The Australian Short Course on Intensive Care Medicine

2001 Handbook
The Australian
Short Course on
Intensive Care Medicine

2001 Handbook

Editor
L.I.G. Worthley
# CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body fluid spaces</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Renal physiology</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Renal hormones</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Pharmacology of the commonly used diuretics</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>Principles of fluid and electrolyte therapy</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Trainee Presentations</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td>131</td>
</tr>
<tr>
<td>Time</td>
<td>26th March</td>
<td>27th March</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>0815</td>
<td>Travel to FMC</td>
<td>Travel to FMC</td>
</tr>
<tr>
<td>0900</td>
<td>Lecture Introduction to the critically ill patient</td>
<td>Interactive ECG's</td>
</tr>
<tr>
<td>1015</td>
<td>Interactive Clinical vignettes</td>
<td>Interactive Presentations</td>
</tr>
<tr>
<td>1130</td>
<td>Clinical cases Pharmacological support of the circulation</td>
<td>Interactive Biochemistry, bacteriology</td>
</tr>
<tr>
<td>1245</td>
<td>Lunch</td>
<td></td>
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<tr>
<td>1400</td>
<td>Interactive Biochemistry, blood gases, bacteriology</td>
<td>Lecture Respiratory assistance in airflow obstruction</td>
</tr>
<tr>
<td>1515</td>
<td>Interactive Presentations</td>
<td>Interactive X-rays</td>
</tr>
<tr>
<td>1630</td>
<td>Interactive Path Forms</td>
<td>Interactive Biochemistry, haematology, coagulation</td>
</tr>
<tr>
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FMC = Flinders Medical Centre  
QEH = Queen Elizabeth Hospital  
WCH = Women’s and Children's Hospital  
RAH = Royal Adelaide Hospital
**REGISTRANTS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>*1</td>
<td>Dr. M. Daley</td>
<td>Intensive Care Unit, St George Hospital, NSW</td>
</tr>
<tr>
<td>*2</td>
<td>Dr. K. Vidhani</td>
<td>Intensive Care Unit, Liverpool Hospital, NSW</td>
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<td>*3</td>
<td>Dr. M. Gillham</td>
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<td>*4</td>
<td>Dr. K. Deshpande</td>
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<td>*5</td>
<td>Dr. R. Fabian</td>
<td>Intensive Care Unit, St George Hospital, NSW</td>
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<td>*6</td>
<td>Dr. C. Fagan</td>
<td>Intensive Care Unit, Royal Perth Hospital, WA</td>
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<td>*7</td>
<td>Dr. A. Delaney</td>
<td>Intensive Care Unit, Gosford Hospital, NSW</td>
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<td>*8</td>
<td>Dr. T. Browne</td>
<td>Intensive Care Unit, Queen Elizabeth Hospital, SA</td>
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<tr>
<td>*9</td>
<td>Dr. S. Baker</td>
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<td>*10</td>
<td>Dr. S. Koottayi</td>
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<td>*11</td>
<td>Dr. D. Collins</td>
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<td>*12</td>
<td>Dr. C. Schneider</td>
<td>Intensive Care Unit, Middlemore Hospital, New Zealand</td>
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<td>*13</td>
<td>Dr. R. Hegde</td>
<td>Department of Critical Care Medicine, Flinders Medical Centre, SA</td>
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<tr>
<td>*14</td>
<td>Dr. R. Holland</td>
<td>Intensive Care Unit, Bankstown Lidcome Hospital, NSW</td>
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<td>*15</td>
<td>Dr. D. Lowe</td>
<td>Intensive Care Unit, St Vincent’s Hospital, NSW</td>
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<td>*16</td>
<td>Dr. R. Plant</td>
<td>Intensive Care Unit, The Alfred Hospital, Victoria</td>
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<td>*17</td>
<td>Dr. B. Turner</td>
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<td>*18</td>
<td>Dr. D. Evans</td>
<td>Intensive Care Unit, Women’s and Children’s Hospital, SA</td>
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<td>*19</td>
<td>Dr. P. Garrett</td>
<td>Intensive Care Unit, Royal Brisbane Hospital, Queensland</td>
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<td>*20</td>
<td>Dr. N. McNelliss</td>
<td>Intensive Care Unit, Canberra Hospital, ACT</td>
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<td>Dr. S. Nolan</td>
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<td>*22</td>
<td>Dr. P. Whyte</td>
<td>Department of Critical Care Medicine, Flinders Medical Centre, SA</td>
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<td>*23</td>
<td>Dr. D. Murphy</td>
<td>Intensive Care Unit, St Vincent’s Hospital, Victoria</td>
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<td>*24</td>
<td>Dr. J. Field</td>
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<td>*25</td>
<td>Dr. J. Shen</td>
<td>Intensive Care Unit, Queen Elizabeth Hospital, Hong Kong</td>
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<td>*26</td>
<td>Dr. K. Lui</td>
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<td>27</td>
<td>Dr. E. Hughes</td>
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<td>28</td>
<td>Dr. S. Perrin</td>
<td>Intensive Care Unit, The Bendigo Hospital, Victoria</td>
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<td>Intensive Care Unit, Townsville General Hospital, Queensland</td>
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<td>32</td>
<td>Dr. L. Ware</td>
<td>Intensive Care Unit, Broken Hill Base Hospital, NSW</td>
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<td>Dr. S. Sviri</td>
<td>Intensive Care Unit, Sir Charles Gairdner Hospital, WA</td>
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<td>34</td>
<td>Dr. K. O’Connor</td>
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<td>35</td>
<td>Dr. S. DeSilva</td>
<td>Intensive Care Unit, MacKay Base Hospital, Queensland</td>
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<td>36</td>
<td>Dr. A. Warmenting</td>
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<tr>
<td>37</td>
<td>Dr. R. Purcell</td>
<td>Intensive Care Unit, The Alfred Hospital, Victoria</td>
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</table>

