The Australian Short Course on Intensive Care Medicine

2004 Handbook
The Australian
Short Course on
Intensive Care Medicine

2004 Handbook

Editor
L.I.G. Worthley
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FMC = Flinders Medical Centre    RAH = Royal Adelaide Hospital

Dinner at:
19:00 hr, Wednesday 31st March 2004
‘House of Chow’
82 Hutt St, Adelaide
REGISTRANTS

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<th>Code</th>
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<tr>
<td>*† 1</td>
<td>Dr. H. So</td>
<td>Intensive Care Unit, PYN Eastern Hospital, Hong Kong</td>
</tr>
<tr>
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<td>Dr. A. Duggan</td>
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<td>*† 4</td>
<td>Dr. R. Lewin</td>
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<td>*† 5</td>
<td>Dr. N. Blackwell</td>
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<td>*† 6</td>
<td>Dr. J. Bates</td>
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<td>*† 7</td>
<td>Dr. J. Ritchie</td>
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<td>*† 8</td>
<td>Dr. M. Scully</td>
<td>Intensive Care Unit, The Alfred Hospital, Victoria</td>
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<td>*† 9</td>
<td>Dr. K. Gandhi</td>
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<td>*†10</td>
<td>Dr. H. Tan</td>
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<td>*†11</td>
<td>Dr. S. Li</td>
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<td>Dr. Y. Goto</td>
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<td>*†14</td>
<td>Dr. B. De Kevlenaer</td>
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<td>*†15</td>
<td>Dr. M. Holland</td>
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<td>*†16</td>
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<td>*†18</td>
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<td>Dr. S. Lane</td>
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<td>* 24</td>
<td>Dr. V. Ho</td>
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<td>* 28</td>
<td>Dr. A. Rashid</td>
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FACULTY

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<td>Dr. L. Worthley (L.W)</td>
<td>Dr. R. Young (R.Y)</td>
<td>Dr. J. Cooper (J.C)</td>
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<tr>
<td>Dr. A. Bersten (A.B)</td>
<td>Dr. M. White (M.W)</td>
<td>Dr. P. Morley (P.M)</td>
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<td>Dr. A. Holt (A.H)</td>
<td>Dr. N. Edwards (N.E)</td>
<td>Dr. C. Joyce (C.J)</td>
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<tr>
<td>Dr. M. Chapman (M.C)</td>
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<tr>
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<td>Dr. M. Yung (M.Y)</td>
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<tr>
<td>Dr. S. Keeley (S.K)</td>
<td>Dr. D. Evans (D.E)</td>
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<td>Dr. A. Slater (A.S)</td>
<td>Dr. A. Flabouris (A.F)</td>
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<tr>
<td>Dr. T. Brownridge (D.C)</td>
<td>Dr. S. Peake (S.P)</td>
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*† = registrants for both sessions
* = registrants for Interactive sessions at the FMC
† = active registrants for Exam oriented sessions at the RAH
‡ = observer registrants for Exam oriented sessions at the RAH
PREFACE

A working knowledge of the basic sciences of anatomy, physiology and pharmacology is the basis for the understanding and management of the critically ill patient. This year the Australian Short Course on Intensive Care Medicine handbook has included a review of the basic sciences of the central nervous system with chapters on cerebrovascular physiology and physiology and pharmacology of the neuromuscular junction. I have also included a chapter on neurological investigations as well as a chapter on acute disorders of consciousness. As with the previous editions, the course registrants presentations (or those that have been submitted on time) have also been included.

This handbook still remains the working document of the Australian Short Course on Intensive Care Medicine and is designed to supplement the course. During the sessions, you may find it useful to mark and note the text to facilitate your recall and review of the course at a later date. Along with the previous editions I trust that you will also find this edition useful.

Dr. L.I.G. Worthley
Adelaide, March 2004
CEREBRAL BLOOD FLOW

The arterial blood supply to the brain is via two carotid and two vertebral arteries. The carotid arteries dividing into anterior and middle cerebral arteries (i.e. anterior circulation) carry the larger percentage of the total cerebral blood supply, and each carries blood distributed almost entirely to the same side of the brain (figure 1 and figure 2).

Figure 1. Arterial supply to the brain with the circle of Willis at the base of the brain formed by the basilar and internal carotid arteries. The left and right internal carotid arteries communicate with the basilar artery via the posterior communicating arteries and the left and right internal carotid arteries communicate anteriorly via the anterior communicating artery (Modified from Gardner E. Fundamentals of neurology, WB Saunders, Philadelphia 1963).
The vertebral arteries (figure 3) unite to form the basilar artery (i.e. posterior circulation; with proximal, middle and distal segments). The circle of Willis is formed by the carotids and the basilar artery (joined by the posterior communicating artery), and is the origin of the six major vessels (i.e. anterior, middle and posterior cerebral arteries) supplying the cerebral cortex. The venous system includes dural sinuses and deep veins which empty into the internal jugular veins.

In normal man, cerebral blood flow (CBF) is autoregulated at 45 - 55 mL/100g/min, between cerebral perfusion pressures of 60 - 130 mmHg (8 - 17 kPa). The grey-matter blood flow averages 69 mL/100g/min, the white matter blood flow averages 28 mL/100g/min and the total cerebral flow ranges from 550 to 750 mL/min (the weight of the adult male brain is 1400 g, the female brain weighs on average 100 g less). Within the limits of autoregulation, cerebral blood flow is independent of pressure and altered only by variation in the cerebral vascular diameter. Loss of autoregulation occurs with cerebral ischaemia and severe closed head injury, and in these conditions cerebral blood flow becomes pressure dependent.

Perfusion pressure

The cerebral perfusion pressure is the difference between the mean intracerebral arterial and venous pressure and is often approximated by the difference between the mean systemic arterial pressure and intracranial pressure, as the intracerebral venous pressure is always maintained at 2 - 4 mmHg above the intracranial pressure. When the jugular venous pressure rises the CSF pressure rises. When cerebral perfusion pressure falls below the lower limit of autoregulation (i.e. 60 mmHg), there is a reduction in cerebral blood flow proportional to the reduction in
Cerebrovascular Physiology

Cerebral perfusion pressure. If the cerebral perfusion pressure falls below a certain value (i.e. critical closing pressure) arterial vessels collapse (due to intrinsic tone of cerebral arterial smooth muscle and extravascular pressure) and blood flow ceases. In normal individuals this varies from 30 to 40 mmHg during the Valsalva manoeuvre.

If the perfusion pressure exceeds the upper limit of autoregulation then cerebral blood flow increases and vasogenic cerebral oedema and hypertensive encephalopathy may occur.

Figure 3. The origin and courses of the carotid and vertebral arteries as they ascend the neck and enter the skull to form the circle of Willis (Modified from Snell RS. Clinical neuroanatomy for medical students. 2nd Ed, Little Brown and Co, Boston 1987).

Cerebral vascular diameter

The cerebral arteriolar diameter may be altered by:

1. Cerebral metabolic rate: cerebral oxygen consumption (and carbon dioxide production, as the cerebral RQ is 1) is 3.5 mL/100g/min (i.e. a total 45 - 50 mL/min) which is approximately 20% of the total resting oxygen consumption. Glucose is the predominant energy source and is used at the rate of 5 mg/100g/min, or a total of 4 g/hr. Cerebral blood flow varies directly with the cerebral metabolic rate, decreasing by 30% with slow wave sleep and increasing significantly with epileptiform seizures and hyperthermia. Within a temperature
range of 22 - 42°C the cerebral metabolic rate changes by 5% for each degree change in temperature (i.e. cerebral metabolic rate is reduced by approximately 25% at 30°C, and 50% at 20°C and is increased by 25% at 42°C). At temperatures above 42°C, there is no increase in cerebral oxygen consumption because enzyme inactivation and cellular damage occurs.

2. Arterial carbon dioxide tension (PaCO₂): at a PaCO₂ of 40 mmHg, the cerebral blood flow varies by 3 - 4% for each 1 mmHg rise or fall in PCO₂, decreasing by 30% at a PaCO₂ of 30 mmHg, with no further reduction in cerebral flow occurring below a PaCO₂ of 20 - 25 mmHg when the CBF is reduced by 40% - 50% and an EEG pattern indistinguishable from hypoxia, of mild or moderate severity, may be observed. Cerebral blood flow increases by approximately 50% and the cerebral blood volume increases by 14 mL (i.e. 20% at a PaCO₂ of 60 mmHg). At a PaCO₂ of 80 mmHg the cerebral blood flow increases by 100%. Hypercapnia up to 80 mmHg is associated with a moderate increase in cerebral metabolic rate. However, at PaCO₂ levels greater than 80 mmHg a progressive reduction in cerebral metabolic rate occurs, which is associated with a progressive reduction in consciousness.

3. Arterial oxygen tension (PaO₂) and oxygen content: cerebral blood flow does not change until the PaO₂ is 60 mmHg, below which the cerebral blood flow increases markedly, increasing by 32% at a PaO₂ of 35 mmHg. A decrease in haemoglobin by 50% (i.e. a reduction in oxygen content) will double the cerebral blood flow. In man, EEG slowing is observed at a PaO₂ of 35 mmHg or when CBF is reduced to 30 mL/100 g/min. The EEG becomes flat at a PaO₂ of 20 mmHg or when the cerebral blood flow is reduced to 15 - 20 mL/100g/min.

CEREBROSPINAL FLUID

The CSF circulates throughout the lateral ventricles which communicate through the foramen of Monro (interventricular foramen) with the unpaired third ventricle of the diencephalon (Figure 4). The third ventricle communicates with the fourth ventricle by way of the aqueduct of Sylvius of the mesencephalon (cerebral aqueduct). About 60% - 70% of the cerebrospinal fluid is formed from the choroid plexus which is located in the roof of the third and fourth ventricles, the other 30% - 40% is formed around the cerebral vessels and along the ventricular walls. The fourth ventricle overlies the brainstem between the pons, medulla and cerebellum and communicates with the subarachnoid space by two lateral foramina (foramen of Luschka) and the median foramen of Magendie, and continues caudally with the central canal of the spinal cord (Figure 4). CSF flows out from ventricular to subarachnoid spaces and is absorbed through the arachnoid villi into the venous sinuses.

The reabsorption of CSF is a mechanical process requiring a pressure gradient to force the CSF through unidirectional microtubules of the arachnoid villi (through which particles of up to 4 - 12 μm in diameter are able to pass, enabling large proteinaceous and cellular debris to be removed from the brain ECF) and into the venous blood. CSF absorption usually ceases at a CSF pressure below 5 mmHg.

Internal (noncommunicating) hydrocephalus occurs if there is a blockage in the foramen of Luschka or Magendie or there is an obstruction within the ventricular system. If the reabsorptive capacity of the arachnoid villi are reduced then external (communicating) hydrocephalus occurs.

The total CSF volume is 150 mL, 50% surrounds the brain and 50% surrounds the spinal cord. The flow through the villi is approximately 500 mL/day (0.35 mL/min). CSF production may decrease with metabolic and respiratory alkalosis, hypothermia and hyperosmolality (there is a 95% reduction of CSF formation with an increase in plasma osmolality of 30 mosmol/kg). When the choroid plexus NaK-ATPase is inhibited using standard doses of digoxin, acetazolamide, frusemide and amiloride, the CSF production may
Cerebrovascular Physiology

decrease by up to 80% of normal (i.e. from 500 to 100 mL/day). An increase in CSF production does not seem to occur under physiological conditions.

Figure 4. Circulation of cerebrospinal fluid. (Reproduced, and redrawn, with permission, from, Chusid JG. Correlative neuroanatomy & functional neurology, 2nd ed. Los Altos, California, Lange Medical Publications 1979: p227).

Cerebrospinal fluid composition

While the composition of the CSF in many ways is like the glomerular filtrate (i.e. an ultrafiltrate of plasma, with differences of electrolyte concentrations being due to a Gibbs-Donnan effect), transport systems exist in the choroid plexus which alter the CSF concentrations of numerous substances (e.g. potassium, calcium, chloride and glucose are less than would be expected if the CSF were simply an ultrafiltrate; Table 1). There are also regional concentration differences in CSF substances. For example, while the cisternal CSF has the same HCO$_3^-$ content as lumbar CSF, it has a protein content 0.10 g/L lower, PCO$_2$ 2.6 mmHg lower and a pH 0.02 higher than lumbar CSF and in disease even larger differences may exist.

CSF rhinorrhoea following a basal skull fracture, which is often transient and only requires prophylactic antibiotic treatment, is identified from other secretions by measuring the glucose content of the fluid (CSF has a glucose content greater than 2.2 mmol/L whereas nasal secretions have no glucose). Interstitial fluid differs from CSF by having a higher protein content (e.g. 3000 compared with 200 mg/L).
Acid-base changes in the CSF

A change in PaCO$_2$ alters the CSF PCO$_2$ and pH rapidly, and in a similar direction to the change in arterial pH and PCO$_2$. During hypercapnia, the CSF HCO$_3^-$ increase is time-dependent, the rapid component is due to HCO$_3^-$/Cl$^-$ exchange across the blood brain barrier (which is inhibited by digoxin and acetazolamide); a slower component follows the increase in plasma HCO$_3^-$ caused by the renal response to chronic hypercapnia. During hypocapnia, approximately 30% of the acute decrease in CSF HCO$_3^-$ is due to an increase in CSF lactate. With prolonged hypocapnia, the CSF lactate decreases and the reduction in CSF HCO$_3^-$ reflects the lower plasma HCO$_3^-$ levels. These effects are not influenced by acetazolamide.

Table 1. Concentrations of substances in human lumbar cerebrospinal fluid (CSF) and plasma

<table>
<thead>
<tr>
<th>Substance</th>
<th>CSF (mmol/L)</th>
<th>Plasma (mmol/L)</th>
<th>CSF:Plasma ratio</th>
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<tr>
<td>Na$^+$</td>
<td>147</td>
<td>150</td>
<td>0.98</td>
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<td>K$^+$</td>
<td>2.9</td>
<td>4.6</td>
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<td>Ca$^{2+}$</td>
<td>1.15</td>
<td>2.35</td>
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<td>Mg$^{2+}$</td>
<td>1.1</td>
<td>0.8</td>
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<td>Cl$^-$</td>
<td>113</td>
<td>99</td>
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<td>HCO$_3^-$</td>
<td>22.9</td>
<td>23.4</td>
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<td>PCO$_2$ (mmHg)</td>
<td>47.9</td>
<td>38.3</td>
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<tr>
<td>pH</td>
<td>7.311</td>
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<td>Osmolality (mosmol/kg)</td>
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<td>Protein (mg/L)</td>
<td>200</td>
<td>6000</td>
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<td>Glucose (mmol/L)</td>
<td>3.5</td>
<td>5.5</td>
<td>0.64</td>
</tr>
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<td>PO$_4$ (inorganic) (mmol/L)</td>
<td>1.1</td>
<td>1.5</td>
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<td>Urea (mmol/L)</td>
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<td>Creatinine (mmol/L)</td>
<td>0.13</td>
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<td>Lactic acid (mmol/L)</td>
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<td>Cholesterol (mmol/L)</td>
<td>0.0052</td>
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With metabolic acidosis or alkalosis the changes observed in CSF pH and HCO$_3^-$ are in the same direction as (but less than) the plasma changes, and are slow to respond to changes in arterial HCO$_3^-$ and pH. The fall in CSF HCO$_3^-$ in metabolic acidosis, is related to the fall in PCO$_2$, as the CSF HCO$_3^-$ reduction is minimal if the PCO$_2$ is not altered. The increase in CSF HCO$_3^-$ associated with metabolic alkalosis is associated with a decrease in Cl$^-$ levels.

An increase in brain lactate production associated with cerebral ischaemia, haemorrhage, infarction and trauma, also influences CSF pH and may be responsible for the hyperpnoea associated with severe cerebral injury.

CSF function

The CSF acts:
1. To buoy 97% of the weight of the brain, protecting it from damage during sudden movement of the head
2. To provide a constant metabolic environment for cerebral tissue (e.g. the blood brain barrier restricts free entry of substances from the plasma to the CSF, for example, K$^+$, Ca$^{2+}$)
and Mg\(^{2+}\) levels in CSF change little in response to plasma fluctuations; once within the CSF, the transition of substances to the cerebral tissue is relatively unrestricted.

3. To transport various intracerebral substances
4. As a sink for waste disposal, to transmit large particles (e.g. protein) from the CSF to the blood stream via the arachnoid villi.\(^{21}\)

**CSF pressure**

The average cranial capacity of an adult is 1400 mL, consisting of 90% brain (1250 mL) 5% blood (75 mL) and 5% CSF (75 mL). As these three elements are relatively incompressible and as the cranium is almost a closed space, the total bulk of these three elements must at all times remain constant (Monro-Kellie doctrine). An increase in brain volume (e.g. cerebral tumour, intracranial, subdural or extradural haematoma, cerebral oedema) can only be accommodated by a reduction in CSF or blood volume. When the effect of the reduction in intracranial CSF volume is maximal, the blood volume is reduced, the CSF pressure rises and cerebral perfusion may be compromised. Raised intracranial pressure can also occur with an increase in CSF volume (e.g. hydrocephalus).

**Methods of measurement**

The CSF pressure may be measured, during a lumbar puncture using a fluid-filled manometer attached to a needle that has entered the subarachnoid space or via a transducer system attached to a catheter or device in contact with the subarachnoid, subdural or epidural space of the head:

1. *Ventricular catheter:* this is normally placed in the frontal horn of the lateral ventricle. It reflects tissue pressure more accurately than other methods, provided that there is no catheter obstruction. It also allows for drainage of CSF and is useful in patients who have had a large subarachnoid haemorrhage and in whom an internal or external hydrocephalus may occur. The disadvantages of this method include difficulty of insertion (particularly in patients who have cerebral trauma, diffuse oedema and compressed ventricles), ventricular haemorrhage and catheter obstruction.

2. *Subdural catheter:* this may be inserted in the subdural space over the frontal lobe of the nondominant hemisphere. This has the advantage of being simple to insert and not requiring penetration of the brain. However, in patients who have unilateral cerebral disease, if the catheter is placed over the normal cerebral hemisphere, the pressure measured may not reflect the increase in intracerebral pressure.\(^{22}\)

3. *Subarachnoid bolt ('Richmond screw'):* this involves the placement of a small hollow bolt into the skull so that its tip lies below the open dura. It has the advantage of a low infection risk due to the arachnoid remaining intact, although it has the disadvantage of not enabling CSF to be drained, high incidence of signal dampening and underestimating ICP values greater than 20 mmHg.\(^{23}\)

4. *Implanted extradural or intracerebral transducer or fibre-optic sensor (Camino laboratories):*\(^{24}\) these catheters are commonly used to measure intracerebral pressures. The disadvantages are, they are expensive, they require specialised equipment and do not allow calibration to check for zero drift.

CSF pressure measurements are made with the patient in the left lateral position, if a lumbar puncture is performed, with the zero reference being the site of the needle entry. When continuous ICP monitoring is being used with a cerebral catheter, the patient is often positioned 15\(^\circ\) head-up with the head in a neutral position\(^{25,26}\) (a posture of head-up greater than 30\(^\circ\) may adversely effect cerebral perfusion pressure).\(^{27,28}\) The zero reference (i.e. at the level of the
foramen of Monro) is taken from a point 2.5 cm upward along a line drawn perpendicular from
the middle and posterior thirds of a line between the tragus of the ear and the lateral angle of
the eye. If cerebral perfusion pressure is to be correctly assessed, the same zero should be used
for the MAP measurement\(^29\) (at a 15° head up position, the foramen of Monro is 8 - 10 cm
higher than the left atrium and therefore the MAP will be approximately 5 - 8 mmHg higher if
measured with the zero at the transection of the 4th intercostal space and midaxillary line).

If the patient is nursed supine and flat, the zero reference is taken at the external auditory
meatus, although ICP values are often 5 mmHg higher than values achieved when using the
above method. One study of 20 patients with ischaemic stroke found that the mid cerebral
artery flow (measured by transcranial Doppler) increased by 12% when the head of the bed was
lowered from a 30° head up position to a 15° head up position and increased by a further 8%
when the head of the bed was lowered from 15° head up position to 0° head up position,
indicating that cerebral blood flow may benefit from lying flat.\(^30\)

**Clinical features of an increased intracranial pressure**

If the intracranial pressure is raised gradually and the structures within the skull maintain
their normal anatomical relationships with no obstruction to the flow of cerebrospinal fluid
(CSF), the intracranial pressure (ICP) may approach the mean arterial pressure (i.e. 40 mmHg)
and the patient remain asymptomatic.\(^31\) However, if the ICP is increased rapidly and the
intracranial structures are compressed or there is blockage to the CSF flow, then the
characteristic symptoms and signs associated with an increase in ICP will commonly occur.
Symptoms include severe headache (worse with coughing), anorexia, nausea, disorientation
and drowsiness. Signs include, projectile vomiting, high pitched cry or scream, lethargy,
strabismus, loss of upward gaze ('sun setting'), papilloedema (which takes 36 hours to develop
with an acute elevation of ICP), absence of retinal venous pulsation and an ability to obliterate
retinal arterioles before obliterating the retinal veins with orbital pressure.\(^32\) Late signs include
the Cushing reflex (e.g. bradycardia, hypertension, irregularity of respiratory rhythm)\(^33\)
pulmonary oedema, bilateral extensor plantar responses, stupor, coma, fixed dilated pupils
(uncal herniation) and brain death.

Rarely, other signs may occur. For example, a transient cutaneous flush of the face,
shoulders, upper arms, upper chest or abdomen that lasts for 5 - 15 minutes has been described
in paediatric patients with a sudden rise in ICP.\(^34\) The flush may be patchy or confluent and
pink or cyanotic. Paediatric patients may also develop a tense anterior fontanelle, splayed
cranial sutures and an increase in head circumference.

**Indications for CSF pressure measurement**

ICP catheters are often used in disorders where cerebral blood flow autoregulation is
deranged and becomes pressure dependent and intracranial pressure may be elevated (e.g.
severe head injury, spontaneous intracranial haemorrhage, post operative brain tumour surgery,
hydrocephalus, encephalitis, cerebral oedema due to liver failure, and postoperative evacuation
of subdural or extradural haematoma). The measurement will permit early identification of
impending clinical deterioration as well as an evaluation of response to therapy.

**Measurements**

Continuous monitoring shows that the normal CSF pressure tracing is pulsatile, with one
component corresponding to arterial pulsations and a slower waveform corresponding to
respiratory movements. It may vary from 0 - 10 mmHg relative to the foramen of Monro
(patient 15° head up) and may transiently rise to 50 mmHg when the patient coughs or strains.
A sustained increase in CSF pressure above 15 mmHg is abnormal; it is usually associated with an increase in amplitude of arterial pulsations and a decrease in respiratory movements. The latter become insignificant when the ICP is raised above 20 mmHg. When the intracranial pressure is elevated to more than 30 mmHg for any period of time, cerebral blood flow is reduced. The resultant ischaemia may stimulate the vasomotor centre and the cardioinhibitory centre, causing a rise in systemic blood pressure and bradycardia, respectively (i.e. Cushing response), although more commonly hypertension and tachycardia occur due to vasomotor centre stimulation.

