

CRITICAL CARE NEUROLOGY AND NEURO CRITICAL CARE

ROADMAP

CRITICAL CARE NEUROLOGY

- **Analgesia, sedation and neuromuscular blockade**
 - Basic principles, goals, general guidelines and assessment
 - Table of established drugs
 - Sedation for endotracheal intubation in critical care
 - Specialist analgesia in critical care
- **Sleep**
- **Neurological dysfunction in critical care**
 - Acute brain dysfunction
 - Delirium
 - Autonomic dysfunction
 - Critical illness neuromyopathy
 - Encephalopathy
 - Disease specific / syndromal encephalopathies (
 - Hypertensive encephalopathies
 - Toxic and metabolic encephalopathies
 - Common infectious and inflammatory diseases of the nervous system
 - Meningitis
 - Encephalitis - generalised and limbic
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 - Acute inflammatory demyelinating polyneuropathy (AIDP)
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 - Persistent disorders of consciousness
 - Brain stem death: diagnosis, pathophysiology and management of the potential organ donor.

CORE TOPICS IN NEURO CRITICAL CARE

- **Secondary brain injury**
 - Pathophysiology – oedema, vascular autoregulation, sodium, glucose, temperature (metabolic supply / demand imbalance), oxygen, carbon dioxide
 - Prevention and neuroprotection – discussed for each topic above plus pharmacological therapies (epo, progesterone, magnesium etc)
- **Brain monitoring, interpretation and management**
 - Intracranial pressure & cerebral perfusion pressure – physiology, targets and medical management
 - External ventricular drains
 - Decompressive craniectomy
 - Tissue oxygen & reverse jugular bulb oximetry
 - Metabolic monitoring and microdialysis
 - EEG
 - Radiology – CT, MRI, angiography, functional imaging
- **Controversies in routine care – packed RBC transfusion, thromboprophylaxis, prophylactic anticonvulsant therapy**

DISEASE SPECIFIC NEURO CRITICAL CARE

- **Structural injury**
 - Post neurosurgical recovery
 - Traumatic brain injury
 - Spontaneous subarachnoid haemorrhage

- **Spontaneous intracerebral haemorrhage**
- **Acute stroke**
- **Spinal cord injury**

General introduction

This module has been split into 2 parts. The first deals with intensive care neurology, whilst the second covers neuro critical care. This is self evidently a somewhat arbitrary and division made for practical reasons.

Part 1 starts with the impact of ICU therapies on the normal brain. Acute brain dysfunction is then considered followed by specific brain conditions that may result in the need for ICU care.

Part 2 starts with a revision of normal neurophysiology followed by detailed reviews of neuropathophysiology and treatment, both general supportive care and specific therapies. Neuroprotective therapies are discussed including therapeutic hypothermia. Finally, a brief section provides an overview and suggested reading regarding specific related topics.

CRITICAL CARE NEUROLOGY

ANALGESIA, SEDATION AND NEUROMUSCULAR BLOCKADE

Analgesia, with or without sedation, is an essential component of the holistic care of critically patients. With the exception of immediate life saving interventions, patient comfort should be the first priority. As with all interventions, it is vital to set goals of treatment, communicate, record and regularly review these. Two excellent general review articles can be found here (Kress and Hall, 2006, Sessler and Varney, 2008)

Goals of analgesia-sedation regimes

- Patients should be comfortable and pain free.
- Anxiety should be minimised.
- Patients must be able to tolerate organ system supportive therapies / nursing care.
- Patients should not be paralysed and aware.
- Ideally, patients should be calm, co-operative, able to communicate and to sleep when undisturbed. From a clinical perspective, the ideal state is to be able to complete a neurological assessment. Coughing and moving are not in themselves reasons to sedate a patient, unless such activity places the patient at risk.

General guidelines

- The commonest indication for the initiation of analgesia-sedation in ICU is endotracheal intubation and ventilation. Some patients may tolerate this without any drugs but most will require analgesia and suppression of airway reflexes. There are important differences between initiation of ICU analgesia-sedation and the induction of routine anaesthesia both in terms of the drugs used, the doses required and the predictable immediate complications (see *link to intubation section below*).
- Most ICUs employ continuous infusions of opiates and sedatives, although boluses regimes are successfully employed especially in resource limited units. The choice of agents depends upon a number of factors including drug pharmacokinetics, cost and personal preference. Some advocate analgesia only sedation with the addition of non-analgesic sedatives only as necessary.
- It is important to note that commonly used combinations of agents have significant pharmacokinetic interactions that tend to potentiate the effects of each agent (Lichtenbelt et al., 2010, Mertens et al., 2004).
- Start with a small bolus dose prior to commencing an infusion. If this is insufficient to achieve the desired level of analgesia / sedation, repeat the small bolus prior to each increase in infusion rate. This is to allow steady state drug levels to be achieved more quickly and reduces total cumulative dosage.
- Neuromuscular blockade should only be considered in patients in whom sedation / analgesia does not achieve the defined goals, most commonly, failure to achieve adequate ventilation or as part of a cooling protocol. Intermittent bolus dosing is usually preferable to IV infusions. If given by infusion, daily cessation should be mandatory. Prolonged use of neuromuscular blocking agents is associated with a higher incidence of critical illness neuromyopathy. There is a very strong case for the mandatory use of continuous depth of sedation monitoring (continuous, processed EEG) in paralysed patients in ICU.
- Before increasing sedation and / or adding neuromuscular blockade:
 - Exclude any avoidable source of physical discomfort.
 - Review the need for all uncomfortable or disturbing interventions.
 - Consider whether the increase in sedation is an index of clinical deterioration.
 - Consider non drug measures e.g. patient positioning.
 - Consider analgesia.
 - Consider a bolus dose rather than an increase in infusion rate, especially if prior to an unpleasant intervention.
 - Over sedation is associated with a higher incidence of ventilator associated pneumonia, prolonged weaning from mechanical ventilation, colonisation with multiply resistant organisms, an increased requirement for neurological investigations, prolonged ICU stay and death.
- All drugs accumulate to some degree, if given to critically ill patients for prolonged periods. It has become a widely accepted / standard practice to perform a daily cessation of the drug regime, which should only be re-started as clinically indicated. Perhaps surprisingly, this strategy stems from a relatively small single centre study [reviewed by (Schweickert and Kress, 2008)] and arguably represents one of the best examples of effective change in ICU practice.
- Regular simple analgesia should always be considered in critically ill patients regardless of

pathology as immobility and critical care interventions are uncomfortable and can be distressing. Multimodal pharmacological analgesia is generally considered the optimal approach in all settings.

- Be aware that sedative drugs do not achieve physiological sleep (as assessed by EEG) and that sleep deprivation is probably one of the principle causes of ICU delirium (see [link to Sleep section below](#)).
- Prolonged use of sedation / analgesia drugs is associated with tachyphylaxis and some degree of neurochemical dependence, and therefore, withdrawal syndromes. Weaning from prolonged use may require staged reduction over a period of days and may be enhanced by the use of alternative drugs, in particular, methadone (prolongs QTc), a benzodiazepine or clonidine. Haloperidol, chlorpromazine, olanzapine and risperidone are also used.

Assessing the quality of analgesia and depth of sedation (Sessler et al., 2008)

Despite the development and validation of numerous scales to semi-objectively assess and target analgesia and sedative therapies, their use remains patchy at best. This is analogous to placing a patient on mechanical ventilation and not assessing any parameters of oxygenation or ventilation. Given that minimising the cumulative dose of sedative drugs is an essential therapeutic goal, in order to reduce the iatrogenic injury they cause, this therapy should be aggressively titrated. The only means of doing this is to set well defined and easily assessable goals that the entire team caring for the patient can unambiguously communicate. Bedside assessment scales are simple and effective. Adding processed EEG / EMG monitoring is of proven benefit when deep sedation or NMB is required. Such technology almost certainly has a role in brain monitoring over and above its ability to track depth of sedation (see [link to EEG section below](#)). Behavioural assessment scales have also been developed that specifically aim to measure the quality of analgesia over and above sedation (Sanna-Mari et al., 2009). As previously stated, there is a considerable overlap between sedation and analgesia. Whether combining available assessment tools is valuable remains to be investigated.

Brief drug monographs

The following tables give brief descriptions of most of the widely used drugs in UK ICU practice. The only 2 notable absences are lorazepam, which is commonly used as an infusion in the US (included in the list of bolus drugs) and sufentanil, which is widely used in Europe. A systematic review of published trials comparing different drug regimes can be found here (Ostermann et al., 2000) – it concludes there is a very poor level of evidence to support the choice of one drug over another. This is another case of “it ain’t what you use it’s the way that you use it.”

Table 1: Commonly used continuous infusion sedative analgesic regimes

<i>Drug</i>	<i>Regime</i>	<i>Notes</i>
Morphine	Loading 5 - 15 mg Maintenance 1 - 12 mg/hr	Slow onset. Long acting. Active metabolites. Consider bolus dosing / PCA in place of infusion. Accumulates in renal and hepatic impairment.
Fentanyl	Loading 25 - 100 mcg Maintenance 25 - 250 mcg/hr	Rapid onset. Modest duration of action. No active metabolites. Renally excreted. Transdermal patches available for longer term use.
Alfentanil	Loading 15 - 50 mcg/kg Maintenance 30 - 85 mcg/kg/hr (1 - 6 mg/hr)	Rapid onset. Relatively short acting. Accumulates in hepatic failure.
Remifentanyl	Dose 0.4 – 45 mcg/kg/hr	Rapid onset and offset of action with minimal if any accumulation of the weakly active metabolite. Significant incidence of problematic bradycardia with bolus dosing.
Clonidine	Dose 1-10 mcg/kg/hr	An α_2 agonist. Has sedative and analgesic effects. Infusion doses up to 25 mcg/kg/hr AND slow bolus doses of 10-20 mcg/kg have been described as being safe with a surprisingly low incidence of hypotension and bradycardia (Liatsi et al., 2009).
Dexmedetomidine (Carollo et al., 2008)	Load 1 mcg/kg over 10 min Maintenance 0.2-1.0 mcg/kg/hr	Also an α_2 agonist but with ~7 times greater binding affinity than clonidine. In addition, it has a much shorter half life. It currently only has a licence in the US but European licensing is likely to be granted in the near future.
Ketamine (Aroni et al., 2009, Morris et al., 2009)	Analgesia 0.2 mg/kg/hr Induction 0.5 - 2.0 mg/kg Maintenance 1 - 2 mg/kg/hr	Atypical analgesic with hypnotic effects at higher doses. Sympathomimetic; associated with emergence phenomena when given at hypnotic doses when usually co-administered with a benzodiazepine. Potentially useful adjunct to opiates (opiate sparing) as part of a mixed analgesic regime

Of note: there is some experimental evidence suggesting that fentanyl and all of its analogues, together with ketamine, increase intra-cranial pressure (ICP) and are thus relatively contra-indicated in situations where ICP is elevated (or suspected to be). However, in clinical practice this does not seem to be significant and indeed, use of these agents has been shown to reduce ICP when used as part of a complete package of care for such patients (Aroni et al., 2009, Albanese et al., 1999).

Table 2: Commonly used continuous infusion sedative regimes

<i>Drug</i>	<i>Regime</i>	<i>Notes</i>
Propofol 1%	Loading 1.5 - 2.5 mg/kg Maintenance 0.5 - 4 mg/kg/hr (0 - 200 mg/hr)	Intravenous anaesthetic agent. Causes vasodilatation and hence hypotension. Extra hepatic metabolism, thus does not accumulate in hepatic failure. Has antiemetic and may have some analgesic properties (Vasileiou et al., 2009, Bandschapp et al.). Made in Intralipid hence maximum long term (hours) infusion rate should be ≤ 200 mg/hr. Propofol infusion syndrome is a serious complication of prolonged and high dose administration with a significant fatality rate. The incidence, pathophysiology and management are reviewed here (Fudickar and Bein, 2009, Iyer et al., 2009, Roberts et al., 2009)
Midazolam	Loading dose 30 - 300 mcg/kg Maintenance 30 - 200 mcg/kg/hr (0 - 14 mg/hr)	Shortest acting benzodiazepine. Active metabolites accumulate in all patients especially in renal failure. Consider intermittent bolus dosing rather than an infusion.

Table 3: Commonly used regular / bolus dose analgesia

<i>Drug</i>	<i>Regime</i>	<i>Notes</i>
Paracetamol	1 g NG / PO 6 hourly or 1 g IV 6 hourly	Starting regime for simple analgesia Only use IV if enteral route unavailable / unreliable OR as part of an opiate sparing regime. Note 1g IV paracetamol \equiv 2.5 – 5mg IV morphine
Diclofenac	50 mg NG / PO 8 hourly or 75 mg IV 12 hourly	As part of an opiate sparing regime but only in well hydrated patients with normal renal function. Usually requires PPI cover. NSAIDs may have a role in reducing hypertrophic acetabular ossification post acetabular fracture repair and as adjunctive anti-pyretics (Cormio and Citerio, 2007).
Codeine, Dihydrocodeine Oramorph	Starting regime: Oramorph 2.5 – 10mg PRN Max. 60mg / 24 hrs	Essentially the same drug (codeine is metabolised to morphine BUT only by 70% of the population). Used regularly in post-op patients to wean from PCA infusions. Avoid in renal failure. Patients must receive aperients. Oramorph is arguably the optimal agent as dose titration is simple.
Oxycodone	5 – 30 mg NG / PO 4 -12 hourly	Safer in renal failure as extensive hepatic metabolism to less active drug.
Methadone	Start 15-30 mg NG / PO daily	Useful daily opiate. Can prolong QT interval.
Tramadol	50 – 100 mg 6 hourly	Mixed weak opiate and noradrenaline re-uptake inhibitor. Highly emetogenic, causes delirium, especially in elderly, and SIADH. Multiple drug interactions therefore contra indicated in patients on any antihypertensives, SSRIs, tricyclics and warfarin.

Immunomodulation due to analgesic and sedative therapies (Webster and Galley, 2009)

There is a large body of circumstantial evidence to suggest that morphine is immunosuppressive (Weinert et al., 2008). These effects are believed to be due to binding to μ_3 receptors on immunologically active cells. Notably, the synthetic opioids (fentanyl / alfentanil / remifentanil) have poor affinity for μ_3 receptors and hence do not appear to have clinically significant immunomodulatory effects. Both propofol and benzodiazepines also have in vitro immunosuppressive effects. However, there is a startling absence of research into whether these effects of commonly used ICU agents have clinically significant effects.

Table 4: Neuromuscular blocking drugs

<i>Drug</i>	<i>Bolus dose</i>	<i>Onset & Duration</i>	<i>Side effects</i>
Suxamethonium	1-2 mg/kg Ampoule 100 mg	30 s 5 mins	Depolarisation. Histamine release. Elevation of plasma K ⁺ by ~1 mmol/l hence contraindicated in hyperkalaemia.
Atracurium	0.3-0.6 mg/kg Ampoule 50 mg	90 - 120 s 60 mins	Racemic mixture. Broken down by serum esterases hence predictable pharmacokinetics in renal and hepatic failure. Causes histamine release hence contra-indicated in acute severe asthma. Inactive metabolite, laudanosine, lowers seizure threshold.
Vecuronium	0.08-0.1 mg/kg Ampoule 10 mg	60 - 120 s 20 - 60 mins	Lipid soluble <i>hence</i> accumulates.
Rocuronium	0.6 mg/kg Ampoule 50 mg	< 60 s 30 - 60 mins	Most rapid onset of non-depolarising blockers. Low incidence of histamine release. Low, but significant incidence of anaphylaxis.

For more detailed information see (Craig and Hunter, 2009, Claudius et al., 2009, Naguib and Brull, 2009)

Table 4: Regular / bolus dose sedation

<i>Drug</i>	<i>Regime</i>	<i>Notes</i>
Haloperidol	2.5 – 5 mg NG / PO / IV Max daily dose 20mg	Often delayed onset of action in patients with agitated ICU delirium.
Chlorpropazime	10 – 250 mg NG / PO / IM	Alternative to haloperidol.
Olanzapine	5 – 15 mg NG / PO daily	Alternative to haloperidol.
Risperidone	1 – 4 mg NG / PO / s/l	Alternative to haloperidol.
Quetiapine	50 – 200mg NG / PO	Alternative to haloperidol (Devlin et al., 2009)
Lorazepam	0.5 – 4 mg s/l / NG / PO / IV PRN	Tablets work well s/l. IV preparation is in ethylene glycol. Give 8 – 12 hourly. Fewer active metabolites / more predictable half life in multiple organ failure (~14 hours) compared to diazepam. Cumulative dose (as with all benzodiazepines) is a risk factor for the development of delirium. Negative Cochrane review (Lonergan et al., 2009)

For a review of antipsychotic use in acute delirium see (Vaios et al., 2009).

Sedation for endotracheal intubation in critical care

Elective induction of anaesthesia for an invasive / distressing procedure IS NOT the same as safe and timely endotracheal intubation for airway protection and / or provision of ventilatory support.

To achieve the later DOES NOT necessitate a deep level of induced general anaesthesia (to obliterate the physiological response to direct laryngoscopy) NOR neuromuscular blockade (NMB). Each patient must be assessed and an appropriate intervention planned including resources for failed intubation and / or ventilation. For example, patients with a depressed level of consciousness may, on occasion, be easily intubated without any sedative drugs. Similarly, technically difficult intubation techniques often employ topical anaesthesia and “awake” intubations. Minimal sedation and avoidance of NMB may safely avoid haemodynamic crises (hypotension due to sudden reduction in sympathetic tone), hypoxia (derecruitment) and hypercapnia (hypoventilation). The risks of gastric aspiration and laryngeal trauma can easily be minimised by applying simple techniques, careful planning and employing an unhurried technique. Rapid sequence induction is not the only OR necessarily the best technique for intubation of the critically ill.

There is no optimal sedative drug or drug combination for intubation in the critically ill. Etomidate, previously favoured for its relative cardiovascular stability has been dropped by many (banned by some) due to its inevitable, if reversible, adrenal suppression effects. Although still the subject of passionate articles, both for (Karis et al., 2009) and against (Dean, 2008), there is always at least an equivalent, if not superior, alternative with ketamine enjoying a resurgence of interest (Jabre et al., 2009, Morris et al., 2009).

Specialist analgesia in critical care

Acute and chronic pain management is a large topic and beyond the scope of this module. However, the same principles of pain management apply to critically ill patients as to all other patients. Appropriately, as “critically-ill” patients are neither well defined nor in any way homogeneous, there aren’t any trials in this area and very few review articles expressing “expert” opinion. However, if this subject interests you, the following 2 articles introduce many of the topical issues (Malchow and Black, 2008, Schulz-Stubner, 2006).

SLEEP

Physiological sleep is an essential requirement for physical and mental health. A basic review of the neurobiology of sleep can be found here (Kalia, 2006) and a more detailed review here (McCarley, 2007).

Studying sleep quality and quantity requires continuous multimodal monitoring including EEG. Understandably therefore, research in the critically ill has been impeded by the logistics of employing such techniques and the interpretation of the accumulated data (Bourne et al., 2007). However, all of the studies published to date, agree that critical illness, sedation, mechanical ventilation and the ICU environment all contribute to dramatic reductions / obliteration, disruption / fragmentation and altered architecture of sleep (Friese, 2008, Drouot et al., 2008).

Exactly how important this is remains unknown. How ICU interventions / environment can be altered to minimise this likely iatrogenic injury is also unknown but several common sense strategies are widely recommended, if perhaps, all too rarely employed. These include:

- Minimising sedation including an early morning cessation of all sedative drugs.
- Adopting a daytime regime of stimulation / physical work (e.g. reduced ventilatory support) alternating with planned quiet periods and minimal interventions with optimal support during the night.
- Sensory minimisation using foam ear plugs and eye shades during quiet periods and / or to simulate a day night cycle.

The only pharmacological intervention to show promise is melatonin (Bourne et al., 2008) although much work remains to be done before this becomes established as a useful therapy.

NEUROLOGICAL DYSFUNCTION IN CRITICAL CARE

Acute brain dysfunction

Systemic pathologies can affect brain function by inducing a wide spectrum of symptoms / signs from subtle deficits in memory or cognition, through to behavioural change, delusions, hallucinations and onto seizures and depressed levels of consciousness. Acute brain dysfunction is a common manifestation of many acute illnesses but in some respects is a neglected component of the multiple organ dysfunction syndrome (MODS). However, all weighted, critical illness, severity of illness scoring systems have the Glasgow Coma Score (GCS) as their strongest predictor of mortality, regardless of primary pathology. Thus, detection, pursuing an exact diagnosis, minimising the risk factors for the development of and, where appropriate, intervening, either empirically or therapeutically, must be clinical priority.

Delirium

Delirium (Girard et al., 2008) is an acute, (at least partially) reversible and fluctuating disturbance of consciousness, cognition and behaviour and by inference, maybe multifactorial. Delirium may be a manifestation of encephalopathy. A diagnosis of delirium during any acute illness is associated with a greater morbidity, length of ICU and hospital stay, prevalence of chronic neuropsychiatric sequelae and mortality.

Delirium has been classified into 3 subtypes based on psychomotor activity: hyperactive, hypoactive and mixed or fluctuating. A number of bedside examination tools have been developed to diagnose and characterise delirium, including several, designed for use in ICU patients, including those intubated and ventilated. These tools assess conscious level, concentration / inattention and some aspects of cognition, often termed, organised thinking.

Prevalence studies utilising these methods have reported incidence rates of 20-80% in ICU patient populations. Despite this wide range, it is generally acknowledged that delirium has historically been under diagnosed and that in part, this is due to the hypoactive subtype being the most prevalent and the purely hyperactive active subtype being comparatively rare.

Delirium is a common manifestation in all acute illnesses. The best established risk factors are increasing age and any form of chronic cognitive decline, perhaps best considered a reduction in functional cognitive reserve. In the ICU population, severity of illness, direct brain injury and chronic hypertension have been identified as patient risk factors. There is also some evidence linking chronic alcohol misuse and acute nicotine withdrawal with the risk of developing delirium. In addition, a number of ICU interventions, in particular, the cumulative dose of benzodiazepines has been shown to significantly increase the risk of developing delirium. Unsurprisingly, sleep deprivation has also been linked to the risk of delirium (Figueroa-Ramos et al., 2009), however, the pathophysiology of sleep disturbance and delirium have a great deal in common and may be two manifestations of the same process rather than cause and effect.

The pathophysiology of delirium is not well characterised (Cerejeira et al., 2010) but inflammation, impaired oxidative metabolism, and alterations in the balance of amino acids and other neurotransmitters, in particular dopamine and acetylcholine, all appear to have a role.

Management recommendations include:

- Daily screening for signs
- Minimising all sedative medication (Treggiari et al., 2009) and avoidance of benzodiazepines altogether
- Identical measures to those described above to optimise the quality and quantity of physiological sleep
- Rescue therapies for hyperactive or mixed subtypes, where agitation impedes care or places the patient at risk of self harm include both traditional and atypical antipsychotics. To date, no single drug or combination of drugs has been demonstrated as superior. However there is some evidence to support the newer, atypical agents due to a reduction in side effects (Rea et al., 2007, Devlin et al., 2009, Vaios et al., 2009).

Studies into the long term neuro-cognitive outcomes of patients following critical illness have been limited but suggest a high incidence of chronic dysfunction associated with a diminished quality of life (Hopkins and Jackson, 2006, Mark et al., 2009). The incidence, severity and duration of delirium are all associated with an increased risk of long term neuro-cognitive dysfunction. Some have hypothesised that critical illness accelerates age related brain atrophy and thereby unmasks otherwise occult, functionally compensated, structural abnormalities (Gunther et al., 2007).

Autonomic dysfunction

The autonomic nervous system has over recent years emerged as crucial player in critical illness. The moment to moment balance between the sympathetic (SNS) and parasympathetic (PNS) nervous systems appears to be analogous to the pro and anti-inflammatory cascades or the clotting and fibrinolytic cascades.

The first set of evidence comes from investigations into surrogate markers of SNS and PNS tone, specifically looking at changes in heart rate variability (Vanderlei et al., 2009) and baroreflex activity / blood pressure control . In health there is a significant level of beat to beat variability that appears to diminish in acute severe illness. This appears to be an early phenomenon and may offer a useful monitoring target (Ahmad et al., 2009). There is also an association with the degree of loss of variability and both severity of multiple organ dysfunction (Papaioannou et al., 2006) and death (Norris et al., 2008). Again, whether this is cause or effect remains unclear.