**FACULTY**

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<th>FMC</th>
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<tbody>
<tr>
<td>Dr. L. Worthley  (L.W)</td>
<td>Dr. M.O’Fathartaigh (M.O’F)</td>
<td>Dr. R. Young (R.Y)</td>
<td>Dr. N. Matthews (NM)</td>
</tr>
<tr>
<td>Dr. A. Vedig (A.V)</td>
<td>Dr. J. Moran (J.M)</td>
<td>Dr. M. Finnis (M.F)</td>
<td>Dr. A. Slater (A.S)</td>
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<tr>
<td>Dr. A. Bersien (A.B)</td>
<td>Dr. P. Panell (P.P)</td>
<td>Dr. P. Thomas (P.T)</td>
<td>Dr. M. Chapman (M.C)</td>
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<tr>
<td>Dr. A. Holt (A.H)</td>
<td>Dr. M. Tie (M.T)</td>
<td>Dr. P. Sharley (P.S)</td>
<td>Dr. C. Joyce (B.V)</td>
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<tr>
<td>Dr. E. Everest (E.E)</td>
<td></td>
<td>Dr. D. Clayton (D.C)</td>
<td>Dr. J. Myburgh (J.M)</td>
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</tbody>
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* registrants willing to undergo a ‘clinical’
# Acute Organ Failure

The RADISSON PLAYFORD HOTEL,  
120 NORTH TCE, ADELAIDE  
SOUTH AUSTRALIA

## March 24th, 2001

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>17:00 - 18:00</td>
<td>Registration</td>
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<tr>
<td>18:00 - 18:30</td>
<td>The Critically Ill Patient</td>
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<tr>
<td>18:30 - 20:00</td>
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## March 25th, 2001

### MORNING

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>08:45 - 09:00</td>
<td>Welcome</td>
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<tr>
<td>09:00 - 09:35</td>
<td>Acute Respiratory Distress Syndrome</td>
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<tr>
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<td>Medical and mechanical treatment</td>
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<td>Prof. A. Bersten</td>
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<tr>
<td>09:35 - 09:45</td>
<td>Discussion</td>
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<tr>
<td>09:45 - 10:20</td>
<td>Acute Renal Failure</td>
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<tr>
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<td>Fluid and dialytic therapy</td>
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<td>Prof. R. Bellomo</td>
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<tr>
<td>10:20 - 10:30</td>
<td>Discussion</td>
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<tr>
<td>10:30 - 11:00</td>
<td>Morning Coffee Break</td>
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<tr>
<td>11:00 - 11:35</td>
<td>Cardiac Arrest</td>
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<td>Current algorithms</td>
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<td>Dr. D. Ernest</td>
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<tr>
<td>11:35 - 11:45</td>
<td>Discussion</td>
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<tr>
<td>11:45: 12:20</td>
<td>Acute Coronary Syndromes</td>
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<td>Pathophysiology and current treatment</td>
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### AFTERNOON