With any pathological increase in the ICP there may be steady increase, a sustained increase, or waves of increased ICP. Lundberg described three pressure wave forms associated with an increase in ICP.\textsuperscript{35} A waves (plateau waves), describing waves of rapidly rising pressure to 50 mmHg or more lasting for 5-20 min, with an equally rapid descent, occurring several times an hour (and are a haemodynamic phenomenon associated with cerebrovascular vasodilation and are observed in patients with preserved cerebral autoregulation but reduced pressure-volume compensatory reserve);\textsuperscript{36} B waves describing sharp peaked waves of variable height occurring at a frequency of 0.2-2 per min rising up to 30 - 60 mmHg and often coinciding with changes in respiration; and C waves occurring at a frequency of 5 - 8 per min which related to the Traube-Herring-Mayer waves of the arterial blood pressure recordings and are often found when the ICP is raised and pulse pressure increases. Since then, numerous other waveforms (e.g. ramp, scallop, preplateau, prolonged plateau) have been described, although rather than the pattern, the important factors in ICP monitoring appear to be the degree and the duration of elevation in ICP.\textsuperscript{37}

In patients who have a closed head injury and cerebral oedema, therapy to lower ICP is usually initiated if the ICP is 25 mmHg or greater for 15 min or longer or 30 mmHg or greater for 1 min or longer. In Reye’s syndrome, ICP monitoring has been reported to improve outcome by guiding optimal therapy to prevent a reduction in CPP below a critical value of 40 mmHg.\textsuperscript{38}

Complications of measurements

As with all forms of measurement the major hazard of ICP monitoring is the recording of incorrect measurements, which precipitate incorrect therapy. Other complications include, ventriculitis and meningitis and infection rates of up to 20% have been recorded,\textsuperscript{39} although with care, infection rates of 1% should be achieved.

BLOOD-BRAIN BARRIER

The rapidity with which substances penetrate brain tissue, is directly related to their lipid solubility and inversely related to their molecular size. Water, carbon dioxide, and oxygen cross the blood brain barrier readily, whereas glucose crosses more slowly. Changes in plasma Na\textsuperscript{+}, K\textsuperscript{+}, Mg\textsuperscript{2+}, Cl\textsuperscript{-}, HCO\textsubscript{3}\textsuperscript{-} and HPO\textsubscript{4}\textsuperscript{2-}, require three to 30 times as long to equilibrate with the CSF as they do with other interstitial fluid areas. The barrier is largely due to the tight endothelial junctions and basement membrane structure, functioning to maintain the consistency of the environment of the neurones in the central nervous system.\textsuperscript{40}

REFERENCES


Chapter 2

PHYSIOLOGY AND PHARMACOLOGY OF THE NEUROMUSCULAR JUNCTION

NORMAL CHOLINERGIC TRANSMISSION

Choline is actively taken up from the ECF by the cholinergic neurone and, in combination with acetyl-CoA from the tricarboxylic acid cycle, is converted by choline acetyltransferase to acetylcholine (ACh) which is stored in presynaptic vesicles at an estimated 10,000 ACh molecules per vesicle. When an action potential travels down the axon to the nerve terminal, calcium from the ECF enters the cytosol via calcium channels (unaffected by verapamil, nifedipine or diltiazem), facilitating the fusion of axonal and vesicular membranes, causing approximately 150 - 200 synaptic vesicles to disrupt and release ACh into the synaptic cleft. The number of synaptic vesicles that disrupt is influenced by the ECF Ca\(^{2+}\) concentration. A doubling of the Ca\(^{2+}\) concentration results in a 16-fold increase in synaptic vesicle ACh release.

The release of ACh by exocytosis is inhibited by botulinus toxin, hypermagnesaemia and hypoccalcaemia. The amount of Ca\(^{2+}\) entering the nerve terminal is also governed by the duration of the action potential (AP) which is terminated by the outward flux of K\(^{+}\). The outward flux of K\(^{+}\) is inhibited by 4-aminopyridine which increases the release of ACh. This agent has been used at a dose of 0.3 mg/kg, to reverse the neuromuscular blockade associated with antibiotics, nondepolarisers, myasthenia gravis and the Eaton-Lambert syndrome, although it is of limited use in botulism and can cause tremor, excitability and seizures.

The acetylcholine receptor

The acetylcholine receptor at the motor end plate has, 5 subunits (two alpha subunits, one beta subunit, one delta subunit and one gamma or one epsilon subunit), a molecular weight of 250,000 and a half-life of 6 - 13 days. The ACh binding sites on the two alpha subunits on the ECF or synaptic surface of the macromolecule are the sites of competition between cholinergic agonists and antagonists (figure 1). When both alpha unit sites are occupied by an agonist, the central channel undergoes a conformational change to allow Na\(^{+}\) and Ca\(^{2+}\) in and K\(^{+}\) out. Both alpha units must be occupied simultaneously by an agonist; if only one site is occupied the channel remains closed.

The influx of Na\(^{+}\) ions depolarises the adjacent membrane. The channel does not permit anions (e.g. Cl\(^{-}\)) to cross the membrane. If the ACh receptor does not open when both binding sites are occupied by an agonist, the receptor is said to be desensitised. Normally, ACh receptors are constantly changing from a sensitised to a desensitised state. Certain agents may increase the number of desensitised receptors and thus weaken neuromuscular transmission or render the patient more susceptible to neuromuscular blocking agents. Cholinergic receptors are muscarinic (subtypes M\(_1\), M\(_2\) and M\(_3\)) or nicotinic (subtypes N\(_1\) and N\(_2\)). The motor end plate acetylcholine receptor is a nicotinic (N\(_2\)) receptor that is sensitive to neuromuscular blocking agents, unlike the sympathetic ganglionic receptors (i.e. N\(_1\) receptors) which are only mildly responsive to some of these agents (e.g. d-Tubocurarine is a mild ganglion blocker).
Physiology and Pharmacology of the Neuromuscular Junction

Figure 1. A diagrammatic representation of acetylcholine receptors, depicting the five subunits (alpha, beta alpha, gamma, delta) around the central ion channel. The main immunogenic region (MIR) is associated with the alpha subunits. The 43 kDa cigar-shaped cytoplasmic structures are cytoskeletal components. Records of the opening and closing of the ion channels are shown. The lower trace indicates that monoclonal antibodies that bind to the MIR have no effect on the channel opening, whereas a monoclonal antibody (antibody No. 10) that binds to certain sites on the alpha and beta subunits, blocks channel opening completely (Reproduced, with permission, from Engel AG. Myasthenia gravis and myasthenic syndromes. Ann Neurol 1984;16:519-534).

Cholinesterase

Acetylcholine is hydrolysed by cholinesterases to choline and acetate terminating the action of the ACh. Acetylcholinesterase (AChE or true cholinesterase) is found in RBCs and at all sites of cholinergic transmission. It is a macromolecule that has a number of active centres where the hydrolysis of ACh may take place. These active centres have two areas that interact with ACh, the anionic site and the esteratic site. The anionic site contains a negatively charged amino acid that binds to the positively charged quaternary amine group of ACh. The esteratic site of the molecule contains a serine molecule that is responsible for breaking the ester linkage of the ACh, forming choline and acetylated acetylcholinesterase. The latter is rapidly hydrolysed regenerating the free enzyme.

Pseudocholinesterase (PChE) is found in plasma, skin and intestine; it hydrolyses succinylcholine and procaine. Its physiological significance is unknown.

DRUGS THAT ACT AT THE NEUROMUSCULAR JUNCTION

Nondepolarising agents

The nondepolarising agents are competitive blockers of ACh, blocking neuromuscular transmission by binding to one or both ACh receptor binding sites without depolarising the
skeletal muscle membrane. Conditions that cause an increased sensitivity to these agents are listed in Table 1.\textsuperscript{5,6,7}

**Table 1. Conditions associated with an increased sensitivity to nondepolarising relaxants**

<table>
<thead>
<tr>
<th>Neuromuscular disorders</th>
<th>Hypokalaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio, motor neurone disease</td>
<td>Myxoedema</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Eaton-Lambert syndrome</td>
<td>Inhibition of motor nerve terminal acetylcholine release</td>
</tr>
<tr>
<td>Myasthenia gravis,</td>
<td>Botulinum toxin, snake venoms</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
<td>Hypermagnesaemia, hypocalcaemia</td>
</tr>
<tr>
<td>Polymyositis, dermatomyositis</td>
<td>Drugs</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>Volatile anaesthetic agents, barbiturates</td>
</tr>
<tr>
<td>Myxoedema</td>
<td>Agents with local anaesthetic properties</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Local anaesthetics</td>
</tr>
<tr>
<td>Inhibition of motor nerve terminal acetylcholine release</td>
<td>Phenothiazines, tricyclic antidepressants</td>
</tr>
<tr>
<td>Botulinum toxin, snake venoms</td>
<td>Beta blockers with membrane stabilising effects (e.g. propranolol)</td>
</tr>
<tr>
<td>Hypermagnesaemia, hypocalcaemia</td>
<td>Lincomycin, clindamycin</td>
</tr>
<tr>
<td></td>
<td>Chloroquine, quinidine, procainamide,</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
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<tr>
<td></td>
<td>Aminoglycosides</td>
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<tr>
<td></td>
<td>Tetracyclines</td>
</tr>
</tbody>
</table>

The pharmacological properties of the commonly used nondepolarising agents are listed in Table 2. Tubocurarine is often unsuitable for use in the intensive care unit because of its hypotensive effects (due to ganglion blocking and histamine release activity) and prolonged duration of action in patients with renal failure. Gallamine and alcuronium similarly have a prolonged action in patients with renal failure. Pancuronium and vecuronium are synthetic steroid-based neuromuscular blocking agents, and both have prolonged actions in patients with renal failure, although pancuronium (unlike vecuronium) has a vagolytic effect (i.e. causes tachycardia). Vecuronium is marketed as a white powder which is soluble but unstable in aqueous solutions. When vecuronium is stored at 25°C in daylight, after being reconstituted to 1 ml, decomposition is approximately 1% - 2% after 24 hr. Mivacurium is a potent nondepolarising relaxant whose onset is as rapid but rate of recovery is twice as rapid as vecuronium due to its metabolism by plasma cholinesterase. Reversal of mivacurium with anticholinesterases is not required and in patients with cholinesterase deficiency prolongation of the neuromuscular blockade (> 6 hours) occurs. Rocuronium is about one sixth as potent as vecuronium but has a more rapid onset.\textsuperscript{8}
Table 2  Pharmacological properties of the nondepolarising agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (µg/kg)</th>
<th>Onset block (min)</th>
<th>Duration block (min)</th>
<th>Receptor N&lt;sub&gt;2&lt;/sub&gt; release</th>
<th>Histamine % renal excretion</th>
<th>CVS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decamethonium</td>
<td>50</td>
<td>1 - 2</td>
<td>15 - 20</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Gallamine</td>
<td>3000</td>
<td>2 - 3</td>
<td>30 - 40</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>300</td>
<td>3 - 5</td>
<td>40 - 60</td>
<td>+</td>
<td>-</td>
<td>70 - 90</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>100</td>
<td>3 - 5</td>
<td>40 - 60</td>
<td>++</td>
<td>-</td>
<td>60 - 80</td>
</tr>
<tr>
<td>D-Tubocurarine</td>
<td>600</td>
<td>3 - 5</td>
<td>40 - 60</td>
<td>++</td>
<td>-</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>100</td>
<td>2 - 3</td>
<td>20 - 40</td>
<td>-</td>
<td>-</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>100</td>
<td>2 - 4</td>
<td>10 - 20</td>
<td>-</td>
<td>+</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>600</td>
<td>1 - 3</td>
<td>30 - 40</td>
<td>-</td>
<td>-</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Atracurium</td>
<td>450</td>
<td>3 - 4</td>
<td>20 - 40</td>
<td>-</td>
<td>+</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>100</td>
<td>4 - 5</td>
<td>40 - 60</td>
<td>-</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1400</td>
<td>0.25 - 0.3</td>
<td>3 - 10 stim</td>
<td>+</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

N<sub>1</sub> = nicotinic ganglion receptors, M<sub>2</sub> = muscarinic cardiac receptors, Dose = intubation dose, Onset = 90 - 100% twitch block after intubation dose, Duration to 25 - 75% twitch recovery after intubation dose. Cardiovascular effects, blood pressure increase = (+), decrease = (-), pulse rate increase = (+), decrease = (-).

Most agents undergo either renal or hepatic degradation and excretion, although both atracurium and cisatracurium largely undergo nonenzymatic degradation to inactive metabolites, without requiring renal or hepatic excretion. Mivacurium is metabolised by plasma cholinesterase.

For continuous relaxation, 20 - 30 min after the initial dose of a nondepolarising agent, a further dose of a third to a fifth of the original dose is used, although with the rapid offset agents (e.g. vecuronium, atracurium, cisatracurium), continuous monitoring of neuromuscular transmission is normally performed to maintain ideal control. 9,10

In the critically ill patient an acute generalised myopathy may develop with prolonged use of the steroid based nondepolarising agents (i.e. vecuronium and pancuronium) particularly when they are administered with corticosteroids. 11

Depolarising agents

The depolarising agents (e.g. succinylcholine, decamethonium) mimic the effect of acetylcholine. However, as they are not hydrolysed by acetylcholinesterase, they have a prolonged action and cause neuromuscular blockade.

Succinylcholine

A solution of succinylcholine hydrolyses at room temperature (e.g. 5% after 1 month and 20% after 12 months), therefore it is usually stored in a refrigerator. The characteristics of the neuromuscular blockade produced by succinylcholine changes when the dose is changed, for example:

1. Phase I block: the intubation dose of 1.4 mg/kg (i.e. 100 mg/70 kg) of succinylcholine causes excitation (i.e. fasciculation) due to its initial attachment and stimulation of the nicotinic (N<sub>2</sub>) motor end plate receptor. With continuous attachment the membrane remains depolarised, causing an inexcitability of the area of muscle surrounding the motor end plate, and a neuromuscular blockade lasting from 3 - 10 min. During this phase, the twitch response is
reduced and the train of 4 (see later) is close to unity. Neither fade nor post-tetanic facilitation occurs.

**Phase II block:** with continuous use of succinylcholine up to 3 - 7 mg/kg (i.e. 200 - 500 mg/70 kg), desensitisation of the ACh receptor occurs, causing a prolonged neuromuscular block of up to 30 min. During this phase, fade and post tetanic facilitation is evident and the ‘train of 4’ is less than unity. Phase II block may be partially reversed by edrophonium or neostigmine.

The action of succinylcholine is terminated by pseudocholinesterase, and the average adult has enough pseudocholinesterase to convert approximately 40 - 80 mg of succinylcholine per minute\textsuperscript{12}. The action of succinylcholine is prolonged when the plasma levels of pseudocholinesterase are low due to an acquired disorder or an hereditary abnormal PChE exists (see Table 3).

### Table 3. Conditions associated with a prolonged action of succinylcholine

<table>
<thead>
<tr>
<th>Reduction in plasma pseudocholinesterase (PChE) levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Pregnancy and immediately postpartum</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Infection, myocardial infarction, pulmonary embolism</td>
</tr>
<tr>
<td>Starvation</td>
</tr>
<tr>
<td>Carcinomatosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition of PChE (eg, anticholinesterases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical plasma PChE</td>
</tr>
</tbody>
</table>

A hereditary disorder caused by an atypical plasma PChE may be diagnosed by assessing the patient’s dibucaine number. This number refers to the percentage inhibition of PChE activity by dibucaine under standard conditions. A $10^{-5}$ molar concentration of dibucaine inhibits normal PChE to a far greater extent than the abnormal PChE. Normal plasma has a dibucaine number of 80, plasma from a heterozygote (containing both normal and abnormal gene) has a dibucaine number between 40 - 70, and plasma from a homozygote has a dibucaine number of less than 30. Alternative routes of elimination of succinylcholine (which assume greater importance when there is a defect in enzymatic hydrolysis) are alkaline hydrolysis (at 5% or less per hour), renal excretion (at 2% or less per hour) and redistribution.

The side effects of succinylcholine include:

1. **Cardiovascular effects:**
   a. Tachycardia and hypertension, due to stimulation of the autonomic ganglion
   b. Bradycardia, salivation and bronchorrhoea, which may occur after the second dose due to vagal stimulation.

2. **Skeletal muscle contraction effects:**
   a. Increased intraocular pressure, due to a continuous increase in extraocular muscle tone
   b. Increased intragastric pressure (up to 85 cm H$_2$O had been recorded\textsuperscript{13})
   c. Muscle pain, the incidence of which varies from 1 to 80%, depending on sex (greater in females), age (less in children and elderly) and degree of ambulation (greater in ambulatory patients)
   d. Myoglobinuria
e. Myotonic response, i.e. contraction rather than relaxation in patients who have myotonic dystrophy, myotonia congenita, motor neurone disease, and patients susceptible to malignant hyperpyrexia

f. Malignant hyperpyrexia

g. Hyperkalaemia: in normal subjects, intravenous succinylcholine increases the plasma K$^+$ by 0.5 - 1 mmol/L. The effect begins after 1 min, reaches a maximum at 3 - 5 min and lasts for 10 - 15 min.\textsuperscript{14} The increase in plasma K$^+$ is increased in patients who have burns,\textsuperscript{15} massive tissue trauma,\textsuperscript{16} rhabdomyolysis, neuroleptic malignant syndrome,\textsuperscript{17} closed head injury, multiple sclerosis, cerebrovascular accidents,\textsuperscript{18} encephalitis, spinal cord injury with hemiparesis or paraplegia,\textsuperscript{19} Guillain-Barré syndrome\textsuperscript{20} and tetanus. The hyperkalaemic effect is usually maximum at 14 days, although the effect may be noticeable from 1 to 25 weeks. The K$^+$ arises from skeletal muscle due to skeletal muscle damage and a proliferation of post synaptic ACh receptors which cause a massive liberation of K$^+$ when the skeletal muscle is stimulated. The hyperkalaemic effect is exaggerated with beta-blockade,\textsuperscript{21} and can be attenuated by pretreatment with intravenous d-tubocurarine, pancuronium, calcium gluconate, magnesium sulphate, dantrolene, diazepam, lignocaine or salbutamol.

\textit{Monitoring neuromuscular blockade}

The assessment of the presence or absence of residual weakness due to neuromuscular blockade is often performed clinically. For example, if the patient can lift his or her head from the pillow for 5 s or more, has a vital capacity of 15 mL/kg and inspiratory force of 20 cm H$_2$O negative pressure, then the residual weakness due to neuromuscular blockade is clinically insignificant. A more objective method to assess the degree of neuromuscular blockade is to stimulate (often by using a peripheral nerve stimulator) an accessible peripheral motor nerve and evaluate the response of the skeletal muscle supplied by that nerve.\textsuperscript{22}

The peripheral nerve stimulator is usually set to deliver a supramaximal (usually 20 - 30 mA, but may be up to 50 mA), square wave pulse of 0.2 s duration to a peripheral nerve (often the ulnar nerve, assessing the response by measuring thumb adduction) at varying frequencies. Examples are given here.

\textit{Single twitch} (i.e. 0.15 - 0.1 Hz or one in 10-15 s). If a neuromuscular blocking agent is used, the control response is measured first. A response of 25% - 75% of the control response is defined as the recovery rate (i.e. a state which requires more neuromuscular blockade, if clinical relaxation is required).

\textit{Tetanic stimulation} (i.e. 50 Hz for 5 s). This may be used to determine the presence or otherwise, of fade, which indicates residual nondepolarising neuromuscular blockade. However, in an awake patient, it is a painful test, and provides no more information than the ‘train of four’.\textsuperscript{23}

\textit{Post-tetanic twitch}. This refers to a repeated single twitch stimulation, 10 s after a tetanic stimulation. Potentiation indicates residual non depolarising neuromuscular blockade.

\textit{‘Train of 4’ stimulation}.\textsuperscript{24} Supramaximal stimuli are administered at 2 Hz for 2 s with a stimulus duration 0.2 s. Each ‘train of 4’ is not repeated more frequently than once every 10 - 12 s. If the fourth response is absent, there is approximately 75% depression of the first response in relation to the control. If the third and fourth responses are absent, 80% suppression of the first response (in relation to the control) is present, and at 90% inhibition the second twitch becomes undetectable. As clinical relaxation is defined as a single twitch height of 5 - 25% of the control, when three responses are detected using a ‘train of 4’ (i.e. no more than 75% blockade exists) a small supplemental dose of muscle relaxant is usually required to maintain clinical relaxation. The ratio of the amplitude of the fourth to the first evoked response
in the same train (e.g. ‘train of 4’ ratio) also provides a convenient method to assess neuromuscular transmission. With a ‘train of 4’ ratio above 60% the patient is usually able to lift his/her head from the pillow for 5 s or more, and a ratio of 75% or greater is correlated with adequate clinical recovery from neuromuscular blockade.25

**Anticholinesterases**

The anticholinesterases inhibit acetylcholinesterase, thereby prolonging the effects of ACh. They can be classified as quaternary amines (e.g. edrophonium), carbamates (e.g. neostigmine, physostigmine, pyridostigmine and carbaryl), and organophosphates.

The quaternary amines attach to the anionic site by electrostatic attachment, competing with ACh for this site (i.e. they provide a competitive block). The carbamates attach to the esteratic site as well as the anionic site of the enzyme. This attachment results in a chemical bonding and hydrolysis of the carbamylated enzyme which lasts for about 1 hr for neostigmine, physostigmine and pyridostigmine, and 6 - 12 hr for carbaryl. The organophosphates phosphorylate the esteratic site of the enzyme. Physostigmine and most organophosphates pass the blood brain barrier causing CNS effects; neostigmine and pyridostigmine do not. The half-life of a low dose of edrophonium (e.g. 10 mg) is only 2 - 5 min, due to redistribution. The half-life of neostigmine, pyridostigmine and high-dose edrophonium (e.g. 35 - 70 mg) is 1 - 2 hr, increasing to 3 - 6 hr if renal failure exists.26,27 Neostigmine is poorly absorbed via the gastrointestinal tract with a 10% bioavailability (e.g. 1 - 2 mg intravenously is equivalent to 15 mg orally) and is excreted unchanged via the kidneys. Pyridostigmine also has a poor oral bioavailability (e.g. 2 mg intravenously is equivalent to 60 mg orally). Physostigmine is readily absorbed by the gastrointestinal tract and is destroyed by cholinesterases, 1 mg intravenously has a half-life of 1 hr irrespective of renal function. The anticholinesterases are often used to reverse competitive neuromuscular blockade. The dosages of the commonly used agents are listed in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>IV (mg)</th>
<th>onset (min)</th>
<th>duration (hr)</th>
<th>renal excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
<td>35 - 70</td>
<td>1 - 2</td>
<td>1 - 2</td>
<td>70</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>2.5</td>
<td>3 - 5</td>
<td>1 - 2</td>
<td>50</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>10</td>
<td>7 - 10</td>
<td>1 - 2</td>
<td>75</td>
</tr>
</tbody>
</table>

**Anticholinesterase poisoning**

Anticholinesterases are often used in agriculture as pesticides. They are either organophosphates (e.g. malathion, dimethoate, metasystox, fenthion, parathion, sarin, soman) or carbamates (e.g. Carbaryl, Baygon).