The second body of evidence stems from the discovery that the autonomic nervous system plays a crucial role in both the innate and adaptive immuno-inflammatory response. The SNS has a complex but overall pro-inflammatory response (Bellinger et al., 2008) whereas the PNS appears to have an anti-inflammatory response (Johnston and Webster, 2009). Over activity and exogenous agonists and antagonists may be responsible for either exacerbating or inhibiting these phenomena. Although no clear therapeutic avenues have emerged they are the subject of much ongoing research.

Lastly, autonomic dysfunction is a well recognised sequelae of both brain and spinal cord injury. In brain injury, paroxysmal sympathetic over activity is seen (Baguley et al., 2008, Papaioannou et al., 2008, Kirkness et al., 2009). The pathophysiology is incompletely understood and treatment essentially empirical with labetalol being the most favoured agent. The pathophysiology and treatment of autonomic dysfunction following spinal cord injury is primarily dependant upon the level of injury. The pathophysiology is comparatively simple and management strategies well established (Furlan and Fehlings, 2008).

Critical illness neuro-myopathy (CINM)

As with delirium and autonomic dysfunction, critical illness affects the peripheral nervous system and skeletal muscle. Bed rest, systemic inflammation, hyperglycaemia, sedation, neuromuscular blockade, exogenous steroid therapy, duration of critical illness and mechanical ventilation have all been implicated in contributing to this clinical problem. The incidence is described as high although accurate estimates depend upon the exact definition and diagnostic criteria.

Perhaps the most obvious and severe consequence of CINM is failure to wean from mechanical ventilation. A recent study into the effects of mandatory mechanical ventilation on diaphragm structure has revealed just how rapid disuse atrophy occurs (Levine et al., 2008). Combined with trunk and limb weakness, the consequences of CINM include increases in ICU and hospital stay, reduced functional recovery and increased mortality (van der Schaaf et al., 2009).

Complete prevention is impractical, however, early screening and intervention are common sense. Therapies with at least some evidence to support their effectiveness include; tight glycaemic control (Hermans et al., 2009), the use of supported spontaneous rather than mandatory ventilation modes, early and aggressive rehabilitation (Schweickert et al., 2009, Perme and Chandrashekar, 2009, Burtin et al., 2009, Morris et al., 2008) and perhaps, electrical stimulation (Gerovasili et al., 2009).

The following 3 review articles are recommended (Schweickert and Hall, 2007, Hermans et al., 2008, Fan et al., 2009). The proceedings of a recent roundtable conference have been published which considers many aspects of CINM in detail (Griffiths and Hall, 2009).

Encephalopathy

Encephalopathy can be defined as brain dysfunction ascribed to a specific aetiology such as a chemical deficiency or toxicity, or a systemic disease such as hypertension or sepsis. In the context of an acute illness, any single organ failure can result in a secondary encephalopathy:

- Cardiovascular failure can cause a hypotensive encephalopathy, which if severe and / or prolonged can result in one or more cerebral infarcts in vulnerable vascular territories (watersheds), classically periventricular white matter and in or around the internal capsule.
- Hypoxaemic and / or hypercapnic respiratory failure can cause an encephalopathy, although in isolation or combination, such encephalopathy is readily reversible unless there is local cerebral, or global, circulatory failure. It is ischaemia, rather than hypoxaemia, that results in permanent brain injury (discussed in detail [HERE \[LINK\]](#)). Whereas, in isolation, hypercapnia is merely anaesthetic with no known level associated with cellular toxicity.
- The pathophysiology and treatment of the encephalopathy associated with liver failure are reviewed in (Shawcross et al.). It is emerging that though ammonia is the principal toxic mediator in hepatic encephalopathy (HE), whose cerebral effects are mainly upon astrocytes, systemic inflammation / infection is an essential co-factor. Ammonia is also toxic to neutrophils resulting in both activation and impaired function of the innate immune system. Cerebral oedema is the predominant pathology in HE. In addition to general supportive care, specific management strategies include limiting ammonia production, pre-emptive antibiotics and albumin replacement. Novel therapies targeting neutrophils are under investigation. Hepatic recovery is associated with complete resolution of HE.
- Encephalopathies associated with renal failure are reviewed in (Brouns and De Deyn, 2004). Uraemic encephalopathy is not merely due to the accumulation of urea but the accumulation of a whole host of cerebrototoxic molecules. This may be further exacerbated by electrolyte disturbance(s) and accumulation of some drugs. Renal replacement therapy (RRT) is usually effective in treating uraemic encephalopathy. However, especially in the acute setting or in high doses, RRT can precipitate an encephalopathy known as the disequilibrium syndrome, although this is usually self limiting. Chronic renal failure, chronic dialysis and renal transplantation all have associated encephalopathies.
- The pathophysiology, differential diagnosis and potential therapies for septic encephalopathy (SE) are reviewed in (Iacobone et al., 2009). Unsurprisingly, the pathology mimics the end organ damage in all other organs. There are no specific therapies, merely supportive care and treatment of the underlying condition. Recovery maybe incomplete. Typical patterns of deficit appear similar to those seen following diffuse traumatic brain injury.
- Self evidently, in the context of MODS, with or without sepsis, the above aetiologies can co-exist.

Disease specific / syndromal encephalopathies

Hypertensive encephalopathies

Classical hypertensive encephalopathy (HE) - the pathophysiology of which is reviewed here (Gardner and Lee, 2007) - is a reversible syndrome of diffuse vasogenic cerebral oedema that develops due to a rapid and precipitous rise in systemic arterial pressure (SAP) as apposed to chronic hypertension, to which adaptive (although incomplete) neurovascular protective mechanisms evolve. This pressure overwhelms the normal cerebral arteriolar vasoconstrictive response to increases in SAP. Cerebral arterioles have a vital autoregulatory function that aims to maintain a near constant cerebral blood flow (CBF) in the face of a wide range of perfusion pressures [LINK to **An overview of brain anatomy, physiology and pathophysiology**]. Failure of this vasoconstrictive protection is patchy but tends to affect the posterior cerebral circulation first. This failure results in uncontrolled vasodilation and high CBFs, which in turn damages the vascular endothelium, which is responsible, at least in part, for mediating the protective vasoconstrictive response. As a result of the endothelial damage and the high local hydrostatic pressures, plasma migrates from the circulation both through (via dysregulated pinocytosis) and around the normally highly impermeable blood brain barrier. The resulting vasogenic oedema appears to start in the cortex and migrates via the interstitial space into the white matter tracts. The endothelial damage also activates the inflammatory and coagulation cascades, increasing the risk of ischaemia and thrombosis. A further exacerbating factor can be hypertensive diuresis / natriuresis, which causes intravascular volume depletion and results in a vasoconstrictive endocrine response.

If untreated, HE can lead to cerebral infarction and / or haemorrhage. However, cerebral ischaemia, infarction and haemorrhage all result in acute systemic hypertension thus, differentiating between the primary and secondary pathologies may be impossible.

There is considerable overlap between hypertensive encephalopathy and the syndrome alternatively described as reversible posterior leukoencephalopathy syndrome or posterior reversible encephalopathy syndrome (PRES), which is reviewed in (Bartynski, 2008b, Bartynski, 2008a, Fugate et al., 2010). This syndrome is also closely linked with reversible cerebral vasoconstriction syndrome (Ducros and Bousser, 2009), which encompasses a spectrum of acute severe headache disorders. These syndromes are increasingly recognised as secondary complications of pre-eclampsia / eclampsia, immunosuppressive therapies and auto-immune diseases (Bartynski et al., 2006, Fugate et al., 2010). However, as the clinical manifestations of PRES overlap with other neurological manifestations of these diseases, prompt imaging with MRI is essential to avoid initiating potentially detrimental therapies (Mak et al., 2008). Another syndrome, that of hyperperfusion after carotid revascularization (Moulakakis et al., 2009) may also share a similar pathophysiology.

The immediate management of HE is a rapid (within 1 hour) 15-25% reduction in mean arterial pressure (Chobanian et al., 2003) using short acting intravenous anti-hypertensives - reviewed here (Marik and Varon, 2007) - followed by a more gradual reduction, if tolerated, to normotensive levels within a few days. Of note, the use of nifedipine, glyceryl tri-nitrate and sodium nitroprusside is contra-indicated in the immediate management of HE. Too precipitous a reduction in SAP can result in end organ ischaemia as vasodilator autoregulatory responses require time to adapt. This is especially true following confirmed cerebral infarction / haemorrhage [LINK to the discussion of blood pressure management in these conditions below] Close attention should also be paid to normalising intravascular volume status and maintaining euvolaemia.

Toxic and metabolic encephalopathies

Exposure to a large number of toxins may result in encephalopathy. These are rare though often difficult diagnoses to make. As with any clinical presentation, the value of a thorough history, clinical examination and the intelligent use of investigations are essential. Exposure to a number of metals, in particular, mercury, lead, manganese and aluminium result in encephalopathy. These metals cause toxicity through astrocyte dysfunction

The commonest metabolic encephalopathies are those associated with dysglycaemia, usually in diabetics, and dysnatraemia [LINK to specific sections below]. Of these, the hyperglycemic hyperosmolar state (HHS) is both the commonest and associated with the highest incidence of encephalopathy. The pathophysiology and management are well defined - reviewed here (Chiasson et al., 2003). Perhaps the commonest mistake in the management of HHS, and indeed other metabolic encephalopathies is attempts to correct the underlying abnormality too quickly with potentially dire consequences. As a rough guide, correction should occur no faster than the period of time over which the abnormality evolved.

The next commonest metabolic encephalopathy is that associated with thiamine deficiency, eponymously known as Wernicke's encephalopathy (WE). Although chronic alcohol misuse has the strongest association with WE, it can occur in other malnourished patients and be a manifestation of the refeeding syndrome (Donnino et al., 2007, Sechi and Serra, 2007). The exact pathophysiology is complex and reviewed here (Hazell and Butterworth, 2009). Controversies remain regarding the optimal dose, frequency and duration of intravenous thiamine therapy (Donnino et al., 2007, Sechi and Serra, 2007).

Common infectious and inflammatory diseases of the nervous system

Meningitis

Community acquired bacterial meningitis - reviewed here (Klein et al., 2009) - is a common and severe illness associated with a significant incidence of severe disabling morbidity and mortality. In adolescents and adults <50 years of age, the vast majority of cases are due to either *Streptococcus pneumoniae* or *Neisseria meningitidis*. In the over 50s, there is a small but significant incidence of *Listeria monocytogenes* meningitis, which requires specific adjunctive therapy with ampicillin. A high index of suspicion and rapid diagnostic investigations, including lumbar puncture, are vital. Time to antibiotics is critical and dramatically affects outcome, although controversy remains regarding pre-hospital administration, especially in patients with systematic sepsis and meningitis. Adjunctive dexamethazone before / with the first dose of antibiotics and continued for 96 hours, is of possible benefit in proven cases of *Strep. pneumoniae* meningitis, in developed countries, in patients with a low index of suspicion of HIV infection, although the most recent meta-analysis casts doubt even in this specific group (van de Beek et al., 2010). The common viral meningitides, which clinically overlap with viral encephalitis (see below), are caused by herpes simplex type 2, varicella zoster and enterovirus and are reviewed here (Big et al., 2009). Sub acute / chronic meningitis including mycobacterial, aseptic, lymphomatous and carcinomatous is reviewed here (Helbok et al., 2009).

Encephalitis - generalised and limbic

Encephalitis is defined as the presence of an inflammatory process in the brain in association with clinical evidence of neurological dysfunction. It can be a diffuse process or affect specific brain regions such as the limbic system. Aetiologies include:

- Acute viral infection (Tunkel et al., 2008, Solomon et al., 2007)
- A variety of autoimmune pathologies (Vernino et al., 2007), which may be idiopathic, or arise post infection, termed acute disseminated encephalomyelitis (ADEM) (Sonneville et al., 2009),
- Paraneoplastic (Didelot and Honnorat, 2009)
- Associated with systemic diseases such as SLE (Muscal and Brey, 2010).

The autoantigens that are the targets of these immunopathologies are increasingly being elucidated (Graus et al., 2010, Irani et al., 2010). These patients present to intensive care most commonly with either depressed levels of consciousness and / or complex epilepsy. Initial management depends upon the most likely diagnosis but classically involves supportive care, exclusion of an infectious aetiology followed by high dose systemic steroids and consideration of other immunotherapies such as plasmapheresis.

A related series of pathologies that affect focal areas in the spinal cord are termed transverse myelitis. The epidemiology and aetiologies of TM are reviewed here (Pandit, 2009, Bhat et al., 2010).

Acute inflammatory demyelinating polyneuropathy (AIDP)

The peripheral nervous system can also be affected by acute immunological pathologies, the commonest being Guillain-Barré syndrome (GBS) - reviewed here (van Doorn et al., 2008). The pathophysiology of AIDP is believed to be due to the induction of specific anti-ganglioside antibodies. These most commonly arise following infection when a surface molecule on the infecting organism cross reacts with one of the endogenous gangliosides. These antibodies bind to neuronal cell surfaces causing complement activation and inflammation. Cranial nerve AIDP known variably as Miller-Fisher variant, Fisher syndrome, Bickerstaff brainstem encephalitis or Fisher–Bickerstaff syndrome is associated with a specific anti-GQ1b antibody but is identical to AIDP in all other respects (Overell and Willison, 2005, Yuki, 2009). The diagnosis of AIDP is based upon the clinical history, examination and progressive (ascending) loss of sensory and motor function. Although no specific test is available, the finding of an elevated CSF protein with oligoclonal bands on electrophoresis but a normal cell count supports the diagnosis. A more detailed analysis of the CSF is not currently routine but maybe useful (Brettschneider et al., 2009). Of note, CSF protein may be normal if analysed during the first week from symptom onset. Nerve conduction studies may be needed to support the diagnosis in difficult cases. Treatment consists of supportive care, in particular, pain maybe a prominent feature. Screening for ventilatory muscle compromise should be routine as should monitoring for autonomic dysfunction. Therapy with intravenous immunoglobulins (IVIg) speeds recovery if started within 2 weeks of disease onset and has similar efficacy to plasma exchange (Hughes et al., 2010). Failure to respond to IVIg may indicate high clearance rates and may warrant consideration of a second course of therapy (Kuitwaard et al., 2009).

Acquired disorders of the neuromuscular junction (Spillane et al., 2010) and myopathies

The commonest acquired disorder of the neuromuscular junction is the autoimmune disease myasthenia gravis (MG) - reviewed here (Juel and Massey, 2007). From a critical care perspective, MG, like GBS, is a cause of progressive neuromuscular ventilatory failure. Having established the diagnosis, immunosuppressive therapy and acetylcholinesterase inhibitors usually reverse the disease process and are reviewed here (Skeie et al., 2010). The differential diagnosis of MG includes:

- GBS (see above)
- The Lambert Eaton myasthenic syndrome, another autoimmune and commonly paraneoplastic syndrome - reviewed here (Spillane et al., 2010).
- Botulism, caused by the neurotoxin of Clostridium botulinum following either ingestion of foods contaminated by toxin or from contaminated injected illicit drugs (most commonly heroin) - reviewed here (Spillane et al., 2010).
- Tick paralysis (in endemic areas) where a high index of suspicion is required and removal of the offending tick result in a cure - reviewed here (Harris and Goonetilleke, 2004).
- Metabolic myopathies - reviewed here (Berardo et al., 2010)
- Motor neuron disease - diagnosis and treatment reviewed here (Bedlack, 2010) and pathophysiology reviewed here - (Bento-Abreu et al., 2010).

Therapeutic plasma exchange (TPE) and IVIg

TPE is used for many immune mediated neurological conditions. IVIg may be an equivalent therapy but there are few comparative trials in any condition. The mechanisms by which IVIg is thought to act are reviewed here (Jacob and Rajabally, 2009). There is no evidence to support the sequential use of TPE followed by IVIg. As TPE removes IVIg TPE following IVIg is illogical. A review of the technique and controversies surrounding it can be found here (McLeod, 2010).

Biomarkers of brain injury

Assessing whether or not a brain injury has occurred is currently, and likely to remain, dependent upon clinical history and examination. Coupled with structural brain imaging, most commonly CT in the acute setting, gives sufficient information to direct both specific and supportive care. Nevertheless, a single or panel of biomarkers that track ongoing brain injury, relate to severity / extent and provide useful prognostic information would be useful diagnostic and monitoring adjuncts. A number of biomarkers have been investigated both individually and in panels {Kochanek, 2008 #2242; Kövesdi, #3039}. Though no single biomarker has proven is worth in the clinical arena, the combination of serial measurements of S100B, neuron-specific enolase, myelin basic protein and glial fibrillary acidic protein {Honda, #3040} holds some promise as a biochemical panel for brain injury, analogous to the so-called "liver function tests" - bilirubin, alanine transferase, aspartate aminotransferase, alkaline phosphatase and gamma glutyltransferase.

Epilepsy and seizures

Epilepsy is a recurrent, episodic, abnormal increase in local or global, neuronal electrical activity. There is a spectrum of epileptic phenotypes most of which have a classical seizure type or clinical manifestation, such as absences or generalised tonic clonic fits. Although all forms of epilepsy start in a focal area, some remain confined to that brain region whilst others, with varying latency, spread widely and become generalised. Following the seizure, a post-ictal state, often with reduced or altered consciousness occurs, for a variable period of seconds to minutes, before recovery to baseline state is observed.

Neither the epileptic phenomenon, nor the pathophysiology that underlies it is completely understood. Epilepsy is associated with the abnormal, synchronous firing of large neuronal populations. Due to the complexity of the phenomenon, a number of models have been developed and are reviewed here (Ullah and Schiff, 2009). Not all such events manifest as obvious seizures and can only be detected by using high spatial and temporal resolution electroencephalography (EEG) (Jiruska et al., 2010, Keller et al., 2010). There are also a myriad of paroxysmal non-epileptic neurological syndromes, a concise review of which can be found here (Crompton and Berkovic, 2009).

EEG

The gold standard investigation for the detection of epilepsy is high fidelity EEG. This should of course be coincident with appropriate investigations into the underlying cause. EEG, unlike ECG, is both highly complex and chaotic making continuous and real time interpretation problematic - for a very readable introduction into EEG see (Bennett et al., 2009). EEG assesses brain function / activity in real time and correlates with measures of regional blood flow and metabolic activity measured using functional imaging techniques (Kurtz et al., 2009).

The utility of full fidelity EEG in the ICU setting is reviewed here (Guérit et al., 2009) and extends beyond the confirmation of epilepsy and the detection of subclinical / non-convulsant epilepsy to other causes of coma, in which EEG has both diagnostic and prognostic value. In addition, the value and utility of continuous EEG (cEEG) monitoring in the comatose ICU patient following brain injury is undisputed (Friedman et al., 2009). To increase the interpretability of cEEG, computerised signal processing and derived variables have been developed (Subha et al., 2010). The use of simplistic cEEG derived variables has an established role in depth of anaesthesia monitoring (Palanca et al., 2009). Of the commercially available monitors the Bispectral index or BIS monitor (<http://www.aspectmedical.com/CriticalCare.aspx>) is perhaps the most widely used. The validity and hence utility of such monitors for continuous bedside functional brain monitoring during neuromuscular blockade (Ball, 2002), therapeutic burst suppression (see below) (Musialowicz et al., 2010, Cottenceau et al., 2008) and in assessing the prognosis of comatose patients (Schnakers et al., 2008, Myles et al., 2009, Wennervirta et al., 2009, Seder et al., Dunham et al., 2009) is rapidly emerging.

Pathophysiology

At a basic level, epileptic foci occur in groups of neurones where there is a persistent net increase in excitatory stimuli. Normally there is a balance between excitatory and inhibitory stimuli with interconnected feedback systems that prevent epileptic discharge. Both increases in excitatory, and reductions in inhibitory processes, are implicated in the pathogenesis. The principal excitatory neurotransmitter is glutamate via the N-methyl-D-aspartate (NMDA) receptor whilst the principal inhibitory neurotransmitter is γ -aminobutyric acid (GABA) via the GABA_A receptor. Propagation, synchronisation and amplification of this excitatory stimulus is believed to be mediated by the abnormal expression or function of voltage gated sodium channels (Mantegazza et al., 2010). G-protein gated potassium channels (Luscher and Slesinger, 2010) and the extracellular matrix (Dityatev, 2010) are also emerging as important elements in the pathophysiology of epilepsy.

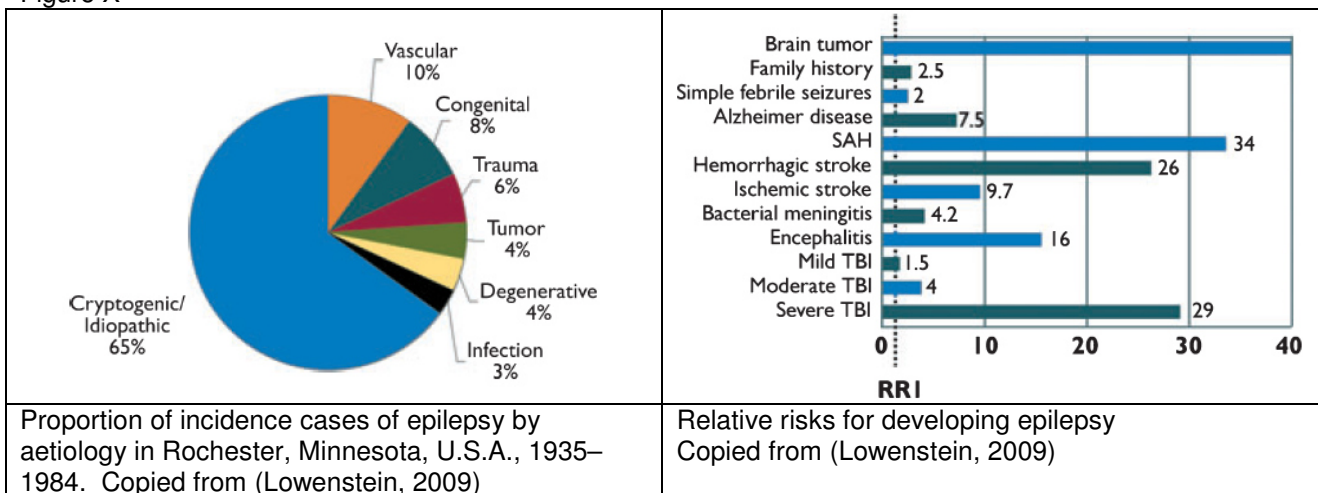
A variety of reversible events (Bleck, 2009), such as pyrexia or alcohol withdrawal, can provoke epilepsy if there is an underlying structural or physiological predisposition. Such events are described as lowering the seizure threshold. Although the concept of a seizure threshold is clinically observed, its clear physiological explanation, beyond the net increase in excitatory stimuli described above, is lacking. Differentiating threshold lowering from toxin induced epilepsy [LINK to proconvulsant drugs] is impossible.

In most instances, seizures spontaneously terminate after seconds to minutes. The physiological explanation for spontaneous seizure termination remains to be clarified (Löscher and Köhling). However, this post ictal phase is notable for an increase in seizure threshold. Thus the mechanisms responsible for spontaneous termination and the refractory post ictal state are obvious, if until recently neglected, areas of interest - reviewed here (Löscher and Köhling)..

Epidemiology and epileptogenesis

Epilepsy does not occur in a “normal” brain although the majority of cases arise in patients in whom no structural abnormality can be demonstrated, see Figure X. The natural history of such idiopathic cases, in adults, is very variable but the majority are controlled with anti-epileptic drugs (AEDs) and are often limited to periods of months to years. There are a number of genetic disorders that predispose to the development of epilepsy. In addition it is well recognised that any form of congenital or acquired structural brain injury, be it traumatic, vascular, inflammatory or infectious, can also predispose to epilepsy, by an incompletely understood process termed epileptogenesis. The proportion of underlying aetiologies and the long term, relative risk of developing epilepsy following various injuries are shown in Figure X. Acquired epilepsies tend to be more resistant to AEDs and sometimes exhibit a progressive course. Therapies that inhibit and even reverse epileptogenesis remain in the experimental arena (Pitkänen), although well known anti-inflammatory and immunosuppressive drugs show some promise. Indeed a number of pro-inflammatory mediators have recently been identified as key players (Maroso et al., 2010, Balosso et al., 2008). The role of AEDs as anti-epileptogenics is unclear (Willmore, 2005), not least as they are a diverse group of drugs. Perhaps surprisingly, proconvulsant drugs may also have a therapeutic role as anti-epileptogens (Pitkänen), a possible explanation for which is seizure preconditioning (Johnson and Simon, 2009).