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 - 13:30</td>
<td>LUNCH</td>
</tr>
<tr>
<td>13:30 - 14:05</td>
<td>Acute Liver Failure</td>
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<tr>
<td></td>
<td>Current supportive therapies</td>
</tr>
<tr>
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<td>Dr. A. Holt</td>
</tr>
<tr>
<td>14:05 - 14:15</td>
<td>Discussion</td>
</tr>
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<td>14:15 - 14:50</td>
<td>Acute Cerebral Trauma</td>
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<td></td>
<td>Neural protection</td>
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<tr>
<td>14:50 - 15:00</td>
<td>Discussion</td>
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<td>15:00 - 15:30</td>
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<td>15:30 - 16:05</td>
<td>Shock</td>
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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 cursory look at the basic sciences of the renal system with chapters on body fluid spaces, renal physiology, renal hormones, pharmacology of the commonly used diuretics and principles of fluid and electrolyte therapy. As with the previous editions, the course registrants presentations (or those that have been submitted on time) have also been included.

The subjects that have been dealt with in the lectures (this year included in the ‘Acute Organ Failure’ meeting) that were included in previous handbooks are now published separately in the journal Critical Care and Resuscitation.

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 2001
An understanding of fluid compartments and electrolyte physiology is required before the clinician is able to rationally prescribe the various intravenous solutions for the acutely ill patient.

**UNITS OF MEASUREMENT**

**Equivalent.** One equivalent of an ion is the amount which can replace or combine with 1 g of hydrogen (i.e. it is the 'equivalent' of 1 g of hydrogen). It is the atomic weight of a substance divided by its valence.

**Mole.** A mole of a substance is the molecular weight of that substance expressed in grams. As substances react in equivalent molar quantities, the mole provides a useful unit of measurement.

**Molality.** The molality of a solution is the number of moles of a solute per 1000 g of a solvent. Molarity of a solution is the number of moles of a solute per litre of a solvent and thus, unlike molality, is dependent on temperature.

**Osmole.** The osmotic effect of a substance in solution depends only on the number of particles dissolved. It is independent of the weight, electric charge, valence or chemical formula. Each mole of an unionised substance equals one osmole. As each molecule of sodium chloride in an ideal solution dissociates into two ions, sodium chloride contributes twice as many osmotically active particles as a non-ionised substance (e.g. glucose). Thus 1 mmol of sodium chloride in solution provides 2 mosmol.

However, body fluids are not ideal solutions and, although the dissociation of electrolytes may be complete, the number of particles exerting an osmotic effect is reduced due to ionic interaction. For sodium chloride a factor of 1.86 makes allowance for the interaction of ions in concentrations that normally exist in plasma water. Thus the osmolality of 0.9% saline, which contains 154 mmol/L of sodium and chloride, is 286.4 and not 308 mosmol/kg.

**Osmolality.** Osmolality is a measure of the total number of particles (i.e. ions or molecules) present in a given weight of solvent. The osmotic effect of a substance in solution depends only on the number of particles dissolved. It is independent of the weight, electric charge, valence or chemical formula. Properties of a solution that depend solely on the number of solute particles present are known as its colligative properties. Addition of a solute to a solvent results in changes in the four colligative properties of the solvent; its freezing point and vapour pressure are lowered, and its boiling point and osmotic pressure are increased. In an aqueous solution the osmolality is commonly determined from a measurement of the freezing point depression (using the fact that each milliosmole/kg increase in osmolality, depresses the freezing point of the solvent, water, by 0.00186°C - although this constant varies with solute concentrations), as direct measurement is difficult (because of the difficulty in obtaining a true semipermeable membrane) and alteration in boiling point is inappropriate for solutions containing substances that are unstable at high temperatures and measurement of vapour pressure is inaccurate in the presence of volatile solutes (e.g. methanol, ethanol).
In health, sodium and its accompanying anion, glucose and urea contribute to almost 100% of the plasma osmolality, allowing for a reasonably accurate estimation of the plasma osmolality by the simple addition of the molar concentrations of these compounds.

