dysfunction, immunomodulating therapy and supportive care.

Respiratory failure is the most serious complication of GBS. The principles of management and criteria for intubation are similar to those for myasthenic crisis (see previous section). Intravenous suxamethonium should not be used for intubation as it may lead to the release of large amounts of potassium, causing ventricular arrhythmias. Early tracheostomy should be considered in patients with a fulminant course with rapid development of quadriplegia, axonal changes on electromyography and no response to plasma exchange or IVIG.⁸⁰

Autonomic dysfunction has a reported incidence of up to 65%.⁸⁹ It is more common in patients with severe motor deficits and respiratory failure than in those with less severe disease. Autonomic dysfunction is commonly heralded by unexplained sinus tachycardia (heart rate >100 beats per minute) that does not require treatment.⁹⁰ Hypertension is a serious autonomic problem.⁹¹ Some patients manifest marked blood pressure lability with rapid and unpredictable swings between hypertension and hypotension. The rapidity of these changes argues for the use of short-acting agents such as esmolol and nitroprusside for treatment of hypertension and dopamine, noradrenaline and phenylephrine for treatment of hypotension. A wide variety of supraventricular and ventricular arrhythmias have been reported. These ranged from atrial flutter, atrial fibrillation, junctional rhythms, atrioventricular block, sinus bradycardia, sinus arrest and ventricular tachycardia.⁹² Bradyarrhythmia is a serious problem which is difficult to

treat; the development of asystole or advanced degrees of heart block may require emergent insertion of a temporary transvenous pacemaker.

Immunomodulating therapy includes either PE or IVIG.^{93,94} Controlled studies have clearly demonstrated that both modalities reduce the time it takes to achieve independent walking, ventilator days and long-term neurologic deficit. They should be given early in the course of crisis. IVIG appears at least as effective as PE, costs less and is much easier to administer.⁹⁵ Patients who relapse after IVIG or PE may benefit from another course of treatment, but data are not available currently.^{96,97}

Supportive treatment includes management of nutrition, ileus, infections, frequent changes in position and splintage, deep vein thrombosis prophylaxis, care of skin, eyes, mouth and management of pain.

Acute Ischaemic Stroke

The role of neurointensive care management in acute ischaemic stroke is three-fold. Firstly, to treat and monitor patients undergoing therapy aimed at reversing or ameliorating neurological deficits.^{98,99} The publication of the NINDS tissue plasminogen activator (tPA) study and FDA approval of tPA have generated much interest in the acute management of brain ischaemia.¹⁰⁰ Until recently, decisions for thrombolysis were based on a negative finding—presence of a normal CT of the brain in a patient with a history and physical examination consistent with a diagnosis of stroke. In the last few years, new ultrafast magnetic resonance imaging (MRI) methods [diffusion-weighted imaging (DWI) and perfusion imaging (PI)] have opened up the possibility of non-invasively detecting and studying the time course of human ischaemic pathophysiology.^{101,102} Table V outlines 6 possible permutations of combined PI and DWI lesions and their potential acute stroke therapies.¹⁰³ These suggested therapies require validation and further investigation in prospective clinical trials. The PI/DWI indexes potentially allow us to identify candidates for thrombolysis beyond the 3-hour therapeutic window and to evaluate the effect of neuroprotectants.¹⁰⁴ The future treatment of acute stroke may involve a “cocktail” of thrombolytics, combination neuroprotectants which act at multiple sites in the ischaemic cascade and trophic growth factors.¹⁰⁵⁻¹⁰⁸ Secondly, neurointensive care management provides special interventions directed towards complications of stroke such as raised intracranial pressure. The mass effect of the stroke and secondary brain oedema leads to raised intracranial pressure, impaired perfusion to the brain, and through shifts of tissue, secondary damage to vital structures deep in the brain and death. Treatment of brain oedema and raised intracranial pressure is a key component in management of patients with large infarct or haematoma.^{80,109,110} Therapeutic options include