Figure X



Epilepsy in the ICU

The 2 commonest scenarios encountered in intensive care are post injury epilepsy and status epilepticus.

Post injury epilepsy (PIE)

Epilepsy post injury is inconsistently classified on the basis of time from injury into immediately (within 24 hours), early or provoked (within the first 7 days) and late or unprovoked (after 7 days). Late epilepsy can occur years after injury (Lowenstein, 2009). The pathogenesis of early and late PIE is probably different and reviewed here (Agrawal et al., 2006, Diaz-Arrastia et al., 2009). The risk of PIE is increased by more extensive injury, any form of haemorrhage (free iron appears to be a potent epileptogen) and penetrating injury, including surgery.

Dead neurones do not generate electrical activity hence the origin / focus of epilepsy is always adjacent or connected to such an area. As electrical activity is dependant upon energy supply, and hence blood supply, the occurrence of an epileptic event following brain injury, where the local or global blood supply may be critically limited, can result in significant secondary ischaemic brain injury, see section on secondary brain injury below [LINK]. The controversy regarding prophylaxis verses treatment is discussed below [LINK].

Status epilepticus (SE)

If the endogenous seizure termination mechanisms fail, prolonged or repetitive seizures ensue. Seizures of >5 minutes, or, two or more sequential seizures without full neurological recovery between episodes is termed status epilepticus (SE) (Behrouz et al., 2009). SE can result in neuronal cell death predominantly through excitotoxicity or ischaemia, although activation of apoptotic cascades may also occur. In addition, SE itself is epileptogenic, although the exact pathophysiology is unclear. SE can be classified into convulsant (Behrouz et al., 2009) and non-convulsant types (Maganti et al., 2008), each of which have been subclassified. Diagnosis may be obvious from clinical observation but may require EEG for confirmation and more importantly exclusion (Crompton and Berkovic, 2009). Management consists of general supportive care and specific therapy. General supportive care includes airway protection, ventilatory support, cardiovascular monitoring for complications of the associated endogenous catecholamine surge (Metcalf et al., 2009, Bealer et al.), temperature and glycaemic control (Kinirons and Doherty, 2008). Specific therapy consists of a well established escalator of AEDs [LINK to AEDs], although this is based on very limited clinical trial data. Reviews of the management of convulsant SE can be found here (Kinirons and Doherty, 2008, Behrouz et al., 2009, Meierkord et al., 2010) and of non-convulsant SE here (Maganti et al., 2008).

In cases where there appears to be ongoing seizures, either clinically or on EEG, SE is considered to be refractory. Conventional therapy for this condition is drug induced coma targeted at achieving a burst suppression (BS) pattern on cEEG (Musialowicz et al., 2010). Neither the optimal agent (thiopental and / or propofol and / or midazolam) (Rossetti, 2007) nor the target level of BS (arbitrarily 3-5 bursts/minute \equiv BIS \sim 15 \equiv BIS suppression ratio >60%) (Musialowicz et al., 2010) nor the optimal duration of therapy (arbitrarily 24-48 hours) have been clearly established. Indeed, the physiology of BS is poorly understood (Amzica, 2009). As a therapy, it is also used as "medical rescue" in the management of otherwise intractable intracranial hypertension [see LINK]. Whatever the arbitrary duration, some advocate gradual withdrawal of anaesthetic therapy, whilst others suggest complete cessation. After \geq 24 hours of usually high doses on any of the conventional agents (either individually or in combination), the time taken to effectively clear the active drug(s) is days, especially thiopental. Recurrence of seizures during this phase is associated with a poor prognosis. Whether to repeat the induction of BS or admit therapeutic failure will depend upon the individual case. If recovery from induced BS is uncomplicated, then full recovery, depending upon the underlying aetiology (Bleck, 2010), can be expected.

There is emerging evidence that in refractory SE, resistance develops to the conventional GABA agonist drugs (Löscher, 2007) and that alternative agents such as the NMDA antagonist, ketamine (Wasterlain and Chen, 2008, Rossetti, 2009) maybe both more logical and effective. The successful use of adjunctive therapeutic hypothermia [LINK to MTH section] has also been reported (Corry et al., 2008).

In the few cases of SE that are truly drug resistant and in which no irreversible underlying pathology is detected, there are anecdotal reports of successful therapy using various forms of electrical brain stimulation, analogous to cardiac defibrillation or overdrive pacing. An overview of such therapies can be found here (Löscher et al., 2009) whilst detailed discussions of each of these approaches and other experimental therapies including cell, gene, novel drug and novel drug delivery can be found in the same issue of the journal (Neurotherapeutics 2009 Volume 6, Issue 2 - Non-traditional Epilepsy Treatment Approaches - available via Science Direct). Perhaps the simplest, most readily available and non-invasive approach is electroconvulsive therapy (ECT). A case series of 3 patients successfully treated with ECT and review of the literature can be found here (Kamel et al., 2010). Finally, surgical resection of radiologically and / or electrophysiologically definable focal brain pathology has been successfully performed in a few cases - reviewed here (Lhatoo and Alexopoulos, 2007).

Antiepileptic drugs (AEDs) (Anderson, 2008)

Drugs with anti-epileptic activity are a highly heterogeneous group whose therapeutic use extends to include migraine, psychiatric conditions, sedation / anaesthesia, and both acute and chronic pain. As a group, they are often divided into established and new. Current UK national guidelines for their use can be found here (NICE, 2004). Not only are there in excess of 13 distinct agents in common use, but their pharmacology, both dynamics but more especially, their kinetics, side effects and drug interactions (Pollard and Delanty, 2007, Diaz et al., 2008) are so complex, that their chronic use is the province of specialists (Anderson, 2008). From an ICU perspective the following facts are of clinical importance:

- First line therapy for self terminating seizures, of almost all types, is sodium valproate (NICE, 2004, Trinkka, 2009). In ICU, the only common problematic drug interaction is with carbapenems, which dramatically increase the clearance of valproate, necessitating either a substantial dose increase or switch to an alternative agent (Mancl and Gidal, 2009).
- First line therapy for rapid seizure termination / SE is a benzodiazepine. Of the benzodiazepines there are data to suggest that lorazepam is the optimal choice over diazepam (Prasad et al., 2005). However, other authors have interpreted this data the other way round and concluded that there is insufficient evidence to clearly recommend lorazepam over diazepam or midazolam (Riss et al., 2008). The optimal route for administration is intravenous (IV) but rectal diazepam or intramuscular, nasal or buccal midazolam are effective alternatives if IV access is unavailable. The optimal dose is also disputed, with most guidance erring on the side of effective overdose (Lowenstein and Cloyd, 2007). If ineffective, repeated dosing is recommended in most guidelines but has a poor and diminishing success rate.
- Phenytoin has highly unpredictable pharmacokinetics, a narrow therapeutic window, as monotherapy achieves seizure control in only a minority of patients, is a potent enzyme inducer, has many drug interactions and is responsible for a high incidence and severity of both acute and chronic side effects. Accordingly it has been relegated to being a third line agent in most chronic epilepsy guidelines. Despite this, it remains the second line (after benzodiazepines) drug of choice in almost all published guidelines for the management of SE and the favoured prophylactic agent post brain injury / surgery in most centres. The only reasons for this state of affairs are a lack of randomised, comparative, head to head trials, some of which are finally being performed. There is compelling evidence and arguments, albeit not based on randomised trials, to use either sodium valproate or levetiracetam in place of phenytoin as the second line agent in SE (Wasterlain and Chen, 2008, Trinkka, 2009). The controversies of seizure prophylaxis are discussed in detail below.
- Due to its efficacy in almost all settings, its complete lack of drug interactions and its availability in both oral and intravenous preparations, levetiracetam is rapidly becoming the first choice AED in ICU (Trinka, 2009, Nau et al., 2009). Its only disadvantages are its comparatively high cost and its idiosyncratic sedative side effect.

The controversy of prophylactic AEDs

On the basis of very limited trial data, many clinicians advocate the use of prophylactic AEDs in all patients with specific diagnoses or on the basis of the extent of injury on CT imaging (Agrawal et al., 2006).

Taking TBI first, the trials of prophylactic AEDs are reviewed here (Temkin, 2009, Chen et al., 2009). To date, only phenytoin has been investigated to any real degree. It reduces the incidence of early (<7days) PIE and therefore maybe efficacious if given for this period. Prophylactic phenytoin doesn't reduce the incidence of late (>7 days) PIE but does appear to have negative effects on neurological outcome if used for extended periods, together with a high incidence of serious side effects. As such, in patients who do develop early PIE despite phenytoin, there is moderately compelling evidence to switch to an alternative AED. As switching can in itself be problematic, using an alternative, such as valproate or levetiracetam as primary prophylaxis would seem logical. It is also worth noting that no trial has demonstrated any outcome benefit from early PIE prevention following TBI (Agrawal et al., 2006). A recent, blinded, prospective trial of 7 days prophylactic AED therapy, randomised (2:1) to either levetiracetam or phenytoin in 52 patients following severe TBI, demonstrated equivalence in the incidence of early PIE but with fewer side effects and superior 3 and 6 month outcome measures in those patients who received levetiracetam (Szaflarski et al., 2010).

Following spontaneous SAH, the prophylactic use of anticonvulsants is associated with a worse outcome (Rosengart et al., 2007), especially phenytoin (Naidech et al., 2005), which interacts with the pharmacokinetics of nimodipine, dramatically reducing its bioavailability (Wong et al., 2005b).

Following spontaneous ICH the incidence of seizures maybe up to 30% in the first 2 weeks. However, clinical seizures have not been associated with worsened neurological outcome or mortality. Two recent studies have however demonstrated a worse outcome in patients given prophylactic phenytoin (Messé et al., 2009, Naidech et al., 2009). The 2010 AHA/ASA guidelines on the management of ICH conclude,

“Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence: B). (New recommendation) (Morgenstern et al., 2010).

The use of prophylactic AEDs is of no benefit and may do some of harm in patients with primary brain tumours (Tremont-Lukats et al., 2008) or cerebral metastases (Mikkelsen et al., 2010).

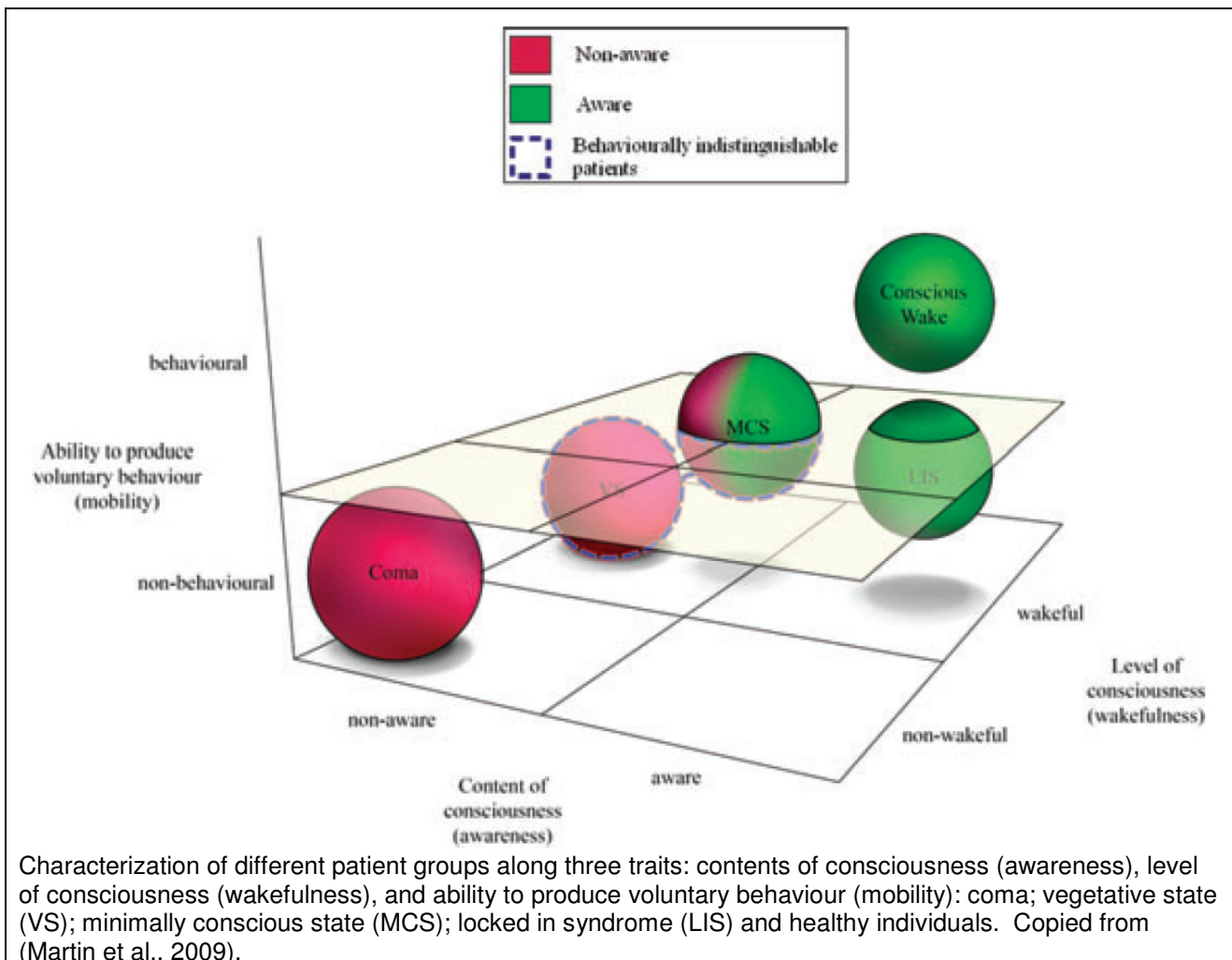
In summary, regardless of the type of brain injury, there is a conspicuous lack of evidence to demonstrate any benefit from the routine use of prophylactic AEDs. Furthermore, if such therapy is to be given, phenytoin may do significant harm, especially if given for >7days.

Proconvulsant drugs (Löscher, 2009)

As with anti-arrhythmic drugs, most AEDs show proconvulsant activity at toxic doses. In addition, certain antibiotics (in particular, beta-lactam containing drugs), local anaesthetics, general anaesthetics (Kofke, 2010), neuroleptics, antidepressants and opioids are considered to lower the seizure threshold. However, such proconvulsant effects are usually only evident at supra-therapeutic levels. The management of SE secondary to drug toxicity can be very challenging as conventional management algorithms often fail, specific antidotes do not exist and enhanced elimination therapies are rarely effective. At therapeutic doses however, many of these drugs exhibit either neutral or anticonvulsant effects such that combination therapy with AEDs and neuroleptics, for example, are safe and efficacious in patients who not uncommonly require therapy for epilepsy and serious mental illness. The concept that too little or too much of a certain drug is proconvulsant, whilst an intermediary level is anticonvulsant, is perhaps best exemplified by the endogenous neurotransmitter noradrenaline, the conflicting data regarding which is reviewed here (Fitzgerald, 2010).

Persistent disorders of consciousness (Bernat, 2006)

Following a severe brain injury, survival with very limited neurological recovery presents diagnostic, therapeutic, ethical, philosophical and legal challenges. Over recent years, there have been moves towards consensus diagnostic criteria for 4, persistent disorders of consciousness: locked in syndrome; the minimally conscious state; the vegetative state and coma (see figure below).



Until the advent of functional brain imaging, differentiating these conscious states was often impossible. However, although positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can demonstrate metabolic activity in specific brain regions and changes in metabolic activity in response to stimuli consistent with normal individuals, the diagnostic conclusion of awareness and volition arguably exceed our current understanding and imaging technology. Potential for further recovery and whether this constitutes “meaningful” recovery are value judgements. The appropriateness of continuing supportive care and the burden of the costs of such care are highly emotive issues and challenge ethical, philosophical and legal boundaries.

Brain stem death (BSD): diagnosis, pathophysiology and management of the potential organ donor.

It is widely recognised that the brainstem, which controls the essential bodily functions, can suffer complete and irreversible injury, most commonly in the context of herniation through the foramen magnum following a catastrophic rise in intracranial pressure. This event constitutes brain death. In an unsupported individual it rapidly results in respiratory followed by cardiac arrest. However, in an individual receiving mechanical ventilation +/- circulatory support, the function of all organs, other than the brain, can be maintained for a protracted period of time.

Controversies remain concerning the clinical diagnosis of death and are reviewed here (Souter and Van Norman, 2010).

BSD is associated with a specific syndrome of pathophysiology, reviewed here (Bugge, 2009). When recognised or suspected, there are a set of bedside tests that can confirm the diagnosis (Academy of Medical Royal Colleges, 2008, Wijdicks et al., 2010). In circumstances where these tests cannot be completed, adjunctive radiological and / or neurophysiological tests may be required. The diagnosis of BSD constitutes grounds for the immediate withdrawal of all supportive care in most countries. However, prior to this, consideration should be made as to whether the patient is eligible and had consented to organ donation. The legislation covering donation after brain death (formerly known as heart beating donation) varies from country to country. Given the supply demand imbalance for organ transplants, maximising the consent and optimising the donor's physiology prior to retrieval are both critical and the subjects of national campaigns, worldwide.

An example of an evidence based and detailed guideline for donor management following brain stem death can be found here: <http://db.tt/cDWU662>

CORE TOPICS IN NEURO CRITICAL CARE

An overview of brain anatomy, physiology and pathophysiology. Based upon (Fitch, 1999):

The anatomy and physiology of the brain is unique amongst organ systems and an understanding, of both normal and pathological neurophysiology, are essential.

The brain is well protected physically and physiologically. Physically, the mass of the brain (approximately 1400±1600g) is supported, and its movements are cushioned, by the cerebrospinal fluid (CSF). It is restrained by the attachments of the falx cerebri, the dentate ligaments and the tentorium cerebellum and, with the exception of the foramen magnum, enclosed, at least in the adult, in a strong, rigid container, the fused skull bones. Although the demand by the brain for energy-generating substrates is substantial (the central nervous system consumes 20% of the oxygen and 25% of the glucose that is utilized by the resting individual under physiological conditions) this is met more than adequately by the 15% of the resting cardiac output (750ml/min) which perfuses the brain (approximately 80% to grey matter and 20% to white matter). Indeed, normally, the supply of oxygen is considerably in excess of requirements such that the brain extracts only 25±30% of that supplied. However, because the brain's own stores of energy-generating substances is small (exhausted in approximately 3 min) it is uniquely dependent on a continuing, and adequate, supply of substrate.

<i>Demand</i>	<i>Supply (normal resting conditions)</i>
170µmol O ₂ per 100g brain tissue per min	
≡ 3±5ml O ₂ per 100g brain tissue per min	
≡ ~40±70ml O ₂ per min	~150ml O ₂ per min
31µmol glucose per 100g brain tissue per min	~250µmol glucose per 100g brain tissue per min

Based upon: mean global cerebral blood flow (CBF) of 50ml per100g brain tissue per min

The contents of the intracranial space can be divided into cellular and fluid components / compartments (see Table 5). Because of the rigidity of the skull, any increase in the volume of one of these compartments must, of necessity, decrease the space available for the other three and / or increase the pressure within the cranial cavity. Fortunately, in the absence of intracranial pathology, minor changes in the volume of one component may be accommodated without difficulty such that the pressure within the container does not change (see Figure 1). The absolute value of the pressure within the intracranial space (or, more correctly, the craniospinal axis) measured with the subject in the horizontal position is 7-12 mmHg (10-16cmsH₂O). It is principally determined by the balance between the rate at which CSF is formed and that at which it is reabsorbed. CSF is formed at a fairly constant rate by diffusion and filtration in the choroid plexus (~50%) with the remainder forming around cerebral vessels and along ventricular walls. CSF is passively absorbed through the arachnoid villi into the venous sinuses but the rate is dependant upon the venous pressure and the resistance of the absorptive mechanism. There is no feedback system between production and absorption and since the latter is relatively easily impaired, the result is accumulation of CSF (hydrocephalus). A review of the different types of hydrocephalus and their management can be found here (Bergsneider et al., 2008).

Table 5: Intracranial tissue and fluid compartments, their volumes and their relative proportions.

Compartments		Approximate volumes	Percentage of total volume
Cellular	Glia	700-900ml	46%
	Neurones	500-700ml	35%
Fluid	Interstitium	75ml	5%
	Blood	100-150ml	7%
	CSF	100-150ml	7%

Of the intracranial compartments, the only one that can rapidly change volume is blood. The cerebral circulation is unique in that the variations in the diameter of the cerebral blood vessels, and the consequent alterations in the total volume of blood in the intracranial space, take place within the confines of an almost completely closed “box”. Although numerous physiological mechanisms mitigate the potential disadvantages of this arrangement these have finite limitations and may be overwhelmed by pathologically induced changes

in intracranial dynamics (See Figure 1). The essential point of this graph is that the contents of the intracranial space can compensate for minor physiological variations and initially, for changes in intracranial volume associated with intracranial pathology (tumour, haematoma, oedema). However, as the relationship moves towards the right-hand side of the graph, the ability to compensate further, becomes exhausted, and any further increase in volume is accompanied by a more marked increase in CSF pressure: the 'tighter' the brain the more marked the induced alterations in CSF pressure. The first compensatory mechanisms are the translocation of CSF from the intracranial space into the spinal subarachnoid space (unless the communication between the 2 spaces is obstructed) and the extrusion of blood from the thin-walled veins on the surface of the brain. As a result there is a limit to the degree of compensation possible. These compensatory mechanisms take some time to develop: hence sudden alterations in volume, regardless of the position of the patient on the curve, will increase intracranial pressure acutely. Only therapeutic interventions that affect the intracerebral blood volume can influence such changes. Other therapeutic interventions may reduce the volume of the interstitial (e.g. mannitol) or CSF (e.g. ventricular or spinal drain) compartments.

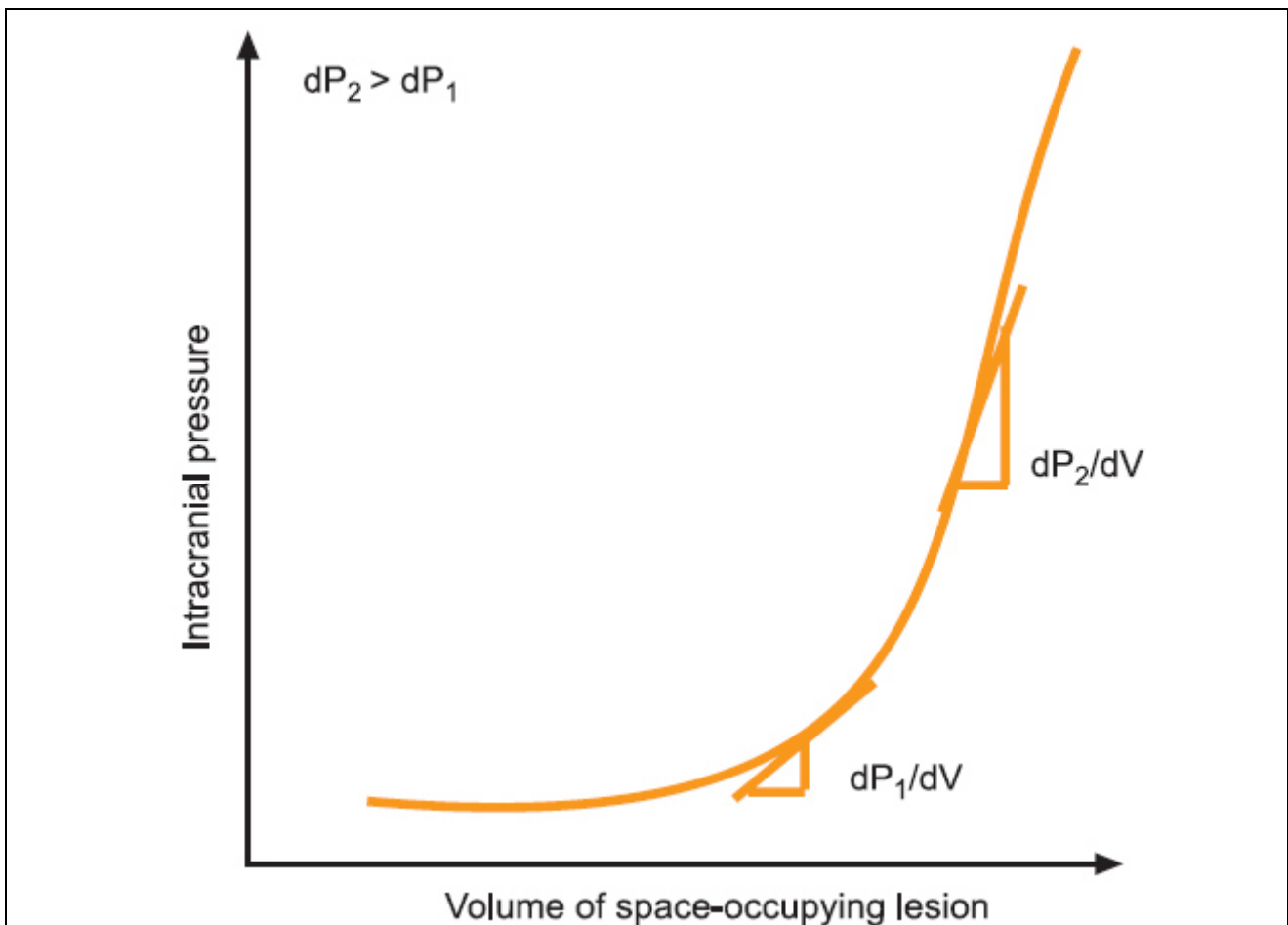


Figure 1: Schematic representation of the changes in CSF pressure associated with progressive increases in intracranial volume. The difference between the pressure change per unit change in volume between the left-hand part of the graph (compensation possible) and that once compensation has been exhausted (right-hand part) is demonstrated. Copied from (Fitch, 1999)

As intracranial pressure (ICP) rises, 2 injurious processes result. Firstly, an increase in perfusion pressure will be required to maintain cerebral blood flow, in particular in the microcirculation. Secondly, as the pressure rises, the floating brain is forced downward into the foramen magnum, compressing the brainstem and the vital structures within it. If untreated, this results in herniation of the brainstem and death.