Organophosphates inactivate cholinesterase by phosphorylating the esteratic site of the enzyme, and unless dephosphorylation by pralidoxime occurs (which needs to be administered within a few hours of the organophosphate ingestion because of an ‘aging’ of the phosphorylated enzyme), new enzyme has to be synthesised before normal synaptic activity can occur (plasma cholinesterase recovers within 3 - 4 weeks, whereas red blood cell cholinesterase may not be fully restored to normal function for several months). Carbamates, on the other hand, combine reversibly with cholinesterase, allowing their effects to persist for only 12 hr or less.
**Clinical features.** There may be acute, intermediate and delayed sequelae in patients who have anticholinesterase poisoning.

1. *Acute cholinergic syndrome.* Acute anticholinesterase poisoning may occur from inhalation, skin absorption, or ingestion, with symptoms characteristically beginning after 30 - 60 min and reaching a maximum after 2 - 8 hr. In some cases, symptomatology may be delayed for up to 12 hr, and with dichlorfenthion and fenthion the onset of symptoms may be delayed by up to 2 and 5 days respectively. With fenthion the symptoms may recur after 24 days. The organophosphate poisoned patient often emits a characteristic odour. The acute clinical picture may be mild, moderate or severe depending upon the quantity of cholinesterase inhibitor ingested. The patient exhibits some or all of the features listed in Table 5.

<table>
<thead>
<tr>
<th>Muscarinic effects</th>
<th>clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular: miosis</td>
<td>blurred vision</td>
</tr>
<tr>
<td>increase lacrimal secretion</td>
<td></td>
</tr>
<tr>
<td>CVS: bradycardia</td>
<td>hypotension</td>
</tr>
<tr>
<td>junctional rhythm</td>
<td></td>
</tr>
<tr>
<td>peripheral vasodilation</td>
<td></td>
</tr>
<tr>
<td>RS: bronchoconstriction</td>
<td>dyspnoea, cyanosis</td>
</tr>
<tr>
<td>bronchorrhoea</td>
<td>cough, crackles, wheezes</td>
</tr>
<tr>
<td>pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>GIT: increase tone and motility</td>
<td>salivation, vomiting</td>
</tr>
<tr>
<td>decrease tone of sphincters</td>
<td>diarrhoea, abdominal cramps</td>
</tr>
<tr>
<td>increase secretion</td>
<td></td>
</tr>
<tr>
<td>GUS: Contraction of detrusor</td>
<td>urinary incontinence</td>
</tr>
<tr>
<td>Skin: Increase sweat production</td>
<td>diaphoresis</td>
</tr>
<tr>
<td>Nicotinic effects</td>
<td></td>
</tr>
<tr>
<td>MSS: Skeletal muscle, initial stimulation followed by paralysis</td>
<td>fasciculations (eyelids, tongue)</td>
</tr>
<tr>
<td>following by paralysis</td>
<td>weakness, paralysis</td>
</tr>
<tr>
<td>CVS: Sympathetic ganglia initial stimulation</td>
<td>tachycardia, hypertension</td>
</tr>
<tr>
<td>following by paralysis</td>
<td>(often overridden by parasympathetic effects)</td>
</tr>
<tr>
<td>CNS: muscarinic and nicotinic effects</td>
<td>bradycardia, hypotension</td>
</tr>
<tr>
<td></td>
<td>tremor, anxiety, confusion, seizures, coma</td>
</tr>
</tbody>
</table>

With severe poisoning, multiple organ failure (e.g., respiratory failure, renal failure, hypotension, complete heart block, ventricular tachycardia and ventricular fibrillation) and even necrotising pancreatitis can develop. While cardiac arrhythmias associated with organophosphate poisoning are usually an initial brief period of sinus tachycardia followed by bradycardia, a rare syndrome of prolonged QTc interval and sudden death has also been reported in patients from 1-15 days after the exposure.
2. Intermediate syndrome. An intermediate syndrome is diagnosed by the onset of motor paralysis developing 1 - 4 days after organophosphate poisoning. It is characterised by an acute respiratory paresis, weakness of proximal limb muscles and muscles supplied by cranial nerves, and depressed tendon reflexes (i.e. a combined pre and postsynaptic dysfunction of neuromuscular transmission), and may require mechanical ventilation for up to 18 days, before it reverses. Parathion is the causitive agent in up to 75% of cases.

3. Delayed sequelae. In some cases (due to the phosphorylation of a peripheral nervous tissue esterase), the acute cholinergic phase may be followed by a delayed peripheral polyneuropathy involving the distal muscles of the extremities. The rapid onset of a distal and symmetrical sensorimotor polyneuropathy (with weakness and ataxia) is diagnostic, appearing 2 - 5 weeks after the exposure. Chronic neuropsychological functional impairment (e.g. impairment of auditory attention, visual memory, problem solving, motor reaction and dexterity) may also occur after an acute episode of organophosphate poisoning, and after long-term occupational exposure.

Investigations. The RBC (true) and plasma (pseudo-) cholinesterase levels are reduced markedly with anticholinesterase poisoning and are usually 30% - 50% of normal by the time symptoms appear. Patients with levels of less than 50% are often symptomatic, although during convalescence the patient may return to normal muscle function with pseudocholinesterase levels of only 20%. Normally, RBC cholinesterase levels return to normal after 5 - 7 weeks and pseudocholinesterase levels return to normal after 4-6 weeks.

Treatment. The treatment may include:

1. Resuscitation: intravenous fluids, intubation ventilation and control of seizures by using benzodiazepines or barbiturates may be required, as well as gastric lavage and oral activated charcoal. Medical and nursing personnel need to wear protective clothing and gloves, when dealing with these patients, to avoid contact with the pesticide.

2. Anticholinergic agents (e.g. atropine, glycopyrrolate): these agents reverse the muscarinic symptoms of bradycardia, and excessive gastrointestinal and respiratory secretions. While one study found that 7.5 mg of glycopyrrolate in 200 ml of 0.9% saline was just as effective as 15 mg of atropine in 100 mL of 0.9% saline (both of which were infused until the heart rate was > 60 and fasciculations were absent), in the management of organophosphate poisoning, atropine is the drug of choice and is administered intravenously in 1 - 5 mg amounts every 5 min until excessive secretions are controlled, the pulse rate is greater than 80 beats per min and the pupils are dilated. Up to 10 - 30 mg of atropine may be required initially, thereafter 1 - 5 mg may be required every 30 min for maintenance. While atropine (unlike glycopyrrolate) crosses the blood brain barrier and reverses some of the CNS effects, it is ineffective against the neuromuscular paralysis. In one case of organophosphate poisoning, 19,590 mg of atropine was administered over 24 days, with 2950 mg administered in one 24 h period.

3. Cholinesterase reactivators (pralidoxime, obidoxime): Pralidoxime is the agent of choice as high doses of obidoxime are hepatotoxic. Pralidoxime (PAM) as the chloride, iodide, mesylate or methylsulphate salt are all equally effective in reactivating cholinesterase. However, pralidoxime chloride is usually recommended, as it has less side-effects than the iodide salt (repeated asystole has been reported with the administration of pralidoxime iodide) and can be used in patients who have iodide sensitivity. Pralidoxime is most effective in treating the nicotinic symptoms (e.g. muscular fasciculations and paralysis) of certain organophosphate poisonings. It appears to be relatively ineffective against dimefox, dimethoate, methyl diazinon, mipafox and scradan and against carbamates (it may even
Physiology and Pharmacology of the Neuromuscular Junction

increase carbamate toxicity because pralidoxime has a weak anticholinesterase activity. Pralidoxime being an ionised compound does not cross the blood brain barrier easily and accordingly has minimal beneficial effects against CNS symptoms. It is also only effective if it is administered within 24 hr of the poisoning, as the organophosphate-cholinesterase bond becomes relatively permanent after 48 - 72 hr.

To reach the effective plasma concentration of 4 mg/L, pralidoxime should be administered as a 1 g intravenous bolus, followed by an infusion of 0.5 g/hr (i.e. 12 g/day). However, higher doses have been recommended (e.g. 30 mg/kg followed by 8 mg/kg/hr, and in children 25-50 mg/kg followed by a continuous infusion of 10 - 20 mg/kg/hr as the dose recommended to attain that which was believed to be the effective plasma concentration of 4 mg/L does not permit the full exploitation of the therapeutic potential of pralidoxime.

Pralidoxime is relatively non toxic, although rapid intravenous administration may be associated with nausea, tachycardia, disturbances of vision, headache, dizziness and weakness due to transient neuromuscular blockade. It has an elimination half-life of 1.2 hr and is normally excreted by the kidneys.

However, some have questioned the effectiveness of pralidoxime, with one stating that ‘PAM has no place’ in the current management of organophosphate poisoning. In one study of 10 cases of organophosphate poisoning, no clinical evidence of reactivation of the phosphorylated cholinesterase was observed, when pralidoxime was used. In another study, the use of pralidoxime (4 gm in the first 24 hr followed by 1 gm daily for 5 days) was not associated with an improvement in outcome. Nevertheless, the doses used in all of these studies may have been insufficient as other studies have reported beneficial effects from high dose pralidoxime administration.

4. Other therapy: replacement of blood volume has been used successfully and plasmapheresis (with fresh frozen plasma replacement) may be of use. In the experimental model, adenosine receptor agonists (5’-N-ethylcarboxamido-adenosine and N6-cyclopentyl adenosine) if given within minutes of organophosphate poisoning, prevent or reduce salivation, seizures and respiratory distress and improve survival.

Magnesium sulphate has been used successfully to control tachycardia, ventricular arrhythmias and muscle fasciculations.

REFERENCES

Chapter 3

NEUROLOGICAL INVESTIGATIONS

LUMBAR PUNCTURE

Indications

A lumbar puncture may be performed to diagnose or treat certain disorders (Table 1) and is only carried out following a CT scan, to exclude a lesion that may increase the possibility of coning after the procedure\textsuperscript{1,2,3} (although coning may still occur after a lumbar puncture even in the presence of a normal CT scan\textsuperscript{4}). The lesions that are likely to provoke coning include a cerebral space-occupying inflammatory lesion (e.g. subdural empyema, brain abscess, toxoplasma encephalitis), tumor, haemorrhagic lesion, cerebral oedema, thrombosis of the sagittal sinus or cortical vein, occlusion of the arachnoid villi or ventriculus foramina.

Table 1. Indications for lumbar puncture

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Antibiotic or cytotoxic treatment</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>Anaesthesia or pain treatment (e.g. local anaesthetics, opiates)</td>
</tr>
<tr>
<td>CNS malignancy</td>
<td>Antispasm therapy (e.g. baclofen)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td></td>
</tr>
<tr>
<td>Spinal obstruction</td>
<td></td>
</tr>
</tbody>
</table>

When a lumbar puncture is used to diagnose a neurological disease, the tests which are commonly performed on the CSF are listed in Table 2.\textsuperscript{5} The characteristic diagnostic features of meningitis, subarachnoid haemorrhage, CNS malignancy and Guillain-Barré syndrome are reviewed.

Meningitis

The normal CSF is clear. It has a mononuclear cell count of 5 per mm\textsuperscript{3} or less, with no polymorphonuclear cells or RBC's, the glucose is usually 2.8 - 4.4 mmol/L, and the protein concentration is 0.15 - 0.45 g/L (which is a mixture of albumin and globulins in a ratio of 8:1). Meningitis commonly causes an increase in CSF pressure, protein and cell count and a decrease in glucose.

1. Bacterial meningitis: a positive CSF culture is found in the majority of patients who have bacterial meningitis, and who have not been treated previously with antibiotics. It is associated with an increased CSF opening pressure (usually > 15 mmH\textsubscript{2}O), polymorphonuclear cell count
(which ranges from 1000 - 100,000/mm$^3$, although is usually between 5000 - 20,000/mm$^3$), and protein concentration greater than 0.45 g/L, and, in 70% of cases, a CSF : serum glucose ratio of less than 0.31. Bacterial antigens for *Neisseria meningitidis*, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae* may be measured in the CSF in patients who have a meningitis with an increased polymorph count (particularly if antibiotics have been previously administered).

**Table 2. Cerebrospinal fluid tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure measurement</td>
<td>60 - 150 mmH$_2$O (abnormal if $\geq$ 190 mmH$_2$O)</td>
</tr>
<tr>
<td>Culture</td>
<td>mononuclear cell count $\leq$ 5 cells/mm$^3$</td>
</tr>
<tr>
<td>Cell count</td>
<td>Mononuclear cell count $\leq$ 5 cells/mm$^3$</td>
</tr>
<tr>
<td>Biochemical tests</td>
<td>Protein $\leq$ 450 mg/L</td>
</tr>
<tr>
<td></td>
<td>Glucose $\geq$ 2.2 mmol/L (or 60% - 70% plasma glucose)</td>
</tr>
</tbody>
</table>

2. **Fungal meningitis:** this is usually cryptococcal and is associated with an elevated CSF opening pressure, protein concentration, and mononuclear cell count, and a normal or low glucose level. The Indian ink stain test detects the *Cryptococcus* by demonstrating a halo around the cell in 20 - 50% of cases. Cryptococcal meningitis has a positive CSF culture in 60% - 70% of patients. The likelihood of a positive culture and demonstration of the cryptococcal cell increases if multiple lumbar punctures are performed. If the CSF mononuclear cell count is greater than 5/mm$^3$, (or the CSF is from an HIV positive patient), latex agglutination test for Cryptococcus should be performed.

3. **Viral meningitis:** the diagnosis of a viral meningitis (e.g. infectious mononucleosis) often relies upon exclusion of other causes. A high cell count with a mononuclear pleocytosis of up to 1000/mm$^3$, normal glucose and normal to elevated protein levels and CSF opening pressure may be found. CSF culture is rarely of value.

4. **Other causes of an increased CSF cell count:** a mononuclear cell reaction may be observed in encephalitis, multiple sclerosis and TB, although it rarely exceeds 300 cells/mm$^3$. A mild increase in mononuclear cells may also be observed in patients who have cerebral tumours, meningeal tumours (which may also be associated with a decreased CSF glucose level) cerebral abscess and intracranial venous thrombosis, and a mixed polymorph and mononuclear pleocytosis may be observed in patients who have cerebral and extradural abscess, TB and in the early stage of poliomyelitis.

**Subarachnoid haemorrhage**

A lumbar puncture is only performed if the CT scan is normal and the diagnosis of subarachnoid haemorrhage is in doubt. If the lumbar puncture is blood stained, then serial samples should be collected and the observation of CSF clearing should be supported by RBC counts of serial specimens to confirm or otherwise a traumatic tap. A sample (usually the last sample) should be centrifuged as soon as possible (and certainly within 1 hr) and the supernatant inspected. If there is a yellow discolouration of the CSF (i.e. xanthochromia),
erythrocyte lysis has occurred which indicates that blood has been in the CSF for more than 1 - 2 hr, although it may not occur for up to 12 hr after a subarachnoid haemorrhage. Xanthochromia always occurs within 24 hr of a subarachnoid haemorrhage, becomes most intense at 7 days and disappears in 3 - 4 weeks.6 If the lumbar puncture sample is clear, the CSF should be submitted for spectrophotometric analysis to completely rule out xanthochromia. After 3 to 7 days, RBCs disappear from the CSF.

CNS malignancy

A lumbar puncture may be of value in patients who have a lymphoma or leukaemia where there may be a suspicion of meningeal spread of the disease. If malignant cells are found, the CSF protein is often raised and the glucose levels are normal.

Guillain-Barré syndrome

While an increase in CSF protein occurs with meningitis, encephalitis, multiple sclerosis, poliomyelitis, cerebral tumours, haemorrhage and cerebral infarction, very high CSF protein levels is a characteristic of the Guillain Barré syndrome, where the CSF protein may increase up to 10 times normal (i.e. 2000 mg/L rather than 200 mg/L) without an associated decrease in glucose or elevation in cell count.

Procedure

The patient is placed in bed curled in the lateral recumbent position with his or her back at the edge of the bed. The vertical plane of the back should be perpendicular to the bed surface. The lumbar puncture is performed below the level of L2 to reduce the risk of spinal cord trauma, because the spinal cord in the adult terminates at the lower border of L1. When the needle enters the subarachnoid space below this level, it is able to push the nerve roots of the cauda equina to one side without causing damage. The dura (and therefore the subarachnoid space) ends at the lower border of S2.

A line is drawn between the highest points of both iliac crests which passes through the spinous process of L4. The interspinous space above this line is L3 - L4, and below this line is L4 - L5; either space may be used. Once the interspinous points are determined, the operator uses a sterile gown, gloves and mask and a solution of povidone iodine and sterile drapes to prepare the area. The subcutaneous area overlying the supraspinous ligament between L4 - L5 or L3 - L4 is anaesthetised with a local anaesthetic and a 20 gauge needle is inserted into the midline at right angles to the skin, with a 5° - 10° tilt cephalad. Once the tip engages the supraspinous ligament the needle stylet is removed and the needle is advanced slowly through the interspinous ligament, ligamentum flavum, epidural space, the dura and arachnoid until CSF drips from the end of the needle indicating that the subarachnoid space has been reached. A manometer is placed on the end of the needle and the pressure is measured (i.e. opening pressure). The Queckenstedt test (i.e. compression of both internal jugular veins which normally produces an increase in the CSF pressure; if there is no rise, the test is positive, and indicative of a spinal block) is now no longer performed. If a spinal obstruction is suspected, a spinal column MRI scan or a myelogram is the test of choice.

Cerebrospinal fluid specimen’s are taken for culture (first specimen), biochemical tests (e.g., protein, glucose; second specimen) and cell count (third specimen).

Complications

The complications associated with a lumbar puncture include:
1. **Coning**: a lumbar puncture is contraindicated in the presence of a cerebral space occupying lesion (e.g. cerebral, subdural or epidural abscess, tumour or haemorrhage) as herniation which occurs in up to 12% of patients with an elevated CSF pressure, has a reported mortality of up to 40%.

2. **Headache**: a post lumbar puncture headache is often attributed to a leakage of CSF through the hole in the dura, leading to a reduction in CSF pressure with traction on pain-sensitive nerve endings in the dura and intracranial vessels. The use of 22 gauge blunt needles (to part rather than cut the dural fibres - needles smaller 22 gauge take longer than 6 minutes to collect 2 mL of fluid) reduces the incidence of headache to 5%. In one study with the use of needles (20 gauge or less) and nursing the patient prone for 2 - 4 hr after the procedure (rather than supine), the incidence of a post lumbar puncture headache was reduced from 10% - 25% to less than 1%. Epidural ‘blood patching’ may be followed by complications and is not recommended for routine use. A supine posture for 24 hr, or laying the patient head down, does not have a consistently greater beneficial effect than lying the patient horizontal and supine for 1 - 2 hr after the lumbar puncture. If a headache develops following a lumbar puncture, it is generally agreed that the patient should lie flat until the headache disappears, although, some studies have found no difference in the rate of headache between patients who have been immediately mobilised or had 2 - 4 hours of bed rest following lumbar puncture.

3. **Pain and paraesthesias**: back pain and paraesthesia following a lumbar puncture may occur in up to 10% of patients. These symptoms are often transient and do not require therapy.

4. **Infection**: if the procedure is performed in an aseptic manner, infection is rare. In one study the incidence of meningeal infection was reported to be no different than that expected to occur by chance alone.

5. **Bleeding**: the incidence of a traumatic tap is between 5 and 20%, although, the incidence of spinal or epidural haematoma following a lumbar puncture is extremely low.

### IMAGING INVESTIGATIONS OF THE CENTRAL NERVOUS SYSTEM

These include,

1. **X-ray techniques**
   - skull X-ray
   - CT scan (which may be performed with intravenous iodinated contrast media to assess vascularity and integrity of the blood brain barrier),
   - cerebral or vertebral angiography (may be performed when aneurysms, AV malformations, cerebral or vertebral artery embolism, thrombosis or stenosis are suspected)
   - digital subtraction angiography (DSA)

2. **MR imaging** which is usually performed when there is a suspicion of a posterior fossa, brainstem or spinal lesion, and is the investigation of choice to diagnose multiple sclerosis
   - MR angiography, which allows noninvasive visualisation of the cerebral vasculature and with use of intravenous gadolinium may provide information about the blood brain barrier
   - MR spectroscopy (providing a noninvasive method to study cerebral metabolites, brain pH, and some neurotransmitters without the use of ionising radiation),

3. **Ultrasonography techniques** with cervical duplex doppler sonography (has an accuracy of 90% in evaluating haemodynamically significant stenosis of the carotid arteries or transcranial doppler ultrasonography (where a probe is applied onto specific windows -temporal bone squama, orbit, foramen magnum to assess blood flow in the middle, proximal anterior, and
Neurological Investigations

posterior cerebral and distal vertebral and basilar arteries) to detect partial (e.g. vasospasm) or complete (thrombus, embolus) vascular occlusion.

4. **Radionuclide scanning** (e.g. brain scan using technetium)
   - Positron-emission tomography (PET)
   - Single-photon-emission computed tomography (SPECT).

**Computed tomography scan**

CT is often used to diagnose intracranial haemorrhage, infarction, infection and intracranial lesions associated with head injury.

*Intracerebral haematoma*

This appears as an obvious area of increased density within the cerebral tissue (figure 1). If there is subarachnoid extension of the intracerebral haemorrhage, the blood is detected as an increased density within the normally low density CSF areas. The high density intracerebral haematoma is usually observed immediately after the haemorrhage, thereafter the density decreases over the subsequent weeks, until a low density cystic area remains.

![Figure 1. Left basal ganglia intracranial haemorrhage](image)

*Subarachnoid haemorrhage*

Subarachnoid haemorrhage may be diagnosed by the presence of high density opacifications (i.e. blood) within the normally low dense CSF areas, intracerebral blood,
infarction/ischaemia, hydrocephalus, and the demonstration of a causative lesion (e.g. berry aneurysm, angioma or tumour).

Cerebral infarction
This may be caused by thrombosis, embolism or severe arterial spasm. The classical sign of infarction is an area of decreased density within the brain substance (figure 2), usually within the territory of a major vessel (e.g. the middle or posterior cerebral arteries). The lesion is often triangular in shape involving both the white and superficial grey matter. An area of reduced density and a mild mass effect may be seen as soon as 6 h after the onset of symptoms, although it is often not seen until 24 h later. Enhancement of an infarct may be observed within a few hours, although it usually only occurs after 2 - 3 days. Two to three weeks later, at the time of resolution of oedema and during the vascular and cellular infiltration, the infarcted area may be less evident than at any other time and may become isodense with the surrounding brain. Over time, the density of the infarcted area progressively decreases until it finally attains the same density as CSF.