**Osmolarity.** The osmolarity of a solution is the number of osmoles of solute per litre of a solution and is therefore dependent on temperature.

**Tonicity.** Body fluid solutes are either permeant [i.e. they are able to permeate throughout the intracellular fluid (ICF) and extracellular fluid (ECF) compartments)]; or impermeant (i.e. they are distributed within the ECF only, because of molecular size, electrical charge or active membrane pumps).

Tonicity is a measure of the impermeant solutes and may be derived by calculating the osmolarity from the molar concentrations of plasma sodium and glucose (2 x Na + glucose), or by measuring the osmolality and reducing this value by the molar concentrations of permeant solutes (i.e., urea, ethanol).

Hyperosmolar states have an increased plasma osmolality due to a decrease in total body water or an increase in body solutes. Hypertonic states have an increased concentration of impermeant solutes and accordingly, due to the ECF/ICF osmotic difference, fluid shifts from the ICF to the ECF compartment, causing a net ICF reduction. This effect, if due to hypertonic substances not containing sodium (e.g. glucose or mannitol), is associated with a predictable reduction in the plasma sodium concentration.

If hypertonic saline or sodium bicarbonate solutions are administered, the plasma sodium rises. The anticipated increase in plasma sodium may be calculated by multiplying the initial plasma sodium by the ratio of the increase in plasma osmolality. For example, in a 70 kg man who has a total body water of 60% and a plasma sodium and osmolality of 140 mmol/L and 286 mosmol/kg, respectively, the rise in plasma sodium due to the administration of 100 mmol (in 100 mL) of sodium bicarbonate (assuming no water or sodium is excreted and the sodium bicarbonate is completely dissociated i.e. discounting the interaction of ions in plasma), may be calculated as follows:

\[
\begin{align*}
\text{Plasma osmolality} & = 286 \text{ mosmol/kg,} \\
\text{Total body water} & = 70 \times 0.6, \\
& = 42 \text{ L.} \\
\text{Total body osmoles} & = 42 \times 286, \\
& = 12012 \text{ mosmol.} \\
\end{align*}
\]

After 100 mmol of sodium bicarbonate,

\[
\begin{align*}
\text{Total body water} & = 42 + 0.1, \\
& = 42.1 \text{ L,} \\
\text{Total body osmoles} & = 12012 + 200, \\
& = 12212 \text{ mosmol,} \\
\text{Plasma osmolality} & = 12212/42.1, \\
& = 290 \text{ mosmol/kg,} \\
\text{Final plasma sodium} & = 290/286 \times 140, \\
& = 142 \text{ mmol/L} \\
\end{align*}
\]

As an approximation, the plasma sodium rises 1 mmol/L for every 42 mmol (numerically the same as patient's total body water) of sodium which is administered without water.
**Osmolar (osmolal) gap.** The osmolar gap is the difference between the measured osmolality and the calculated osmolarity. The simplest (and most accurate) formula for calculating osmolarity is

\[
\text{Osmolarity} = 2 \times \text{Na}^+ + \text{glucose} + \text{urea}
\]

where the plasma sodium, glucose and urea are measured in millimoles per litre.\(^3\) The osmolar gap is normally less than 10. The gap increases in conditions of ‘factitious’ hyponatraemia where plasma water is less than normal, or in the presence of unmeasured osmotically active compounds such as ethanol, methanol, isopropyl alcohol, ethylene glycol, paraldehyde, ether, trichloroethylene, acetone, mannitol, glycerol, sorbitol, glycine and fructose.\(^3\) The osmolar gap is also elevated in patients with chronic renal failure\(^4\) and in keto and lactic acidosis,\(^5\) the causes of which are not entirely clear.