TABLE V: PI AND DWI ACUTE STROKE PATTERNS AND POTENTIAL IMPLICATIONS FOR ACUTE STROKE THERAPY⁹⁸

Pattern no.	Acute PI/DWI patterns	Potential therapy*
1	PI > DWI	reperfusion (e.g. thrombolysis)
2	PI = DWI	neuroprotectant
3	PI < DWI	neuroprotectant
4	DWI only	neuroprotectant
5	PI only	reperfusion (e.g. thrombolysis)
6	neither DWI nor PI	No acute intervention

PI: perfusion imaging; DWI: diffusion-weighted imaging

* These hypotheses require further investigation in prospective clinical trials.

hyperventilation, osmotherapy, cerebrospinal fluid diversion procedures and surgical decompression. Thirdly, clinical deterioration due to co-existent medical problems such as sepsis, heart disease (myocardial infarct, cardiac failure, arrhythmias), pulmonary problems (pneumonia and pulmonary embolism), seizures and acute renal failure are best managed in an ICU environment. Successful therapy often depends on early and aggressive intervention.

REFERENCES

1. Lew T W K, Darby J M. Central nervous system. In: Shoemaker W, Ayres S M, Grenvik A N A, Holbrook P R, editors. *Pocket Companion to Textbook of Critical Care*. Philadelphia: WB Saunders Co, 1996: 564-612.
2. Young M P, Birkmeyer J D. Potential reduction in mortality rates using an intensivist model to manage intensive care units. *Eff Clin Pract* 2000; 3:284-9.
3. Hanson C W, Deutschman C S, Anderson H L, Reilly P M, Behringer E C, Schwab C W, et al. Effects of an organized critical care service on outcomes and resource utilization: a cohort study. *Crit Care Med* 1999; 27:270-4.
4. Carlson R W, Weiland D E, Srivathsan K. Does a full-time, 24-hour intensivist improve care and efficiency? *Crit Care Clin* 1996; 12: 525-51.
5. Milzman D P, Hinson D, Magnant C M. Overview and outcomes. *Crit Care Clin* 1993; 9:633-56.
6. Obrist W D, Langfitt T W, Jaggi J L, Cruz J, Gennarelli T A. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. *J Neurosurg* 1984; 61:241-53.
7. Bouma G J, Muizelaar J P, Choi S C, Newlon P G, Young H F. Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. *J Neurosurg* 1991; 75:685-93.
8. Kotapka M J, Graham D I, Adam J H, Gennarelli T A. Hippocampal pathology in fatal human brain injury without intracranial pressure. *J Neurotrauma* 1994; 11:317-24.
9. Lipton S A, Rosenberg P A. Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med* 1994; 330:613-22.
10. MacManus J P, Hill I E, Huang Z G, Rasquinha I, Xue D, Buchan A M. DNA damage consistent with apoptosis in transient ischaemic neocortex. *Neuroreport* 1994; 5:493-6.
11. Ng I, Yeo T T, Tang W Y, Soong R, Ng P Y, Smith D R, et al. Apoptosis occurs after cerebral contusions in humans. *Neurosurgery* 2000; 46: 949-56.
12. Chestnut R M, Marshall L F, Klauber M R. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; 34:216-22.
13. Powers W J. Acute hypertension after stroke: the scientific basis for treatment decisions. *Neurology* 1993; 43:461-7.
14. Suarez J I, Qureshi A I, Bhardwaj A, Williams M A, Schnitzer M S, Mirski M, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med* 1998; 26:1118-23.
15. Rapp R P, Young B, Twyman D, Bivins B A, Haack D, Tibbs P A, et al. The favourable effect of early parenteral feeding on survival in head-injured patients. *J Neurosurg* 1983; 58:906-12.