Figure 2. A large infarct in the right middle cerebral artery territory
Neurological Investigations

Cranial trauma

CT scanning is often performed in head-injured patients, particularly those who are admitted with a GCS of 8 or less or those who have a deteriorating state of consciousness, to detect:

1. **Extradural haematoma:** this appears as a biconvex (i.e. lens like) high-density area most often seen in the frontoparietal regions (figure 3). The underlying brain is displaced, with the sulci and lateral ventricles being compressed. The classic biconvex shape may not occur if the extradural haematoma develops after surgery.

![Figure 3. A right extradural haematoma and small haemorrhagic contusion in the left posterior parietal lobe.](image)

2. **Subdural haematoma:** an acute subdural haematoma often appears as an area of increased density overlying the brain and has a border that may run almost parallel to the adjacent brain (compared with the convex border of an extradural haematoma). Due to the nature of the trauma responsible for subdural haematomas (i.e. a shearing force which tears the subdural veins), these patients often have intracerebral haemorrhages and cerebral oedema as well (figure 4). Subdural haematomas have an increased density during the first 2 weeks, thereafter the density decreases and the lesions become isodense with the underlying brain over 2 to 4 weeks. Chronic subdural haematomas have a density similar to that of CSF.
3. **Intracranial haematoma:** this may appear similar to a spontaneous intracerebral haemorrhages, although intracerebral haemorrhages due to trauma are often multifocal, occur in the frontal and temporal regions, and are associated with subarachnoid blood and cerebral oedema.

4. **Cerebral oedema:** this may be focal or generalised, and may be associated with compression of sulci and ventricles (figure 5). However, the CT scan may be within normal limits in the presence of marked cerebral oedema and intracranial hypertension.

![Figure 4. An organising subdural haematoma (*) that is difficult to delineate from the surrounding brain parenchyma as it changes from the hyperdense to the hypodense phase.](image)

5. **Other lesions:** skull fractures, air, foreign bodies and hydrocephalus may also be seen.

**Infections**

Features of the CT scan in infective cerebral lesions include:

1. **Abscesses:** these may occur anywhere in the brain or subdural space, particularly if they are secondary to bacterial endocarditis or chronic pulmonary infection. Frontal lobe abscesses may be secondary to infection of the frontal sinuses and temporal lobe abscesses may be caused by an extension of a mastoid infection. The CT scan reveals an area of low density which has, when contrast is injected, a peripheral capsule enhancement.
2. *Encephalitis*: the majority of encephalitidies do not have CT scan abnormalities. Herpes simplex encephalitis characteristically reveals a bilateral reduction in density (although it may be unilateral in the beginning) and surrounding compression of the temporal lobes.

3. *Meningitis*: patients who have bacterial meningitis often have a normal CT scan, although meningeal enhancement is often noticed when contrast is used.

![Diffuse cerebral oedema](image)

**Figure 5.** Diffuse cerebral oedema

**OTHER NEUROLOGICAL INVESTIGATIONS**

**Electroencephalogram**

Normal electroencephalogram (EEG) rhythm consists of alpha and beta wave activity. Alpha waves have a frequency of 8 - 13 Hz and are most marked in parieto-occipital area. They are observed in adults at rest, when the eyes are closed and the mind is wandering. They are slowed by hypoglycaemia, hypercapnia, hypothermia, and increased during hypocapnia. When
the eyes are open and the individual concentrates, beta wave activity predominates. These waves have a frequency of 14 - 25 Hz and are smaller in amplitude.

An EEG is indicated to detect the type of cerebral disturbance and its location. The amplitude and frequency of the common EEG waves are listed in Table 3. In the intensive care patient, however, artifact and sedative agents renders the EEG difficult to interpret, and it is rarely performed. Evoked potentials (auditory or visual) are not commonly used in the management of critically ill patients, although they have been used for prognosis in head injury and anoxic-ischaemic encephalopathy.13

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Electroencephalogram waves</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (Hz)</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>8 - 13</td>
</tr>
<tr>
<td>Beta</td>
<td>14 - 25</td>
</tr>
<tr>
<td><strong>Abnormal</strong></td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td>&gt; 26</td>
</tr>
<tr>
<td>Delta</td>
<td>0.5 - 3.5</td>
</tr>
<tr>
<td>Theta</td>
<td>4 - 7</td>
</tr>
</tbody>
</table>

Nerve conduction studies

Nerve conduction studies may be performed to confirm, or otherwise, the presence of a peripheral neuropathy.

Electromyography

Normal muscle is electrically silent at rest. With activity, potentials from one or more motor units may be recorded using electromyography and may be indicated in the diagnosis of muscle disorders (e.g. myopathies). Muscle potential abnormalities include, spontaneous depolarisations at rest (fasciculations), abnormalities in amplitude, shape and duration of single motor unit potentials, decrease in number of motor units that may be recruited, and alteration in size, duration and interval between potentials during graded muscular activity.

Muscle biopsy

The indications for a muscle biopsy include the investigation of muscle disorders (e.g. neurotrophic atrophy, dystrophy, metabolic myopathy and polymyositis), diffuse diseases (e.g. SLE or polyarteritis nodosa), infective muscle lesions (e.g. trichinosis or toxoplasmosis), and metabolic muscle diseases.

REFERENCES

ACUTE DISORDERS OF CONSCIOUSNESS

ACUTE CONFUSIONAL STATES

Confusion is a state of cognitive impairment where the patient is unable to think with the customary speed and clarity. Disorientation is a state of cognitive impairment with impaired attention, concentration, and an inability to register immediate happenings and to recall them later. Delirium is a state of increased arousal and cognitive impairment which is characterised by agitation, delusions, hallucinations, seizures and autonomic overactivity (e.g. insomnia, diaphoresis, fever, tachycardia, tremor, diarrhoea). An hallucination is a false sensory perception, occurring without any external stimulus, and a delusion is a fixed irrational belief not consistent with the patient’s cultural norms.

Causes

An acute confusional state (particularly in the elderly) may develop in association with the conditions listed in Table 1.

Treatment

Treatment of an acute confusional state includes resuscitation and supportive therapy and physical and pharmacological restraint.

Resuscitation and supportive therapy

While fluid, glucose and electrolyte maintenance, vitamin supplementation and treatment of the underlying disorder are standard considerations in the management of the hyperactive patient, reducing the number of procedures that cause sleep interruption, provision of a familiar environment (e.g. cards, pictures of family, clock, flowers and radio or television) and allowing familiar faces (e.g. family) to visit frequently (but not for prolonged periods) should also be used to settle the agitated intensive care patient. Any discussion with the patient should appear helpful and agreeable, and not appear as a disagreement or hindrance (even when dealing with the patient’s delusions) as the latter will only increase the patient’s agitation.

Physical restraint

To protect the patient from self-injury or to stop the patient removing intravenous lines, drainage tubes or respirator connections, physical (e.g. glove and feet restrainers to limit limb movement) or pharmacological restraint (i.e. tranquillisers) may be required.

Pharmacological restraint

1. Benzodiazepines: these act on the benzodiazepine-receptor enhancing GABA-mediated post synaptic inhibition. Intravenous diazepam 5 mg hourly up to 20 mg may provide sedation in some patients, although in the severely agitated patient its action is often short lived and usually only partially effective.

2. Phenothiazines: these are DA_1 and DA_2 dopamine receptor blockers, which may block muscarinic M_1, α_1-adrenergic, α_2-adrenergic and H_1 histamine receptors as well. Their
antipsychotic activity is due largely to their DA₂ dopamine receptor blocking effect in the limbic system.

Table 1. Causes of an acute confusional state

<table>
<thead>
<tr>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td>Sepsis, septicaemia</td>
</tr>
<tr>
<td>Severe burns</td>
</tr>
<tr>
<td>Postoperative</td>
</tr>
<tr>
<td>Due to hypoxia, hypercapnia, pain, full bladder, anaesthetic drugs</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Cerebrovascular disorders</td>
</tr>
<tr>
<td>TIlAs, subdural haematoma, hydrocephalus</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Fat embolism</td>
</tr>
<tr>
<td>Heat stroke, hyperpyrexia</td>
</tr>
<tr>
<td>Acute drug withdrawal</td>
</tr>
<tr>
<td>e.g. 1-3 days after sedative, tranquilliser, opiate, antidepressant, alcohol or corticosteroid withdrawal</td>
</tr>
<tr>
<td>Drug toxicity</td>
</tr>
<tr>
<td>Anticholinergics (e.g. atropine, scopolamine)</td>
</tr>
<tr>
<td>antihistamines, antidepressants, tranquillisers, cimetidine, digoxin, local anaesthetic agents (e.g. lignocaine), opiates, corticosteroids</td>
</tr>
<tr>
<td>LSD, amphetamines, phencyclidine, sympathomimetics, aminophylline</td>
</tr>
<tr>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Hepatic failure, renal failure, thyrotoxicosis, myxoedema, porphyria</td>
</tr>
<tr>
<td>hypocalcaemia, hypercalcaemia, hyponatraemia, hypernatraemia</td>
</tr>
<tr>
<td>metabolic alkalosis, respiratory alkalosis, hypoxia, hypercapnia</td>
</tr>
<tr>
<td>hypoglycaemia</td>
</tr>
<tr>
<td>Environmental factors (e.g. ‘intensive care syndrome’)</td>
</tr>
<tr>
<td>sleep deprivation, noise, foreign and windowless environment</td>
</tr>
<tr>
<td>sensory overload, diurnal cycle impairment (constant lighting time disorientation), communication impairment, dependency, immobilisation</td>
</tr>
</tbody>
</table>

Chlorpromazine is the standard phenothiazine tranquilliser. An initial oral or intramuscular dose of 50 - 100 mg is commonly administered to manage an agitated patient and its effect is usually assessed 1 hr later. If required, further doses of 50 - 100 mg may be administered hourly. While up to 1000 mg has been used in some severely disoriented patients, if 400 - 600 mg does not produce the desired effect, then supplemental doses of a benzodiazepine (e.g. diazepam 2 - 10 mg) will act synergistically and produce profound sedation which often lasts for 24 - 48 hr. While an intravenous bolus dose of 2.5 - 10 mg of chlorpromazine often causes severe hypotension, an intravenous infusion at 10-20 mg/hr usually does not, and can be used safely. The elimination half-life of chlorpromazine is 24 - 48 hr.

The side-effects of phenothiazines include dry mouth, constipation, urinary retention and blurred vision (due to a muscarinic receptor blocking effect) and hypotension and hypothermia (due to an α₁-adrenoreceptor blocking effect). Parkinsonian side-effects occur due to nigrostriatal dopamine-receptor blockade which may cause acute extrapyramidal effects (e.g. oculogyric crisis or akathisia, which may be treated with intravenous benztropine 1 - 2 mg) or a late-onset, tardive dyskinesia. The other side effects include QTc interval prolongation with torsade de
pointes, malignant neuroleptic syndrome, leucopenia, eosinophilia, cholestatic jaundice and photosensitivity.

3. **Butyrophenones:** haloperidol is most commonly used butyrophenone in the intensive care unit, although 5 - 10 mg i.v. may not provide the same sedative effect as chlorpromazine and thus may not be as effective as chlorpromazine for the severely agitated patient. In one study haloperidol infusions ranging from 3 to 25 mg/hr were used successfully to control agitation in critically ill patients, although complete heart block, ventricular tachycardia and QTc prolongation (with the risk of torsade de pointes) which were also described indicates that this form of therapy may not be without risk.

4. **Atypical neuroleptic agents:**
   a) Clozapine: has significant 5HT receptor (largely 5HT2A) as well as D2 receptor antagonism, reducing extrapyramidal side effects. It is effective in 50% of patients unresponsive to conventional neuroleptics. The dose ranges from 300 to 900 mg a day. Side effects include sedation and anticholinergic properties (due to H1 histamine and muscarinic M1 receptor antagonism, respectively), agranulocytosis (weekly blood tests for 18 weeks then monthly blood tests should be performed in all patients during therapy), seizures, hypotension, hypersalivation, weight gain, myocarditis and cardiomyopathy.
   b) Risperidone: has significant 5HT2 as well as D2 receptor antagonism and while it is not as effective as clozapine, it does not cause agranulocytosis and has a lower rate of extrapyramidal adverse effects. The dose ranges from 2 to 6 mg a day (e.g. 1 - 3 mg 12-hourly).
   c) Olanzapine: has significant 5HT2 as well as D2 receptor antagonism but unlike clozapine and risperidone it does not antagonise α2-adrenergic receptors as well, and has not been associated with a reduction in seizure threshold. The dose ranges from 5 to 20 mg a day and is usually given as a single daily dose. Side effects include sedation, somnolence, weight gain and anticholinergic properties (due to H1 histamine and muscarinic M1 receptor antagonism, respectively). While it does not cause agranulocytosis and has a lower rate of extrapyramidal adverse effects, neutropenia, seizures and neuroleptic malignant syndrome have also been reported.
   d) Sertindole, ziprasidone and quetiapine are newer atypical neuroleptic agents which are reported to have lower rates of extrapyramidal adverse effects. However QTc prolongation (sertindole) and sedation (ziprasidone) indicate that they are not free of side effects.

5. **Ethyl alcohol:** in the acutely ill alcohol-dependent patient, intravenous ethanol (5% ethanol in 5% dextrose, i.e. 50 ml of 100% alcohol per litre of 5% dextrose at 50 - 100 mL/hr) has been used successfully, for both delirium tremens prophylaxis and for pre-delirium tremens agitation. The serum ethanol levels are reportedly low or unmeasurable and patients are usually able to be weaned from the mixture after 3 - 7 days.

6. **Propranolol:** the sympathetic effects of acute agitation following withdrawal of sedative drugs (e.g. tachycardia, hypertension, diaphoresis) have been treated successfully with beta-blockers (e.g. propranolol 40 - 80 mg orally 4 hourly, or 5 mg intravenously 2- to 4-hourly).

REDUCED STATES OF CONSCIOUSNESS

Consciousness is a normal state of arousal and cognitive function. Clouding of consciousness is a state in which both arousal and cognition is impaired. Stupor is a sleep-like state from which the patient can be aroused only by vigorous and persistent stimulation. Coma is a sleep-like state from which the subject cannot be aroused.
Causes

There are many conditions that can cause a reduced state of consciousness. In the intensive care patient, a common clinical problem is that of a patient who fails to awaken (e.g. remains unconscious when the acute illness has subsided and the sedative, opiate and relaxant drugs have been withdrawn). Those conditions which may lead to coma are listed in Table 2. The metabolic encephalopathies, in the absence of structural brain damage, are usually reversible when the underlying cause (e.g. sepsis, renal failure, hepatic failure) is corrected.12,13,14,15

Table 2. Causes of coma

<table>
<thead>
<tr>
<th>Cerebral functional abnormality</th>
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</thead>
<tbody>
<tr>
<td>Concussion</td>
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<tr>
<td>Postepileptic</td>
</tr>
<tr>
<td>Vasovagal attack, syncope</td>
</tr>
<tr>
<td>Electrocution</td>
</tr>
<tr>
<td>Intracranial lesions</td>
</tr>
<tr>
<td>Subdural, epidural, intracerebral, space-occupying lesion</td>
</tr>
<tr>
<td>(e.g., haematoma, abscess, tumour)</td>
</tr>
<tr>
<td>Cerebral or brainstem haemorrhage, embolus, infarct</td>
</tr>
<tr>
<td>Sub arachnoid haemorrhage</td>
</tr>
<tr>
<td>Closed head injury</td>
</tr>
<tr>
<td>Encephalitis, meningitis</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
</tr>
<tr>
<td>Global hypoxia (e.g. cardiac arrest, carbon monoxide poisoning, near drowning)</td>
</tr>
<tr>
<td>Drug intoxications, poisonings, or overdosage (e.g. drug accumulation)</td>
</tr>
<tr>
<td>Sepsis, septicaemia, multiple trauma</td>
</tr>
<tr>
<td>Reye’s syndrome</td>
</tr>
<tr>
<td>Dialysis induced</td>
</tr>
<tr>
<td>Hypo and hyper (tension, thermia, capnia, glycaemia, natraemia)</td>
</tr>
<tr>
<td>calcaemia, magnesaemia)</td>
</tr>
<tr>
<td>Hypophosphataemia, hypokalaemia</td>
</tr>
<tr>
<td>Hepatic failure, renal failure</td>
</tr>
<tr>
<td>Cofactor deficiency (e.g. thiamine, pyridoxine, vitamin B12)</td>
</tr>
<tr>
<td>Pancreatitis, porphyria</td>
</tr>
<tr>
<td>Small vessel disease (e.g. fat embolism, air embolism, post-cardiopulmonary bypass cholesterol embolism, systemic lupus erythematosus, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, bacterial endocarditis)</td>
</tr>
<tr>
<td>Myxoedema, thyrotoxicosis, hypopituitarism</td>
</tr>
<tr>
<td>Psychogenic &quot;coma&quot;</td>
</tr>
<tr>
<td>Hysteria, catatonic schizophrenia</td>
</tr>
</tbody>
</table>

The diagnosis is made from:

1. The history: for example, does the patient have a head injury, is he/she epileptic, is there any evidence of a drug overdose?
2. The examination: for example, the degree of consciousness (e.g. GCS), signs of head injury, pupillary reflexes, fundi, limb responses to pain, tone, reflexes and Babinski reflex. For example, patients who have coma due to a metabolic encephalopathy (cf. coma due to a
Acute Disorders of Consciousness

structural brain disorder) usually have a pupillary response to light, flexor or no response to pain, are hypotonic and do not have a positive Babinski reflex.

3. The venous blood: for glucose, urea, creatinine, osmolality, sodium, potassium, calcium, phosphate, magnesium, transaminases, complete blood picture, platelet count, prothrombin time, APTT and culture.

4. The arterial blood: for pH, HCO$_3^-$, PCO$_2$ and PO$_2$ estimations.

5. The urine and blood: to detect presence of sedative drugs.

6. Radiological studies: for example, skull, cervical spine X-ray, cerebral CT scan.

7. Lumbar puncture: performed in the presence of meningeal irritation and in the absence of a space-occupying lesion on CT scan. In septic encephalopathy the CSF and the CT scan are usually within normal limits.

8. EEG: this has been reported to be a sensitive index of brain function in septic encephalopathy, with the severity of the encephalopathy being reflected by changes in the EEG from normal, to excessive theta, predominant delta, triphasic waves, and suppression or burst suppresion activity.

Treatment of coma

The management of a patient in coma requires:

1. Resuscitation: this is performed to ensure an adequate airway, ventilation and circulation, and an adequate delivery of oxygen and glucose to the brain. Seizures are managed by treating the underlying condition (e.g. hypoglycaemia, hyponatraemia, etc.) and with antiepileptic therapy.

2. General care of an unconscious patient:
   a) Physiotherapy: passive leg movement 8-hourly, and splinting of ankles and wrists to prevent contractures.
   b) Eye care: As the corneal reflex is often depressed, the eyes are taped at the angles to ensure that they are closed at all times to reduce the incidence of corneal trauma, keratopathy and infection. Artificial tears and antibiotic ointment are used if the conjunctiva is exposed, and if the cornea is exposed other methods may also be necessary to ensure closure of the lids including the use of a Donaldson eye patch (using a Velcro fastener), a 5 O’ silk suture of upper and lower lid margins, polyacrylamide gel patches with high water content or cling wrap. While conjunctival oedema may be caused by trauma to the unprotected eye, it may also be caused by severe extracellular oedema. Severe nosocomial eye infections in the critically ill patient are usually caused by Pseudomonas aeruginosa which often arises from Pseudomonas aeruginosa chest infections. Damage to the eye with keratopathy and corneal trauma requires urgent ophthalmological advice.
   c) Posture: Neutral limb and head postures are carefully maintained to reduce tendon, muscular and nerve injury (e.g. brachial plexus injury associated with hyperextension of the upper limb).
   d) Mouth and nose toilet: (particularly when nasal and oral tubes are present) to reduce the collection of secretions (with subsequent development of sinusitis) and nystatin drops to prevent candida infection.
   e) Pressure point care (i.e. shift the position of the patient) to prevent dermal ulceration (bed sores of sacrum, heels elbows, occiput), peripheral nerve injury and rhabdomyolysis.
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f) Aseptic management of cannulae and tubes (e.g. central venous and Swan-Ganz catheters, suctioning of endotracheal tubes, urinary catheters, enterostomy bags, and abdominal drains)
g) Fluid, electrolyte and nutritional care.
h) Pulmonary embolism prophylaxis.


SEPTIC ENCEPHALOPATHY

Septic encephalopathy is a diffuse yet reversible cerebral dysfunction that occurs in up to 70% of patients with sepsis. The aetiology is most likely multifactorial with the proposed causes including, reduced cerebral blood flow, impaired cerebral oxygen utilisation, cerebral oedema, abnormal neurotransmitter composition (due to alterations in serum amino acid levels similar in some respects to that observed with hepatic encephalopathy) and disruption of the blood brain barrier (caused by the circulating inflammatory mediators of tumor necrosis factor-α, interleukin-1 and interleukin -2). It presents clinically with confusion, disorientation, agitation and fluctuations in level of consciousness. In severe cases the decrease in level of consciousness may even result in coma. Bilateral signs of hyperreflexia and grasp reflex may be elicited and abnormal movements such as myoclonus, tremor or asterixis can occur.

The diagnosis of septic encephalopathy is difficult as it first requires the exclusion of structural abnormalities (e.g. normal CT and MRI scans), and an absence of other metabolic (hypotension, hypoglycaemia, hypocalcaemia, etc), organ failure (hepatic, renal, hypertensive), drug induced (sedatives, opiates) toxic and cerebral infectious (e.g., meningitis or encephalitis) causes. The EEG has been reported to be a sensitive index of brain function with the severity of an encephalopathy being reflected by changes in the EEG from normal, to excessive theta, predominant delta, triphasic waves, and suppression or burst suppression activity. However, as it is difficult to achieve an EEG recording without artifact at the bedside this investigation is not often performed.

Although patients with septic encephalopathy severe enough to produce coma have a mortality that approaches 50%, this largely reflects the severity of the underlying illness and is not a direct result of the encephalopathy.

There is no specific treatment for septic encephalopathy although successful treatment of the underlying cause of the sepsis almost always results in complete resolution of the encephalopathy, without residual neurological deficits.

Recently, a series of three cases of multifocal necrotising leukoencephalopathy (normally associated with HIV infection or chemotherapy or radiotherapy for cerebral cancer) have been described caused by septic shock.

THE VEGETATIVE STATE

This is a state of consciousness that may follow an episode of severe brain injury, where the individual appears to awaken after 2 - 4 weeks but has no conscious intelligence. Unlike brain death, these individuals have a functioning brain stem, although they appear to have no higher cortical function.