SECONDARY BRAIN INJURY

Introduction

Traumatic brain injury, stroke and spontaneous subarachnoid / intracerebral haemorrhage are very common and potent causes of premature death, and severe disability in survivors. Neuro critical care is concerned with the supportive care of the brain and all the other organ systems following brain injury. It is considered a subspecialty of intensive care and there are, specialist, stand alone units. However, patients with brain injuries often have other injuries / pathologies and are susceptible to all of the same ICU complications as other critically ill patients. It is also common for patients with brain injuries to be cared for in general critical care units and thus “brain supportive care” must be familiar to every intensive care practitioner.

As explained in the previous section, the brain is very sensitive to ischaemia with loss of consciousness within seconds and irreversible damage occurring within a few minutes of normothermic circulatory arrest (Schneider et al., 2009). Different parts of the brain exhibit variable tolerances to ischaemia, which continues to challenge the concepts surrounding the diagnosis of brain death, most especially in the area of organ donation following cardiac death (Verheijde et al., 2009, 2008){Souter, 2010 #3050}.

The commonest mechanisms of primary brain injury are direct mechanical insults and vascular disruption, which often occur in concert. As brain function is dependant upon the integrity of fragile axonal tracts and billions of inter-neuronal and neuro-glial connections, even relative trivial shear-strain forces can result in long term cognitive deficits. Such injuries are often referred to as diffuse axonal injury (DAI).

Following this primary injury, brain tissue undergoes a complex series of further insults over minutes to days, referred to as secondary injury (del Zoppo, 2008, Park et al., 2008) illustrated in Figures 2, 3 and Table 6.

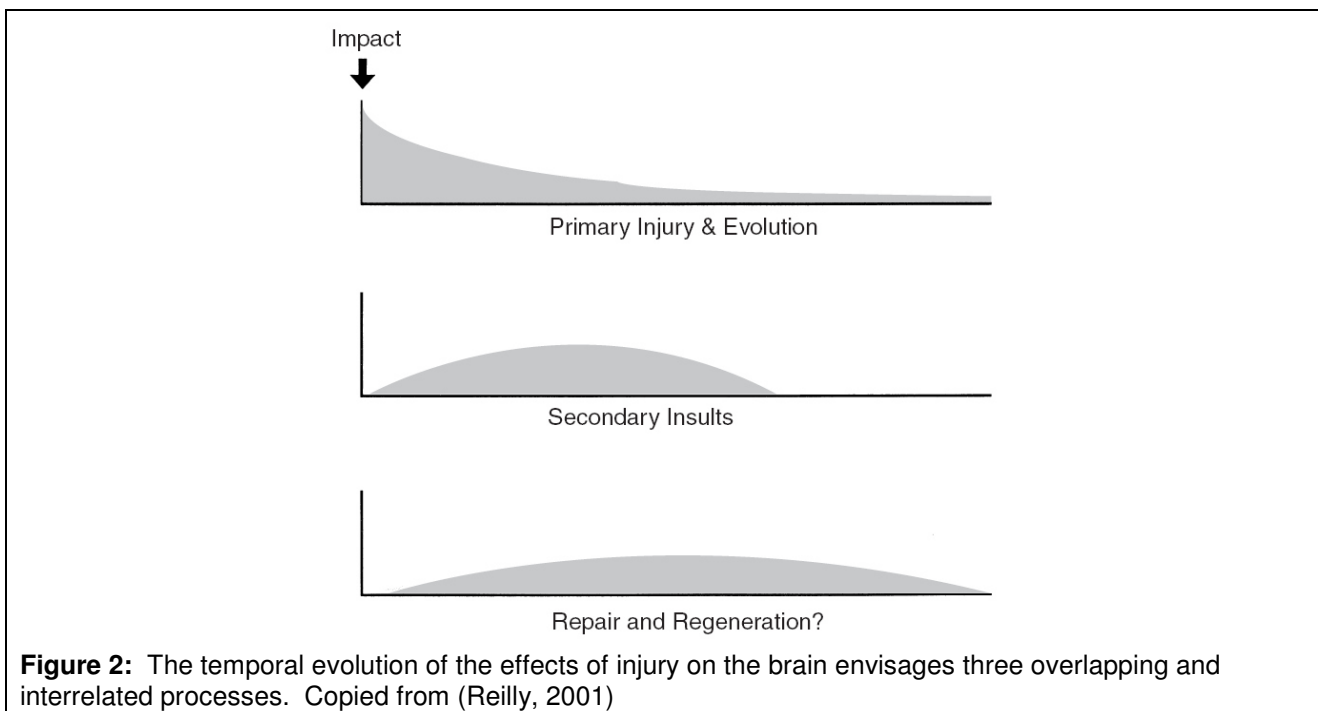


Figure 2: The temporal evolution of the effects of injury on the brain envisages three overlapping and interrelated processes. Copied from (Reilly, 2001)

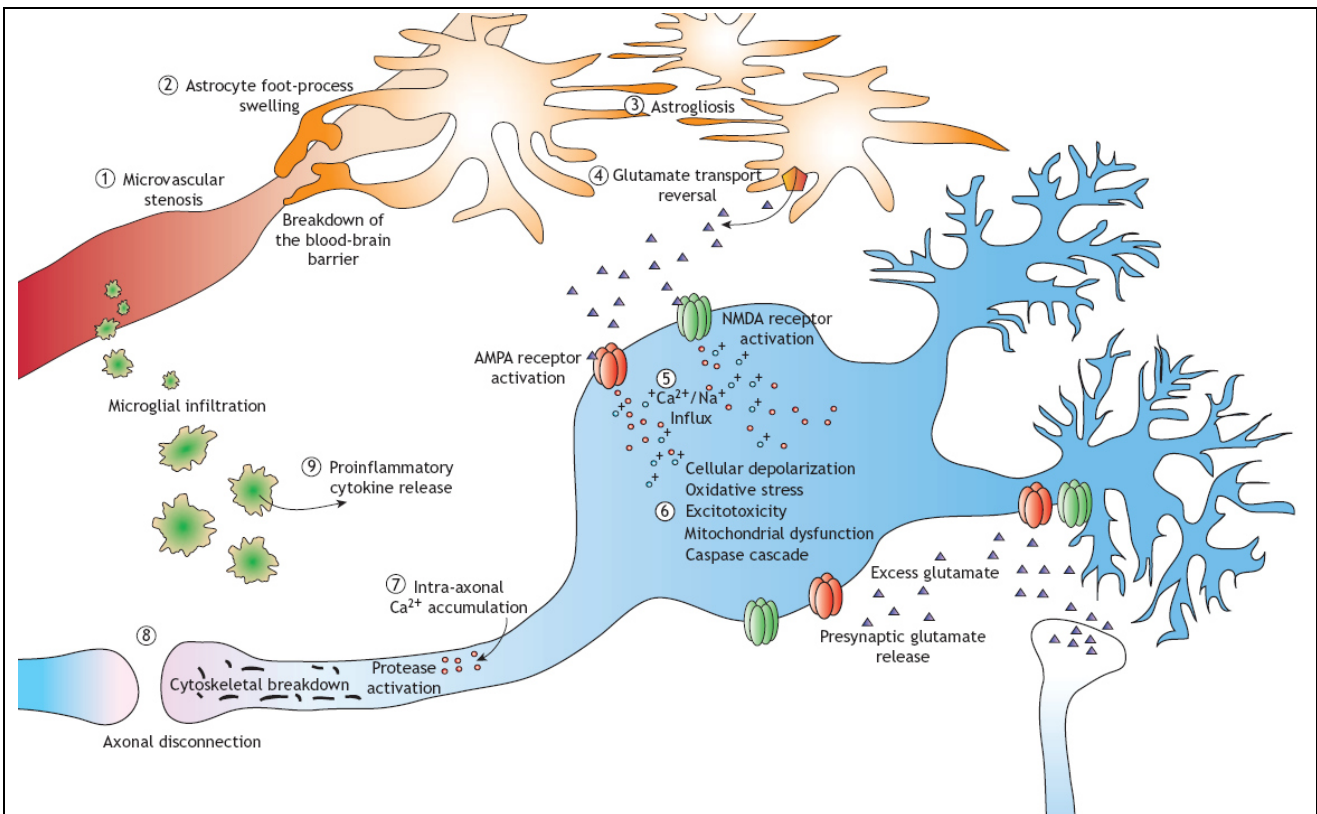


Figure 3: The major pathways associated with the progression of secondary injury after a brain injury. Microcirculatory derangements involve stenosis (1) and loss of microvasculature, and the blood–brain barrier may break down as a result of astrocyte foot processes swelling (2). Proliferation of astrocytes (“astrogliosis”) (3) is a characteristic of injuries to the central nervous system, and their dysfunction results in a reversal of glutamate uptake (4) and neuronal depolarization through excitotoxic mechanisms. In injuries to white and grey matter, calcium influx (5) is a key initiating event in a series of molecular cascades resulting in delayed cell death or dysfunction as well as delayed axonal disconnection. In neurons, calcium and zinc influx through channels in the AMPA and NMDA receptors results in excitotoxicity (6), generation of free radicals, mitochondrial dysfunction and postsynaptic receptor modifications. These mechanisms are not ubiquitous in the traumatized brain but are dependent on the subcellular routes of calcium influx and the degree of injury. Calcium influx into axons (7) initiates a series of protein degradation cascades that result in axonal disconnection (8). Inflammatory cells also mediate secondary injury, through the release of proinflammatory cytokines (9) that contribute to the activation of cell-death cascades or postsynaptic receptor modifications. Copied from (Park et al., 2008).

Table 6: Secondary injury events in timescale. Copied from (Margulies and Hicks, 2009)

Within minutes	Minutes–24h	24–72h
<p>Cell / axon stretching, compaction of neurofilaments, impaired axonal transport, axonal swelling, axonal disconnection</p> <p>Disruption of the blood brain barrier</p> <p>Excessive neuronal activity: Glutamate release</p> <p>Widespread changes in neurotransmitters: Catecholamines, serotonin, histamine, GABA, acetylcholine</p> <p>Haemorrhage (haeme, iron-mediated toxicity)</p> <p>Seizures</p> <p>Physiologic disturbances: Decreased cerebral blood flow, hypotension, hypoxemia, increased intracranial pressure, decreased cerebral perfusion pressure</p> <p>Increased free radical production</p> <p>Disruption of calcium homeostasis</p> <p>Mitochondrial disturbances</p>	<p>Oxidative damage: Increased reactive oxygen and nitrogen species (lipid peroxidation, protein oxidation, peroxynitrite), reduction in endogenous antioxidants (e.g., glutathione)</p> <p>Ischemia</p> <p>Oedema: Cytotoxic, vasogenic</p> <p>Enzymatic activation: kallikrein-kinins, calpains, caspases, endonucleases, metalloproteinases</p> <p>Decreased ATP: Changes in brain metabolism (altered glucose utilization and switch to alternative fuels), elevated lactate</p> <p>Cytoskeleton changes in cell somas and axons</p> <p>Widespread changes in gene expression: cell cycle, metabolism, inflammation, receptors, channels and transporters, signal transduction, cytoskeleton, membrane proteins, neuropeptides, growth factors, and proteins involved in transcription / translation</p> <p>Inflammation: Cytokines, chemokines, cell adhesion molecules, influx of leukocytes, activation of resident macrophages</p>	<p>Non-ischemic metabolic failure</p>
<p>Traumatic brain injury rapidly initiates a series of secondary events that collectively contribute to cell injury and / or repair. These secondary events often create long-term neurological consequences, including cognitive dysfunction. Based primarily upon rodent models of brain injury, these early events can generally be divided into three periods, beginning with those that arise within minutes after injury, to those that evolve over the first 24 h, and finally to events that may be more delayed in onset, appearing between 24 and 72h post-injury.</p> <p>Each of these periods reflects only an estimation of the onset of these pathogenic events, as details about their temporal profile and interactions are incompletely understood, but most extend for days post brain injury. Variability in onset and frequency, as well as the duration of these events, is governed in part by the type and magnitude of the injury.</p>		

Brain injury may be focal (e.g. traumatic or spontaneous haematoma, thromboembolic stroke), diffuse (e.g. rapid deceleration – diffuse axonal injury) or global (e.g. cardiac arrest). Regardless, a commonly used concept is that of a focus of dead / dying (unsalvageable) brain tissue, a surrounding penumbra of injured (but salvageable tissue) and beyond this, uninjured brain tissue. It is the secondary injury processes, that if unchecked, cause the central focus and penumbra to enlarge. It is the aim of the supportive care strategies to minimise this secondary injury.

The broad concepts of brain supportive care are simple and familiar; deliver enough, but not too much, oxygen and glucose, whilst removing enough, but not too much, carbon dioxide and other waste products, to the penumbra and remaining normal brain.

Secondary injury does not necessarily lead to functional loss and numerous neuroprotective interventions continue to be actively investigated (see **NEUROPROTECTIVE THERAPIES** section below). Regeneration of damaged brain tissue, once thought to be non-existent, is increasingly recognised as occurring and may be positively influenced by medical therapies.

Thus the aim of neuro critical care is to maximise recovery by providing a period of “best supportive care”. What has become clear, and indeed neuro critical care may be considered the pioneer in this respect, is that “best supportive care” for the brain, is a delicate balance between normalising whole body physiology and iatrogenic injury, in order to minimise the secondary injury that the brain is uniquely susceptible to.

There are of course both medical (e.g. thrombolysis for thromboembolic stroke) and neurosurgical (e.g. evacuation of haematoma, insertion of external ventricular drain and decompressive craniectomy) time critical, brain tissue / life saving interventions; but these are arguably just extensions of the best supportive care paradigm.

Normal cerebral perfusion

The brain enjoys an excess delivery of essential substrates, and as a consequence has a tolerance to global hypoxia / hypoglycaemia, as long that is, as cerebral perfusion is maintained. In addition, the cerebral circulation has many unique features (see Table 7) that, in effect, create a functional reserve.

Table 7: Unique features of the cerebral circulation (Kulik et al., 2008).

Element	Unique feature	Consequence
Arterial histology	CNS arteries lack vasa vasorum. Cerebral arteries have only a single elastic lamina.	They derive their nutrition from CSF, perhaps making them more resistant to the effects of hypotension and ischemia. May influence their response to alterations in luminal pressure.
Collateral arterial circulation	A redundancy of arterial supply.	Protects most areas of the brain from ischaemia following a single arterial failure, however so-called "watershed" territories of marginal co-lateral supply remain vulnerable.
Venous drainage	Pial veins do not travel with pial arteries. Pial veins do not significantly change in diameter with physiologic changes in blood flow.	
The blood-brain barrier. Detailed reviews (Wolburg et al., 2009, Engelhardt and Sorokin, 2009)	Cerebrovascular endothelium has tight junctions, limited transport by pinocytic vesicles and has 5–6 times more mitochondria	Limits the paracellular flux of hydrophilic molecules but allows small lipophilic molecules to diffuse freely across plasma membranes along their concentration gradient
Astrocytic influence on cerebral vessels	Integrate neuronal activity and link neuronal activity to the vascular network. Critical in the development and/or maintenance of blood-brain barrier characteristics	
Direct neural influence on cerebral blood flow	Both local neurons and autonomic neurons innervate cerebral blood vessels	Possible efferent limb of the rapid autoregulatory response

The cerebral circulation can be categorised based both on vessel size, into macro and micro circulations, and on location, specifically in relation to the parenchyma, into extrinsic and intrinsic components. Global cerebral blood flow (CBF) is dependant upon a high degree of both spatial and temporal complexity that remains incompletely understood (Panerai, 2009). In order to meet the demands of the brain (see previous sections), its circulation has evolved a complex, rapid response, local system of autoregulation, the purpose of which, is the maintenance of a near constant blood flow in the face of quite marked variations in cardiac output and systemic arterial blood pressure, see Figure 4 (Panerai, 2009). For example, normal CBF is maintained during intense exercise, however, exactly how cerebrovascular autoregulation is regulated under such physiological stresses remains incompletely understood (Ogoh and Ainslie, 2009). In addition, cerebrovascular autoregulation ensures blood flow increases to provide a greater supply of substrate to more metabolically active areas of the brain as cerebral metabolic activity is dependent on cerebral function (as exemplified by functional brain imaging studies (Peter, 2009)).

Stimuli that effect local CBF include systemic blood pressure (SBP), intracranial pressure (ICP), arterial and brain tissue partial pressures of oxygen and carbon dioxide, together with local metabolic demands / neuronal activity.

Nitric oxide is arguably the principal mediator in cerebrovascular autoregulation. The large volume of research into NO and cerebrovascular autoregulation is reviewed here (Toda et al., 2009).

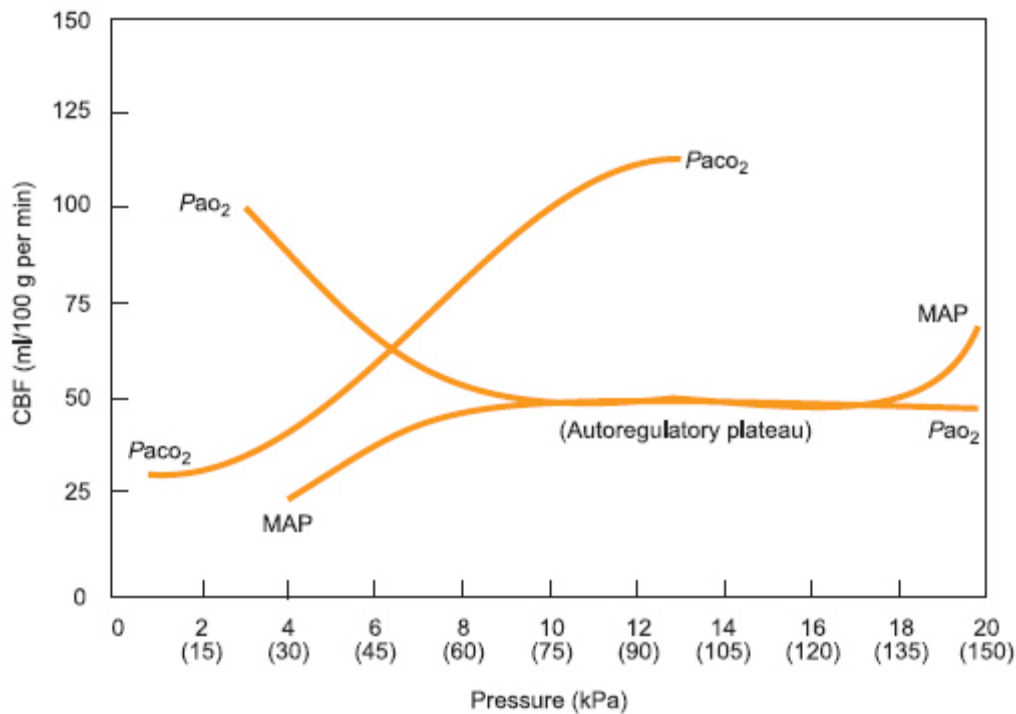


Figure 4: Cerebrovascular autoregulation - A schematic representation of the interrelationships between alterations in mean systemic arterial pressure and in the partial pressures of carbon dioxide (P_{aCO_2}) and oxygen (P_{aO_2}) and CBF. Values of pressure in parenthesis are in mmHg. A decrease in systemic arterial pressure causes dilatation of the pial vessels whilst increases in arterial pressure induce vasoconstriction of the pial vessels. This graph is, in a way, an abstraction. It relates mean systemic arterial (aortic) pressure to overall cerebral perfusion whereas the important pressure, as far as tissue perfusion is concerned, is the pressure gradient across the vasculature, the cerebral perfusion pressure (CPP) (mean systemic arterial pressure minus mean cerebral venous pressure *or* mean intracranial pressure, whichever is the greater). However, under physiological conditions, the differences between mean arterial pressure and CPP hardly matter because both intracranial pressure and cerebral venous pressure are low, and systemic arterial pressure becomes the principal determinant of CPP. However, in the presence of space-occupying pathology, intracranial pressure becomes a significant component and the determination of CPP is essential, in order to determine physiological targets of supportive care, in particular, MAP. Autoregulation has limits, above, and below which, CBF relates directly to perfusion pressure. The limits per se are not static but vary dynamically, being modulated by activity in the autonomic nervous system, by the vessel wall rennin-angiotensin system, by those factors which affect the tone in the walls of the cerebral blood vessels (P_{aCO_2} ; vasoactive agents) and by morphological changes in the vessel walls themselves. However, whatever the absolute value, it is reasonable to assume that below the lower limit, CBF will decrease linearly as perfusion pressure decreases until ischaemic thresholds are reached. However, it is important to note that the lower limit of autoregulation is that arterial pressure at which flow begins to decrease: it has no significance of itself as an indicator of cerebral ischaemia. At the other end of the pressure-flow plateau, high perfusion pressure leads to a forced dilatation of the cerebral arterioles, disruption of the blood-brain barrier, reversal of hydrostatic gradients and the formation of cerebral oedema. Copied from (Fitch, 1999)

Cerebral blood flow following brain injury

Brain injury may result in absent, impaired or excessive cerebral blood flow (CBF) and depending upon the injury, these may co-exist in different brain areas and / or occur sequentially over time.

Ideally, supportive therapies following brain injury would maintain CBF above an ischaemic threshold to all areas of the brain. To do this would require both accurate, regional, continuous, bedside monitors of CBF and therapies that can influence

Cerebrovascular autoregulatory failure

Perhaps unsurprisingly, cerebrovascular autoregulation is often an early casualty of brain injury and its failure results in conflicting supportive care targets. In response to a falling CPP, the local autoregulatory mechanisms that maintain CBF fail, resulting in ischaemia. Thus, supportive care aims to maintain CPP by influencing the MAP and where possible the ICP and CVP. However, if systemic arterial pressure is too high it may promote local haemorrhage and a high intracerebral blood volume. As discussed in the previous section ([link to **An overview of brain anatomy, physiology and pathophysiology**](#)), as the brain is encased in a rigid box, it has a very limited capacity to adapt to effective reductions in the available volume, hence, even relatively small increases in blood volume or haematoma can have detrimental effects on CPP. In short, following brain injury, there is an optimal CPP above and below which ischaemia occurs. One way to determine this optimal CPP is to continuously monitor cerebral autoregulation. The most reliable methods require continuous measurements of CBF, most easily achieved using transcranial Doppler (Czosnyka et al., 2009). However, such techniques are impractical outside the research arena. The most reliable alternative, is to continuously monitor the dynamic response of ICP to minor fluctuations in MAP, most commonly associated with the respiratory cycle (Czosnyka et al., 2009). From such monitoring, the pressure reactivity index can be continuously calculated and displayed permitting MAP and ICP therapies to be titrated {Jaeger, #2846}.