16. Young B, Ott L, Kasarkis E. Zinc supplementation is associated with improved neurological recovery rate and visceral protein levels of patients with severe closed head injury. *J Neurotrauma* 1996; 13:25-34.
17. Smith J Jr, Martin L F, Young W W, Maciocce D P. Do trauma centers improve outcome over non-trauma centers? *J Trauma* 1990; 30: 1533-8.
18. Ng I, Lew T W K, Yeo T T, Ong P L, Tan K K, Seow W T, et al. Outcome of patients with traumatic brain injury managed on a standardized head injury protocol. *Ann Acad Med Singapore* 1998; 27:332-9.
19. Rosner M J, Daughton S. Cerebral perfusion pressure management on head injured patients. *J Trauma* 1990; 30:933-40.
20. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. *Crit Care Med* 1998; 26:344-51.
21. Marshall L F, Gattula T, Klauber M R, Marshall L F. The outcome of severe closed head injury. *J Neurosurg* 1991; 75(Suppl)1: S287-92.
22. Jaggi J L, Obrist W D, Gennarelli T A. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. *J Neurosurg* 1990; 72:176-82.
23. Chesnut R M. Hyperventilation versus cerebral perfusion pressure management: Time to change the question. *Crit Care Med* 1998; 26:210-2.
24. Chan K, Miller J D, Dearden N M, Andrews P J D, Midgley S. The effects of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular venous oxygen saturation after severe brain injury. *J Neurosurg* 1992; 77:55-61.
25. Ng I, Wong A, Lew T W K, Yeo T T. Correlation of favourable patient outcome in a standardised head injury management protocol to the level of cerebral perfusion pressure achieved. *Crit Care Med* 1997; 25:A74.
26. Cormio M, Valadka A B, Robertson C S. Elevated jugular venous oxygen saturation after severe head injury. *J Neurosurg* 1999; 90:9-15.
27. Gopinath S P, Robertson C S, Contant C F, Hayes C, Feldman Z, Narayan R K, et al. Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psych* 1994; 57:717-23.
28. Polin R S, Shaffrey M E, Bogaev C A, Tisdale N, Germanos T, Bocchicchio B, et al. Decompressive bifrontal craniectomy in the treatment of severe refractory posttraumatic cerebral edema. *Neurosurgery* 1997; 41:84-92.
29. Asgeirsson B, Grande P O, Nordstrom C H. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. *Intensive Care Med* 1994; 20:260-7.
30. Eker C, Asgeirsson B, Grande P O, Schalen W, Nordstrom C H. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. *Crit Care Med* 1998; 26:1881-7.
31. Marion D W, Penrod L E, Kelsey S F, Obrist W D, Kochanek P M, Palmer A M, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997; 336:540-6.
32. Harders A, Kakarieka A, Braakman R. Traumatic subarachnoid haemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; 85:82-9.
33. Sarti C, Tuomilehto J, Salomaa V, Sivenius J, Kaarsalo E, Narva E V, et al. Epidemiology of subarachnoid hemorrhage in Finland from 1983 to 1985. *Stroke* 1991; 22:848-53.
34. Lai S H, Lau G, Chao T C. Berry aneurysms: a cross-sectional study of 105 autopsy cases recorded between 1982 and 1996 [abstract]. Abstract Handbook of the 32nd Singapore-Malaysia Congress of Medicine; 1998 August 13-16; Singapore. Singapore: Academy of Medicine, Singapore, 1998:397.