Osmolality may be measured in plasma or serum (as haemolysis does not change osmolality). While the heparin in a plasma sample can artefactually elevate the osmolality by up to 0.6 mosmol/kg,\(^6\) in practice this is regarded to be negligible.\(^7\) However, if a blood specimen is left standing for some time before the osmolality is measured, the formation of lactate may artefactually increase the osmolality by up to 8 mosmol/kg.\(^8\)

**Anion gap.** Chemical compounds in solution may either remain intact (i.e. undissociated), in which case they are called non-electrolytes (e.g. glucose, urea), or dissociate to form ions, in which case they are called electrolytes. Ions carry an electrical charge (e.g. \(\text{Na}^+\), \(\text{Cl}^-\)). Ions with a positive charge are attracted to a negative electrode or cathode, and hence are called ‘cations’. Conversely, ions with a negative charge travel towards a positive electrode or anode and are called ‘anions’. To maintain a solution’s electrical neutrality, the number of anions must equal the number of cations. The plasma ‘anion gap’ is calculated from the formula

\[
\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)
\]

(where \(\text{Na}^+\), \(\text{K}^+\), \(\text{Cl}^-\) and \(\text{HCO}_3^-\) are measured in mEq/L), and is an index of the gap between the ‘unmeasured cations’ (e.g. Ca 5 mEq/L and Mg 1.5 mEq/L) and the ‘unmeasured anions’ (e.g. plasma proteins 15 mEq/L, phosphate 2 mEq/L, sulphate 0.5 mEq/L, lactate, citrate and ketones 3 mEq/L). Albumin has a molar equivalent of 18, (i.e. 18 mEq for each 6.9 g), therefore a normal albumin level of 4.2 g is responsible for 11 of the 15 ‘plasma protein’ milliequivalents.\(^9\) The unmeasured cations total 6.5 mEq/L and the unmeasured anions total 20.5 mEq/L, accordingly the normal mean anion gap is 14.0 mEq/L.

The normal ‘gap’ ranges between 8 and 16 mEq/L, although with ion-selective electrode systems this may be 2 mEq/L lower due largely to an upward shift of the measured chloride values.\(^9\)

**An increased anion gap** (i.e. > 16 mEq/L) may be due to:\(^{10}\)

1. A non carbonic, non hydrochloric, acidosis (e.g. d or l lactic acidosis, ketoacidosis), poisoning acidosis (e.g. ethylene glycol, methanol, ethanol, paraldehyde, salicylate), or renal failure acidosis (due to phosphate and sulphate anions)
2. Therapy with sodium salts of strong acids (e.g. acetate, citrate, lactate)
3. High dose penicillin therapy (i.e. excess penicillin anion)
4. Alkalaemia (due to an increased protein anion equivalent,\(^{11}\) of 0.01 mEq/L per g/L of protein for each increment in pH of 0.10 units\(^{12}\))
5. Hypermotraemia (by unknown mechanisms\(^8\))
Body Fluid Spaces

6. ECF volume contraction (due to a higher net anionic charge on plasma proteins or an increase in anions that are restricted to the intravascular compartment).  

A decreased anion gap (i.e., < 8 mEq/L) may be due to:

1. Technique-dependent error, for example:
   a. Bromism: bromide toxicity occurs with plasma levels greater than 50 mg/100 mL (6.25 mEq/L) and in severe toxicity levels up to 200 mg/100 mL (25 mEq/L) may occur; as the colorimetric and ion-selective methods used to estimate chloride is more sensitive to bromide, the chloride level is artificially elevated and the anion gap is reduced.  
   b. Hyperlipidaemia: high lipid levels interfere with some of the methods used to measure chloride, causing an artificial elevation of the plasma chloride, and a decreased anion gap.

2. Miscellaneous effect, for example:
   a. Reducing the albumin level by half will reduce the anion gap by 5.5 mEq/L (one study documented a decrease in the anion gap by 2.5 mEq/L for each 10 g/L reduction in albumin – as measured by bromocresol purple – below 44g/L).
   b. Increasing the unmeasured cations of calcium and magnesium, will reduce the anion gap by up to 2 - 4 mEq/L.
   c. High levels of IgG (a cationic protein) may also reduce the anion gap.
   d. Water excess, due to unknown mechanisms, will cause a decrease of the anion gap approximately twice that which would be expected from dilution alone.