The characteristic features of the vegetative state include: 1) no evidence of awareness of the self or the environment and an inability to interact with others; 2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli; 3) no evidence of language comprehension or expression; 4) intermittent wakefulness manifest by the preservation of sleep-wake cycles; 5) sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing
Acute Disorders of Consciousness

care; 6) bowel and bladder incontinence; 7) variably preserved cranial nerve reflexes (pupillary, oculocephalic, corneal, oculovestibular, gag) and spinal reflexes.\(^{31}\)

If the vegetative state persists for longer than one month it is classified as a \textit{persistent} vegetative state. Recovery of consciousness from a posttraumatic persistent vegetative state is unlikely after 12 months and therefore is regarded as a \textit{permanent} vegetative state (PVS) if it lasts 12 months or more.\(^{32}\) However, improvements in consciousness after posttraumatic persistent vegetative states lasting 15 months\(^{33}\) and and 21 months\(^{34}\) have been reported, prompting some to believe that improvement in consciousness after 12 months (particularly in young patients) may not be rare.\(^{33}\) Recovery from a nontraumatic persistent vegetative state after three months is rare and therefore regarded as a \textit{permanent} vegetative state (PVS) if it lasts 3 months or more.

BRAIN DEATH

The diagnosis and management of brain death is presented in the chapter on clinical features of neurological diseases (Chapter 6) in “clinical examination of the critically ill patient”.

MANAGEMENT OF THE ORGAN DONOR

Organ donation (98\% of whom originate from intensive care units\(^{35}\)) proceeds through the stages of identifying a potential donor, certification of brain death, consent to organ donation, management of the organ donor (maintaining optimal organ function), and organ procurement (e.g. organisation, operation, organ preservation and delivery).

\textit{Identifying a potential donor}

Any patient in coma with irreversible cerebral disease who is likely to progress to brain death prior to cardiac arrest (e.g. severe brain trauma, subarachnoid haemorrhage, stroke, resuscitated cardiac arrest, asphyxia, drowning, primary brain tumors, drug overdosage) should be considered a potential organ donor. Exclusion criteria include a number of infective conditions (e.g. untreated or resistant septicaemia, active tuberculosis, viral hepatitis, viral encephalitis, HIV - or activity likely to be associated with HIV) and malignancy (other than primary brain tumor, local skin or in situ uterine cervix carcinomas), well as injury to the specific donor organ (although acute renal dysfunction, that is recovering, will not exclude renal organ donation).\(^{36}\) Age is no longer an absolute exclusion criterion with most organs being acceptable in patients up to the age of 70 (kidneys up to 75, and corneas will be acceptable at any age).

Laboratory testing varies depending on the organ donated but often includes blood typing (ABO), tissue typing, serological tests (HBV, HCV, HIV, HTLV1, CMV), plasma electrolytes, creatinine and urea, arterial blood gas analysis (lung donation requires a $\text{PaO}_2 > 300 \text{ mmHg}$ with $\text{FiO}_2 1.0$ and 5 cm PEEP), liver function tests, chest Xray, ECG and (particularly with cardiac donation) echocardiography.

\textit{Brain death certification (see previously)}

\textit{Consent to organ donation}

This legal requirements for consent to organ donation varies between countries but often includes written consent from the patient (i.e. prior to brain death), patient’s relatives, guardian, or coroner. In some countries organ donation is undertaken as the default wish of the patient, unless he or she has expressed a prior wish not to donate organs.\(^{37}\)

If the patient has not given prior consent or the relatives refuse organ donation then life support becomes futile and withdrawal of therapy is discussed with the family. Most
understand the concept, although some require a day or so to become comfortable with the act of discontinuing mechanical ventilation (some time may also be requested to allow distant relatives to visit). Some family members may request to be present during discontinuation of ventilatory support. In such circumstances they must be informed of the occasional spinal reflex movements (twitching of limbs, elevation of legs or arms, opisthotonos) that may occur during the patients final moments (‘Lazarus signs’).38

Management of the organ donor

The principles of management of the organ donor include early recognition and treatment of haemodynamic instability (e.g. hypertension, hypotension and arrhythmias) to maintain a systemic perfusion pressure that maximises donor organ function, treatment of complications related to brain death (e.g. fluid and electrolyte abnormalities, diabetes insipidus, hypothermia) and maintenance of supportive care (e.g. vascular access, respiratory, skin and corneal care - to reduce the incidence of infection and pressure).

Haemodynamic instability: The haemodynamic disturbances that are found in the potential organ donor are hypertension, hypotension and arrhythmias (tachycardias and bradycardias) and reflect the progressive rostral to caudal (i.e. cerebral, midbrain and brainstem) deterioration of the brain function. The hypertensive response caused by progressive brainstem ischaemia is due to increased sympathetic activity (which may cause focal ischaemic damage to the myocardium and tachycardias) and esmolol can be used to manage this.36 If bradycardia exists with the hypertensive response (i.e. the ‘Cushing response’), intravenous nitroprusside may be used to reduce the blood pressure. Some believe that as the hypertension is short lived it does not require treatment.39

Hypotension (i.e. systolic blood pressure of 90 mmHg or less or mean arterial pressure of 60 mmHg or less with urine output less than 1.5 mL/kg/hr and poor peripheral perfusion) occurs with destruction of the pontine and medullary vasomotor centers (i.e. with brain stem herniation) due to loss of arterial and venous sympathetic tone (leading to an effective reduction in blood volume and a reduction in myocardial contractility) and volume depletion (usually secondary to diabetes insipidus or prior use of diuretics and fluid restriction). Management requires intravenous fluids to increase the central venous pressure up to 10 – 12 mmHg (using blood, if the haemoglobin is less than 100 g/L, or albumin and saline solutions if the haemoglobin is greater than 100 g/L). If hypotension is resistant to intravenous fluid therapy then positive inotropic agents (e.g. adrenaline, dobutamine, dopamine, noradrenaline) may be used. If increasing quantities of inotropic agents are required, arginine vasopressin (1 – 2 U/hr) has been used to increase the vascular sensitivity to catecholamines.40 Hydrocortisone (250 mg intravenously followed by an infusion of 5mg/hr), has also been recommended for resistant hypotension39 (even though plasma cortisol levels are not significantly lower in hypotensive brain dead patients compared to normotensive brain dead patients41).

The recommended upper limit to the systolic blood pressure is 120 mmHg (mean arterial pressure 90 mmHg) as pressures higher than this are often associated with pulmonary oedema (due to excessive intravenous fluids), or reduced organ flow with damage (due to excessive vasopressor activity).42,43

Respiratory function: The patient is mechanically ventilated maintaining the PaCO₂ between 35-45 mmHg and PaO₂ > 60 mmHg. Pulmonary oedema is treated conventionally using PEEP and attempting to lower the pulmonary artery occlusion pressure.

Diabetes insipidus: destruction of the hypothalamic-pituitary axis results in a decrease in antidiuretic hormone secretion leading to a central diabetes insipidus in up to 80% of patients with brain death.36 The diagnosis is confirmed with polyuria (urine output ≥ 2 mL/kg/hr), hypernatraemia (plasma sodium > 145 mmol/L), plasma osmolality > 300 mOsm/kg and urine
osmolality < 300 mOsm/kg. When urinary losses exceed 4 mL/kg/hr a vasopressin preparation should be administered (e.g. desmopressin 1 µg i.v. 2 hourly – which has no detrimental effect on renal graft function in the recipient). Arginine vasopressin has the advantage that it increases the sensitivity of the brain dead patient to catecholamine therapy, and is used as a continuous infusion (e.g. 0.5 – 15 U/hr titrated to maintain a urine output > 1.5 mL/kg/hr and < 4 mL/kg/hr or > 100 mL/70 kg/hr and < 250 mL/70kg/hr).

A reduction in antidiuretic hormone (ADH) secretion will lead to renal water loss of water only (causing hypernatraemia), so the abnormalities of hypokalaemia, hypophosphataemia, hypocalcaemia and hypomagnesaemia (as well as hypermagnesaemia, hyperkalaemia, hypercalcaemia and hyperglycaemia) that may be present, relate to prior deficiencies (or excesses), or inaccuracies in fluid and electrolyte replacement rather than ADH deficiency.

**Hypothermia:** The temperature should be kept above 35°C as mild hypothermia (<35°C) prevents the diagnosis of brain death and severe hypothermia (< 30°C) cardiovascular instability occurs (e.g. bradycardia, atrial fibrillation, VF asystole). The intravenous fluids should be warmed and as the patient is poikilothermic warming blankets may be required.

**Other therapy:**

a) Coagulation factors (e.g. platelets, fresh frozen plasma, fibrinogen) are administered if a consumption coagulopathy exists. Fibrinolytic inhibitors are not used as they can lead to microvascular thrombosis within donor organs.

b) Hormone therapy (e.g. triiodothyronine, hydrocortisone). With the observation of a reduction in circulating triiodothyronine and cortisol following brain death, intravenous triiodothyronine (2-4 µg/hr) and cortisol (100 mg/hr) has been recommended in the haemodynamically unstable patient. However, as others have found residual hypothalamic-pituitary endocrine activity in brain dead patients, with normal circulating cortisol levels and the only evidence of thyroid dysfunction being the presence of a euthyroid sick syndrome, routine replacement of triiodothyronine or cortisol is currently not recommended in brain dead organ donors.

**Organ procurement**

Before the operation prednisolone 1 gm, pancuronium 8 mg (to prevent reflex contraction with surgical stimulation), cephalothin 2 gm and gentamicin 80 mg are often administered intravenously. During the operation heparin, mannitol, and sympathomimetic agents may also be required.

**REFERENCES**


# Trainee Presentations

Each registrant has prepared a five minute talk and summary on the topics listed below. The summaries that were received in time for publication have been included (unedited).

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Dr. A. Rashid
WHAT ARE THE ACTIONS, INDICATIONS AND COMPLICATIONS OF RECOMBINANT FACTOR VIIA?

Dr. J. Bates. Intensive Care Unit, The Alfred Hospital, Victoria

Actions

- Recombinant Factor VIIa (rFVIIa) can initiate coagulation upon contacting TF in the absence of other factors which act more proximally in the clotting cascade, such as factors VIII, IX, and XI (bypass effect). The TF-FVIIa complex activates factor X which binds to factor Va (forming the prothrombinase complex) and cleaves prothrombin to thrombin. Thrombin subsequently cleaves fibrinogen to fibrin, thus leading to the formation of clot. This effect only occurs at sites of endothelial damage as rFVIIa requires TF for activation.
- The TF-FVIIa complex also activates factor IX, which, along with factor XI is responsible for the formation of thrombin-activatable fibrinolysis inhibitor (TAFI). TAFI protects the newly formed clot from premature fibrinolysis. Pharmacological doses of FVIIa can activate TAFI even in the absence of factor XI.
- Platelet availability is rate limiting for the production of thrombin and FVIIa can bind directly to the surface of activated platelets (a process which does not require TF) to increase the rate of thrombin formation. This effect is seen in thrombocytopenic patients.
- The therapeutic effect of rFVIIa occurs at concentrations up to 10 times greater than the physiological concentration of endogenous FVII. It is thus a pharmacological intervention rather than a replacement treatment. The half life of rFVIIa is 2.5 hours.

Indications

rFVIIa is indicated for the prevention or control of bleeding in the following patient groups:

- Haemophilia A (F VIII deficiency) and Haemophilia B (F IX deficiency):
  rFVIIa is indicated for hemostasis of patients with hemophilia A and B especially when inhibitors to FVIII or FIX are present in the circulation. It was originally developed for treatment of such patients. It has been used successfully to prevent excessive bleeding in elective surgery (both major and minor) in these patients at a dose of 90 µg/kg 2 hourly for 24 hours.
  FVIIA is effective in treating serious intracranial, retroperitoneal, intraperitoneal and intramuscular bleeds as well as hemarthroses in hemophiliacs.
- Extensive surgery or trauma with severe bleeding:
  Patients with extensive bleeding following trauma or extensive surgery, requiring massive transfusion have defective thrombin formation. In such patients rFVIIa may have a hemostatic effect even when transfusion of other blood products (FFP, cryo, platelets) has been unsuccessful. The doses used in these patients have ranged from 40-120 µg/kg
- Patients with thrombocytopenia and functional platelet defects:
  rFVIIa can shorten bleeding time and stop bleeding in thrombocytopenic patients (even when the platelet count is less than 10,000 per µL) and in patients with functional platelet defects.
- Congenital FVII deficiency.
- Hemostasis in patients taking oral anticoagulants
- Hemostasis in patients on low-molecular weight heparin (2 case reports)
- Patients with impaired liver function (including those undergoing liver transplant surgery)
- Massive GI or other internal organ bleeding not responsive to usual measures
The evidence for efficacy of rFVIIa comes mainly from case reports and series. The few clinical trials that have been conducted to date involved hemophilia patients only.

**Complications**
Because rFVIIa is not itself enzymatically active, it does not activate factor X until it contacts TF or activated platelets and thus diffuse intravascular coagulation does not occur. It has a very good safety profile (only 5 episodes of thrombosis in one series of 170,000 doses administered).
The following have all been reported in patients given rFVIIa.

- Superficial thrombophlebitis
- Thrombosis associated with indwelling catheters (jugular and femoral vein thrombosis)
- DVT (upper and lower limb)
- Pulmonary embolism
- Acute myocardial infarction
- Cerebrovascular accident
- Inadequate treatment

**References**
1. Hedner U, Erhardt sen E. Potential role for rFVIIa in transfusion medicine. Transfusion 2002;42;114-124
DISCUSS THE USE OF FRUSEMIDE IN THE MANAGEMENT OF ACUTE RENAL FAILURE

Dr. S. Moodie. Intensive Care Unit, Royal Adelaide Hospital, South Australia

Acute renal failure occurs in around 30% of all critically ill patients
Mortality of ARF in critically ill population is 75%.¹

Causes:

Pre-renal: hypo perfusion

Intrinsic renal: Acute GN
Nephrotoxins
Interstitial nephritis

Post-renal: outflow obstruction

In the ICU environment the usual acute renal failure encountered is multifactorial in origin and loosely described as Acute Tubulular Necrosis (ATN). This is probably a combination of prerenal and intrinsic renal with medullary ischemia, renovascular vasoconstriction from vasoactive septic inflammatory mediators and iatrogenic nephrotoxins. There is also an obstructive component with tubular obstruction from interstitial oedema and tubular debris from ischaemic tubules. For the past 30 years frusemide has had widespread use in an attempt to prevent or modify ARF in critically ill patients.

Frusemide
Chemically is a sulphamamide derivative, is given i.v as a dose of 10 - 500mg daily, has a half life of 90 minutes and duration of action is around 6 hr (hence ‘Lasix’ as it lasts six hours). It acts by inhibiting NaCl reabsorption primarily in the thick ascending loop of Henle, but also the proximal tubule. Mechanism is by binding to the Cl⁻ symporter and thus blocking the Na⁺ K⁺ 2Cl⁻ luminal co-transporter and thus preventing associated reabsorption of water. The luminal Na⁺ would normally then be transported to the interstitium by a Na⁺ K⁺-ATPase. This accounts for 80% of the O₂ and metabolic requirement of the kidney. Theoretically, therefore, blocking this should protect the kidney by reducing metabolic requirements during times of hypoxia and ischaemia as well as flushing the tubules free of debris and tubular casts with the polyuria.

Supportive experimental evidence
In rats given radiocontrast agents, medullary PO₂ decreases but returns to normal with frusemide treatment. Also shown to be protective against radiocontrast media induced renal failure when given with saline.²

In healthy volunteers, frusemide improves regional oxygenation (usual medullary PO₂ is 10 mmHg, 50mmHg in cortex)

Clinical trials
Unfortunately clinical trials do not support experimental findings. Some older studies show a reduction in duration of oliguria and a reduction in need for dialysis, others have only shown a reduction in oliguria. No studies have convincingly shown a reduction in mortality.³⁴
More recent and rigorously constructed trials have shown even less benefit with no effect on duration of renal function, requirement for dialysis or mortality. Most studies do agree a marginal increase in urine output with no effect on outcome of renal dysfunction or mortality.

**SUMMARY**

All the current evidence indicates the role of frusemide in ARF is only to optimise fluid balance as a diuretic. It has no role in preventing or modifying ARF and has no effect on need for dialysis or mortality. Considering the multifactorial cause of ARF in the critical care population, it is not surprising that a single agent has no real effect and therapy should be aimed at treating the precipitant of a multisystem disorder and not “saving the kidney”

**References**

DISCUSS THE CAUSES, CLINICAL FEATURES AND MANAGEMENT OF A PATIENT WITH ACUTE VIRAL ENCEPHALITIS

Dr. M. J. Holland. Intensive Care Unit, Townsville Hospital, Queensland

Viral encephalitis: Often a severe illness with symptoms and signs of inflammation of the parenchyma of the brain

Clinical features: Acute febrile illness
Headache
Mental aberrations: Behavioural changes
Hallucinations
Agitation
Personality change
Frank psychosis
Altered consciousness: mild lethargy to deep coma
Focal or diffuse neurological signs: Aphasia
Ataxia
Hemiparesis
Involuntary movements
Cranial n. palsies

Involvement of the hypothalamic – pit axis: Temp dysregulation
SIADH
DI

Causes: DNA viruses: Herpes viruses: HSV 1 + 2*, VZV, CMV, EBV
Adenoviruses
RNA viruses: Enteroviruses*: Cocksackie A + B, echovirus, poliovirus, 9 + 71
Orthomyxovirus: Influenza
Paramyxoviruses: Mumps*, rubella, measles, Nipah
Rhabdoviruses: Rabies, Australian bat lyssa virus
Arboviruses*: Dengue, Japanese B, West Nile, Murray valley
Arenaviruses: Lymphocytic choriomeningitis virus
Retroviruses: HIV, HTLV
*commonest

Diagnosis: High index of clinical suspicion
Neuroimaging: MRI better than CT (will exclude other diagnoses)
Fronto-temporal changes in HSE
Thalamic haemorrhages in Japanese B enceph
EEG: Distinguish focal encephalitis from diffuse encephalopathy
also rule out non convulsive status
CSF analysis: Lymphocytic pleocytosis (usu < 500/ml), N gluc, N or sl. ↑ protein
CSF PCR (HSV, VZV, CMV, EBV, Lyssa virus) and Culture
Viral specific IgM immunoassays e.g. Japanese B encephalitis
Serological studies (acute phase and convalescent)
Viral Isolation: throat swabs, stool, blood and urine
Treatment: Supportive Rx, ABC, careful monitoring for ↑ ICP and treatment of increased ICP as clinically indicated. Control of seizures and prophylaxis. Prevention of DVT, aspiration pneumonia, and 2nd bacterial infections. Empirical aciclovir 10mg/kg tds. until HSV, VZV or EBV ruled out. Ganciclovir +/- Foscarnet if CMV; antiretroviral Rx if HIV

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1. Chaudhuri A et al; Diagnosis and treatment of viral enc; Postgrad Med J. 2002;78:575-583
2. McCormack et al; emerging viral infections in Australia; MJA;2002 vol177:45-49
3. Solomon T;Exotic and emerging viral enceph Curr Op Neurol; 2003 vol16(3) 411-418
4. Braunwald et al Harrison’s Principles of Int Med
DISCUSS THE MANAGEMENT OF A PATIENT WITH DILTIAZEM OVERDOSAGE

Dr. S. Raja. Department of Critical Care Medicine, Flinders Medical Centre, South Australia

Introduction:
Diltiazem is a calcium channel blocker. It acts on the 'L' subtype of voltage sensitive calcium channels and reduce the calcium influx into the cells. It inhibits phase '0' depolarisation in cardiac pacemaker cells, and the phase '2' plateau in myocytes, purkinje cells and vascular smooth muscle cells. In doing so, it causes vasodilatation, depresses myocardial contractility, and sinus and atrioventricular nodal conduction.

Due to extensive first pass hepatic metabolism, blood levels after a standard dose can vary over tenfold, limiting the usefulness of blood levels in overdose cases. It is highly protein bound (80-90%). Based on the pharmacokinetic profiles, extracorporeal removal procedures would have minimal or no effect on diltiazem elimination. Clearance of diltiazem after oral ingestion follows first order kinetics, with the half life of 5 - 10hrs, independent of the amount ingested.

Delayed toxicity from sustained release preparations may be greater than 12hrs after ingestion. So all patients with sustained release diltiazem overdose should be hospitalised even if they are asymptomatic initially.

Toxic dose in man is not known. The oral LD 50 in mice and rats range from 415 to 740mg/kg and from 560 to 810 mg/kg respectively. There have been reports of diltiazem overdose in amounts ranging from < 1 gm to 18g. Most patients recovered with treatment. In cases of fatal outcome, there was multiple drug ingestion.

Clinical features:

**Bradycardia, Asystole & High degree AV block:**
Diltiazem prolongs the AV node refractory period without significantly prolong sinus node recovery time except in patients with sick sinus syndrome.

**Cardiac failure:**
Haemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor negative inotropic effects. But caution should be used when it is combined with beta-blockers or in patients with underlying ventricular dysfunction.

**Hypotension:** results from low cardiac output and vasodilation

**Metabolic effects:**
1. Hyperglycemia due to inhibition of insulin release from pancreas.
2. Metabolic acidosis. It can worsen diltiazem toxicity by increasing the ionised drug available for channel blockade.

**Neurological effects:** Lethargy, grand mal seizure and coma.

**Acute hepatic Injury:**
Significant elevations in transaminases and alkaline phosphatases consistent with hepatic injury can happen with diltiazem. But usually reversible with discontinuation of the drug.

**Hematological:**
It can cause bone marrow depression very rarely even at therapeutic doses.

Management:
Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.
Supportive management:
This inculdes administration of activated charcoal through nasogastric tube and whole bowel irrigation using polyethylene glycol solution. Correction of metabolic problems and treatment of seizures if any.

Haemodynamic management:
Patients need invasive haemodynamic monitoring if they have haemodynamic compromise.

Bradycardia: Administer atropine (0.6- 1mg). If there is no response to vagal blockade, administer isoproterenol cautiously. High dose intravenous calcium is recommended if bradycardia progresses to asystole or if there is refractory shock. Optimum dose is yet to be determined. Hypercalcaemia may become significant if >45 meq/L of calcium is administered.

High Degree AV block: Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, dobutamine) and diuretics. Electromechanical supports like IABP may be needed in concert with cardiac pacing.

Hypotension: Fluids and Vasopressors. Intravenous Calcium for refractory shock.

Other:
Some experimental studies show benefit with euglycemic insulin therapy and calcium channel agonists like 4-Aminopyridines.

References
5. The Pharmacological Basis of Therapeutics:Goodman & Gilman's
WHAT ARE THE ACTIONS OF, INDICATIONS FOR AND COMPLICATIONS OF PENTOXIFYLLINE

Dr. J. Ritchie. Intensive Care Unit, Greenlane, New Zealand

**Pentoxifylline** (3,7-dimethyl-1-(5-oxohexyl)-xanthine)
*Trade name:* Trental
*Metabolism:* renal and hepatic
*Cost:* NZ$24.86/5 x 100mg IV
*Dose:*
  - PO: 400mg TDS
  - IV doses used: 1-1.5mg/kg/hr (<100mg/hr), 100 - 2500mg/day

**Actions**
- Methylxanthine derivative and non-specific PDE inhibitor

**Effects on microcirculation**
- Decreases blood viscosity and plasma fibrinogen.
- Increases erythrocyte deformability/flexibility.
- Modulates platelet aggregation; increases endothelial prostacyclin production and inhibits thromboxane A2 synthesis, which increases microcirculation blood flow and enhances tissue oxygenation.1

**Effects on the inflammatory cascade**
- Inhibits phosphatidic acid generation.
- Decreases calcium influx:
  - Reduces neutrophil oxidative burst/free radical generation
  - Reduces neutrophil chemotaxis, adherence, degranulation and phagocytosis.
- Inhibition of cytokine production (TNF-α, IL-1 and 8, but not IL-6 or IL-10).1,4
  - Via PDE IV inhibition.