35. Locksley H B. Report on the cooperative study of intracranial aneurysms and subarachnoid haemorrhage. In: Sahs A L, Perret G E, Locksley H B, editors. *Intracranial Aneurysms and Subarachnoid Haemorrhage*. Philadelphia: JB Lippincott, 1969:219-368.
36. Mayberg M R, Batjer H H, Dacey R, Diringer M, Haley C, Heros R C, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke* 1994; 25:2315-28.
37. Kassell N F, Torner J C. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery* 1983; 13:479-81.
38. Friedman A H. Timing of aneurysm surgery. In: Wilkins R H, Rengachary S S, editors. *Neurosurgery*. 2nd ed. USA: McGraw Hill Inc., 1996: 2255-60.
39. Kassell N F, Torner J C, Haley E C Jr, Jane J A, Adams H P, Kongable G L. The international cooperative study on the timing of aneurysm surgery. *J Neurosurg* 1990; 73:18-47.
40. Weir B, Findlay J M. Subarachnoid hemorrhage. In: Carter L P, Spetzler R F, editors. *Neurovascular Surgery*. USA: McGraw Hill Inc., 1995:557-81.
41. Eskridge J M, Song J K. Endovascular embolisation of 150 basilar tip aneurysms with GDC coils: results of FDA multicentre clinical trial. *J Neurosurg* 1998; 89:81-6.
42. Weir B, Grace M, Hansen J. Time course of vasospasm in man. *Neurosurgery* 1978; 48:173-8.
43. Eskridge J M, McAuliffe W, Song J K, Deliganis A V, Newell D W, Lewis D H, et al. Balloon angioplasty for the treatment of vasospasm: results of first 50 cases. *Neurosurgery* 1998; 42:510-7.
44. Polin R S, Hansen C A, German P, Chaddock J B, Kassell N F. Intraarterially administered papaverine for the treatment of symptomatic cerebral vasospasm. *Neurosurgery* 1998; 42:1256-67.
45. Ng P Y, Ong P L, Tan K K. Outcome of ruptured cerebral aneurysms managed with surgery and intensive hemodynamic support. Tan Tock Seng Hospital 6th Annual Scientific Meeting; 1998 Nov 7; Singapore. Singapore: Tan Tock Seng Hospital, 1998:13.
46. Venketasubramanian N, Sadasivan B, Tan A K Y. Stroke patterns in a Singapore hospital based stroke data bank. *Cerebrovasc Dis* 1994; 4:250.
47. Broderick J P, Adams H P Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, et al. Guidelines for the management of healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke* 1999; 30:905-15.
48. Hankey G J, Hon C. Surgery for primary intracerebral haemorrhage: is it safe and effective? *Stroke* 1997; 28:2126-32.
49. Morgenstern L B, Frankowski R F, Shedden P, Pasteur W, Grotta J C. Surgical treatment for intracerebral haemorrhage. A single centre randomized clinical trial. *Neurology* 1998; 51:1359-63.
50. Bone R C. Treatment of convulsive status epilepticus. *JAMA* 1993; 270:854-9.
51. Lowenstein D H, Bleck T, Macdonald R L. It's time to revise the definition of status epilepticus. *Epilepsia* 1999; 40:120-2.
52. Waterhouse E J. Classification and outcomes of status epilepticus. Proceedings of the American Academy of Neurology 51st Annual Meeting; 1999 April 17-24; Toronto, Ontario, Canada. 4:7DS.001.
53. DeLorenzo R J, Garnett L K, Towne A R, Waterhouse E J, Boggs J G, Morton L, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. *Epilepsia* 1999; 40: 164-9.
54. Lowenstein D H, Alldredge B K. Status epilepticus. *N Engl J Med* 1998; 14:970-6.