TOTAL BODY WATER (TBW)

In man, water contributes to approximately 60% of the body weight, with various organs contributing different amounts of water in relation to their weight (Table 1.1).

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<tr>
<th>Tissue</th>
<th>%</th>
<th>Water Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

The variation of the percentage of total body weight as water, between individuals, is largely governed by the amount of adipose tissue. Men normally have less body fat than women. Accordingly, an average male will have a higher percentage of body weight as water. The average water content as a percentage of total body weight is 60% for males and 50% for females. Of the remaining 40 - 50% of total body weight, 18% is protein, 7% is mineral and 15 - 25% is fat. Total body water as a percentage of total body weight decreases with age, due to a progressive loss of muscle mass, allowing bone, connective tissue and adipose tissue to assume a greater percentage of total body weight (Table 1.2).
Table 1.2. Water content as a percentage of total body weight

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males (%)</th>
<th>Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 15</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>15 - 40</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>40 - 60</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>50</td>
<td>45</td>
</tr>
</tbody>
</table>

Measurement of total body water utilises techniques involving dilution of substances which are distributed throughout the total body water space. Antipyrine is one such substance which is easily measured and slowly metabolised and excreted. Alternatively, isotopes of water may be used. Deuterium oxide ($\text{D}_2\text{O}$) is nonradioactive and thus difficult to measure, whereas tritium (THO) is a weak beta-emitter and can be measured easily. Equilibrium of a small dose takes 4 - 6 hr and provide values that are predictable to within $\pm 2\%$. \(^{21,22}\)

FLUID COMPARTMENTS
The TBW may be divided into two functional volumes, the ICF and ECF.\(^{20}\)

The ICF is defined as all the body water within cells. The ECF is defined as all the body water external to the cell, and, while it may be divided into five or more compartments,\(^{23}\) it is commonly subdivided into plasma and interstitial fluid volumes (Table 1.3, Figure 1.1).

Sodium balance regulates the ECF volume. Water balance regulates the ICF volume. Sodium excretion is normally regulated by various hormonal and physical ECF volume sensors, whereas water balance is normally regulated by hypothalamic osmolar sensors.\(^{24}\)

![Body fluid compartments](image)

**Figure 1.1.** Body fluid compartments
Table 1.3. **Body fluid compartments**

<table>
<thead>
<tr>
<th>Fluid Compartment</th>
<th>Volume (mL/kg)</th>
<th>% Total Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume</td>
<td>45</td>
<td>4.5</td>
</tr>
<tr>
<td>Blood volume</td>
<td>75</td>
<td>7.5</td>
</tr>
<tr>
<td>Interstitial volume</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td>Extracellular fluid volume</td>
<td>250</td>
<td>25</td>
</tr>
<tr>
<td>Intracellular fluid volume</td>
<td>350</td>
<td>35</td>
</tr>
<tr>
<td>Total body fluid volume</td>
<td>600</td>
<td>60</td>
</tr>
</tbody>
</table>

**Extracellular fluid compartment**

Measurement of this space is performed by using substances (tracers) that diffuse throughout the ECF space without penetrating the cell. The volume measured ranges from 15 to 27% of total body weight and depends on the tracer used. Tracers are either ionic (isotopes of bromide, chloride, or sulphate) or non-ionic (inulin, mannitol, and sucrose). The non-ionic tracers are large molecules that often fail to distribute throughout all of the ECF in a reasonable time, whereas the ionic tracers distribute not only throughout the ECF compartment, but also partly through the ICF compartment as well. Thus, the ionic substances give larger measurements of the ECF volume than the non-ionic substances.