Vasogenic and cytotoxic cerebral oedema

The second circulatory consideration following injury is the normally tight blood-brain barrier, which serves to isolate the brain's unique extracellular milieu from plasma and limits the diffusion of free water (Hawkins and Davis, 2005). Brain injury causes this to fail and results in local (so-called vasogenic) oedema as well as exposure to undesirable circulating molecules, inflammatory cells and potentially, pathogens. Brain oedema has a second and arguably more important second component, so-called cytotoxic oedema. Cellular injury, in particular ischaemia results in energetic failure, which in turn results in intracellular ionic homeostasis failure and a net influx of ions and solutes, especially sodium. Water passively follows, resulting in swelling of the cell. This process increases the diffusion gradient from the intravascular space to the extracellular space to the intracellular space but requires endothelial injury / failure to permit molecular transit. The complex process is reviewed here (Kahle et al., 2009). A crucial early player in these events is the NKCC1, cation-chloride co-transporter. This transporter is inhibited by low doses of bumetanide, the therapeutic role of which is currently under investigation. Of equal importance, cerebral oedema results in the upregulation of the NCCa-ATP channel, which passively opens permitting the intracellular influx of water and solute. Inhibition of this channel can be achieved with low doses of glibenclamide. These recent insights into the cellular pathophysiological processes that result in cerebral oedema raise the prospect of specifically targeted combination therapy (Simard et al.), in addition to the more global medical and surgical therapies discussed below.

Brain oedema, not only creates detrimental local pressure effects, it also increases the bi-directional diffusion distance of essential molecules, be they local transmitters, fuels or toxic waste products. Thus therapeutic strategies have been devised that aim to minimise oedema formation and rescue therapies to reduce the volume.

Intracranial hypertension

As a result of the rigid box (skull) and the fact that all brain injuries result in an increase in undesirable intracranial contents, for which there is limited compensatory mechanisms, a central tenant of cerebral perfusion monitoring is the continuous measurement of ICP.

Raised ICP, or intracranial hyper tension

To further exacerbate the demadthe situation with deficient or excessive (toxic) global delivery; add the increased metabolic demands of pyrexia; and “best supportive care” to a non-uniformly injured brain becomes a complex challenge of conflicting targets. All this, in the potential scenario of say a victim of polytrauma with multiple other competing and conflicting demands and you are faced with trying to do the least harm. Thus many supportive care recommendations boil down to targeting physiological values at one end of the normal spectrum.

As CBF, both global and regional, is difficult to

Clinical practice

The initial assessment of the extent and severity of brain injury is assessed by clinical neurological examination, in particular the Glasgow Coma Score (GCS). In acute pathologies, any loss of consciousness, diminished conscious level, generalised seizure or focal neurological deficit is a clear indication for urgent structural brain imaging. Due to its speed of acquisition and wide availability computerised tomography (CT) is the method of choice. Although very sensitive to acute haemorrhage and mass effects, this technique has limitations in detecting acute ischaemia, axonal and dendritic injury. CT does not clearly differentiate normal, injured and dead brain tissue.

Pathophysiology of ischaemia reperfusion - bioenergetics (Hertz, 2008, Sims and Muyderman, 2010)
Oedema and swelling (Elkin et al., 2010, Kahle et al., 2009) – steroids / sodium / mannitol / hypertonic solutions

Vasospasm?

Diffuse (Diff ax inj vs cardia arrest) vs. focal injury (haemorrhage / haemotoma / contusion / stroke)

ICP CPP measurement and targets {Smith, 2008 #2200}

Zero drift problems with trnasducers {Al-Tamimi, 2009 #3093}

ICP plateau waves (Castellani et al., 2009) probably not important

concept of “dose” of intracranial hypertension {Vik, 2008 #2231}.

Patterns - bimodal and late rises {O'Phelan, 2009 #2220}

Gr:Gc ratio ? {Roustan, 2009 #3092}

Medical therapies osmotic - mannitol vs hypertonic saline vs hypertonic sodium lactate
sedation

mild hypothermia

Increase MAP using inoconstrictors to maintain a CPP in the face of an

elevated or rising ICP

alternative oedema minimisation therapy - Lund concept - maintain

normovolaemia, normal haematocrit (using pRBC Tx), normal plasma oncotic pressure (using hypertonic 20-25% albumin) and if possible use β_1 -antagonist and α_2 -agonist therapy +/- ARBs see {Grände, 2006 #2803}

surgical therapies - external ventricular drains / evacuation of haematomas / decompressive craniectomy

Neurogenic stunned myocardium

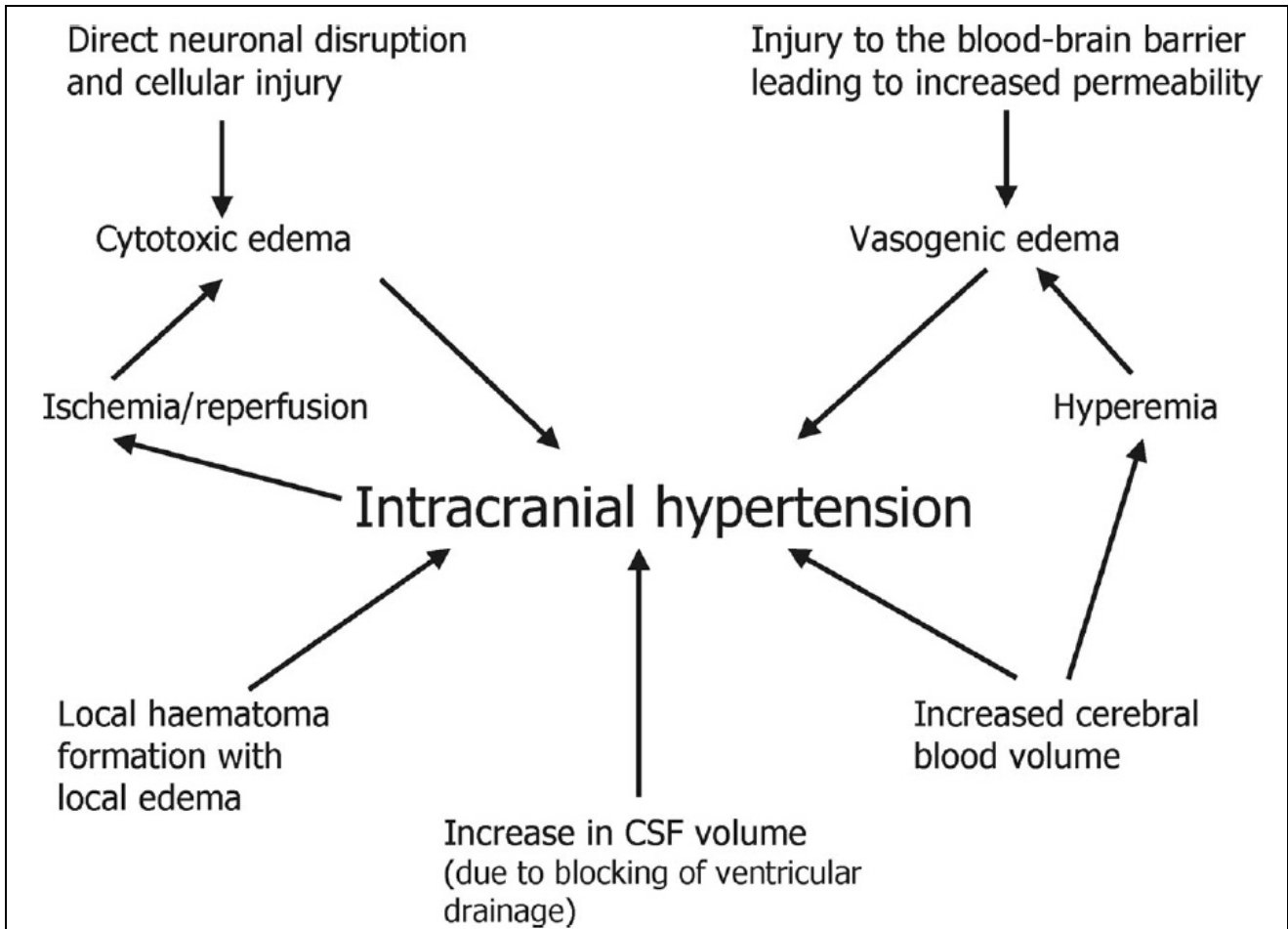
Pathophysiology {Nguyen, 2009 #3091; Nef, 2010 #3089}

treatment

hyperinsulinaemic euglycaemia ? {Vanderschuren, 2009 #3082}
levosimendan {Busani, #3087}

MANAGEMENT OF RAISED ICP – starting ref (Kumar et al., 2009)

- Intracranial pressure & cerebral perfusion pressure – physiology, targets and medical management
- Cerebral blood flow (Botteri et al., 2008)
- External ventricular drains
- Decompressive craniectomy

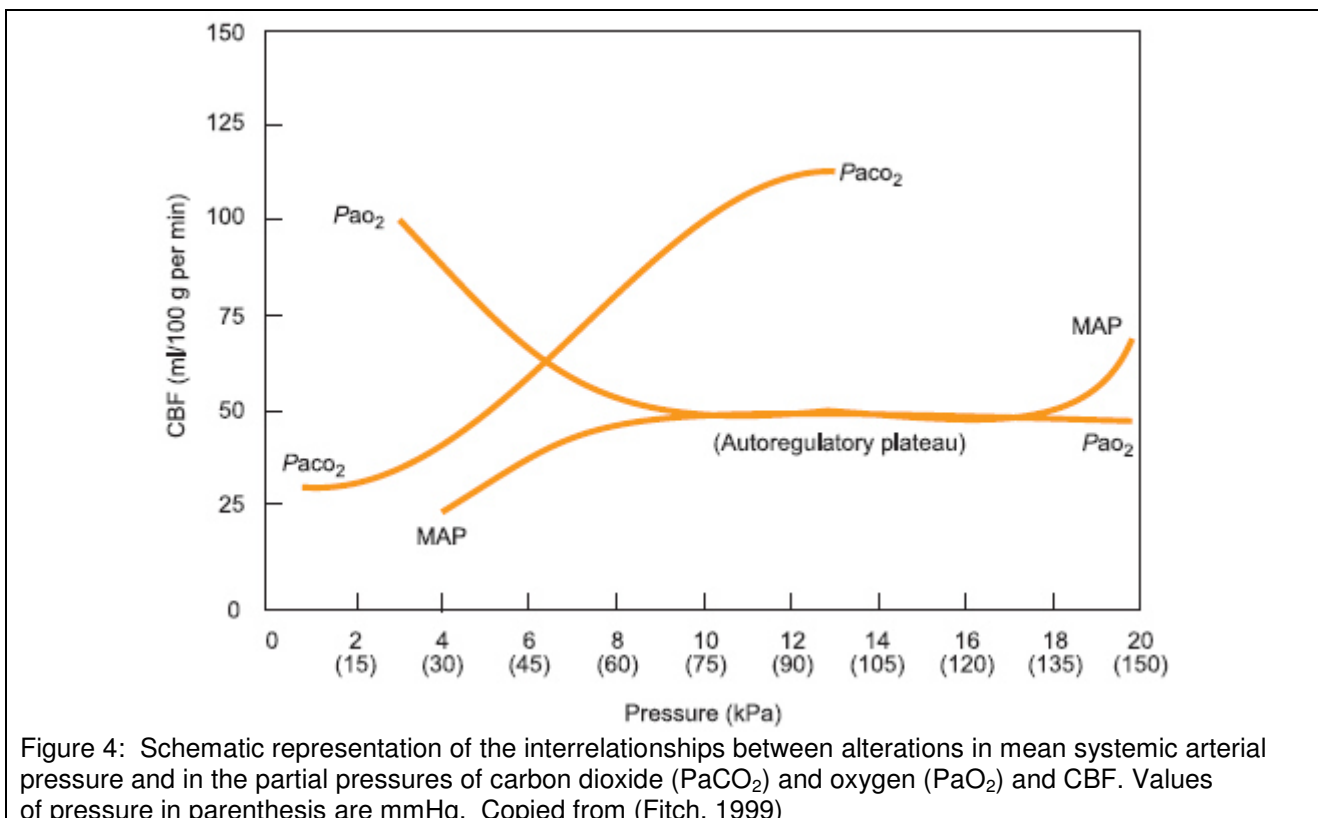


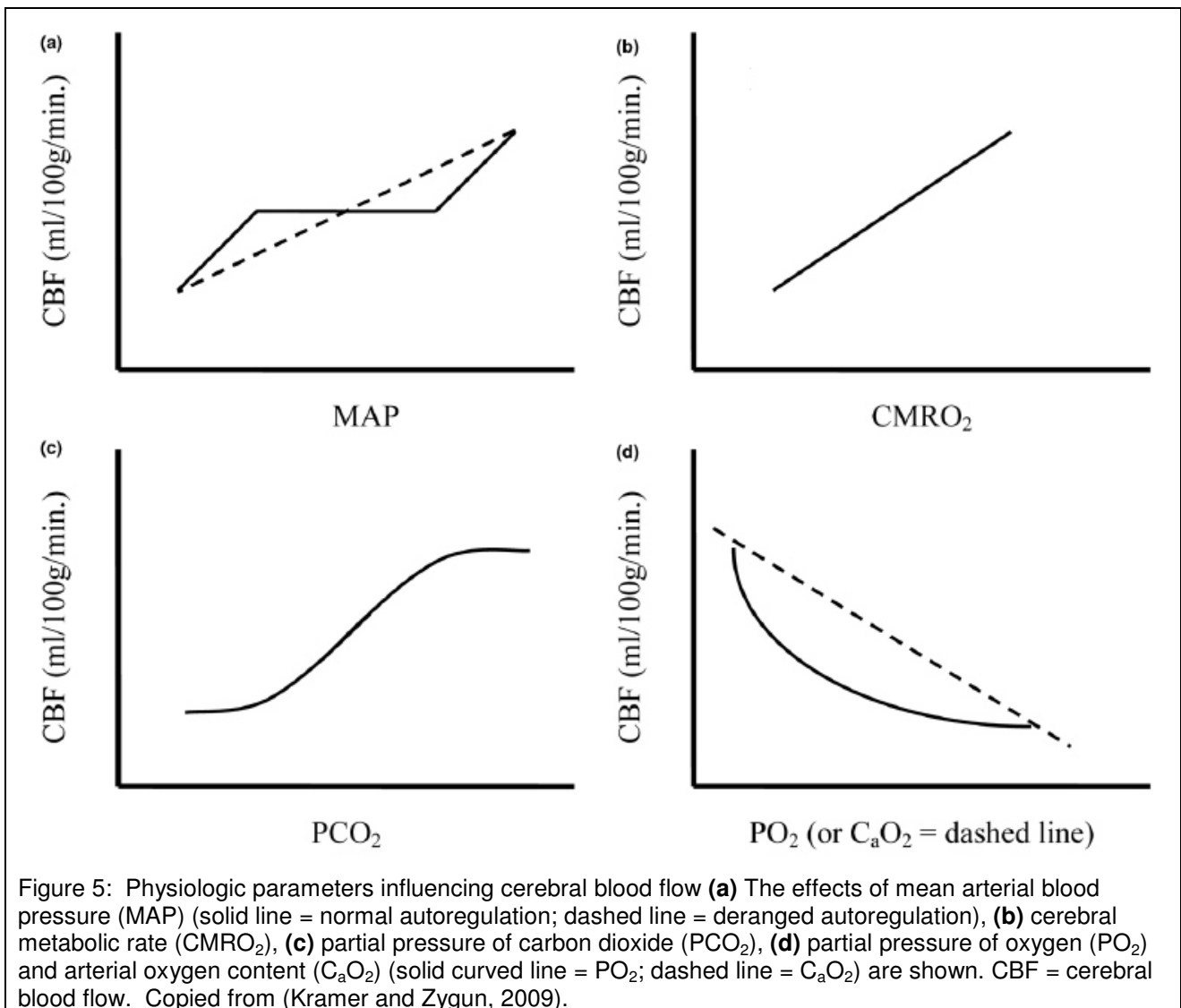
Schematic depiction of the potential role of intracranial pressure as both a marker of ongoing brain injury and a potential cause of additional injury, and of the factors that may contribute to a rise in intracranial pressure. CSF, cerebrospinal fluid. Copied from (Polderman, 2009).

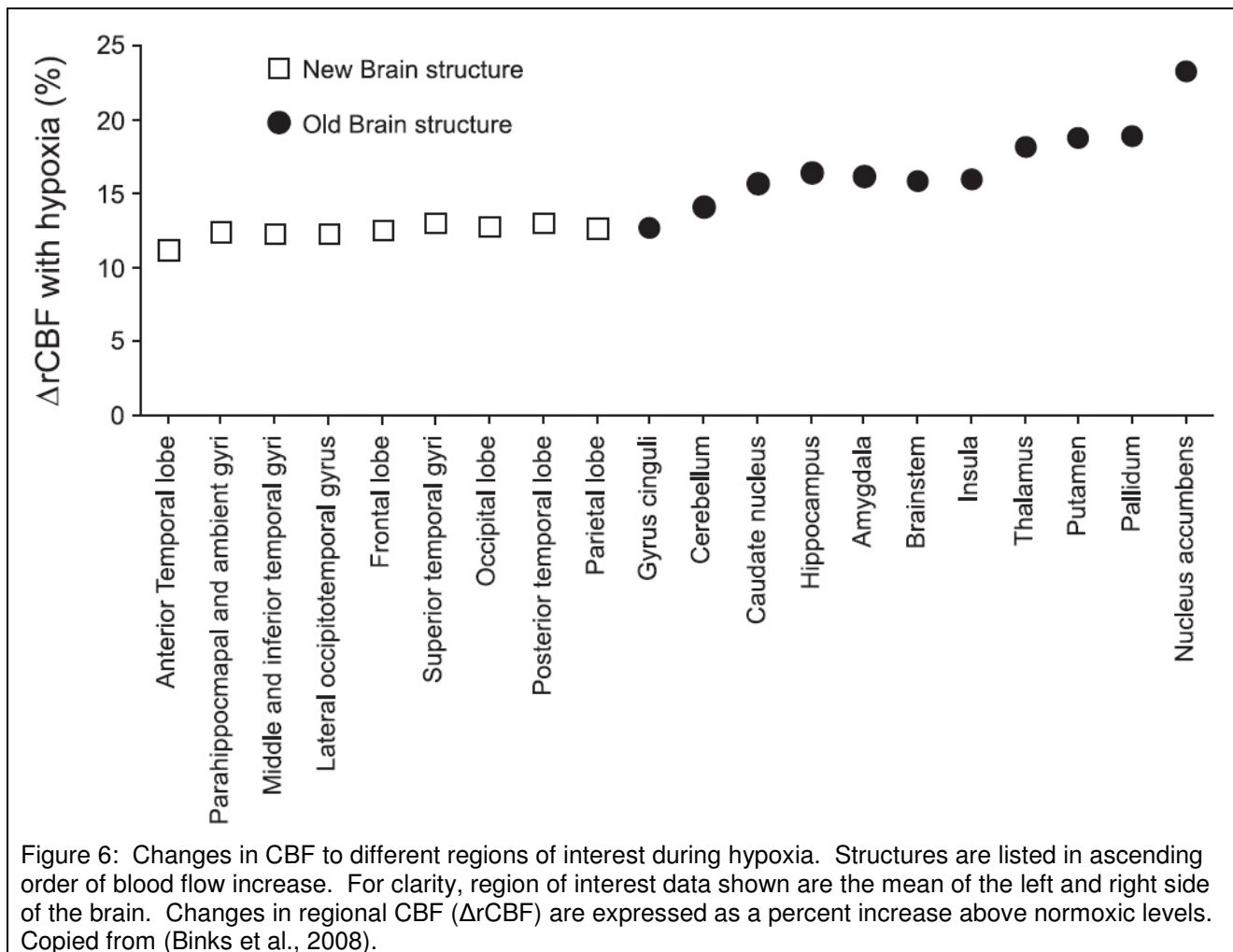
- Hyperperfusion syndrome after carotid revascularization (Moulakakis et al., 2009)
- Cardiac arrest (Schneider et al., 2009)

Oxygen delivery and utilisation

The brain is tolerant to mild levels of hypoxia as long as CBF is maintained. Local autoregulation of CBF is comparatively insensitive to changes in PaO_2 within the normal physiological range, see Figures 4 and 5. Increases in PaO_2 cause very modest decreases in flow: the administration of 100% oxygen will decrease flow by approximately 10%. Similarly, decreases in PaO_2 have little effect on CBF until values of less than 6.8 kPa have been achieved. There is however, significant regional variation, see Figure 6. As noted previously, under physiological conditions, the cerebral oxygen extraction is relatively low (25-30%) and the relationship between CBF and PaO_2 may relate merely to the fact that flow does not increase until the oxygen extraction has been maximized. On the other hand, it may be that flow is more closely allied to arterial oxygen content (CaO_2 which = oxygen carried by haemoglobin + dissolved oxygen) than to PaO_2 . Certainly, the sigmoid shape of the oxygen dissociation curve ensures that CaO_2 is maintained at near-physiological values until a PaO_2 of approximately 6.8kPa. The coincidence of this value with the threshold PaO_2 noted above supports the view that CaO_2 is the principal determinant of CBF during hypoxia, as does the demonstration that the total delivery of oxygen to the brain ($\text{CBF} \times \text{CaO}_2$) is maintained at normal values during normocapnic hypoxia. CaO_2 is essentially determined by the amount of oxygen bound to haemoglobin given that so little oxygen is dissolved in plasma. Numerous studies have sought to unravel the relationships between CBF, haemoglobin concentration and blood viscosity. These have shown that polycythaemia is associated with a decrease in CBF and that CBF is increased in anaemia. However, the balanced view would support the conclusion that CaO_2 , and not the accompanying changes in blood viscosity, is the principal determinant of CBF (Fitch, 1999).







Hypoxia

The effects of acute hypoxia on the higher functions of the brain have been extensively investigated. Models studied include hypobaric hypoxia (Wilson et al., 2009), carbon monoxide poisoning (Prockop and Chichkova, 2007) and sleep disordered breathing (Brzecka, 2007). The severity of the effects is dependant upon both the degree, the rapidity and the duration of the hypoxia. The interdependence between PaO_2 , $PaCO_2$, CBF and brain tissue oxygenation ($PbtO_2$) has also been investigated (van Dorp et al., 2007). These studies confirm that the combination of mild hypoxia, hypocapnia and reduced CBF are highly neurotoxic but mild hypoxia with normo or even hypercapnia and normal / increased CBF is well tolerated. Data from altitude and aviation studies suggest that although acute hypoxia (usually in concert with hypocapnia) affects higher cognitive functions, it isn't usually associated with permanent neuronal injury. The brain's ability to completely adapt to chronic hypoxia is well established both from altitude studies and investigations into the cognitive function of patients with hypoxic cardiorespiratory diseases. The earliest pathophysiological changes associated with acute hypoxia appears to be cerebral venous hypertension and oedema (Dubowitz et al., 2009, Wilson et al., 2009).

$PbtO_2$ in clinical practice

Routine continuous monitoring of $PbtO_2$ is now feasible using electrodes placed within regions of interest within brain parenchyma. (Barazangi and Hemphill lli, 2008). Continuous non-invasive monitoring using reflectance near-infrared spectroscopy remains confined to the research arena (Murkin and Arango, 2009). There is no universally agreed definition of brain tissue hypoxia: Definitions range from a $PbtO_2 < 10$ to < 25 mmHg for > 15 -30 minutes. Regardless, the incidence is common following brain injury and unsurprisingly, increases with the severity of injury. Peak incidence occurs ~5 days post injury (Adamides et al., 2009). Higher cumulative incidences of brain tissue hypoxia are associated with a worse outcome (Maloney-Wilensky et al., 2009). Brain tissue hypoxia occurs in the context of the current therapeutic target ranges for ICP, CPP and MAP, and has no clear association with FiO_2 , [Hb] or $PaCO_2$ (Chang et al., 2009, Radolovich et al., 2009). Two cohort studies have investigated a goal directed therapy algorithm targeting a $PbtO_2 > 20$ mmHg by manipulation of ICP, CPP, MAP, CaO_2 , $PaCO_2$ etc (Narotam et al., 2009, Adamides et al., 2009). Both studies demonstrated the ability to increase $PbtO_2$ but the effect on outcome is unclear. A large retrospective cohort analysis of $PbtO_2$ guided therapy in another centre failed to demonstrate any

outcome benefit from utilisation of this technique (Martini et al., 2009). The enthusiasts claim that such algorithms should become the standard of care as they allow individualisation of physiological targets. In addition, failure to respond is associated with a higher degree of prognostic certainty than ICP / CPP monitoring. As with all highly localised brain monitoring the number and positioning of PbtO₂ probes is problematic. Until techniques exist that provide regional (with whole brain coverage), continuous, bedside monitoring that directs global therapies to protect the maximum brain volume, PbtO₂ guided therapy will remain controversial at best, especially if multiple areas of the brain are injured.