55. Leppik I E, Derivan A T, Homan R W, Walker J, Ramsay R E, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; 249:1452-4.
56. Browne T R, Kugler A R, Eldon M A. Pharmacology and pharmacokinetics of fosphenytoin. *Neurology* 1996; 46(Suppl 1):S3-S7.
57. Leppik I E, Boucher B A, Wilder B J, Murthy V S, Watridge C, Graves N M, et al. Pharmacokinetics and safety of a phenytoin prodrug given IM or IV in patients. *Neurology* 1990; 40(3 part 1):456-60.
58. Shorvon S. Status epilepticus: Its clinical features and treatment in children and adults. Cambridge: Cambridge Univ Press, 1994.
59. Young G B, Blume W T, Bolton C F, Warren K G. Anesthetic barbiturates in refractory status epilepticus. *Can J Neurol Sci* 1980; 7:291-2.
60. Partinen M, Kovanen J, Nilsson E. Status epilepticus treated by barbiturate anaesthesia with continuous monitoring of cerebral function. *Br Med J (Clin Res Ed)* 1981; 282:520-1.
61. Orlowski J P, Erenberg G, Lueders H, Cruse R P. Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med* 1984; 12:367-72.
62. Rashkin M C, Youngs C, Penovich P. Pentobarbital treatment of refractory status epilepticus. *Neurology* 1987; 37:500-3.
63. Lowenstein D H, Aminoff M J, Simon R P. Barbiturate anesthesia in the treatment of status epilepticus: clinical experience with 14 patients. *Neurology* 1988; 38:395-400.
64. Crawford T O, Mitchell W G, Fishman L S, Snodgrass S R. Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology* 1988; 38:1035-40.
65. Osorio I, Reed R C. Treatment of refractory generalized tonic-clonic status epilepticus with pentobarbital anesthesia after high-dose phenytoin. *Epilepsia* 1989; 30:464-71.
66. Van Ness P C. Pentobarbital and EEG burst suppression in treatment of status epilepticus refractory to benzodiazepines and phenytoin. *Epilepsia* 1990; 31:61-7.
67. Yaffe K, Lowenstein D H. Prognostic factors of pentobarbital therapy for refractory generalized status epilepticus. *Neurology* 1993; 43:895-900.
68. Krishnamurthy K B, Drislane F W. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia* 1999; 40:759-62.
69. Chua H C, Tan A K Y, Tan C B, Tjia H. High dose phenobarbitone for status epilepticus. *Neurol J Southeast Asia* 1999; 4:25-9.
70. Giroud M, Gras D, Escousse A, Dumas R, Venaud G. Use of injectable valproic acid in status epilepticus. A pilot study. *Drug Invest* 1993; 5:154-9.
71. Price D J. Intravenous valproate: experience in neurosurgery. *R Soc Med Int Congr Symp Ser* 1989; 152:197-203.
72. Moore A J, Bell B A, Berry D J. Intravenous sodium valproate in neurosurgery: repeat dose pharmacokinetic study and safety assessment in neurosurgical patients. *R Soc Med Int Congr Symp Ser* 1989; 152:204-7.
73. Kaplan P W. Intravenous valproate treatment of generalized nonconvulsive status epilepticus. *Clin Electroencephalogr* 1999; 30: 1-4.
74. Fulton B, Park G R. Intravenous chlormethiazole. *Br J Hosp Med* 1992; 48:742-7.
75. Hanley D F Jr, Pozo M. Treatment of status epilepticus with midazolam in the critical care setting. *Int J Clin Pract* 2000; 54:30-5.
76. Fountain N B, Adams R E. Midazolam treatment of acute and refractory status epilepticus. *Clin Neuropharmacol* 1999; 22:261-7.
77. Bleck T P. Management approaches to prolonged seizures and status epilepticus. *Epilepsia* 1999; 40(Suppl 1):S59-63.