Bromide equilibrates in about 20 - 24 hr, during which time 3 - 5% is lost in the urine. The latter can be measured and allowed for in the calculations, to give results with a variability of ± 2%. When reporting ECF volumes, the tracer used should be stated as well as the time taken for that tracer to equilibrate. For example, one should talk about a 20 hr bromide space rather than the ECF space. Most ECF tracers show two decay curves. The first is a rapidly equilibrating pool of 20 min, delineating an ECF space which is in dynamic equilibrium with the plasma. This is about 20% of the total body water or about 8 - 10 L in volume. The second is a slowly equilibrating ECF space (24 hr), and includes the ECF of dense connective tissue and bone. Electrical conductivity methods can be applied simply at the bedside, and have been used to measure the ratio of TBW and ECF volumes. If the TBW is also measured, then the ECF volume can be derived. However, the accuracy of this method compared to conventional methods, particularly in patients with liver disease, has not been confirmed.

In clinical practice, ECF is normally considered to be 40% of total body water, and 25% of total body weight. The ECF volume, as a percentage of total body weight, shows little change with age; most of the change in total body water due to age is due to a decrease in ICF volume. With acute or chronic illness ICF volume is reduced and ECF volume is increased and may even exceed the ICF volume.

A reduction in the ECF volume is often observed clinically by a reduction in the plasma volume. For example, postural hypotension, tachycardia, reduced peripheral perfusion and low urine output, indicate a reduction in plasma volume and therefore ECF volume. Clinical assessment, however, is often of limited sensitivity in patients who are not hypotensive. In these circumstances, plasma urea, urinary sodium, and urine volume responsiveness to intravenous saline administration may be used to separate normovolaemic patients from hypovolaemic patients. An increase in the ECF volume may be observed clinically by subcutaneous oedema (prominent in the flanks of the body in the supine patient), ascites, pleural effusions and pulmonary oedema.
Body Fluid Spaces

Plasma volume

This may be measured using Evans blue, indocyanine green, hydroxyethylstarch, or radioiodine-labelled albumin.\textsuperscript{27,28} As 7 - 10% of $^{125}$I-albumin escapes from the vascular compartment per hour, the plasma volume may be overestimated using the latter method. To counter this effect, multiple readings may be taken to allow extrapolation to zero time.\textsuperscript{23}

Red blood cell volume

This is part of the ICF volume. However, if a chloride tracer is used to measure ECF volume, then much of the RBC volume is included, as red blood cell chloride levels are 60 - 70 mmol/L (unlike normal ICF chloride levels, which are 3 mmol/L).

The RBC volume may be calculated from plasma volume and haematocrit values. However, RBC mass may be overestimated by about 5 - 7% when using this method, which is thought to be due to total blood haematocrit being about 85 - 92% of venous haematocrit (e.g. a correction factor of 0.91 is often applied). Recently, the assumption that there is a difference in total body haematocrit and venous haematocrit has been questioned, as experimental data have tended to support the hypothesis that plasma markers (e.g. Evans blue, albumin) partly disappear during the mixing period (i.e. first 7 minutes) and therefore yield a false-high determination of the plasma and blood volume.\textsuperscript{28}

Tagging RBCs with chromium ($^{51}$Cr)\textsuperscript{23} or technetium ($^{99m}$Tc)\textsuperscript{27} will give more accurate recordings which are generally used as the ‘gold standard’.

Interstitial fluid volume

This cannot be measured directly and is often calculated as the difference between ECF volume and plasma volume. In clinical practice, transcellular fluids (i.e. fluids formed by transport activity of cells, such as gastrointestinal secretions, pleural or peritoneal fluids) are usually considered as part of the interstitial volume, because an increase or decrease in transcellular fluid volume commonly occurs with a reciprocal change in the ECF volume. The transcellular fluid volume may vary from 1 - 10 L, the larger volumes occurring in diseased states such as bowel obstruction or ascites.

Intracellular fluid compartment

The ICF compartment, unlike the ECF compartment, is a nonhomogeneous, multicompartmental entity, with pH and ionic composition differing between the various organ tissues. The ICF volume is often determined by inference, from the difference in measurements of the TBW and ECF spaces. This measure suffers from the inaccuracies inherent in both ECF and TBW measurements. In general, the ICF volume is considered to be 60% of TBW and 35% of total body weight.