Hyperoxia

Increasing the fraction of inspired O₂ is often one of the first therapeutic responses to acute or sudden illness, especially in an ICU setting. However, as with many substances, too much O₂ has the potential to be a lethal cellular toxin. In humans, CNS oxygen toxicity occurs only following exposure to hyperbaric conditions and manifests itself as self limiting generalised seizures, which in themselves, do not cause permanent neuronal injury (Bitterman, 2004). Of interest, the toxic dose threshold appears to be increased by repetitive subtoxic exposure to hyperbaric hyperoxia suggesting an inducible adaptive response. The fact that land mammals should have such a response suggests that we must have evolved from sea dwelling creatures.

There is data to suggest that normobaric hyperoxia has significant physiological effects on normal brain tissue (Hinkelbein et al., 2010) the significance of which is unknown. In the injured brain, the clinical significance of these effects remains inconclusive but limited data suggests that they maybe beneficial (Kumaria and Talias, 2009).

Hyperbaric O₂ therapy is neither widely available nor easily performed on critically ill patients. However, it has been the subject of limited clinical trials and appears to achieve both physiological (Matchett et al., 2009) and apparent functional outcome benefits (Rockswold et al., 2009). Inevitably, there remain sceptics (Diringer, 2008). The advocates (Bullock, 2009) claim that newer, smaller, cheaper chambers are both safe and can easily be integrated into the ICU environment.

For hyperoxia therapy to be effective it must be started within minutes to hours of injury and continued until the risk of hypoxic injury has past. The potential detrimental effects, principally pulmonary toxicity, remain controversial (Gillbe et al., 1980, Carvalho et al., 1998, Altemeier and Sinclair, 2007).

Target PaO₂

In summary, with regard to oxygen, hypoxia of sufficient degree, rapidity of onset and duration is lethal to neurones. Brain injury impairs the diffusion of oxygen from the circulation to brain tissue. Hyperoxia, may overcome these impediments to oxygen diffusion in injury penumbra and thereby prevent this secondary injury, but only if given early enough, at sufficient dose and continued until the risk of injury has past. Pragmatically, maintaining arterial oxygen tensions within at least the normal range, whilst minimising mechanical (and oxygen induced?) lung injury is the standard of care.

Oxygen carrying capacity - Anaemia

Since CaO₂ not PaO₂ is a critical determinant of CBF, and CaO₂ is principally determined by haemoglobin concentration ([Hb]), the effects of anaemia and packed red blood cell transfusion (pRBC Tx) on CBF and PbtO₂ are of great interest. It is worth repeating that pRBC Tx not only increases [Hb], it also increases blood viscosity (link to Module 2 / CARDIOVASCULAR FAILURE: FLUID THERAPIES, PHARMACOLOGICAL AND MECHANICAL SUPPORT / PRBC Tx). However, pRBC Tx does not achieve physiological normalisation of either O₂ carriage nor blood rheology.

Anaemia is very common in critically ill patients and is associated with a worse outcome following acute brain injury (multiple aetiologies) (Kramer and Zygun, 2009). The physiological response of the brain to anaemia is reviewed here (Hare et al., 2008) – the significance of which in the management of brain injured patients remains uncertain. Numerous studies also associate pRBC Tx with a worse outcome following brain injury (Kramer and Zygun, 2009). In short, anaemia is a problem but pRBC Tx doesn't appear to be the solution. What does appear to be emerging, is that pRBC Tx increases PbtO₂ but doesn't increase O₂ utilisation and is therefore of questionable benefit and possibly a source of secondary brain injury (Zygun et al., 2009). Thus, in brain injured patients (as in all other critically ill patients) a transfusion trigger of [Hb] 7.0g/dL appears to be reasonable.

Oxygen utilisation & metabolic brain monitoring

In order to assess the extent of brain injury and the response to resuscitation / supportive care, both hemispheric / global - reverse jugular venous bulb oximetry (SjvO₂) (White and Baker, 2002) - and focal - microdialysis (Nordström, 2010) - measures of oxygen utilisation and metabolic normality are possible.

Adding these technologies to ICP and PbtO₂ monitoring may in the future facilitate best supportive care (Low et al., 2009). However, investigational neuroimaging technologies, such as functional magnetic resonance imaging (fMRI), combined MRI and positron emission tomography (PET), magnetic resonance spectroscopy (MRS) and voxel-based morphometry clearly demonstrate both the heterogeneity and dynamic fluctuations of regional brain oxygenation and metabolic activity following both diffuse and apparently focal brain injury. As many patients present with either diffuse or multiple foci of injury, deciding where to place your monitor, whether to use more than one, and what to target with which priority becomes difficult. For example, using hemispheric monitoring, such as SjvO₂, forces the question, do you target the more or less injured side, or insert bilateral catheters and look to simultaneously optimise the values and minimise the difference? Similarly, if placing PbtO₂ or microdialysis probes, do you insert them into the penumbra or adjacent normal brain. Is one probe enough and are you targeting the most vulnerable region? Are such monitors merely prognostic or can they be used to guide therapy? Is a failure to improve the monitored variables by manipulation of ICP / CPP, CaO₂ and PaCO₂ going to accurately predict functional outcome, and if so permit earlier discussions about the futility of continuing best supportive care? In short, advances in technology are yet to be matched by advances in clinical care.

Normocapnia

Changes in the partial pressure of carbon dioxide in arterial blood (PaCO_2) have a potent effect on the cerebral vasculature, largely because carbon dioxide can diffuse rapidly across the blood-brain barrier and alter the hydrogen ion concentration of the cerebral extracellular fluid. Indeed, the responsiveness of the cerebral circulation to changes in PaCO_2 is so predictable that the degree of reactivity to carbon dioxide has been used to validate other techniques by which the cerebral circulation may be assessed. Similarly, in association with intracranial pathology, focal or global changes in the responsiveness to carbon dioxide may be indicative of the level of physiological failure and have been shown to be predictive of outcome in patients with traumatic brain damage (Schalen et al., 1991).

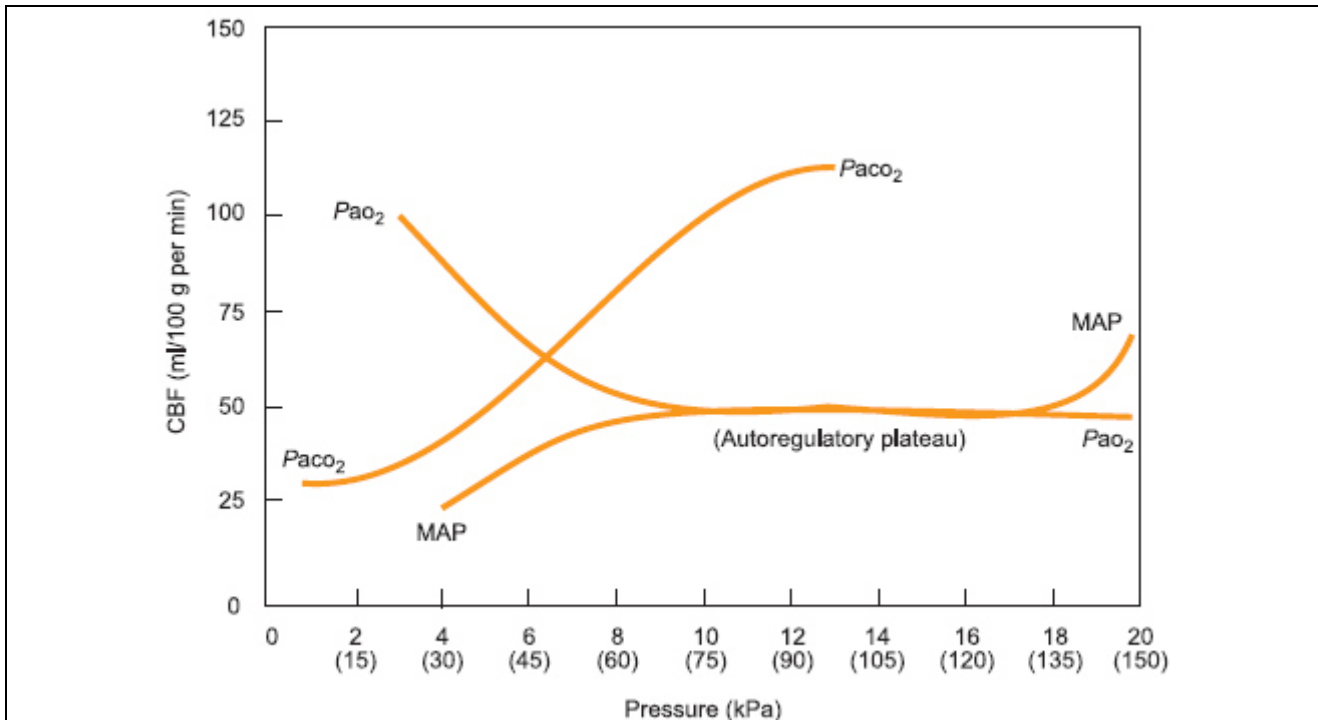


Figure 4: Schematic representation of the interrelationships between alterations in mean systemic arterial pressure and in the partial pressures of carbon dioxide (PaCO_2) and oxygen (PaO_2) and CBF. Values of pressure in parenthesis are in mmHg. Any increase in PaCO_2 will increase flow while, conversely, a decrease in PaCO_2 will increase cerebrovascular resistance. At physiological values of systemic arterial pressure the relationship between PaCO_2 and CBF is essentially linear (over the PaCO_2 range 3-10 kPa). An increase in PaCO_2 from its physiological value to approximately 10.6 kPa will more than double flow whereas decreasing the PaCO_2 to 2.7 kPa will decrease flow by approximately 50%. In essence, CBF changes by around 25% for each kilopascal change in PaCO_2 (3% for each mmHg change in PaCO_2). At more extreme values of PaCO_2 , the change in CBF per unit change in PaCO_2 decreases owing, no doubt, to the inability of the cerebral vasculature to dilate, or constrict, further. The duration of any change in CBF is finite (half-life ~6 hours), even if the change in PaCO_2 is maintained, as more slowly evolving changes in CSF bicarbonate concentration influence the PaCO_2 induced changes in CSF hydrogen ion concentration. Copied from (Fitch, 1999)

Therapeutic targets for PaCO_2 (Curley et al.)

PaCO_2 levels acutely affect CBF and cerebral blood volume. Although reducing PaCO_2 will reduce cerebral blood volume, this is at the expense of CBF, O_2 delivery and potentially cause direct neuronal injury. Furthermore, any beneficial effects on ICP / CPP will be short lived (hours) as the buffering in CSF compensates for the relative hypocapnia. Thus the only role for therapeutic hypocapnia is as an acute rescue therapy for ICP / CPP crises, and probably only as a temporising measure whilst other therapies are instigated. Accordingly, most guidelines advocate strict normocapnia. Some clinicians favour the lower end of this range but this is arguably a poor choice as it gives less room for manoeuvre if an acute reduction in ICP is needed, especially if the patient has any form of lung injury to which the institution of hyperventilation may cause further injury.

Given the necessity to tightly control PaCO_2 following brain injury, the use of continuous monitoring with either end tidal (ETCO_2) or transcutaneous CO_2 (TcCO_2) monitors is desirable. It is essential however to establish and monitor the $\text{PaCO}_2 - \text{ETCO}_2$ (or TcCO_2) difference (Lee et al., 2009).

Dysglycaemia

The brain is predominantly made up of 2 types of cells, neurones and glia. Although often quoted, glucose is not the only metabolic fuel used by the brain. Lactate, acetate and glutamate, in addition to glucose, all appear to act as fuels and appear to be trafficked between neurones and glia cells (Gallagher et al., 2009). Exactly how brain injury alters this complex metabolism is unknown. However lactate is emerging as potentially the preferred neuronal fuel in this setting.

In normal, healthy subjects, blood glucose concentration and extracellular brain glucose concentration appear to have a linear relationship. However, this relationship becomes more complex and essentially unpredictable following brain injury as a number of adaptive responses occur (Zahed and Gupta, 2009), although whether these responses are beneficial or detrimental is unclear.

Simultaneously, brain injury is associated with stress dysglycaemia (Van Cromphaut et al., 2008). This phenomenon, frequently misnamed stress hyperglycaemia, is associated with an initial hyperglycaemic phase, which may be followed by a spontaneous hypoglycaemic phase. When the latter does occur, it is associated with the severity of insult and a poor outcome. Like most physiological responses to injury, the initial hyperglycaemia can be reasonably assumed to be beneficial. However, if an as yet undefined threshold level is crossed and / or the duration prolonged beyond an as yet undefined period, then detrimental effects become evident in most, if not all, organs. Such effects, principally metabolic and pro-inflammatory, are associated with increased complications and worse outcomes in all acute illnesses. As a result, there has been and continues to be a search for the optimal blood glucose level to target following brain injury, as both hypo and hyperglycaemia can cause secondary brain injury.

Observational studies have found that early dysglycaemia is associated with worse outcomes following TBI (Liu-DeRyke et al., 2009) and SAH (Hanafy et al., 2010). Other studies have refined these observations to suggest that episodic hyperglycaemia (but not hypoglycaemia) is associated with worse outcomes following brain injury (Griesdale et al., 2009, Bilotta et al., 2008, Coester et al., 2009). In addition, the greater the range and frequency of glycaemic variability the worse the outcome (Jacka et al., 2009) suggesting that dysglycaemia is a marker of severity of illness as well as a pathological factor (hyperglycaemia at least).

The mechanisms believed to be responsible for hyperglycaemic secondary brain injury are reviewed here (Bémeur et al., 2007, Tsuruta et al.).

As with hyperglycaemia, the threshold level below which hypoglycaemia becomes injurious, to either the normal or injured brain, has not been clearly defined (Van Cromphaut et al., 2008). This situation is exacerbated by the fact that near patient testing devices are only accurate to within 20% and tend to overestimate both plasma and whole blood glucose at levels below the normal range (Moghissi et al., 2009). In short, although not widely appreciated, accurate monitoring remains a significant barrier to diagnosing hypoglycaemia and guiding optimal glycaemic control. As mentioned above, hypoglycaemia can occur spontaneously following injury / insult but whether this causes further injury or is merely an epiphenomenon is unclear. Insulin therapy for hyperglycaemia unequivocally increases the incidence of hypoglycaemia but given the doubts regarding both measurement and toxicity, the importance of such events remains controversial (Van Cromphaut et al., 2008). It is also not widely appreciated that rapid correction of hypoglycaemia induces an injury akin to ischaemia reperfusion (Van Cromphaut et al., 2008).

Following the landmark study of tight glycaemic control (TGC), which was performed in a group of predominantly cardiac surgical ICU patients (Van den Berghe et al., 2001), a large number of similar trials in both selected and unselected groups have been undertaken. Despite this unprecedented degree of investigation, many issues remain unresolved (Jan and Greet Van den, 2010). A small number of trials of TGC have been undertaken in patients with severe TBI (Yang et al., 2009, Coester et al., 2009, Bilotta et al., 2008). In all 3 trials, there was a high incidence of hypoglycaemic episodes in treatment groups. However, there was no mortality difference and a trend towards a reduction in nosocomial infection and better Glasgow outcome scores in the treatment group in all 3 studies.

All of the trials of TGC are confounded by many unresolved issues (Jan and Greet Van den, 2010). Firstly, the amount and composition of nutritional therapy co-administered may induce other relevant metabolic effects such as elevated triglyceride levels (Mesotten et al., 2004). The second and related confounder is that insulin has myriad other potentially beneficial effects in critical illness, a state that can in part be defined by acute insulin resistance. Such effects include anti-inflammatory, anti-apoptotic and anabolic (Johan Groeneveld et al., 2002, Van Cromphaut et al., 2008). Accordingly, it may be that insulin therapy has beneficial effects in addition to maintaining a "normal" range of blood glucose for the patient's condition. For a more detailed consideration of this issue see (Weekers et al., 2003, Vanhorebeek et al., 2009). The problem remains defining the optimal glycaemic range.

In summary, hyperglycaemia is both a marker of the severity of brain injury and a significant, but modifiable contributor to secondary brain injury. The secondary brain injury attributable to iatrogenic hypoglycaemia, due to exogenous insulin administration, is unknown but appears to be small, although the degree and the duration are no doubt important determining factors. Two recent studies suggest that targeting a blood glucose of 6-8mmol/l may be the optimal strategy to minimise dysglycaemic secondary brain injury (Holbein et al., 2009, Meierhans et al., 2010).

The controversy of dyshthermia

In healthy humans, a very narrow range of thermal homeostasis is maintained. This is an active process with both core and peripheral sensors and effectors, principally co-ordinated by the hypothalamus. Hyperthermia, fever and pyrexia all have precise definitions but are frequently, and inaccurately, used interchangeably. In response to infection, inflammation and injury there is often a physiological response, which results in local or systemic temperature elevation. This has beneficial effects for the individual by enhancing the inflammatory-immune response.

Research in this area has in part been hampered by the poor accuracy of some methods of core temperature monitoring (Hooper and Andrews, 2006). Physiologically, and possibly clinically, significant core-brain temperature differences following brain injury are a common finding (Childs, 2008). The accuracy of direct brain temperature measurements, which are a relatively new clinical technology, appears to be reliable (Childs and Machin, 2009). To complicate matters further there is a significant temperature gradient between the central brain structures and the brain surface. Following brain injury, the brain may be up to 2°C higher than core temperature (Sahuquillo and Vilalta, 2007).

There is a widely held belief that any increase in brain temperature, post injury, increases the risk of secondary injury. The rationale goes that in any brain tissue with impaired perfusion, an increase in temperature will increase the oxygen consumption, metabolic rate and excitatory stimuli, thereby increasing the supply demand imbalance and inducing further injury. A recent meta analysis reports that the association between "fever" and worse clinical outcome is unequivocal (Greer et al., 2008). However, there remain sceptics (Thompson et al., 2003, Childs et al., 2009), who present convincing arguments that this association is not borne out by close examination of the data. There is unequivocal evidence however, that as brain temperatures exceed 42°C, neuronal injury occurs, and cerebral oxygen uptake decreases.

By contrast, neurones are very tolerant of induced hypothermia. Hypothermia produces a decrease in cerebral oxygen uptake of ~5-7% per °C, such that at 27°C oxygen uptake is about 50% of normal. At this temperature, cerebrovascular autoregulation and reactivity to carbon dioxide remain intact, as does the coupling between function, metabolism and CBF, at least in the healthy brain. Theoretically, therefore, the hypothermic brain should be able to withstand a critical decrease in supply for longer than the normothermic brain. The brain is more tolerant to hypothermia than the cardiovascular system, which starts to fail at temperatures below 32°C. Indeed, neurones can withstand very low temperatures indeed if the circulation is supported artificially (Fitch, 1999).

It is worth noting however, that spontaneous low brain temperature following brain injury is associated with a poor outcome, possibly because such events are caused by inadequate global cerebral perfusion and / or critical injury to the hypothalamus.

Current recommendations advocate aggressive maintenance of brain normothermia, however, this is often not easy to achieve, presumes continuous brain temperature measurement and is currently untried (Badjatia, 2009). It should be noted, that the drugs and technologies capable of achieving therapeutic normothermia have potentially undesirable side effects, not least of which is interference with the apparently beneficial, physiological adaptive response (pyrexia).

The controversies surrounding therapeutic hypothermia are discussed below.

The controversy of dysnatraemia

Sodium is the predominant extracellular cation and is a principal determinant of serum and extracellular fluid osmolality. Sodium is actively transported across cell membranes and is passively followed by water. The brain plays a pivotal role, in concert with the kidneys, in sodium and water homeostasis. Brain injury can impair this process. Together with the contribution of other injuries / pathologies and treatment given, dysnatraemia is a frequent phenomenon in Neuro ICU patients and is associated with a higher morbidity and mortality.

Hyponatraemia

Hyponatraemia (serum sodium <135mmol/l) occurs in 30-50% of Neuro ICU patients. Depending upon the severity, the rate of decrease and the rate of correction, hyponatraemia can cause, or worsen, cerebral oedema, vasospasm and seizures. In Neuro ICU, the commonest causes of hyponatraemia (excluding iatrogenic causes) are 2 specific pathophysiologicals, the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) and cerebral salt wasting (CSW). Diagnosing which aetiology is responsible is often difficult, but essential, as the treatment is diametrically opposed. Both are characterised by normal adrenal and thyroid function, hyponatremia, hypouricemia, concentrated urine with urinary sodium usually >20mmol/l, and fractional excretion of urate >10%. At onset, euolemia in SIADH and extracellular volume (ECV) depletion in CSW is the only variable that differentiates the 2 conditions. However, simple and reliable bedside measures of ECV are lacking, in particular central venous pressure is completely unreliable. As both conditions progress, attempts at physiological compensation cloud the picture, especially in the ICU setting, where sodium loading from intravenous fluids and drugs together with controlled intravenous and enteral water obscure the picture even further. A review of the pathophysiology can be found here (Maesaka et al., 2009). A recently published systematic review of the diagnosis and management of hyponatraemia in all forms of brain injury can be found here (Rahman and Friedman, 2009).

Osmotic demyelination syndrome (ODS), formerly known as central pontine myelinolysis, is characterized by loss of myelin sheaths with relative sparing of axons and neurons in sharply demarcated lesions, most commonly but not exclusively in the central pons. Although ODS has been most commonly reported in the context of rapid correction of hyponatraemia (>8-10mmol/l/day), a number of other conditions have emerged, which have been associated with the development of ODS with or without a substantial change in serum sodium, suggesting that the finding of myelinolysis may be a more generalized injury pattern to changes in extracellular fluid osmolality. A recent review of this condition can be found here (King and Rosner, 2010).

Hypovolaemic hypernatraemia

Following injury to the hypothalamus or posterior pituitary the production and / or secretion of arginine vasopressin can fail resulting in unrestrained diuresis (diabetes insipidus (DI)) with consequent hypovolaemia and hypernatraemia. Central (neurogenic) DI is most commonly seen in the context of brain stem death, where it is estimated to occur in ~65% of cases. The diagnosis should be suspected in the context of unprovoked dilute, polyuria (>2.5ml/kg/hr, urine specific gravity \leq 1.005, urine osmolality \leq 200mOsm/kg) and rapidly rising serum sodium. Management consists of intravascular fluid replacement. As the loss is water, replacement with 5% dextrose rather than sodium containing crystalloids is logical, especially if the serum sodium is \geq 145mmol/l. Replacement of arginine vasopressin is typically achieved with bolus intravenous doses of desmopressin repeated as necessary depending on response. In Neuro ICU the administration of mannitol for intracranial hypertension can also produce a hypovolaemic hypernatraemia, which can mask the co-existence of DI. In this setting, correction of hypovolaemia may be preferable with aliquots of isotonic sodium containing crystalloids or colloids and functional haemodynamic monitoring is advisable, together with frequent measures of serum sodium.

Euvolaemic / hypervolaemic hypernatraemia

Hypernatraemia is a common consequence of Intensive Care therapy and is primarily the result intravenous sodium from fluids and drugs, which grossly exceeds physiological requirements and losses. Humans are physiologically designed to conserve sodium and have a limited capacity for natriuresis, thus this iatrogenic positive sodium balance rapidly accumulates. In Neuro Critical Care, where avoidance of hyponatraemia is considered best practice and osmotherapy for intracranial hypertension routine, the sodium load is frequently even higher. Importantly this may be yet another significant source of iatrogenic and therefore preventable injury. Two recent observation studies have found hypernatraemia in Neuro ICU patients to be associated with an increased risk of death (Maggiore et al., 2009, Aiyagari et al., 2006). However, whether hypernatraemia is merely a surrogate marker for the severity of brain injury or has a direct causal relationship is unclear. The precise pathophysiological mechanism by which euvolaemic / hypervolaemic hypernatraemia causes neuronal injury has not been defined but the most obvious mechanism would be intracellular dehydration / hypovolaemia since intracellular water is lost to the extracellular and intravascular spaces via passive diffusion secondary to the osmotic gradient.