**Approved indications**
- Peripheral vascular disease.
- Circulatory disorders of the eye or ear.

**Contraindications**
- Recent cerebral and/or retinal haemorrhage or previous intolerance to methylxanthines.

**Animal studies**
- Pentoxifylline and its more potent metabolite lisofylline have been studied in multiple animal models and shown to have beneficial effects in:
  - **Haemorrhagic and septic shock.** Maintains organ function, and improves tissue oxygenation and microcirculation.
  - **E Coli sepsis.** Enhances RES and bacteria clearance, but inhibits excessive neutrophil activation (which may be responsible for the deleterious effects of inflammation).
  - **Reperfusion injury**
    - **Liver**
      - Inhibits the increase in hepatocyte Ca2+ influx that is associated with a decrease in hepatocyte lipid peroxidation.
    - **Transplant organ survival / function**
      - Rat liver transplantation; improves the viability of the liver grafts.
Porcine lung transplant models; pentoxifylline increases oxygenation and reduces pulmonary vascular resistance

**Prevention of secondary head injury**
Inhibition of TNF-α production or activity lessens peak oedema formation and facilitates recovery of motor function.

- **Protection against acid aspiration injury.** Pre-treatment attenuates increase in endothelial permeability leading to restoration of normal gas exchange.
- **Inhalational injury.** Combined treatment with nebulised heparin and systemic lisofylline had beneficial effects on pulmonary function in association with a decrease in blood flow to poorly ventilated areas and less lipid peroxidation.
- **Treatment of frostbite.** Improves tissue survival.

**Human Studies**

**Sepsis/anti inflammatory**
- Studies have been contradictory; often failing to demonstrate improved haemodynamics, oxygenation or mortality, despite a decrease in cytokine levels.
- 51 patients in a surgical ICU treated with 28/7 pentoxifylline infusion 1mg/kg/hr (up to 1800mg/24hours) had improved haemodynamics, MODS scores, but no change in serum endotoxin levels, TNF-α or IL-6 bioactivity.\(^5\)

**Neonatal sepsis**
- Pentoxifylline significantly affects synthesis of TNF and IL-6 as well as reduces the mortality rate in premature infants with sepsis.\(^3\)

**ARDS**
- There is no evidence that pentoxifylline or lisofylline have any beneficial effects in ARDS.\(^6\)

**Lung transplant**
- Treatment with NO and pentoxifylline before and during reperfusion in 23 consecutive patients markedly decreased the incidence of allograft dysfunction, with decreased oedema, improved oxygenation, decreased ventilator days, and decreased mortality.\(^7\)

**Renal transplant recipients**
- Pentoxifylline combined with cyclosporin and prednisone improved cadaveric kidney grafts survival.\(^8\)
- Thought to have a protective effect against cyclosporin-induced nephrotoxicity.\(^9\)

**Post cardiac surgery**
- Pretreatment with infusion of pentoxifylline at induction, continued until day 2 in patients aged >80 years undergoing cardiac surgery, attenuated deterioration of renal, and liver function.\(^10\)
- Pentoxifylline treated patients with an APACHE II score >19 experienced fewer ventilation and CRRT days, reduced ICU stay, with no change in mortality.\(^11\)

**Severe heart failure/dilated cardiomyopathy**
- In patients with severe idiopathic dilated cardiomyopathy, the addition of pentoxifylline to treatment with digoxin, ACE inhibitors, and carvedilol significantly reduced TNF-α levels, improved symptoms, NYHA classification and left ventricular function.\(^12,13\)

**Ischaemic stroke**
- Non-significant trend to less deaths\(^14\) and improvement in vascular dementia but not enough evidence to assess the overall effectiveness and safety.

**Other**
- 6 months treatment of combined pentoxifylline/Vitamin E reduced superficial radiation induced fibrosis after radiotherapy for breast cancer.\(^15\)
Complications

Usually well tolerated.

Gastrointestinal:
- Most frequent including: nausea, dyspepsia, vomiting, belching/flatus/bloating, abdominal pain and diarrhea. Isolated cases of intrahepatic cholestasis and transaminase elevation.

Central Nervous System:
- Dizziness, headache, insomnia, blurred vision, agitation/nervousness, drowsiness and tremor.
- Report of aseptic meningitis.

Cardiovascular:
- Flushing and arrhythmia/palpitations.
- Hypotension, angina/chest pain (rare).

Haematological:
- Decreased fibrinogen, pancytopenia, purpura, aplastic anaemia and leucopenia. Isolated reports of thrombocytopenia.
- Reports of bleeding (e.g. skin, mucosa, gastrointestinal tract) and/or prolonged prothrombin time (occurs rarely in patients without concomitant anticoagulants or platelet inhibitors).

Respiratory:
- Rare reports of epistaxis, flu-like symptoms, laryngitis and nasal congestion.

Hypersensitivity:
- Pruritus, rashes and urticaria.
- Anaphylactoid reaction (isolated cases).

Interactions
- May potentiate effects of: warfarin, antihypertensives, hypoglycaemic agents.
- Combined use with other xanthines (theophylline - increased levels) or with sympathomimetics may cause excessive CNS stimulation.

Overdose
- Dose-related.
- Flushing, hypotension, convulsions, somnolence, loss of consciousness, fever and agitation.
- Occurs 4-5 hours after ingestion and lasts about 12 hours.
- All patients reported have recovered.

Summary
- Multiple potential uses including attenuating the effects of sepsis, reperfusion and microvascular disorders.
- Encouraging animal studies, but usually with pre-treatment.
- Conflicting human results with mostly small RCT’s having positive results but large studies, e.g. ARDSNET showing no benefit with use.
- Well tolerated with few drug interactions.
- Cheap.

References
**LIST THE DIFFERENCES BETWEEN MONOPHASIC AND DIPHASIC DEFIBRILLATORS**

*Dr. T. Li. Intensive Care Unit, Prince of Wales Hospital, Hong Kong*

<table>
<thead>
<tr>
<th></th>
<th>Monophasic</th>
<th>Diphasic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction of flow of electric current between paddles</td>
<td>One direction</td>
<td>Two directions</td>
</tr>
<tr>
<td>Waveform</td>
<td>Single positive phase returning to zero voltage Either gradually (damped sinusoidal waveform) or abruptly (truncated exponential waveform)</td>
<td>First phase is positive. Second phase is negative</td>
</tr>
<tr>
<td>Application</td>
<td>Traditionally used in external defibrillators</td>
<td>Initially used in endocardial defibrillation in implantable cardioverter defibrillators. Recently also available for external defibrillators</td>
</tr>
<tr>
<td>Defibrillation energy level for VF in adults</td>
<td>200 J → 200 J or 300 J → 360 J and subsequent 360 J</td>
<td>150 J → 150 → 150 J Low energy and non-escalating</td>
</tr>
<tr>
<td>Defibrillation energy level for VF or pulseless VT in children</td>
<td>4 J/ kg</td>
<td>1 to 2 J/kg</td>
</tr>
<tr>
<td>Maximum recommended energy</td>
<td>360 J</td>
<td>200 J</td>
</tr>
<tr>
<td>Defibrillation threshold for VT</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Impedance compensating</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Transthoracic cardioversion of AF</td>
<td>Higher energy requirement</td>
<td>Lower energy requirement</td>
</tr>
<tr>
<td>Postresuscitation myocardial damage</td>
<td>Higher frequency</td>
<td>Lower frequency</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>Bigger</td>
<td>Smaller size</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Heavier</td>
<td>Lighter</td>
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<td></td>
<td>More expensive</td>
<td>Less expensive</td>
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<tr>
<td>Technical advantages</td>
<td>More demand of battery</td>
<td>Less demand of battery</td>
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</table>
References
DISCUSS THE USE OF rFVIIa IN THE MANAGEMENT OF THE CRITICALLY ILL BLEEDING PATIENT

Dr. S. Lam. Intensive Care Unit, Royal Adelaide Hospital, South Australia

Clotting cascade as it involves FVII
- Injured vessel exposes tissue factor (TF) on extravascular cells to the circulation.
- Factor VIIa binds to TF to form TF:VIIa complex
- TF:VIIa Complex activates FIX and FX
- FVIIIa and FIXa also activate FX → FXa
- FXa with its cofactor FVa bind to activated platelets to form Prothrombinase
- Prothrombinase, along with Ca^{++} and platelet phospholipids, converts prothrombin (FII) to thrombin (FIIa)
- Which converts fibrinogen (FII) to fibrin (FIIa)
- Fibrin monomers for polymers in platelet plug
Local FVIIa, FIXa, and FXa give positive feedback and activate more FVII.

rFVIIa Mode of action (see Figure 1)
- Recombinant, no human proteins or blood products
- Functions per endogenous FVIIa – ie TF dependent
- Being TF dependent, is thought to limit activation of clotting to site of vascular injury, without systemic activation of clotting
- Also has TF independent action - dose dependent direct activation of FX on platelets, thus able to produce prothrombinase activity without needing FVIIa or FIXa.
- Concentration required for this TF independent effect is higher than normal levels of FVIIa.
- Thus, at high doses, rFVIIa can directly activate clotting, but appears to remain only on activated platelets at the site of vascular injury.

Clinical Use
Originally introduced for haemophiliacs (deficient in Factor VIII or IX) with bleeding refractory to factor replacement due to inhibitory antibodies.
- Has been shown in trials to be effective in achieving haemostasis in over 90% of patients with inhibitors within 48 hours, including in double blinded RCT\(^1\).
- Has also been demonstrated to be effective in open labeled trial\(^2\) of patients with acquired haemophilia due to de novo production of antibodies blocking/reducing clotting factors. Often idiopathic, may be associated with connective tissue disease or pregnancy. Early use of rFVIIa appeared to give better response than with use as ‘salvage’ therapy.

In the last few years, case reports have emerged on its use in non-haemophiliacs. No blinded or randomised controlled trials published to date.
- Mostly for achieving haemostasis in trauma and surgical patients after massive transfusion with continued bleeding and coagulopathy despite ‘conventional’ treatment with maximal surgical haemostasis, platelet transfusion, FFP, cryoprecipitate, aprotonin, protamine if heparinised, and treatment of hypothermia.
These include multitrauma/stabbings/gunshot wounds/etc, abdominal/urological/orthopaedic/cardiac surgery, obstetric bleeding, and during liver transplantation. Small studies have found reduction in bleeding times in thrombocytopenic patients with some anecdotal reports of dramatic response in bleeding thrombocytopenic patients undergoing chemotherapy. Found in phase II studies to be effective even at low dose (20mcg/kg) to rapidly normalise INR in healthy patients anticoagulated with Warfarin. 2 cases reported of successful use in preterm neonates with visceral bleeding (liver, spleen, lung). Case series have reported rapid achievement of haemostasis and improvement or normalisation of INR and aPTT with even single doses (about 30-100mcg/kg IV), within 24-48 hours and as quickly as 10 minutes. Trial ongoing to determine if rFVIIa in patients with intracranial haemorrhage and normal coagulation can reduce haemorrhage volume and hence outcome.

Current Role in the treatment of bleeding ICU patients

- For haemophiliacs with bleeding and high levels of factor inhibitors.
  - Low level inhibitors who don’t have amnestic response may respond to higher doses of factor or porcine FVIII (haemophilia A).
  - Also may be used for patients with acquired haemophilia (factor inhibitors) with bleeding.
- Non-haemophiliacs – main published reports only used in desperate circumstances
may be considered if life threatening bleeding with ongoing coagulopathy and/or thrombocytopaenia despite maximal 'conventional’ medical therapy and appropriate procedural/surgical haemostasis.

Safety and Adverse Effects
- Recombinant, no human proteins or blood products
- Incidence of thromboembolism < 1%
- Small incidence of fever, headache, vomiting, rash. All self limiting and mild.
- No data on use in pregnancy.

Dosage and administration
- IV bolus, effective within minutes
- 50-100mcg/kg q2-4hourly until haemostasis achieved
- t1/2 is 2.5 hours
- no dose adjustment in liver/renal impairment

Monitoring and Coagulation studies
- FVIIa concentration > 30U/ml, but not readily available in urgent clinical situation
- INR becomes normal at about 5U/ml
- aPTT may not normalise
- titrate to clinical effect and requirement

References
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DESCRIBE THE METHOD USED AND THE INDICATIONS FOR THE POSITIONS OF INSERTION OF AN INTERCOSTAL DRAIN

Dr. V. Kulkarni. Intensive Care Unit, St George Hospital, Sydney, NSW

Indications:
- Pneumothorax
  - in any ventilated patient
  - tension pneumothorax (after initial needle relief)
  - recurrent pneumothorax after repeated aspiration
  - large spontaneous pneumothorax in any patient over 50 years
- Malignant pleural effusion
- Empyema and parapneumonic effusion
- Traumatic haemopneumothorax
- Postoperative – elective thoracic or cardiac surgery.

Pre-drainage assessment
Confirm diagnosis and assess risk of bleeding from any coagulopathy. Check for any bullous disease (emphysema), lung adherent to the chest wall, post-pneumonectomy state. Post-pneumonectomy space drainage should be carried out only after consultation with a cardiothoracic surgeon.

Method of Insertion -
- Consent and premedication (benzodiazepines and opioids, unless contraindicated)
- Position – Arm on the side of lesion behind the patient’s head to expose the axilla, in supine position\(^1,2\). As an alternative position, the patient may be made to sit upright, leaning on a table with a pillow or in a lateral decubitus position.
- Chest radiograph to be available at the time of insertion, except in case of tension pneumothorax.
- Confirm site of drain insertion by imaging and needle aspiration.
- Preferred site of insertion – triangular space bounded by anterior border of latissimus dorsi, lateral border of pectoralis major, horizontal line from superior border of nipple. A more posterior position may be chosen if suggested by presence of a locule.
- Prophylactic antibiotics should be given in trauma cases\(^3\).
- Aseptic technique should be employed by appropriate cleaning, draping the site, wearing surgical gown and gloves as for a surgical procedure.
- Anaesthesia – Local anaesthetic solution (lignocaine up to 3 mg/kg) should be infiltrated at the site by raising an intradermal bleb before deeper infiltration of intercostal muscles and pleural space.
- Incision (appropriate for the size of chest tube) is made above and parallel to the rib. Blunt dissection is carried out using a curved clamp to reach the pleural cavity in the intercostal space at the upper border of rib to avoid injury to the neurovascular bundle lying in the groove running along the inferior border of the rib. The pleural cavity is explored by the operator’s finger to release any adhesions and the tube mounted on the clamp is then inserted into the pleural cavity making sure that the distal hole on the drain tube is inside the thoracic cavity.
- Size of chest tube: Small bore chest tubes (8-14 Fr) are inserted by Seldinger technique, without any blunt dissection. Medium size drains can be inserted by either technique. Large drains (above 28-30 Fr) are recommended for acute hemothorax and to monitor blood loss\(^5\).

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\(^1\) Dr. V. Kulkarni. Intensive Care Unit, St George Hospital, Sydney, NSW

\(^2\) Method of Insertion - Consent and premedication (benzodiazepines and opioids, unless contraindicated)

\(^3\) Preferred site of insertion – triangular space bounded by anterior border of latissimus dorsi, lateral border of pectoralis major, horizontal line from superior border of nipple. A more posterior position may be chosen if suggested by presence of a locule.

\(^4\) Prophylactic antibiotics should be given in trauma cases.

\(^5\) Aseptic technique should be employed by appropriate cleaning, draping the site, wearing surgical gown and gloves as for a surgical procedure.

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Chest drain insertion should be performed without any substantial force.

The tube is connected to an underwater seal and secured in place with a silk (1" 0) suture. The air-fluid level in the drain bottle should swing with respiration. The tip of the tube in the bottle should be about 3-4 cms below the water level. The skin around the tube should be tightly approximated to avoid leak around the tube.

A chest X ray is taken to confirm the position of the tube and its effect.

Management of drainage system – All tubes should be connected to a single tube drainage system (underwater seal or flutter valve). A bubbling chest tube should never be clamped. Drainage of a large pleural effusion should be controlled to prevent re-expansion pulmonary edema. If a chest tube has to be clamped, it should always be under the supervision of a cardiothoracic surgeon.

High volume/low pressure suction pumps have been advocated for non-resolving pneumothorax, chemical pleurodesis.

Positions of insertion

For apical pneumothoraces, the second intercostal space in midclavicular line is sometimes chosen but not routinely recommended as it may be uncomfortable to the patient and may leave a unsightly scar.

Loculated apical pneumothoraces may be drained by a posteriorly sited (suprascapular) apical chest tube (performed by an operator experienced in this technique).

The tube may be directed towards the apex in case of pneumothorax or basally for an effusion. A trocar, maintained within a few centimetres behind the tube tip, may be used to guide the position accordingly.

Use of ultrasonography guided insertion is useful for empyema and effusions as it defines the position of diaphragm, presence of loculations and pleural thickening. Successful drainage can still be achieved when the drain is not placed in an ideal position. Effectively functioning tubes should not be repositioned solely due to suboptimal radiologic positioning.

Patients with chest drains should be managed on special wards where the staff are trained in chest drain management.

References

WHAT ARE THE INDICATIONS FOR AND COMPLICATIONS OF ACTIVATED CHARCOAL

Dr M. Maiden. Intensive Care Unit, Royal Adelaide Hospital, South Australia

- Charcoal is “activated” by treatment in acid and steam → removes charcoal impurities and greatly increases the surface area for binding (2000 m²/g).
- Reduces GIT absorption more than induced emesis or gastric lavage.
- Charcoal does NOT adsorb:
  - Alcohols (e.g. ethanol, ethylene glycol, methanol, isopropanol)
  - Metals (e.g. iron, lead, lithium, potassium)
  - Corrosives (e.g. acids, alkali, hydrocarbons)

- Recommendations regarding GIT decontamination have been changing.
  - 1980’s – ipecac, emesis, lavage.
  - 1990’s – charcoal better and safer than emesis.
  - Now – charcoal of limited value.

SINGLE DOSE CHARCOAL (American & European Position statement† 1997)

- Activated charcoal should not be administered routinely in poisoned patients.
- Based on volunteer studies, the effectiveness of activated charcoal decreases with time; the greatest benefit is within 1 hour of ingestion
  - E.g. randomised crossover volunteer study of activated charcoal at 1, 2, and 3 hours after paracetamol ingestion².
  - Charcoal at 1 hour reduced absorption by 30%.
  - Charcoal at 2 or 3 hours did not reduce absorption.
- Consider charcoal if a patient has ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal) up to 1 hour previously
  - Dose 0.5-1 g/kg.
  - Administer as a drink, mousse or via NG tube.
  - If airway unsecured, intubate before giving via NG tube.
- There is no evidence that activated charcoal improves clinical outcomes
  - E.g. RCT of charcoal in self-poisoned adult patients³.
  - 1479 patients over 2 years.
  - No difference in ventilation time, length of hospital stay or overdose complications.
  - Charcoal had a higher incidence of vomiting and longer length of ED stay. It did not improve outcome.

SORBITOL

- A poorly absorbed alcohol.
- Often premixed in charcoal bags.
- May increase palatability, avoid constipation and prevent unbinding of toxins in GIT if prolonged transit time⁴.
- There is NO evidence that the addition of a cathartic improves outcomes.
- Problems with sorbitol:
  - Fluid and electrolyte changes (esp. children).
  - Worse aspiration pneumonia than charcoal alone.
MULTI-DOSE CHARCOAL (American & European Position statement5 1997)

- The charcoal adsorbs drugs and maintains a drug concentration gradient between mucosal blood and gut lumen ("gastrointestinal dialysis").
- May be effective for drugs that are sustained release, form concretions or undergo enterohepatic recirculation.
- Proven to increase drug elimination.
- Yet to been shown in a controlled study to reduce morbidity and mortality.
- Dose 50g repeated 4 hourly.
- Likely benefit for:
  - Carbamazepine.
  - Phenobarbitone.
  - Quinine.
  - Theophylline.
  - Salicylates (controversial).
- Possible benefit for Amitriptyline, Dextropropoxyphene, Digoxin, Disopyramide, Phenytoin, Piroxicam, Sotalol.
- Should not be used if unsecured airway or ileus / GIT obstruction.

COMPLICATIONS

- Vomiting.
  - 30% (women > men).
  - May be decreased with anti-emetic.
  - Incidence unrelated to rate of administration.
- Aspiration pneumonia.
  - Australian retrospective review of poisonings at Newcastle over 5 years6.
  - 71 / 4562 (1.6%) developed aspiration pneumonitis.
  - Mortality 8.5% (aspiration) vs. 0.4% (no aspiration).
  - Higher intensive care unit admission rate.
  - Median LoS 126 hrs vs. 14.7 hrs.
- Charcoal aspiration.
  - Presents as respiratory failure with minimal CXR changes.
  - Treatment requires bronchoscopic removal of charcoal particles.
  - Beware the patient who may dislodge NG tube between charcoal doses.
- Messy.
- Constipation.
- ↓ Absorption of other medications e.g. OCP.
- Black stools.

Should the paramedics be giving charcoal? Probably not. They usually arrive >1 hour after ingestion, poisonings are usually not life-threatening and charcoal will increase the risk of aspiration.

References

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4. Dunn R et al. The emergency medicine manual. 2nd Ed. 2000 pg. 536
Dr. R. Lewin. Intensive Care Unit, Sydney Children’s Hospital, New South Wales

Amniotic fluid embolism:
First described in 1926, a rare obstetric complication, with a reported incidence varying from 1 in 20,000 to 1 in 80,000. The mortality rate is as high as 85%, and accounts for up to 10% of obstetric deaths in countries where comprehensive obstetric care is available.

Presentation:
Cases reported at any time during pregnancy, but especially immediately prior to, or during labour, or during caesarean section. Cases have been reported during first and second trimester abortions, second trimester pregnancy, abdominal trauma, and amniocentesis or for up to 48 hours after delivery.
- Foetal distress in 100% if not already delivered
- Dyspnoea in 100% if not already intubated, hypoxia, pulmonary oedema or ARDS in up to 90%
- Hypotension in 100%, cyanosis in 40%, cardiopulmonary arrest in 40%
- Coagulopathy in 40%
- Seizure as presenting feature in 10 to 20%
- Uterine atony in 10%, post partum haemorrhage

Differential diagnosis:
Anaesthetic mishap: allergy, anaphylaxis, medication error, aspiration pneumonitis, high spinal, local anaesthetic toxicity, inadvertent spinal injection of epidural dose, supine hypotension, haemorrhagic shock, malignant hyperthermia, air embolism.