78. Labar D R, Ali A, Root J. High-dose intravenous lorazepam for the treatment of refractory status epilepticus. *Neurology* 1994; 44:1400-3.
79. Brown L A, Levin G M. Role of propofol in refractory status epilepticus. *Ann Pharmacother* 1998; 32:1053-9.
80. Wijdicks E F M. *The clinical practice of critical care neurology*. Philadelphia: Lippincott-Raven Publishers, 1997:279-89.
81. Thomas C E, Mayer S A, Gungor Y, Swarup R, Webster E A, Chang I, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology* 1997; 48:1253-60.
82. Grob D, Arsura E L, Brunner N G, Namba T. The course of myasthenia gravis and therapies affecting outcome. *Ann N Y Acad Sci* 1987; 505:472-99.
83. Derdak S. Neuromuscular disorders. In: Civetta J M, Taylor R W, Kirby R R, editors. *Critical Care*. 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1997:2005-16.
84. Fink M E. Treatment of the critically ill patient with myasthenia gravis. In: Ropper A H, editor. *Neurological and Neurosurgical Intensive Care*. 3rd ed. New York: Raven Press, 1993:351-62.
85. Qureshi A I, Choudhry M A, Akbar M S, Mohammad Y, Chua H C, Yahia A M, et al. Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 1999; 52:629-32.
86. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol* 1997; 41:789-96.
87. Kornfeld P, Ambinder E P, Mittag T, Bender A N, Papatestas A E, Goldberg J, et al. Plasmapheresis in refractory generalized myasthenia gravis. *Arch Neurol* 1981; 38:478-81.
88. Arsura E L, Brunner N G, Namba T. High-dose intravenous methylprednisolone in myasthenia gravis. *Arch Neurol* 1985; 42:1149-53.
89. Ropper A H, Wijdicks E F M. Blood pressure fluctuations in the dysautonomia of Guillain-Barre syndrome. *Arch Neurol* 1990; 47:706-8.
90. Frison J C, Sanchez L, Garnacho A, Bofill J, Olivero R, Miquel C. Heart rate variations in Guillain-Barre syndrome. *BMJ* 1980; 281:649.
91. Ferraro-Herrera A S, Kern H B, Nagler W. Autonomic dysfunction as the presenting feature of Guillain-Barre syndrome. *Arch Phys Med Rehabil* 1997; 78:777-9.
92. Greenland P, Griggs R C. Arrhythmic complications in the Guillain-Barre syndrome. *Arch Intern Med* 1980; 140:1053-5.
93. The Guillain-Barre Syndrome Study Group. Plasmapheresis and acute Guillain-Barre syndrome. *Neurology* 1985; 35:1096-104.
94. French Cooperative Group on Plasma Exchange in Guillain-Barre syndrome. Efficiency of plasma exchange in Guillain-Barre syndrome: role of replacement fluids. *Ann Neurol* 1987; 22:753-61.
95. Van der Meche F G, Schmitz P I, and the Dutch Guillain-Barre Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. *N Engl J Med* 1992; 326:1123-9.
96. Castro L H, Ropper A H. Human immune globulin infusion in Guillain-Barre syndrome: worsening during and after treatment. *Neurology* 1993; 43:1034-6.
97. Kleyweg R P, Van der Meche F G A. Treatment related fluctuations in Guillain-Barre syndrome after high-dose immunoglobulins or plasma exchange. *J Neurol Neurosurg Psychiatry* 1991; 54:957-60.
98. Hacke W, Schwab S, De Georgia M. Intensive care of acute ischemic stroke. *Cerebrovasc Dis* 1994; 4:385-92.
99. Hund E, Grau A, Hacke W. Neurocritical care for acute ischemic stroke. *Neurosurg Clin N Am* 1997; 8:271-82.
100. National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for the treatment of acute ischemic stroke. *N Engl J Med* 1995; 333:1581-7.
101. Albers G W. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. *Stroke* 1999; 30:2230-7.
102. Schlaug G, Benfield A, Baird A E, Siewert B, Lovblad K O, Parker R A, et al. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. *Neurology* 1999; 53:1528-37.
103. Barber P A, Darby D G, Desmond P M, Yang Q, Gerraty R P, Jolley D, et al. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. *Neurology* 1998; 51:418-26.
104. Li F, Carano R A, Irie K, Tatlisumak T, Silva M D, Pschorni U, et al. Neuroprotective effects of a novel broad-spectrum cation channel blocker, LOE 908 MS, on experimental focal ischemia: a multispectral study. *J Magn Reson Imaging* 1999; 10:138-45.
105. Lindsberg P J, Roine R O, Tatlisumak T, Sairanen T, Kaste M. The future of stroke treatment. *Neurol Clin* 2000; 18:495-510.
106. Muir K W, Grosset D G. Neuroprotection for acute stroke: making clinical trials work. *Stroke* 1999; 30:180-2.
107. Heiss W D, Thiel A, Grond M, Graf R. Which targets are relevant for therapy of acute ischemic stroke? *Stroke* 1999; 30:1486-9.
108. Chua H C, Ng P Y. Neuroprotection in acute stroke. *Ann Acad Med Singapore* 2001; 30:134-42.
109. Ropper A H, Shafran B. Brain edema after stroke: clinical syndrome and intracranial pressure. *Arch Neurol* 1984; 41:26-9.
110. Rosner M J. Pathophysiology and management of increased intracranial pressure. In: Andrews B T, editor. *Neurosurgical Intensive Care*. New York: McGraw-Hill Book Co, 1993:57-112.