In summary, dysnatraemia is common and associated with secondary brain injury and an increased mortality. Maintenance of serum sodium in the 135-145mmol/l range is optimal. Diagnosis of the underlying cause of any abnormality is vital but can be difficult. Close attention should be paid to daily sodium and water balance and frequent monitoring of serum sodium is essential. Management depends upon diagnosis.

Coagulopathy following brain injury and prophylaxis of venous thromboembolism (VTE)

Brain tissue contains a high concentration of both tissue factor and phospholipids. Hence exposure of brain tissue to blood, either in situ, or embolically, is a very potent initiator of both the clotting and fibrinolytic cascades. Accordingly, brain injury, especially TBI, causes a state of disseminated intravascular coagulation (DIC) (Hess and Lawson, 2006). The magnitude of the clotting / fibrinolytic derangement correlates very strongly with the severity / extent of brain injury and outcome (Wafaisade et al., 2010, Harhangi et al., 2008). The natural history of DIC, following brain injury, is that it exists in a fibrinolytic (haemorrhagic) phenotype, for approximately the first 24 hours, and then evolves into an antifibrinolytic (thrombotic) phenotype which typically persists for a median of 48 hours (Lustenberger et al., 2010, Gando, 2009). Thus initially, the risk of bleeding exceeds the risk of microvascular thrombosis but this balance is then reversed.

Diagnosis and monitoring is far from straightforward as conventional clotting assays are neither sensitive, specific nor accurately direct therapy (Frith and Brohi, 2010). Adjunctive tests such as platelet count, fibrinogen assay and quantitative d-dimer / fibrin degradation product assays are valuable, but again, offer limited therapeutic guidance as they measure quantity not function. Thromboelastography (Reikvam et al., 2009), though imperfect, probably offers the best diagnostic and monitoring tool currently available.

As regards treatment, there is little in the way of randomised controlled trials however the early and short term use of antifibrinolytics (<24 hours) appears to be safe and has a small but clinically significant beneficial effect (Shakur et al., 2010). Thereafter, the use of heparin may be beneficial in limiting thrombosis (Levi et al., 2009, Wada et al., 2010). The pros and cons of unfractionated versus low molecular weight heparin and the optimal dose / therapeutic target remain to be clarified. In addition the risk / benefit profile must be considered in the context of the individual patient's condition, however, there is currently insufficient clinical data to accurately inform decision making.

Temporary immobility is a near ubiquitous consequence of any serious brain injury. Hence all Neuro ICU patients are at increased risk of VTE. In addition, as explained above, a prothrombotic coagulation disorder may accompany many brain injuries. Mechanical thromboprophylaxis should be used whenever feasible. However, the efficacy of specific devices, used in isolation or combination, is lacking (Morris and Woodcock, 2010). The addition of pharmacological prophylaxis almost certainly further reduces but does not eliminate the risk of VTE and may, in fact, have a therapeutic role in the management of thrombotic DIC (Wada et al., 2010). The obvious concern however, is balancing the risk of VTE against the risk of increasing the extent of intracranial haemorrhage. There is conflicting data regarding the risk / benefit profile of initiating early pharmacological prophylaxis, within 24 hours of brain injury / surgery (Scales et al., 2010). To complicate matters further, there is unequivocal evidence that even standard high dose pharmacological prophylaxis is inadequate in critical care patients (Levi, 2010). A summary of current consensus guidelines on thromboprophylaxis in neuro critical care can be found in the Table below and in detail, here (Raslan et al., 2010).

Summary of consensus guidelines for the Prophylaxis for VTE in neuro critical care (Raslan et al., 2010)

Pathology	Recommendations
Brain Neoplasm	<p>No clear guidelines.</p> <p>Patients with hemorrhagic tumours as well as multiple metastasis from known hemorrhagic primary tumours (thyroid, renal cell, chorioncarcinoma and melanoma) should not receive pharmacologic prophylaxis.</p> <p>Probably safe to use pharmacologic prophylaxis after surgery as early as 12 hours LMWH and UFH are probably equally effective.</p>
Acute ischaemic stroke (AIS)	<p>2007 AHA/ASA guidelines recommend the use of CS / ICD and UFH or LMWH for VTE prophylaxis.</p> <p>2008 ACCP guidelines also endorse the use of UFH or LMWH for VTE prophylaxis in patients with AIS with impaired mobility starting 24 h after the event, for as long as there is impaired mobility, and recommend ICD with or without CS in patients in whom heparins are contra-indicated</p> <p>Special consideration should be given to patients who receive thrombolysis, diabetics and large volume strokes</p>
Intracranial (ICH) and spontaneous subarachnoid haemorrhage (SAH)	<p>AHA/ASA guidelines recommend CS / ICD with consideration of pharmacological prophylaxis after documentation of cessation of growth of ICH</p> <p>ACCP guidelines suggest that early pharmacologic prophylaxis be considered 48 hours after onset of ICH and recommend ICD as initial therapy</p> <p>In SAH, aneurysms should be secured prior to initiation of pharmacologic prophylaxis</p>
Post neurosurgical procedures	<p>The ACCP guidelines recommend ICD for neurosurgical patients undergoing major elective neurosurgical procedures</p> <p>The addition of LMWH or UFH should be considered for high risk patients and initiated 12 hours post procedure.</p>
Traumatic brain injury (TBI)	<p>2007 Brain Trauma Foundation guidelines recommend the use of mechanical thromboprophylaxis with ICD or CS in all patients with TBI until ambulatory, unless lower extremity injury precludes their use</p> <p>Pharmacologic prophylaxis with LMWH or UFH should be considered in addition to mechanical prophylaxis, but they may carry an increased risk of ICH expansion</p>
Spinal cord injury (SCI)	<p>LMWH is the standard prophylaxis of VTE in patients with acute SCI</p> <p>Prophylactic IVC filters are not indicated in patients with acute SCI</p>
<p>Key: LMWH - low molecular weight heparin UFH - unfractionated heparin AHA/ASA - American Heart Association/American Stroke Association CS - compression stockings ICD - intermittent compression device ACCP - American College of Chest Physicians</p>	

Radiology – CT basic reviews - (Downer and Pretorius, 2009, Harden et al., 2007) , MRI, angiography, functional imaging. (Zhang et al.)

NEUROPROTECTIVE THERAPIES

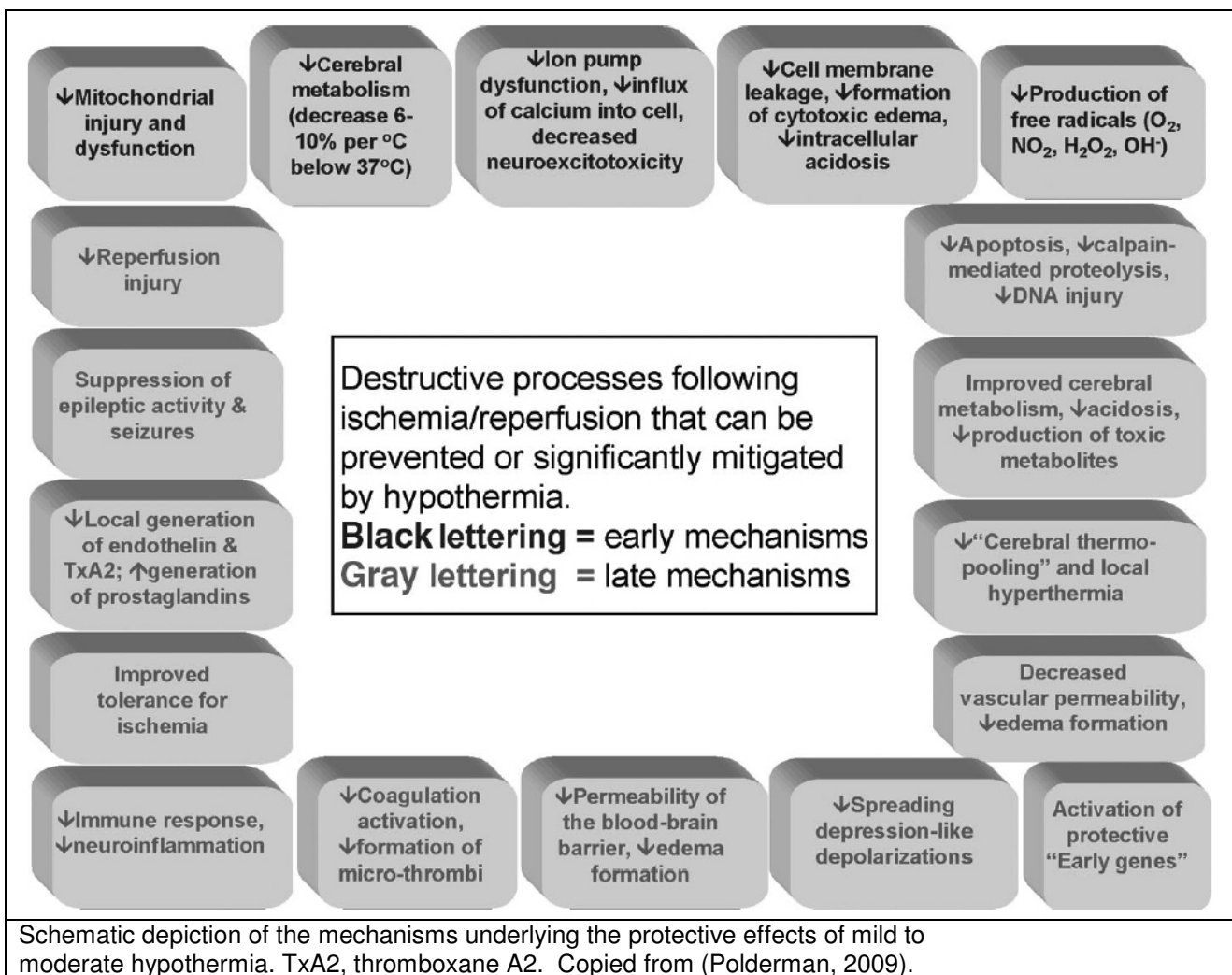
Our knowledge of the cascade of events from injury to neuronal cell death is extensive, if incomplete. As this knowledge has grown the question as to whether we can intervene and limit the damage has been doggedly pursued. In excess of 140 separate compounds and strategies have been investigated for their potential neuro-protective effects (Ginsberg, 2008a, Vink and Nimmo, 2009). There has been much justified criticism of the poor quality of phase I and II trials, which have arguably brought the field into disrepute (Philip et al., 2009). Many therapies, that had shown initial promise in animal models, have failed to demonstrate any clinical benefit when trialled in patients. One potential explanation is that they are given too late in the clinical course of events, when the damage is irreversible. A second and related explanation is the failure of the neuro-microcirculation, which results in inadequate or no delivery of the trial agent to the injured, but potentially salvageable, neuronal tissue (del Zoppo, 2009, del Zoppo, 2008, Andreas, 2009). A third explanation is that no single agent is ever going to be effective as it cannot treat even a fraction of the myriad processes and cell types involved (Barone, 2009). The following section will briefly consider those therapies still under active investigation or that may yet have some useful clinical role to play.

Mild therapeutic hypothermia (MTH)

Rationale

Most of the deleterious neurochemical cascades triggered by brain injury are sensitive to even mild changes in temperature. The mechanisms through which hypothermia is believed to afford neuroprotection are multifactorial and include (Sahuquillo and Vilalta, 2007, Polderman, 2009):

- A reduction in brain metabolic rate
- A reduction in regional cerebral blood flow and an overall reduction in cerebral blood volume
- A reduction of the critical threshold for oxygen delivery
- A blockade of excitotoxic mechanisms
- Antagonism of intracellular calcium influx
- A preservation of protein synthesis
- A reduction of brain thermopooling
- A decrease in oedema formation
- Modulation of the inflammatory response
- Neuroprotection of the white matter
- Modulation of apoptotic cell death



Indications

MTH has been trialed and is currently used following cardiac arrest (Nolan et al., 2008), following spinal cord injury (Dietrich, 2009) and following TBI as a rescue therapy for persistently elevated ICP (Bratton et al., 2007, Andrews) although its use in these patients remains controversial (Grände et al., 2009). It has also been used as a rescue therapy in patients following stroke (Linares and Mayer, 2009), patients with intractable status epilepticus (Corry et al., 2008) and in patients with acute liver failure and raised ICP (Dmello et al., 2010). Its use has also been considered as a strategy following exsanguinating trauma (Fukudome and Alam, 2009), in severe acute respiratory distress syndrome (Villar and Slutsky, 1993, Pernerstorfer et al., 1995) and in patients with cardiogenic shock (Götberg et al.).

Global side effects

MTH is a whole body therapy and has significant and potentially detrimental effects on cellular / organ function that in some instances may mitigate against the neuroprotective effects. Table X summaries these effects.

Thermoregulation - activation of counter-regulatory mechanisms to decrease heat loss (peripheral vasoconstriction) and increase heat production (shivering) (Polderman and Herold, 2009)	Peripheral vasoconstriction occurs at ~ 36.5°C. The major effect of which is to limit the efficacy of surface cooling methods. If prolonged, it increases the risk of pressure injuries. Shivering tends to occur at core temperatures ~35.5°C. Shivering, not only limits induction / maintenance of MTH it also increases O ₂ consumption in the setting of a reduced supply. Shivering stops below core temperatures ~33.5°C and the response can be blunted using a variety of pharmacological agents
Cardiovascular - heart rate and rhythm	Bradycardia and slowing of intracardiac conduction. Arrhythmias develop at temp ≤30°C
Cardiovascular (& renal) - preload	Venoconstriction increases preload but cold diuresis can result in hypovolaemia and an increase in blood viscosity.
Cardiovascular (& coagulation) - preload and O ₂ carrying capacity	MTH induces a mild coagulopathy. This is only important if there is bleeding within the brain or elsewhere. If within the brain then haematoma size and mass effect will be increased. If elsewhere, then ongoing haemorrhage, consumptive coagulopathy and potentially shock may result
Cardiovascular - myocardial contractility	The effect of hypothermia on myocardial contractility is strongly dependent on heart rate. If the heart rate is allowed to decrease along with the temperature, myocardial contractility / systolic function usually increases, although there may be a mild degree of diastolic dysfunction. However, if the heart rate is artificially increased through administration of chronotropic drugs or a pacing wire, myocardial contractility decreases significantly. Whether MTH is beneficial or detrimental on cardiac outcomes following cardiac arrest remains unclear and is dependant upon both the cause of the cardiac arrest and the management of this pathology (Parham et al., 2009, Kelly and Nolan).
Cardiovascular - afterload	Mean arterial pressure typically increases slightly (~10 mmHg) during mild hypothermia.
Overall cardiovascular - global O ₂ delivery and supply demand balance	Cardiac output decreases, due to a fall in heart rate, but this reduction tends to be equal to or less than the decrease in metabolic rate. The net result is unchanged or improved balance between supply and demand, assuming that arterial O ₂ content remains unchanged.
Respiratory - assuming mechanical ventilation	MTH reduces O ₂ consumption and CO ₂ production hence FiO ₂ and minute ventilation should be modified to maintain normal blood gas values.
Respiratory - barrier defences	MTH impairs all the elements of mechanical and barrier defences in the respiratory tract, which coupled with the inevitable immobility results in an increased risk of pneumonia.
Immune function	Hypothermia causes both innate and adaptive immunosuppression and a consequent increased risk of, and slower recovery from, nosocomial infections, especially pneumonia (see above).
Gastrointestinal tract	Delayed gastric emptying and ileus. Despite this, reduced dose / volume (concentrated) enteral feeding should be attempted (cooling decreases calorie requirements by 7% to 10% per °C decrease below 37°C).
Endocrine / metabolic	The principal endocrine effect is insulin resistance causing hyperglycaemia and ketoacidosis. This can be overcome by insulin infusion. Therapy will require careful down titration during rewarming.
Electrolytes - K, Mg, Ca and P	MTH induces increased renal losses of K, Mg, Ca and P and intracellular shift of K and Mg. Hypomagnesaemia, in particular, may exacerbate neuronal injury and pro-active supplementation is advised (see later section). Rebound hyperkalaemia on rewarming can be dramatic and induce cardiac dysrhythmias and is another reason for slow and controlled rewarming.
Metabolic / laboratory	Mild lactic acidosis, elevated hepatic enzymes, elevated amylase, thrombocytopenia.
Metabolic / pharmacokinetic	Global reduction in metabolism of drugs. Especially important for sedative and neuromuscular blocking drugs.

The application of MTH has 3 distinct phases, induction, maintenance and rewarming. Continuous and accurate temperature monitoring is essential. Brain temperature is ideal and is the gold standard. Central brain temperature may be up to 2°C higher than core temperature (depending on measurement site). The pros and cons of various sites and methodologies of core temperature measurement are reviewed here (Polderman and Herold, 2009).

Induction

As with all neuroprotective interventions, the greater the delay in initiating therapy and achieving therapeutic targets, the less efficacious the intervention is likely to be. Accordingly, in order to maximise any benefits from MTH, it should ideally be induced within minutes of injury. However, given that at least some of the beneficial effects of MTH occur hours or even days following injury and that optimal target brain temperature remains to be clarified (Tokutomi et al., 2009, Nielsen and Friberg), the optimal induction regime is yet to be defined.

In terms of cooling method, induction of cooling must be simple, require a minimum amount of preparation / equipment but does not have to achieve target temperature. Accordingly, perhaps the easiest and most effective method is the bolus administration (10-30ml/kg) of 4°C crystalloid. Environmental management including clothing and bedding should be optimised for heat loss. Surface cooling packs may be useful adjuncts and are reviewed here (Polderman and Herold, 2009).

Maintenance

The unresolved issues here remain optimal target temperature and duration of therapy (Marion and Bullock, 2009). Current guidelines favour a target core temperature of 33 °C. Post global ischaemic hypoxic brain injury (e.g. cardiac arrest) the consensus appears to favour 24 hours of therapy from time of event. In intractable intracranial hypertension guidelines tend to recommend 48-96 hours of therapy. A review of maintenance techniques and adjunctive therapies can be found here (Polderman and Herold, 2009, Seder and Van der Kloot, 2009).

Rewarming

The rate at which patients are rewarmed appears to have a profound effect on outcome, much more so than either time to induction, time to target temperature or duration at target temperature. The mechanisms by which too rapid rewarming appears to cause or worsen neurological injury are discussed here (Povlishock and Wei, 2009, Grigore et al., 2009). Current recommendations state that temperature increases should be limited to a maximum of 0.25°C/hour (Polderman and Herold, 2009).

Combination therapy

Given its global effects, combining MTH with other therapies is appealing. It may extend the period during which initiation of other therapies can be still be beneficial and due to the inhibitory effects of MTH on drug metabolism, it may result in advantageous pharmacokinetic profiles.

Albumin

High dose albumin therapy has been shown to be highly neuroprotective in numerous animal models of TBI as well as focal and global cerebral ischemia, if given within 4 hours of the index event (Ginsberg, 2008a).

Albumin is thought to exert its neuroprotective actions by the following means:

- It is a potent antioxidant
- It maintains plasma colloid oncotic pressure whilst inducing haemodilution, which in turn, both optimises microvascular permeability and decreases red blood cell sedimentation under low-flow conditions. This results in a reduction in oedema formation, an increase in blood flow to injured zones and a reduction in infarct volume.
- It reacts with nitric oxide to form a stable S-nitrosothiol that acts as a local vasodilator
- It plays a crucial role in binding and transport of essential fatty acids

Following a positive pilot outcome study in acute ischaemic stroke patients (Palesch et al., 2006) a large randomised control trial of 2.0g/kg of albumin (given as a 25% solution) within 5 hours of the index event, in patients both eligible and ineligible for thrombolysis, is currently underway (Ginsberg et al., 2006).

In TBI, a post hoc analysis of the SAFE trial (TheSAFEStudyInvestigators, 2007) suggested an association between 4% albumin solution used for resuscitation and a worse outcome. This data has been refuted by both rationale argument (Ginsberg, 2008b) and a somewhat complex, prospective cohort study (Rodling Wahlstrom et al., 2009). However, no data exists to demonstrate the efficacy of high dose albumin therapy following TBI.

Magnesium (Sen and Gulati, 2010)

Magnesium can be considered as an endogenous calcium antagonist that may protect neurones via multiple mechanisms, including NMDA receptor blockade, inhibition of excitatory neurotransmitter release, blockade of calcium channels, as well as vascular smooth muscle relaxation. However, experimental evidence suggests that magnesium is only weakly neuroprotectant and that to achieve even a modest effect requires prolonged and high dose administration. The pharmacokinetics of intravenously administered magnesium sulphate in terms of its neuronal bioavailability in both normal and injured brain remains unclear. Given its safety and ease of use, combination therapy for neuroprotection is being investigated. The best emerging candidates are mild hypothermia (Meloni et al., 2009) and polyethylene glycol (Kwon et al., 2010).

Post conditioning

In sublethal ischaemia reperfusion injury, there is a primary hypoxic / hypoglycaemic insult followed by the secondary hyperaemic reperfusion injury. Pre conditioning is the observed phenomenon, that tissue exposed to mild ischaemia reperfusion becomes tolerant to the damaging effects of more profound challenges (Dirnagl et al., 2009). Post conditioning appears to be a similar phenomenon, that may be induced by limited / controlled reperfusion and has been extensively investigated in animal models of brain injury with some success (Giuseppe et al., 2009, Zhao, 2009). However, translating these findings into the clinical arena is a distant and arguably flawed strategy.

Endogenous hormones with therapeutic potential

Erythropoietin (EPO) (Sirén et al., 2009)

EPO is an essential paracrine hormone in the CNS. It is produced by neurones and glial cells and has a myriad of growth, development and anti-apoptotic effects. Due to its molecular size, shape and charge, only ~1% crosses the intact blood brain barrier, hence trials of recombinant therapy in a variety of brain injury models has required very high dose administration with consequent undesirable side effects of excessive erythro- and thrombopoiesis. A variety of techniques are being investigated to overcome these problems and early clinical trials in patients with acute ischaemic stroke, schizophrenia, and chronic progressive multiple sclerosis show both efficacy and safety. The precise molecular biology remains controversial and is discussed here (Brines, 2010).

Oestrogens and progesterone

The female steroid sex hormones play a vital role in normal neuronal biology in both sexes. Reduced physiological levels are associated with more extensive injury following ischaemia reperfusion. Maintaining physiological levels may be of benefit. As with all other hormones, the definition of the levels that produce physiological function following brain injury may in fact be supra physiological.

17 β -oestradiol (E₂), at physiological doses, may have a role in reducing ischaemia reperfusion injury and enhancing recovery by inducing neuronal regeneration (Suzuki et al., 2009). Although much work has established the benefit of physiological doses of E₂ prior to brain injury, acute therapy at supraphysiological doses shows some evidence of benefit in animal models (Lebesgue et al., 2009). To date there are no studies in humans or trials in progress.

Progesterone is a pleiotropic drug that has been shown to have the following effects on injured brain (Margulies and Hicks, 2009):

- Protect and reconstitute the blood–brain barrier
- Reduce cerebral oedema through decreasing vasogenic and cytotoxic oedema and modulating brain water regulation via aquaporin channels
- Downregulate the inflammatory cascade and pro-inflammatory cytokines in response to neurotrauma
- Reduce free radicals and lipid peroxidation
- Decrease apoptosis

Being highly lipophilic, progesterone readily crosses the blood brain barrier and being readily available, cheap and with an excellent safety and tolerability profile is an ideal candidate neuroprotective therapy. Two phase II trials have demonstrated safety and potential benefits of acute progesterone therapy administered within hours of TBI and continued for 5 days (Wright et al., 2007, Xiao et al., 2008). Optimal dosing strategies remain to be established but those within the range administered from gynaecological indications appear to be efficacious. Thus mildly supraphysiological doses appear to be an attractive candidate neuroprotectant therapy and a large scale phase III clinical trial in TBI is scheduled to complete recruiting in June 2015 (<http://www.clinicaltrials.gov/ct2/show/NCT00822900>). Combining progesterone therapy with other neuroprotectants and / or in combination with MTH also holds promise (Margulies and Hicks, 2009).