Maternal: Congenital or acquired cardiovascular disease, pre-eclampsia, eclampsia, sepsis, pulmonary thrombo- embolism, intracranial haemorrhage.

Uterine: Uterine rupture or laceration, uterine atony, massive blood loss, placental abruption.

Foetus: Foetal death in utero, sepsis, foetal deterioration from other causes.

Pathophysiology: Clinical picture of cardiovascular collapse, cyanosis, haemorrhage, DIC:
Amniotic fluid enters maternal circulation via endocervical and uterine veins. Amniotic fluid contains PG/LT/foetal debris. Leads to complement activation, pulmonary vasoconstriction, with possible physical blockage of pulmonary capillaries.
- Similar clinical presentation to anaphylaxis / septic shock rather than massive PE.

Biphasic haemodynamic response:
1. Early: Severe hypoxia, right heart failure with pulmonary hypertension secondary to vasoconstriction.
2. Delayed: Left ventricular failure secondary to hypoxia and/or release of inflammatory mediators, associated with DIC and hypovolaemia with altered capillary permeability.
Management: Successful outcome based on early recognition of crisis, and obtaining adequate assistance for this rare and unpredictable condition. Establishing the diagnosis is secondary to initiating comprehensive supportive management for other treatable causes of cardiorespiratory collapse in an obstetric patient with a possibly viable foetus.

a. Immediate supportive interventions

Airway: Secure, ETT
Breathing: Ensure adequate ventilation with 100 % oxygen
Circulation: Adequate IV access, IV fluids and inotrope support.
  Consider immediate delivery including peri mortem caesarean section
  Consider circulation support with: CPR, IABP, open cardiac massage, CPBypass, ECMO.
  Blood products as required to support circulation, replace losses and correct coagulopathy.
Disability: control seizures, consider initial treatment with MgSO4. Cannot assume no ongoing seizures if patient paralysed. Role for EEG monitoring?
Exposure: Maintain normothermia
Fluid balance: Consider swan-ganz catheter or picco monitoring in addition to IDC
Gastrointestinal system: Nasogastric tube, ulcer prophylaxis

b. Diagnostic interventions

Comprehensive monitoring including pulse oximetry, ECG, pulse, BP, temp. CVC and arterial line. CTG if appropriate. EEG if paralysed for ventilation support with suspected seizure activity.
FBC, Coags, EUCr, BSL, LFTs, blood cultures, ABGs and lactate, monoclonal antibody TKAH-2. Repeat blood investigations if clinical change.
CXR, CTBrain, lung scan
TOE / ECHO if available.
Consider invasive monitoring of cardiac output if not already done.
Aspiration of swan-ganz catheter to look for foetal squamous cells.

c. Specific treatment for consideration based on pathophysiology

Nitric oxide
PGI$_2$
Steroids
Haemodiafiltration
aPC
Antibiotics
d. Consider transferral to a specialist centre

Outcome:
Survivors average 33 units blood products.
Many survivors will have hypoxia-induced neurological impairment.
50% die within one hour, during the initial phase of pulmonary hypertension and right sided heart failure.
Overall mortality 85%, secondary to cardiopulmonary collapse or uncontrolled haemorrhage with DIC.
References
7. Ayoub, Zreik, Dabbous, Baraka. Amniotic fluid embolus: can we affect the outcome? Curr Opin Anaesthesiol 16:257-261
DISCUSS THE ACTIONS AND INDICATIONS FOR INTRAVENOUS GLUCAGON

Dr. W-P. Chan. Intensive Care Unit, John Hunter Hospital, NSW

Mode of action
1) activation of G protein second messenger system to increase cAMP resulting in the cascade of protein kinases.
2) increase in inositol triphosphate.

Route of administration
IV/IM/SC. Acts within 1/60 IV, 8-10/60 IM/SC. Degradation by liver, kidney and plasma. T1/2 10-20/60.

Actions
- Metabolic – glycogenolysis, gluconeogenesis, lipolysis, proteolysis, ketogenesis.
- Hormonal – inc insulin secretion, inc catecholamine secretion.
- CVS – pos ionotropy and chronotropy
- GIT/UGT – smooth muscle relaxation, biliary smooth muscle relaxation, urinary smooth muscle relaxation, inc GFR.

Indications
Hypoglycaemia – reversing insulin induced hypoglycaemia. Needs adequate hepatic glycogen stores. Oral hypoglycaemic induced hypoglycaemia harder to treat (insulin present.) First line therapy usually dextrose. IM glucagon useful if difficulty obtaining IV access.

Toxicology
- beta blocker OD cardiotoxicity. Inc ionotropic and chronotropic effect independent of blocked B adrenoceptors. Used with atropine and ionotropes. 5mg bolus or 50 - 150mcg/kg repeated in 15/60 or 5-10 mg/hr, therefore need an extensive supply.
- Calcium channel blocker OD – after trial of atropine, Calcium, normalized ionized Ca, insulin/dextrose euglycaemia.
- TCA OD – NaBic still agent of choice.
- Asthma/Anaphylaxis –Some patients on a B blocker may not respond, Asthma – not routine use.

Oesophageal obstruction - Reduces resting pressure of lower oesophageal sphincter without changing oesophageal peristalsis. Disagreement over its effectiveness.

Other GIT effects – acute pancreatitis, inhibits secretion. Ureteric colic and biliary colic, acute diverticulitis.

Procedures – ERCP when hyoscine contraindicated.

Side effects
Nausea and vomiting usually when >5mg and diarrhoea.

References
2. Sasada M, Smith S. Drugs in Anaesthesia & Intensive Care 1999
DISCUSS THE USE OF ISOPRENALINE IN THE INTENSIVE CARE PATIENT

Dr. H. Ramaswamykanive. Intensive Care Unit, Concord Hospital, New South Wales

Introduction:
Isoprenaline (Isoproterenol) is a synthetic sympathomimetic having actions on beta₁ and beta₂ adrenergic receptors with little effect on alpha receptors.

Pharmacokinetics:
The half-life is about 2.5 - 5 minutes. Absorption of orally given isoprenaline is unreliable but it is readily absorbed when given intravenously or via aerosol. It is principally metabolised by COMT. MAO plays less of a role in its metabolism compared with epinephrine/norepinephrine. It is metabolised to sulphate conjugates. Around 50% - 75% of the given dose is excreted unchanged drug in urine following intravenous injection.

<table>
<thead>
<tr>
<th>Onset of action</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/V: Immediate</td>
<td>1-5 minutes</td>
</tr>
<tr>
<td>Inhalation: 2-5 min</td>
<td>30 min to 2 hours</td>
</tr>
<tr>
<td>SIC or Sublingual: 10-15 min</td>
<td>1 to 2 hours</td>
</tr>
</tbody>
</table>

Pharmacodynamics:
Isoprenaline is a positive inotropic and chronotropic drug having actions on heart, bronchial, uterine and alimentary tract smooth muscle. It is also a CNS stimulant. Myocardial contractility and heart rate increase due to activation of beta₁ receptors and systemic vascular resistance falls due to a beta₂ receptor-mediated vasodilation. Its lack of alpha agonist properties renders it ineffective to raise perfusion pressure in shock.

The marked reduction in systemic vascular resistance can produce significant hypotension and compromise myocardial perfusion pressure. Decreased diastolic perfusion time due to excessive tachycardia may also impair myocardial perfusion.

Myocardial oxygen requirements increase concurrently and myocardial oxygen balance worsens. Potential exists for an increase in ischaemia and extent of myocardial injury despite increase in cardiac performance. At low doses isoprenaline may increase coronary blood flow to the subendocardium and subepicardium and at high doses subendocardial and subepicardial perfusion decrease owing to decreased perfusion pressure and diastolic perfusion time.

Augmented cardiac output is usually distributed to skeletal muscles. Renal blood flow tends to increase in patients with cardiogenic shock. But there may be redistribution of flow from renal cortex to renal medulla causing no improvement or even deterioration of renal function.

Therapeutic Applications:
In the past, isoprenaline was used in bradycardia or heart block resistant to atropine, but it is no longer part of the American Heart Association Advanced Cardiac Life Support protocol.

a) Isoprenaline is used in patients with bradycardia or complete A V block before a temporary pacer can be inserted. It may also be useful in lowering the pacing threshold. Isoprenaline is frequently used in denervated heart (Post cardiac transplant) to maintain adequate heart rate.
b) Isoprenaline is also useful in patients with pulmonary hypertension as it is a potential pulmonary vasodilator. It decreases the pulmonary artery pressure and reduces the pulmonary vascular resistance
c) Isoprenaline may be used to improve haemodynamics in patients with low cardiac output.
resulting from increased pulmonary vascular resistance as in Mitral valve surgery.

d) In contrast to dopamine, isoprenaline may also increase the arterial oxygenation in patients with pulmonary oedema or acute respiratory distress syndrome due to reduction in pulmonary artery occlusion pressure.

e) Isoprenaline is used in diagnosis of Neurocardiogenic syncope (Tilt table test). Isoprenaline increases the left ventricular contractility while reducing the left ventricular volume. A passive upright tilt exaggerates these responses because the tilt also reduces the venous return and prevents isoprenaline from increasing the cardiac output.

f) Isoprenaline infusion may be used to simulate dynamic exercise in HaCM and Mitral stenosis as it increases the gradient because of its inotropic and chronotropic effects. However the utility of the drug is limited because of its side effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Activation</th>
<th>Hemodynamic Effects</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>α</td>
<td>β₁</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Metaraminol</td>
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<td>-</td>
</tr>
<tr>
<td>Salbutamol</td>
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<td>+</td>
</tr>
<tr>
<td>Pindolol</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Prenalterol</td>
<td>-</td>
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<td>TA 064</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Butapamine</td>
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<td>+</td>
</tr>
<tr>
<td>Levololopa</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ilopropanol</td>
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<td>+</td>
</tr>
<tr>
<td>Dopexamine</td>
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<td>+</td>
</tr>
<tr>
<td>Propranolol</td>
<td>-</td>
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<tr>
<td>Fenoldopam</td>
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Figure 1. Haemodynamic effects of sympathomimetic drugs.

Presentation and Administration:

- Available in: 1 in 5000 (0.2 mg/ml) or 1 in 50000 (0.02 mg/ml).
- Aerosol: 80 micrograms/160 micrograms. Sublingual/rectal: 10mg/15 mg.
- Isoprenaline can be given I/M; SIC; I/V; Sublingual, Meter dose inhalation.
- Dilute 1 mg in 250 ml dextrose/water or normal saline (4 micrograms/ml). Recommended isoprenaline dose for intravenous infusion is 2 to 10 micrograms/minute titrated to heart rate and blood pressure response.
**Adverse effects:**

- Isoprenaline is a potent arrhythmogenic drug. Isoprenaline essentially has the side effects of adrenaline. Ventricular tachyarrhythmia is common with larger doses.
- Dizziness, faintness, headache, nervousness, tremor and weakness observed during isoprenaline treatment. Ulceration, dry mouth, tooth discoloration, urinary hesitancy are some other side effects of isoprenaline. It also increases the blood glucose.
- These undesirable haemodynamic and metabolic effects of isoprenaline along with arrhythmogenicity have restricted the use in day-to-day clinical practice.

**References**

2. Micromedix@ Health care series.
WHAT ANTIBIOTICS WOULD YOU USE TO TREAT A PATIENT WHO HAD AN ALLERGY TO VANCOMYCIN AND HAD AN MRSA ENDOCARDITIS

Dr. N. Blackwell. Intensive Care Unit, The Prince Charles Hospital, Queensland

Manage in conjunction with cardiac surgeon and clinical microbiologist

Clarify:

- MRSA – exactly what sensitivities/resistances?
- Nosocomial or community acquired?
  - Associated with an infected prosthetic device
- If so remove (source control)
- Endocarditis – which valve/?Native or prosthetic/?associated cardiac function
- Allergy – truly allergic or red-man syndrome?

Therapeutic options:

1) Vancomycin by continuous infusion +/- anti-histamines if red-man syndrome not true allergy
2) Desensitize to vancomycin– not feasible given time constraints of reaching therapeutic levels in this patient
3) Teicoplanin – some cross-sensitivity – depends on history of vancomycin reaction
4) Depending on sensitivity profile of organism – clindamycin (high relapse rate) or ciprofloxacin plus rifampicin - problem with development of resistance to ciprofloxacin with protracted course
5) Linezolid (watch for myelotoxicity)
6) Quinupristin/dalfopristin
7) ?Role of adding gentamicin with prosthetic valve endocarditis if not gentamicin resistant

Not forgetting the role of cardiac surgery/valve replacement if indicated.

References
DISCUSS THE IMMUNIZATION SCHEDULE IN A POST OPERATIVE TRAUMA PATIENT WHO UNDERWENT A SPLENECTOMY

Dr. S. Hockley, Intensive Care Unit, Royal Adelaide Hospital, South Australia

Surgical removal of the spleen may be performed for severe splenic trauma, splenic cysts, or as part of resective procedures for tumours of the spleen or adjacent organs. Splenic macrophages play a major role in filtering, and phagocytizing bacteria and parasitised blood cells from the circulation as well as a significant source of antibody production. Partial splenectomy and splenic autotransplantation within the mesentery with retention of some splenic tissue is increasingly practiced in cases of splenic trauma, but overall effectiveness of this procedure remains unknown. Therefore, similar antimicrobial and immunisation protocols should be instituted to prevent Overwhelming Post Splenectomy Infection (OPSI) in these patients as for known asplenic subjects.

Asplenic children <5 yrs, especially infants splenectomised for trauma, may have an infection rate of >10%. Several studies have shown that 50% to 70% of admissions to hospital for serious infections occur within the first 2 yrs following splenectomy. Some degree of risk persists for the duration of life. Thirty-three percent of postsplenectomy pneumococcal infections and 42% of OPSI occurred >5 yrs postsplenectomy.

Causative Organisms

**Encapsulated bacteria.** Pneumococcus (Streptococcus pneumoniae) 50% to 90% of cases, mortality 10% to 60%. Haemophilus influenzae type B (important in children), meningococcus, and group A Streptococci account for an additional 25% of infections.

**Rarely noted organisms.** Capnocytophaga canimorsus, Group B streptococci, Enterococcus sp, Bacteroides sp, Salmonella sp, and Bartonella, Plesiomonas shigelloides, Eubacterium plautii, and Burkholderia pseudomallei. Fatal falciparum malaria has also been noted more frequently in asplenic persons. Protozoan infections following tick bites (Babesia microti in the United States or B. bovi in Europe).

Immunisation schedule

All patients to receive -
- pneumococcal polysaccharide vaccine (Pneumovax – repeat every 5 yrs)
- Haemophilus influenzae type b (Hib) vaccination
- Meningococcal C conjugate vaccine, followed 2 or more weeks later by a single dose of the tetravalent meningococcal polysaccharide vaccine (repeat every 3 yrs)

**Timing:** administration ideally 2 weeks prior to splenectomy, post splenectomy administration should be in the postoperative period when the patient is recovered and no intercurrent infection exists. Vaccination should not be performed during a febrile illness or where contraindication exists and may be deferred in pregnant women.

Antibiotic prophylaxis should be assessed for each patient individually, particularly those at highest risk:

- asplenic children under 5 years of age
- during the first 2 years following splenectomy
- patients with severe underlying immunosuppression (Lifelong).
For children under 2 years, use
amoxycillin 20 mg/kg orally, daily or phenoxympenicillin 125 mg orally, 12-hourly

For adults and older children, use
amoxycillin 250 mg orally, daily or phenoxympenicillin 250 mg orally, 12-hourly

For patients hypersensitive to penicillin, use
roxithromycin (child: 4 mg/kg up to) 150 mg orally, daily or erythromycin (all ages) 250 mg orally, daily

Education of Patient.
Patients should understand the potential seriousness of OPSI and the possible rapid time course of progression. In the event of any acute febrile illness they should seek medical attention, especially if associated with rigors or systemic symptoms.

Self-administration of 3 g of amoxycillin is advised. They should inform any new healthcare professionals, including dentists, of their asplenic status. Patients also need to be informed of an increased risk for travel-related infections such as babesiosis and malaria, as well as animal bite bacteria.

Maintenance of their immunisation status in consultation with their GP is the mainstay of immunoprophylaxis.

Medic-Alert bracelet should be worn.

One study indicated up to 40% of post splenectomy patients remain unaware of their increased risk for serious infection or the appropriate health precautions that should be undertaken despite being informed by their surgeon.

Empiric treatment for suspected overwhelming postsplenectomy infection³

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose⁴</th>
<th>Pediatric Dose⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>2 g iv every 8 hrs</td>
<td>25-50 mg/kg iv every 6 hrs</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g iv every 12-24 hrs</td>
<td>50 mg/kg iv every 12 hrs</td>
</tr>
<tr>
<td>+/- Gentamycin⁸</td>
<td>5-7 mg/kg iv every 24 hrs</td>
<td>2.5 mg/kg iv every 8 hrs</td>
</tr>
<tr>
<td>+/- Ciprofloxacin⁴⁺⁻</td>
<td>400 mg iv every 12 hrs</td>
<td></td>
</tr>
<tr>
<td>+/- Vancomycin⁴</td>
<td>1-1.5 g iv every 12 hrs</td>
<td>30 mg/kg iv every 12 hrs</td>
</tr>
</tbody>
</table>

⁴Doses are for normal renal function and should be adjusted if creatinine clearance is reduced; ⁸gantamycin or ciprofloxacin may be added if an enteric or urologic source of infection is suspected; ⁴ciprofloxacin is not indicated for children; ⁴vancomycin should be added when pneumococcus with high-level penicillin resistance is likely.

References
Dr. H. L. Tan. Intensive Care Unit, Sir Charles Gairdner Hospital, Western Australia

NONKETOTIC HYPERGLYCAEMIC COMA
Definition: Extreme presentation of diabetes due to the relative lack of insulin. Seen more often in elderly with NIDDM Dominant feature is hyperosmolality

Management Principles
Fluid replacement
Insulin therapy to gradually correct hyperglycaemic
Gradual correction of electrolyte disturbance
Treat underlying cause
Supportive therapy
Monitoring

Fluid Therapy
1. Dehydration and sodium depletion results from osmotic diuresis
2. Typical deficit: 9L H₂O, Na 5 to 13 mEq/kg
3. Initial priority is to restore intravascular volume:
   • In hypotensive patients, colloid achieve this faster than crystalloids
4. Once BP is stabilised, gradual replacement of total water deficit over next 24 to 48 hours. Over-aggressive replacement can precipitate cerebral/other oedema.
5. Invasive monitoring useful. Individual variation in fluid requirement
6. Fluid challenge with frequent assessment of response
7. Choice of fluid: debatable
   • Avoid overshoot in sodium and osmolality (associated with pontine myelinosis)
   • Suggested regime:
     0 - 1H 0.9% Saline 15 to 20 mL/kg/h
     1 - 3H 4 to 14 mL/kg/h
       If sodium low: 0.9% Saline
       If sodium high: 0.45% Saline
     4 - 48H 2 to 5 mL/kg/h
       If sodium low: 0.9% Saline
       If sodium high: 0.45% Saline
       Keep sodium 140 to 150 mmol/L
       Add dextrose 5% when BSL < 15 mmol/L
       Adjust for urine output
       Consider early CVVHDF if ARF
**Insulin Therapy**
1. Need less than DKA
2. Gradual correction if hyperglycaemia reduces mortality in DKA
3. Initial bolus dose 0.1 to 0.2 U/kg
4. Low dose 0.1U/kg/h (5 to 10 U/H)
5. Monitor BSL hourly till stable
6. Inadequate BSL normalisation may indicate inadequate rehydration

**Electrolyte Therapy**

**Potassium**
1. Hyperosmolality causes K shift to extracellular space
3. Typical total body deficit = 4 - 6 mEq/kg
4. Replace as combination of chloride and phosphate to avoid hyperchloraemia and hyperphosphataemia
5. Commence replacement when K < 5.3 mmol/L
6. Generally require 20 to 30 mmol/h
7. If K < 3.3mmol/L = profound deficit, start replacement before insulin therapy, 20 to 40 mmol/L, with ECG monitoring

**Phosphate**
1. Same mechanism of loss as K
2. Typical deficit 1mmol/kg
3. Routine phosphate replacement not shown to be beneficial
4. Treat severe deficit: < 0.4 mmol/L
5. Monitor serum calcium during replacement

**Magnesium**
1. Chronic Mg deficiency may be present.
2. Benefits of routine replacement not proven.

**NB:** Monitoring
4 to 8 hourly serum electrolyte/osmolality monitoring till stable
Check for acidosis, ketones (1/3 cases have mixed features)

**References**
Define the management of a patient who develops acute respiratory failure due to diffuse alveolar haemorrhage after allogenic haematopoietic stem-cell transplantation.

Dr. K. Gandhi. Intensive Care Unit, St George Hospital, New South Wales

**Definition:**

Diffuse alveolar hemorrhage (DAH) is a noninfectious pulmonary complication that is associated with hematopoietic stem-cell transplant (HSCT) and may contribute to significant morbidity and mortality. Overall DAH is reported in 5% of all bone marrow transplant. Recipients of autologous transplants are at higher risk than recipients of allogenic transplants. The reported in hospital mortality rate associated with DAH is as high as 80%.

**Criteria’s for the diagnosis of DAH:**

- A. Diffuse bilateral pulmonary infiltrates on chest radiographs.
- B. Progressively bloodier BAL [broncho-alveolar lavage] fluid with each instilled aliquot of normal saline solution from at least 3 separate lobes.
- C. Acute hypoxemic respiratory failure defined as PaO$_2$/FiO$_2$ ratio of < 150, requiring supplemental oxygen and ventilatory support.
- D. No clear bacterial, viral or fungal pathogens detected in BAL fluid.
- E. No improvement with correction of underlying coagulopathy and/or fluid overload and no evidence of cardiogenic pulmonary oedema.

**Pathophysiology:**

Pathophysiology of DAH is unclear, and possibly multifactorial. Different pulmonary structures have been partly damaged after chemotherapy and/or irradiation become more vulnerable to the toxic effects of neutrophils, which invade the lung causing pulmonary damage by their proteases and free radicals. Another mechanism could be inflammatory cells-induced cytokine storm, occurring periengraftment period as mediator of endothelial injury. These injury leads to alveolar desquamation, hyaline membrane formation and diffuse alveolar damage.

**Management:**

Management of pts. with DAH and acute respiratory failure:

- A. Supplemental oxygen therapy
- B. Ventilation
  - In selected hypoxemic patients EARLY initiation of noninvasive ventilation is associated with reductions in rates of intubations and serious complications.
  - If intubation and ventilation is required, care should be taken since many of these pts have severe mucositis, bleeding tendencies and upper airway swelling.
  - Ventilatory strategy for severe lung injury with decreased lung compliances should be of pressure limited ventilation, adequate positive end-expiratory pressure [PEEP]; and accepting permissive hypercapnoea.
  - Use of high-frequency oscillatory ventilation [HFOV] is described in pediatric literature as a safe and effective ventilatory alternative in pts with DAH and acute respiratory failure in
The goal of HFOV is to recruit and maintain “ideal” lung volume and to improve gas exchange while minimizing further lung injury.

C. Maintain euvoeemia with appropriate intravenous fluid therapy and vasopressors should be used to maintain adequate end-organ perfusion once euvoeemia established. Diuretics should be used if there is evidence of cardiogenic pulmonary oedema along with PEEP.

D. Other supportive ICU care – like renal replacement therapy, correction of coagulopathy, nutrition support, should be commenced as needed and if indicated. Use of routine prophylactic broad spectrum antibiotics including antifungal, PCP prophylaxis may be warranted pending definitive culture results including BAL fluid.

E. Glucocorticoids:
High dose corticosteroids [more than 30 mgs of methylprednisolone or its equivalent] have shown to be associated with improved total survival, survival to hospital discharge and decreased development of respiratory failure in the pts with DAH related to bone marrow transplant.6

F. Recombinant factor VIIa
Use of Recombinant factor VIIa has been described in literature for treatment of diffuse alveolar hemorrhage after allogenic bone marrow transplant.7

G. Pts should have diagnostic imaging like CT chest and if warranted bronchoscopy and BAL and open lung biopsy should be performed to rule out other differential diagnosis.

H. Further studies require for use of extracorporeal membrane oxygen therapy and other immunomodulation therapy in DAH associated with HSCT since not much has been written in literature.

Prognosis:
Diffuse alveolar hemorrhage in pts with allogenic hemopoietic stem cell transplant is associated with high mortality rate, and mortality rate upto 80% has been described in literature and hence prognosis should be discussed with pt. and family members including end of life issues.

References

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DISCUSS YOUR CHOICE OF ANTIBIOTIC(S) IN A PATIENT WHO HAS
SUSPECTED PYELONEPHRITIS

Dr. A. Wurm, Intensive Care Unit, Royal Adelaide Hospital, South Australia

<table>
<thead>
<tr>
<th>PATIENT FACTORS</th>
<th>PHARMACOLOGIC FACTORS</th>
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<tr>
<td>Severity of illness</td>
<td>Antibiotic spectrum of activity</td>
</tr>
<tr>
<td>Allergies</td>
<td>Antibiotic concentration in urine</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Side effects of antibiotic</td>
</tr>
<tr>
<td>Hepatic/renal function</td>
<td>Cost</td>
</tr>
<tr>
<td>Paediatric/pregnant patients</td>
<td></td>
</tr>
<tr>
<td>Failure of previous antibiotic therapy</td>
<td></td>
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<tr>
<td>Previous infection with known resistant organism</td>
<td></td>
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</tbody>
</table>

Mild cases (i.e. no sepsis, dehydration, significant comorbidities etc) can be managed as outpatient with oral therapy eg Augmentin, cephalexin, trimethoprim

All other cases treated as inpatient with iv antibiotics:
- Amoxycillin 1g 6/24 + Gentamicin 4-6 mg/kg/day (penicillin allergy: use gent.alone)

If aminoglycoside use is undesirable:
- Ceftriaxone 50 mg/kg up to 1g daily

Recurrences >2 weeks after the cessation of therapy nearly always represent reinfection with a new strain

Complicated UTIs (those arising in a setting of catheterization, instrumentation, urologic anatomic or functional abnormalities, stones, obstruction, immunosuppression, renal disease, or diabetes) are typically due to hospital-acquired bacteria, including *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Pseudomonas*, enterococci, and staphylococci: may be antibiotic-resistant strains.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use in Pregnancy</th>
<th>Daily cost ($)</th>
<th>Precautions</th>
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</thead>
<tbody>
<tr>
<td>Amoxycillin IV</td>
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<tr>
<td>Amoxycillin oral</td>
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</table>

References
DEFINE AND LIST THE CAUSES AND MANAGEMENT OF A VENTILATOR ASSOCIATED PNEUMONIA

Dr. H. Tewari. Department of Critical Care Medicine, Flinders Medical Centre, SA

Definition: VAP is defined by means of the following clinical and radiological criteria:
1. A new and persistent infiltration in the chest X-ray in patients mechanically ventilated for more than 48 hr.
2. Body temperature above 38.5 or below 36°C.
3. White cell count above 12,000/µL or below 4000/µL.
4. Purulent tracheobronchial secretion (TBS).
5. Impairment of pulmonary function as defined by the PaO₂/FiO₂ ratio.
6. The absence of alternative sources of infection such as urinary tract infection or peritonitis.

A score of 6 or more points using the Clinical Pulmonary Infection Score (CPIS) criteria is needed to define pneumonia. The CPIS is a composite of clinical, microbiologic and oxygen related criteria.

Predisposing factors for VAP:
- underlying chronic lung diseases, neurological disease, diabetes mellitus, renal & liver failure, thoracic or upper abdominal surgery, malnutrition, alcoholism & immunosuppression.
- presence of upper airway colonisation
- use of a nasogastric tube;
- reintubation; and emergency intubation
- supine patient positioning;
- duration of mechanical ventilation (MV);
- prior antibiotic exposure
- administration of histamine-2 receptor antagonists or antacids.
- excessive use of sedatives, paralytic agents, corticosteroids.
- frequent ventilator tubing changes.

Causative Agents:
- Staphylococcus aureus (most common), Pseudomonas aeruginosa, Haemophilus influenza, Serratia marcescens, Streptococcus pneumoniae, Alcaligenes faecalis & A. odorens, Enteroccoci, Acinetobacter calcoaceticus, Bacteroides fragilis, Escherichia coli, Branhamella catarrhalis.
- Rarely, Mycoplasma pneumoniae and Chlamydia pneumoniae.
- In the immunocompromised patients - Mycobacterium tuberculosis, Pneumocystis carinii.
- Fungi - like Aspergillus.
- Viruses - Influenza and Parainfluenza virus, Respiratory syncitial virus and Varicella.

Prevention of VAP:
- Environmental control:- most importantly hand washing. Ventilator circuit changes should not be done before 48 hours, proper disinfection of nebulisation equipment and the use of heat moisture exchangers.
- Control of respiratory secretions:- use of continuous lateral rotation, more regular suctioning of secretions before they can accumulate.
- Prophylactic Antibiotics: - There has been a resurgence, recently, on selective digestive
decontamination. These are attempts to sterilize the oral cavity of all gram negative organisms using oral applications of paste of Polymyxin, Tobramycin and Amphotericin and various other related agents. This approach has been blamed for emergence of resistant bacteria.

- Role of non-Invasive ventilation and early extubation to non-invasive ventilation.
- Role of Antibiotic rotation in ICUs to minimize the emergence of resistance.
- Avoidance of overtreatment with antimicrobial drugs has the propensity of selection of multi-drug resistant pathogens hence a worse prognosis.
- Keeping ventilated patients propped up, avoiding excessive use of H2 blocking agents.

MANAGEMENT OF V AP:

Diagnosing Ventilator Associated Pneumonia:
1. The Clinical Criteria for VAP gives a strong clinical index of suspicion.
2. Routine bloods, x-ray chest and blood serology.
3. Specialized Diagnostic Techniques:

| Diagnostic Tests for Ventilator-Associated Pneumonia how effective: |
|---------------------------------|---------|----------|---------|
| Technique                      | Threshold | Sensitivity (%) | Specificity (%) |
| Endotracheal aspirate           | Any pathogen | 70 - 95 | < 50 |
| Endotracheal Aspirate           | = 10⁵ cfu/mL | 25 - 70 | 70 - 85 |
| Bronchoscopy PSB culture        | = 10³ cfu/mL | 30 - 100 | 80 - 100 |
| BAL culture                     | = 10⁴ cfu/mL | 55 - 95 | 70 - 100 |
| BAL cytology                    | 2 - 7% CAB | 30 - 85 | 65 - 100 |
| Non-Bronchoscopic PSB           | 10³ cfu/mL | 60 - 100 | 75 - 100 |
| Non-Bronchoscopic BAL           | 10⁴ cfu/mL | 70 - 100 | 65 - 95 |

cfu/mL = colony-forming units per milliliter; PSB = protected specimen brush; BAL = bronchoalverolar lavage; CAB = cell-associated bacteria.

TREATMENT OF VAP:

Supportive Therapy:
1) Nutritional Therapy: Evidence implicating malnutrition as a cofactor in Pneumonia is substantial. Early enteral feeding, by a small-bore tube placed in the jejunum, with a continuous infusion method is vital.
2) Vigorous chest physiotherapy, regular suctioning of respiratory secretions with the help of positioning and rotation.
3) Aerosols, Bronchodilators and Humidification.

**Definitive Therapy:**

**Based on recommendations of the American College of Chest Physicians**

- The treatment of ventilator-associated pneumonia is at least partially empirical. A strong clinical suspicion justifies early commencement of antibiotic therapy once the diagnostic tests are done.
- **Polymicrobial infections** are common, and the isolation of one pathogen does not preclude others.
- Initial therapy should be directed at **Gram negative bacilli** and **S. aureus**, guided by local hospital flora and resistance patterns.
- Acceptable choices include a **third generation cephalosporin**, alone or in combination with an **aminoglycoside**; a **beta-lactam/beta-lactamase inhibitor** combination with an aminoglycoside; a **carbapenem**; **clindamycin combined with aztreonam**; or a **parenteral fluoroquinolone**.
- Single agents are often acceptable for mild-moderate infections occurring early in the hospital course.
- If **P. aeruginosa** or other multi-resistant pathogen is a strong possibility because of a prolonged ICU stay and/or prior exposure to broad-spectrum antibiotics, then treatment should include an anti-pseudomonal beta-lactam in combination with an aminoglycoside, and consideration should be given to adding vancomycin for methicillin-resistant **S. aureus**.
- A **fluoroquinolone** should be included in hospitals with endemic **legionellosis**. There is evidence that initial antibiotic treatment is an important determinant of outcome, but no empiric regimen can cover all potential pathogens.
- For an immunocompromised host based on the clinical picture, radiological and blood tests, other treatment i.e antiviral, antitubercular, fungal and therapy for pneumocystis-cariini should be added at the earliest.

**References**

LIST YOUR INVESTIGATIONS IN AN IMMUNE COMPETENT ADULT WHO HAS BEEN ADMITTED TO THE INTENSIVE CARE UNIT WITH ACUTE RESPIRATORY FAILURE CAUSED BY AN “ATYPICAL PNEUMONIA”

Dr. Y. Gotto. Intensive Care Unit, Royal Perth Hospital, Western Australia

**Definition of atypical pneumonia**

Chest infection which can not be identified by standard diagnostic techniques and do not respond to therapy with beta-lactam antibiotics.

**Atypical pathogens;**
Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamidia psittaci, Legionella pneumophila, Coxiella burnetii, Histoplasma capsulatum,

**Investigations**

**WCC**

Chest radiography

Non-specific

Radiographic abnormalities may be more prominent than would be predicted by auscultation of the chest

Pleural effusion is evident in one-third of cases of Legionella pneumophila

Gram’s stain of respiratory secretions

Numerous neutrophils but no organisms revealed

Regular sputum or blood-culture bacteriologic media

No growth of bacteria

Acute and convalescent serology (IgM antibody, IgG antibody)

Retrospective diagnosis

Need to demonstrate at least a four fold rise in convalescent –phase antibody titre

Culture in specific media

Direct fluorescent antibody staining

DNA detection using PCR (Polymerase chain reaction) assay

Not yet readily available clinically

Urinary antigen test

Highly sensitive and specific test to detect L. pneumophila serogroup 1

Serum sodium

Hyponatremia (serum sodium level of <131 mmol/L) with Legionnaires’ disease
DISCUSS THE MANAGEMENT OF A PATIENT WHO HAS ACUTE IRON POISONING

Dr. V. Ho. Intensive Care Unit, Concord Hospital, New South Wales

Iron poisoning is one of the leading causes of death in children less than six years of age. Iron is especially tempting to this age group due to the fact that it appears in forms that look like candy. Iron toxicity can be classified as corrosive or cellular. Corrosive toxicity is due to the fact that iron is an extremely corrosive substance to the GI tract. It affects the mucosal tissue and causes acute hemorrhagic gastritis, massive fluid loss (because of third spacing), bleeding and shock. Cellular toxicity is due to excessive iron build-up resulting in systemic iron toxicity. When serum iron level exceeds the body’s binding capacity, free iron produces an increase in reactive oxygen species. The formation of reactive oxygen species causes cellular death in the liver, heart, kidneys, lungs and the haematological system. This results in metabolic acidosis and multiple organ failure.

Stages of iron poisoning
Iron poisoning has 4 stages. There are no particular times associated with the stages and not every patient will go through each stage.

Stage-I (Stage of gastrointestinal toxicity): GI effects may contribute to systemic hypovolemia through ‘third spacing’ of fluid into the small bowel. CNS depression and cardiovascular collapse may occur in this stage in severe cases.

Stage-II (Quiescent phase): This stage which may be bypassed, consists of the resolution of GI symptoms with the patient appearing to improve and recover. This deceptive stage can start 6 hours after ingestion and may last up to 24 hours.

Stage-III (Stage of mitochondrial toxicity): In this stage in addition to hepatic injury, acute tubular necrosis, pulmonary hemorrhage, hypothrombinemia, hypoglycemia and ARDS may occur.

Stage-IV (Stage of gastric scarring): This typically occurs 2-6 weeks after severe acute iron poisoning and usually presents with recurrent vomiting secondary to gastric outlet obstruction.

Assessment
The precise iron preparation consumed and the maximum quantity taken must be determined on history. The amount of elemental iron is a fraction of the weight of the tablet and can be calculated for different iron salts e.g. 200 mg of ferrous sulphate contains 65 mg of elemental iron; 300 mg of ferrous gluconate contains 35 mg. Asymptomatic children that have a definitive history of consuming less than 30 mg/kg of elemental iron do not require any further investigation. Due to the inherent unreliability in poisoning and overdose stories, always take the higher estimate of the amount of tablets ingested when calculating the quantity of elemental iron consumed.

Initial assessment of patients should include careful recording of:
- vital signs
- mental status
- abdominal x-ray
- full blood count
- blood glucose
- coagulation studies
hepatic enzymes
blood gases
urea and electrolytes
serum iron levels ideally between 4-6 hours post-ingestion

Features of elevated serum iron are:6
- Significant vomiting or diarrhea
- Shock and coma
- Iron tablets on abdominal radiograph
- Coagulopathy
- Metabolic acidosis (serum bicarbonate <15 mEq/L)
- Hyperglycemia (blood sugar >8.3 mmol/L)
- Leucocytosis (WCC >15)

If serum iron >55 µmol/L or any of the features of elevated serum iron develop, the child must be admitted.4,5 If child remains asymptomatic for 6 to 8 hours after ingestion, serum iron <55 µmol/L4,5 and other laboratory results are unremarkable, further intervention is usually not required and the child can be discharged.

Treatment

Decontamination. Gastric lavage with the largest available tube and using normal saline should be done at the first port-of-call health care facility if a child has ingested iron in excess of 30 mg/kg or is symptomatic.4 A post lavage abdominal radiograph should be obtained to ascertain the success of lavage in clearing tablets from the stomach.4

Whole bowel irrigation This is of benefit in children in whom the abdominal radiograph reveals tablets beyond the pylorus or throughout the gastrointestinal tract.7 Whole bowel irrigation is also indicated when the serum iron level continues to rise in spite of proven decontamination efforts.2 Polyethylene glycol lavage solution is recommended for lavage with a rate of 30-40 ml/kg/hr for 4-8 hours.4 Irrigation should continue until abdominal films are clear of undissolved tablets.8

Iron Chelation Therapy Desferrioxamine chelates free iron. It does this by binding to elemental iron to produce ferrioxamine complex, which is excreted by the kidney.9 Patients with a serum iron level greater than 90 µmol should receive treatment with intravenous desferrioxamine.5

Desferrioxamine is given as a continuous intravenous infusion in normal saline at 15 mg/kg/hour.9 A clinically stable patient combined with a vin-rose urine color response to desferrioxamine (i.e. a ferrioxamine complex) and a serum iron <90 µmol/L,4,5 represents an appropriate point to cease desferrioxamine infusion.

Severe iron poisoning
Children with iron poisoning should be referred to a tertiary care center as early as possible. Children with severe iron poisoning should be managed in a Pediatric Intensive Care Unit.

Initial resuscitation involves managing:4
- Airway
- Breathing
- Circulation – Fluid replacement; CVP line and inotropes if required
- Blood transfusion to replace blood loss in haematemesis and malaena
- Monitoring for vital signs, GI haemorrhage, fluid balance, blood gases and electrolytes
Maintenance of good urine output > 1 mL/kg/hr is essential to prevent renal failure and to promote excretion of ferri-xamine complex.

**Outcome**

Most patients with iron poisoning respond well to conservative therapy. However it is critical to treat shock early. Early chelation therapy will also reduce mortality. The onset of acute liver failure with iron poisoning is associated with a high mortality. Early liver transplant should be considered in those that develop hepatic necrosis. Fortunately, the majority of survivors of iron poisoning have a normal outcome and an excellent long-term prognosis.

**References**

WHAT ARE THE IDEAL FEATURES OF A SEVERITY OF ILLNESS SCORING SYSTEM

Dr. D. So. Intensive Care Unit, PYN Eastern Hospital, Hong Kong

Easy to use

Minimal cost

Minimal work for staff

Good discrimination

- accuracy of a given prediction
- e.g., when a scoring instrument predicts a mortality of 90%, discrimination is perfect if the observed mortality is 90%

Good calibration

- how instrument performs over a wide range of predicted mortalities
- in e.g. above, a predictive instrument would be highly calibrated if it were accurate at mortalities of 90%, 50%, and 20%

Data built up from a large critical care population

Frequently updated clinical information

Widely studied and widely used

No lead time bias - take into account of pre-ICU care

Provide a foundation for research

Permit evaluation of ICU effectiveness and efficiency

Able for interhospital comparisons of ICU

Able to predict course of critical illness and help clinical decision making

Help with resource management

References
2. Hall, Schmidt, Wood. Principles of Critical Care 2nd Ed, p 57-70
DESCRIBE THE CLINICAL AND BIOCHEMICAL FEATURES OF ‘SHO-SHIN’ BERI-BERI

Dr. M. Scully. Intensive Care Unit, The Alfred Hospital, Victoria

Definition:
A fulminant variant of cardiovascular beriberi, characterised by hypotension, congestive heart failure and peripheral vasodilatation. Death can occur within hours unless thiamine supplementation is administered.¹

Pathophysiology.
Beriberi is caused by thiamine deficiency (Vitamin B₁). Thiamine combines with adenosine triphosphate in the liver and kidneys to form thiamine pyrophosphate. This acts as a coenzyme for transketolase in the pentose monophosphate pathway during gluconeogenesis and also in the decarboxylation of alpha-ketoacids.² Deficiency leads to impaired tissue oxygenation through inhibition of the citric acid cycle and the hexose monophosphate shunt.³ Clinical manifestations are either predominantly neurological (“dry beriberi”) and cardiovascular (“wet beriberi”).¹⁴

Clinical Features:
Shoshin beriberi can occur either as a deterioration of classical cardiovascular beriberi or arise de novo as a fulminant aggressive variant.⁴ The hallmarks of early cardiovascular beriberi are peripheral vasodilatation, sodium and water retention and high cardiac output.⁵ Patients complain of dyspnoea, malaise and palpitations and on examination have peripheral oedema, hepatic engorgement and tachycardia. Features of neurological beriberi (especially peripheral neuropathies) and other nutritional deficiencies (anaemia with iron/folate deficiency) may co-exist. Untreated this form can progress to decompensated ventricular failure with cardiovascular collapse (Shoshin beriberi).⁶ In this variant, direct myocardial depression is the dominant cardiovascular abnormality. Pyruvate is an important energy source in the heart; thiamine pyrophosphate is needed for the decarboxylation of pyruvate and its subsequent oxidation in the citric acid cycle. Thiamine deficiency blocks this step, leading to high pyruvate and lactate levels and diminished energy source. Clinical feature are restlessness, cold and cyanosed peripheries, distended neck veins, tachycardia and hypotension. Poor tissue perfusion and arterio-venous shunting lead to renal failure and multi-organ dysfunction. If this form arises rapidly tissue oedema may not be present. Urgent treatment is required to prevent fatality.

Investigations:
1: High lactate levels, due to poor tissue perfusion and blocked lactate metabolism as described above. Serum pyruvate levels are also elevated.
2: ECG; low voltage QRS complex, prolonged QT interval and T wave inversion have been described.⁷ However the ECG may be normal.¹
3: Chest X-ray usually shows pulmonary oedema.⁷
4: Left ventricular contractility is usually depressed but hyperdynamic changes on echocardiography have been described. Classically right ventricular involvement is pronounced in the early stages.
5: High cardiac index and low peripheral vascular resistance have been described, although a clinical spectrum of findings may occur. High mixed venous-oxygen saturations have been reported.⁸
6: Assessing the response to empirical thiamine therapy has been suggested as a diagnostic test.9

7: Low red cell transketolase levels and low urinary thiamine excretion confirm vitamin deficiency are seen.1 Whole blood or red cell transketolase activity can be assessed by measuring the thiamine pyrophosphate effect (TPPE). An increase in enzyme activity greater than 15% confirms deficiency. If greater than 25% severe deficiency is present.7

Incidence:
In Western societies the incidence of Shoshin syndrome is unknown but is believed to be very low. However isolated case reports suggest the true incidence may be higher than expected and a high index of suspicion maintained.9

Risk factors:
1: Alcoholism; this is the major risk factor in Western societies.1 Although dietary intake is not necessarily diminished, these patients have a relatively high carbohydrate intake which increases their metabolic demands for thiamine. Jejunal absorption is also impaired.3 HIV-associated thiamine cardiomyopathy has been reported.1,7
2: Dietary; this is important in societies with high intakes of polished rice. Worldwide most cases occur in South-East Asia. In Western countries the second commonest cause of thiamine deficiency are anorexia nervosa and diets deficient in thiamine, both of which can produce depletion within 21 days.
3: TPN associated thiamine deficiency producing shoshin beriberi has been reported.10
4: Conditions associated with increased thiamine metabolism include hyperthyroidism, fever, lactation and pregnancy. Thiamine losses occur with both haemodialysis, peritoneal dialysis and diarrhoea. Frusenide increases urinary thiamine excretion.3
5: Folate deficiency impairs the formation of thiamine pyrophosphate, producing an indirect thiamine deficiency as the active form cannot be generated.

Differential diagnosis:
1: Alcoholic cardiomyopathy.
2: Sepsis.
3: Thyrotoxicosis.

Treatment:
Thiamine 100mg intravenously is required, followed by 25mg daily for one to two weeks. Clinical improvement is usually detected within 12 hours and resolution occurs within 24 to 48 hours.1,7 Thiamine is safe and even with renal failure toxicity does not occur. Peripheral vasodilatation typically recovers before myocardial dysfunction; diuretics and digoxin have been used successfully to prevent pulmonary oedema until myocardial recovery occurs.1,3

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