Drugs

Citicoline (Margulies and Hicks, 2009)

Citicoline is a naturally occurring endogenous compound that may exert acute neuroprotective effects, as well as potentiate neurorecovery following TBI and stroke. Citicoline has virtually no side effects, excellent tolerance, and well described pharmacokinetics, toxicity, and bioavailability profiles. Animal data suggest that citicoline works via numerous mechanisms to attenuate neuronal injury after TBI, including increased synthesis of phosphatidylcholine, inhibition of oxidative stress and apoptotic pathways, and activation of pro-survival pathways and cholinergic and dopaminergic neurotransmission. The diversity of citicoline's mechanisms of action and pre-clinical efficacy data make it an attractive candidate for therapeutic development, and a large multicenter trial for TBI is currently underway. Citicoline has already been used for pre-clinical stroke studies in combination with tPA, urokinase, or MK-801. For TBI, citicoline should be combined with treatments that complement its actions on neuronal injury, such as drugs that target axonal injury or have anti-inflammatory actions. Promising potential agents to combine with citicoline include hypertonic saline, statins, progesterone, erythropoietin, and cyclosporine A. Detailed investigations regarding route of administration and brain uptake are needed, as well as mechanistic studies to evaluate the effect of a second treatment on citicoline's therapeutic effects.

Cerebrolysin

Cerebrolysin is a porcine brain-derived peptide preparation that has pharmacodynamic properties similar to those of endogenous neurotrophic factors. It has been principally trialled in patients with Alzheimer's disease and appears to have some efficacy (Wei et al., 2007). Preliminary trials in TBI (Wong et al., 2005a) and stroke (Ladurner et al., 2005) have prompted ongoing investigations. Uniquely, this therapy may be most effective in the post acute phase following brain injury (Onose et al., 2009).

Cyclosporine A (Margulies and Hicks, 2009)

Cyclosporine A (CsA) attenuates mitochondrial failure, which is known to be an important injury mechanism in TBI. Mitochondrial failure leads to energy imbalance, ionic imbalance, swelling of mitochondria, pro-apoptotic events, reduced brain ATP levels, and release of cytochrome C. The locus of action for CsA is in stabilizing the mitochondrial transition pore. Several pre-clinical TBI and ischemia studies (mostly in rodents) have demonstrated neuroprotection. CsA has well-described safety and dosing profiles. CsA is also one of the most potent stabilizers of the mitochondrial transition pore. Secondary to the inhibition of mitochondrial transition pore opening, CsA also attenuates mitochondrial free radical oxidative damage to mitochondrial proteins and thus it acts as an indirect antioxidant. A disadvantage is that chronic usage adversely impacts the immune system, but acute usage for TBI neuroprotection satisfied a broad range of safety parameters in a Phase I clinical trial. Another disadvantage is that CsA has relatively poor brain penetration; however, improvements in increased cerebral perfusion pressure, improved glucose levels, and reduced brain swelling were noted in the Phase I trial. Efforts to block excretion of CsA from the brain with ketoconazole were not successful. Phase III trials for CsA are now in preparation. Because of its slow entry into the brain (6 h), the mitochondrial benefits of CsA might be enhanced if combined with hypothermia, by both prolonging the treatment window and through their synergistic effects on preservation of brain bioenergetics, but combining CsA with hypothermia has the potential risk of infection because of the immune suppression. Because of this potential risk, one might exclude patients with multiple injuries from combined treatment with CsA and hypothermia. CsA might also be used in combination with NMDA inhibitors to block calcium flux, a precipitator for the mitochondrial damage, thus enhancing mitochondrial protection. One pharmacological caveat is that the neuroprotective dose-response curve for CsA is biphasic, so using it in combination would require a very careful evaluation of the pharmacokinetics and dose response.

Statins (Margulies and Hicks, 2009)

There is growing pre-clinical and clinical evidence that the statin class of drugs may have additional pleiotropic properties that are potentially neuroprotective, independent of their effect on serum cholesterol. For example, in the acute phase of TBI, statins exert anti-inflammatory effects, which may reduce the later development of cerebral oedema and intracranial hypertension. Statins also cause an upregulation of eNOS and stabilize endothelial surfaces, which may result in improved cerebral perfusion following trauma. In the subacute period and chronic period following cerebral injury, statins may facilitate recovery via their effects on neurogenesis and angiogenesis. In addition to these multiple mechanisms of action, there are a number of features that make the use of statins attractive in the treatment of acute brain injury. Based on pre-clinical observations in a murine model of SAH, statins have been demonstrated to reduce clinical and radiographic vasospasm and improve outcome following aneurysmal SAH. Pre-clinical evidence also suggests that the use of statins improve outcomes in rodent models of TBI and intracranial haemorrhage. Statins are well tolerated, easy to administer, and have a long, safe clinical track record. Adverse events, primarily myopathy and transaminitis, have been well defined and can be easily monitored. Moreover, clinical experience suggests that statins are well-tolerated in patients with life-threatening neurological disease. Thus statins may represent a novel adjunct strategy in combination therapy treatments for TBI.

Hypertonic sodium solutions

Hypertonic sodium chloride is an attractive treatment for TBI because it restores blood pressure, increases organ blood flow, exerts a positive inotropic effect, and is thought to mobilize water across the intact blood–brain barrier by dehydrating endothelial cells and erythrocytes (Margulies and Hicks, 2009). It also affects leukocyte adhesion and reduces the inflammatory response to injury. The effects of hypertonic saline on TBI include improved haemodynamics through plasma volume expansion, vasoregulation via effects on vascular endothelium, a decrease in cerebral oedema, and cellular modulation through both immunologic and excitotoxic effects. Hypertonic saline has been used extensively in the pre-hospital arena and in ICUs around the world. There have been several clinical trials evaluating hypertonic saline in TBI. The safety profile is good and improvements in intracranial pressure and survival have been observed, but no improvements have been seen in functional outcomes. Currently a large randomized clinical trial of pre-hospital treatment with hypertonic saline versus normal saline in patients with TBI is in progress. Hypertonic saline should be strongly considered for use in conjunction with other promising therapies that target neuronal and axonal injury mechanisms.

Hypertonic sodium lactate may offer some advantages over hypertonic sodium chloride and is at least as effective as mannitol, as an osmotherapy for acute intracranial hypertension (Ichai et al., 2009).

Inhalational and intravenous anaesthetics, noble gases and hydrogen

The ability of anaesthetic agents to limit ischaemia reperfusion injury has a long history. There is some evidence to support the use of anaesthetic agents in limiting myocardial ischaemia reperfusion injury, reviewed here (Frassdorf et al., 2009, Landoni et al., 2009). In brain ischaemia reperfusion, there remains no proven efficacy in humans, reviewed here (Kitano et al., 2006, Werner, 2009). Nitrous oxide appears as a Jekyll and Hyde player in this story (Haelewyn et al., 2008). The noble gas, xenon, which has anaesthetic properties, may also have neuroprotective effects (Derwall et al., 2009), however its use has been limited by its high price and technical restraints regarding economic delivery. Argon, a cheaper and more readily available noble gas, shares many of xenon's properties and has also been proposed as a neuroprotectant (Loetscher et al., 2009). Of the remaining noble gases, neon and krypton do not appear to have any such effects (Jawad et al., 2009). There is conflicting data regarding helium (Coburn et al., 2008, Jawad et al., 2009) but this is probably explained by its cooling effects in certain experimental designs (David et al., 2009). In stark contrast to the inert noble gases, hydrogen, which is fiercely reactive, has also been investigated due to its oxygen free radical scavenging ability coupled with very rapid diffusability. Its efficacy in animal models is dramatic but only if administered prior to reperfusion (Wood and Gladwin, 2007).

Iron chelation

There is convincing evidence that following intracranial haemorrhage, free iron exerts local toxicity resulting in oedema formation and neuronal death (Weinreb et al., 2010). Importantly, this toxicity occurs gradually over hours to days. Hence iron chelation therapy is an attractive neuroprotection strategy. An optimal timing and duration of therapy study in rats suggests that there is a 12 hour therapeutic time window to initiate therapy, with maximal benefit requiring ≥ 7 days treatment (Okauchi et al.). Deferoxamine, is a well established iron chelation therapy, is comparatively cheap and has an excellent safety profile.

Other promising candidates

In an animal model of acute ischaemic stroke, administration of rosiglitazone 24 and 48 hours after the index event resulted in dramatic reductions in infarct volume and secondary brain injury (Allahtavakoli et al., 2009). Thiazolidinediones are potent anti-inflammatory and anti-apoptotic drugs, whose effects on the injured brain are mediated through a number of delayed secondary injury processes. Further investigations are underway.

Trans-sodium crocetin is a member of the carotenoid family of compounds and is a potent anti-oxidant. In addition, however, it appears to increase the amount of hydrogen bonding in aqueous solutions and thereby significantly increases the rate of diffusion of small molecules such as oxygen and glucose (Stennett et al., 2007). It has been in development as a battlefield treatment of haemorrhagic shock and has thus far been found to be safe, its efficacy is untested. Due to its apparent ability to safely increase oxygen delivery without hyperoxia, a number of animal studies have been undertaken to test its efficacy in reducing cerebral infarct volume (Lapchak, 2010, Manabe et al.). These suggest that early (within 3 hours) administration, with or without reperfusion, is beneficial. Further studies are awaited.

Anti epileptic s (AEDs) [LINK] are a diverse group of drugs with a myriad of pharmacodynamic properties. There are good pharmacodynamic and pharmacokinetic reasons to consider single agent and combination therapy anticonvulsants in post injury neuroprotection trials, above and beyond seizure prevention. However, many of these drugs, especially older agents and in particular phenytoin, have detrimental pharmacodynamic, side effect and pharmacokinetic properties. A brief overview of subject can be found

here (Willmore, 2005). A recent study using a TBI rodent model found that very high dose sodium valproate given 30 minutes post injury had demonstrable neuroprotective effects (Dash et al., 2010). A second recent study demonstrated neuroprotective effects of levetiracetam in murine models of closed head injury and subarachnoid haemorrhage (Wang et al., 2006).

Caloric restriction and / or a ketogenic diet may be a comparatively simple, late but efficacious option in neuroprotection. For a recent review see (Maalouf et al., 2009)

DISEASE SPECIFIC NEURO CRITICAL CARE

Structural injury

- **Post neurosurgical recovery**
- **Traumatic brain injury**

Mechanical damage / axonal injury

- **Spinal cord injury**
- **Spontaneous (aneurismal) subarachnoid haemorrhage – review (Diringer, 2009, Rinkel and Klijn, 2009)**
- **American guidelines (Bederson et al., 2009)**

Early signs predicting poor outcome (Hanafy et al., 2010)

Quadruple therapy? (Walid and Zaytseva, 2009)

Glial cell dysfunction aetiology of vasospasm (Mutch)

Coiling is better than clipping (Molyneux et al., 2009). Late coiling failure rate (Ferns et al., 2009).

Early vs. late intervention? No one knows (Whitfield Peter and Kirkpatrick, 2001)

Nimodipine, probably a good thing (Dorhout Mees et al., 2007)

Intravenous MgSO₄ probably a good thing (Zhao et al., 2009). Definitely a good thing (Westermaier et al., 2010)?

Review of Mx (Rabinstein et al., 2010, Naval et al., 2006)

Prophylactic use of anticonvulsants in associated with a worse outcome (Rosengart et al., 2007), especially phenytoin (Naidech et al., 2005), which interacts with the pharmacokinetics of nimodipine, dramatically reducing its bioavailability (Wong et al., 2005b).

Optimal CPP in severe SAH (Bijlenga et al., 2010)

- **Spontaneous intracerebral haemorrhage – review (Rincon and Mayer, 2008)**

Risk factors / pathophysiol "strain vessel hypothesis (Ito et al., 2009)

Early aggressive BP control – initial studies suggest this is a safe and efficacious strategy however, clinical outcome studies are awaited. (Anderson et al., 2010, Anderson et al., 2008, Antihypertensive Treatment of Acute Cerebral Hemorrhage investigators, 2010)

General review (Elliott and Smith, 2010)

AHA/ASA Mx guidelines (Morgenstern et al., 2010)

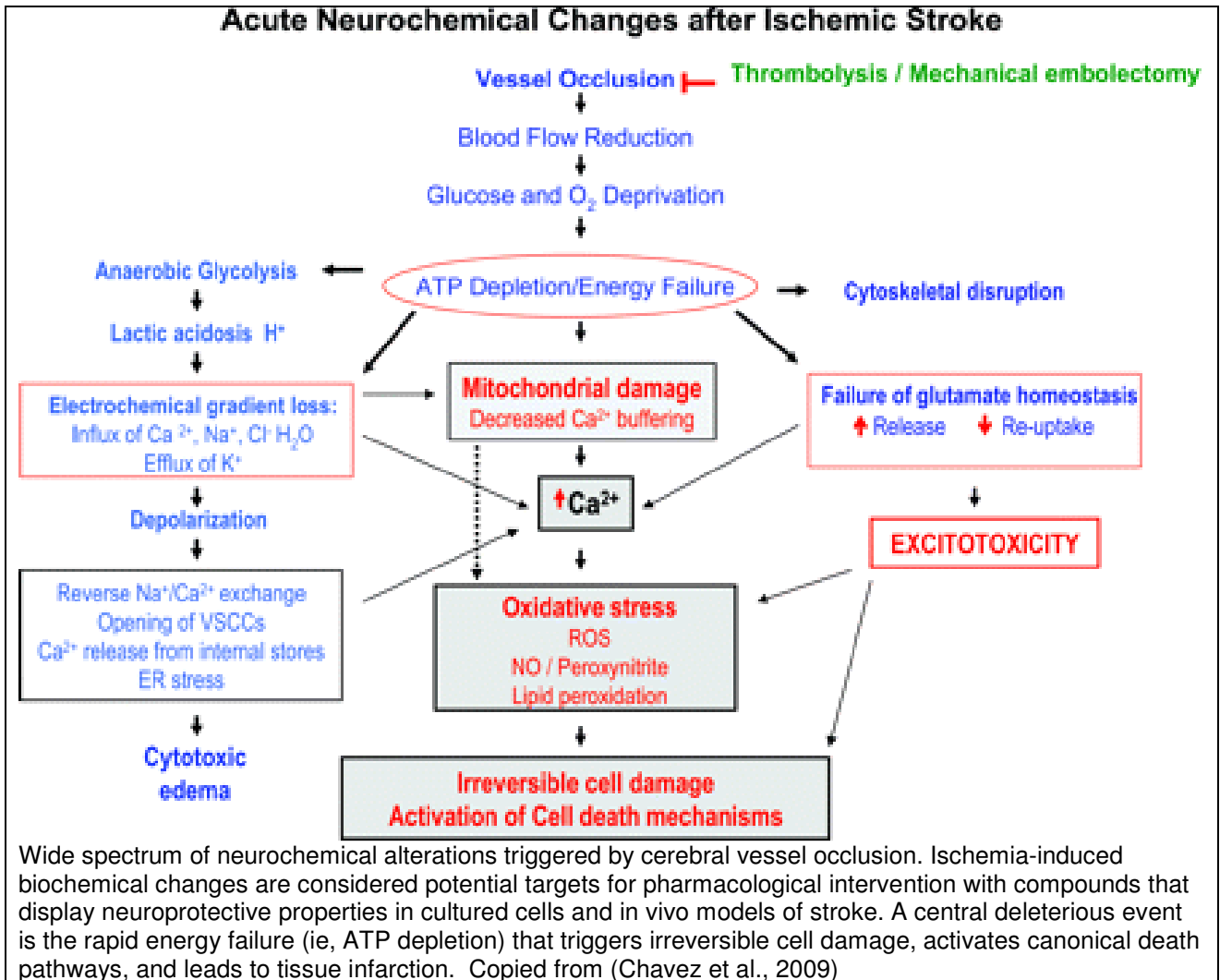
Cerebral abscess

Epidemiology and surgical management (Hall and Truwit, 2008)

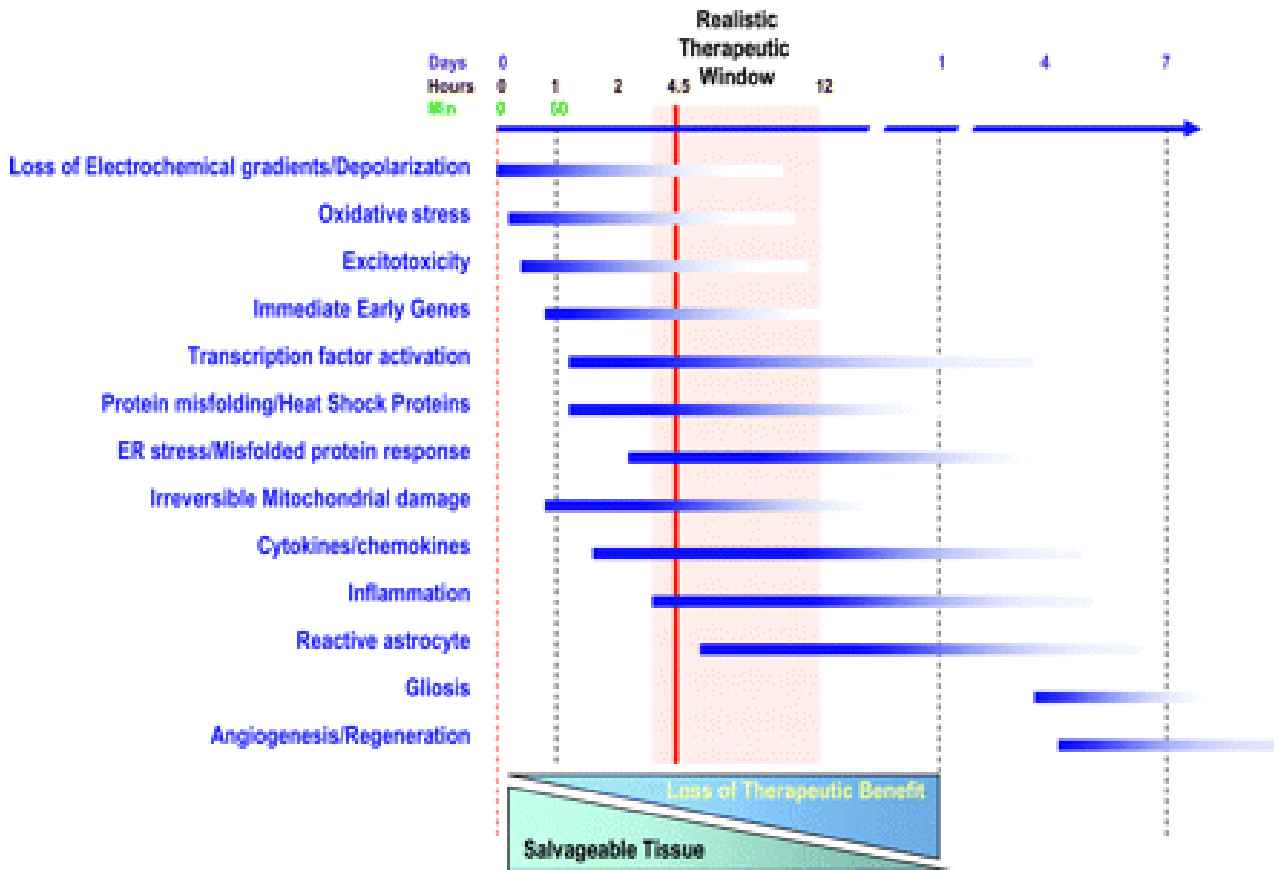
Nosocomial ventriculitis and meningitis

Review article (Beer et al., 2008)

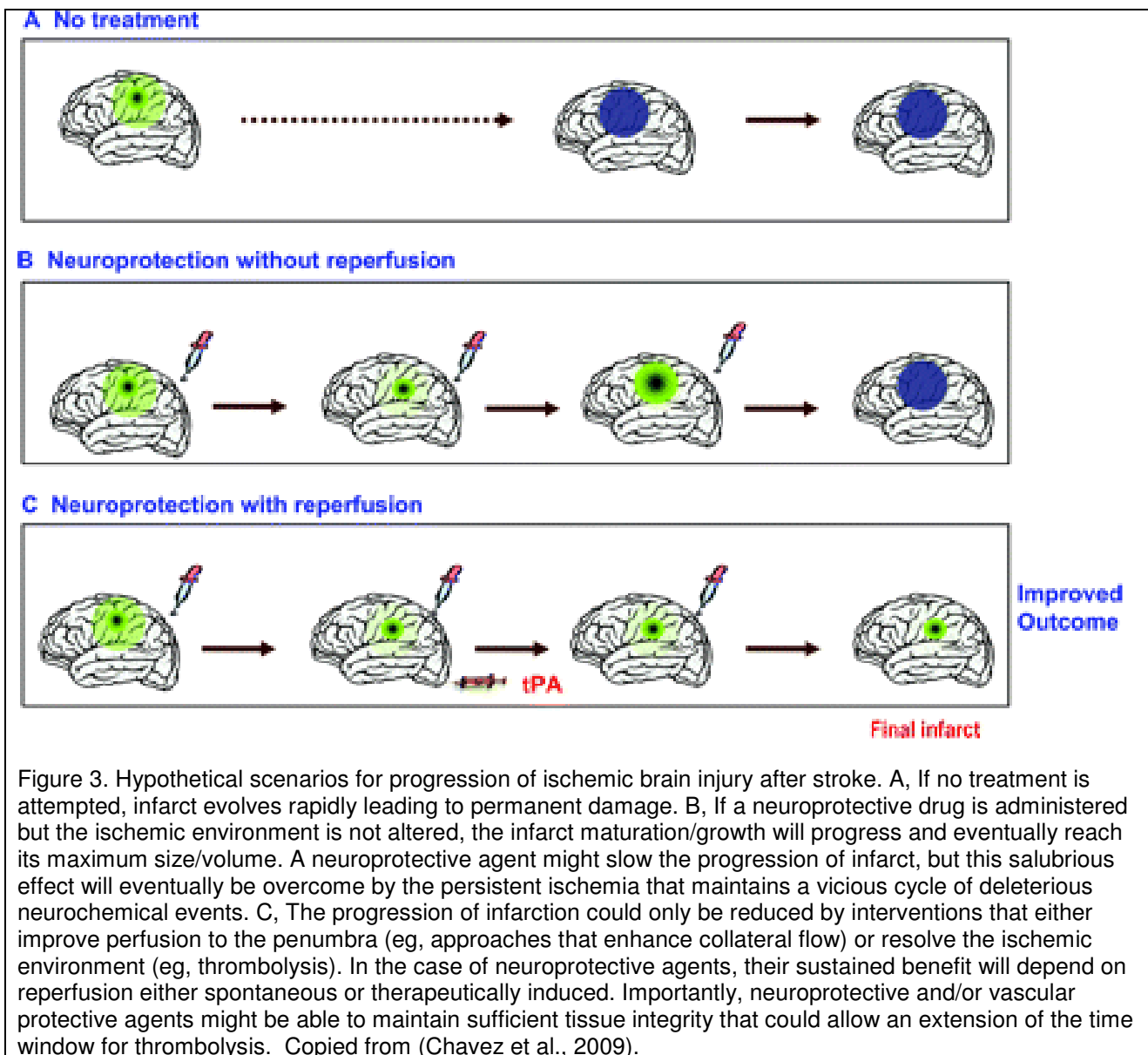
Acute stroke – excellent pathophys rev paper with diagrams (Emsley et al., 2008)



Timeline overview of Stroke induced response



Approximate timeline of stroke-induced responses in the brain parenchyma. The therapeutic time window of novel neuroprotective drug candidates has dual restrictions; first, the variable time it takes for patients to reach clinical centres and be properly diagnosed; second, any therapeutic benefit will depend on the presence of potentially salvageable tissue or penumbra. Drug candidates targeting neurochemical / molecular events outside this realistic window are unlikely to provide meaningful benefit. As a reference, a 3-hour limit for the time window of thrombolysis with tissue plasminogen activator is shown (dashed red line). Copied from (Chavez et al., 2009).



Thrombolysis within 3 hours

“Late” thrombolysis (3.0-4.5 hours after symptom onset) is safe and beneficial (Bluhmki et al., 2009) and recommended (del Zoppo et al., 2009) and evaluated (Ahmed et al.).

Experimental adjunctive therapies {Alexandrov, 2010 #3094}

An overview of stroke epidemiology, primary and secondary prevention and management can be found here - (Marsh and Keyrouz, 2010)

Acute neurorehab
Drugs (Liepert, 2008)

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