As cell membranes are highly permeable to water, the cell volume can be altered by changes to the ICF or ECF osmolality. In health, as cells tend to accumulate osmotically active substances (e.g. amino acids), a decrease in the intracellular Na$^+$ (and chloride and other anions) concentration, driven largely by the Na/K pump, counterbalances the osmotic change and maintains the ICF volume.\textsuperscript{29} To maintain this steady state, the Na/K pump utilises an estimated 30% of the resting energy expenditure.\textsuperscript{30} Changes in cell volume induced suddenly by extracellular hypotonicity or hypertonicity is rapidly countered (i.e. over minutes) by cell loss of potassium chloride (due to activation of separate potassium and chloride channels or activation of the K$^+$/Cl$^-$ cotransporter) during hypotonicity, and uptake of potassium and sodium chloride (due to activation of the Na$^+/\text{H}^+$ and Cl$^-$/HCO$_3^-$ exchangers or Na$^+/K^+/2\text{Cl}^-$ cotransporter) during hypertonicity. If the change in tonicity remains, then the regulation of the cell volume occurs (over many hours) by an alteration in cell organic osmolites. The organic
osmolites responsible for this effect are grouped into three distinct classes: polyols (e.g. sorbitol, myo-inositol), amino acids and their derivatives (e.g. taurine, alanine, proline, N-acetylaspartate), and methylamines (e.g. betaine, glycerylphosphorylcholine). These compounds (which have been called ‘idiogenic osmoles’ in studies on cerebral tissue) have unique properties of compatibility which allow them to accumulate within cells over a wide range of concentrations without disrupting cell function or structure. They accumulate primarily by uptake from extracellular fluids through the activation of sodium-dependent cotransporters. Organic solutes accumulate more rapidly than they are dissipated (particularly in cerebral tissue), largely because solute efflux occurs through one broadly selective organic-osmolite efflux channel, of which myo-inositol (which is the predominant organic osmolite) is at the upper size limit of solutes that can permeate the channel. In addition, particularly in cerebral tissue, the sodium dependent pathways of myo-inositol uptake induced by chronic hypertonic stress remain activated for prolonged periods.

**Composition of body fluids**

Each body water compartment contains electrolytes with different composition and concentration. As the intracellular electrolyte composition varies from organ to organ, the values are often averaged (Table 1.4).

**Table 1.4 Mean Electrolyte Composition of Body Fluid Compartments (mmol/L)**

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Extracellular Fluid</th>
<th>Intracellular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>Whole Water</td>
</tr>
<tr>
<td>Sodium</td>
<td>140</td>
<td>150</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.7</td>
<td>4</td>
</tr>
<tr>
<td>Chloride</td>
<td>101</td>
<td>109</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Calcium (ionised)</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Magnesium (ionised)</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Osmolality</td>
<td>291.3</td>
<td>291.3</td>
</tr>
</tbody>
</table>

**Physiological regulation of the compartments**

**Compartment wall**

The difference in concentration of substances between compartments is due in part to the barrier separating the compartments. The composition of the interstitial fluid is similar to that of plasma because the former is an ultrafiltrate of the latter. The protein content of plasma is 70 g/L and that of the interstitial fluid is 10 g/L, accounting for the lower Na⁺ and higher Cl⁻ content in the interstitial fluid due to the Gibbs-Donnan effect (see later). The cell wall separates the interstitial fluid from the ICF, and the Na/K pump is responsible for the major concentration differences of these ions between these compartments. Apart from small specialised areas there are no osmolar gradients between compartments.

**Solute movement**

Body solute moves in response to a number of factors and transport mechanisms can be active or passive.
Passive transport mechanisms

1. **Diffusion**: this describes the physical property of all solutes in solvents, which is characterised by a movement from an area of higher concentration to one of a lower concentration.

2. **Nonionic diffusion**: undissociated molecules of weak acids and bases often cross a cell membrane with greater ease than the ionic form. Upon crossing the membrane, they may then dissociate, which characterises the condition of non-ionic diffusion.

3. **Gibbs-Donnan effect**: the unequal distribution of diffusible ions on either side of a membrane can be explained if one side contains a poorly diffusible ion. At equilibrium:
   a. The product of the concentrations of diffusible ions in one compartment will equal the product of the same ions in the other compartment
   b. Within each compartment the total cationic charges equal the total anionic charges
   c. The diffusible cations are greater in the compartment with the nondiffusible anion, and the diffusible anions are greater in the other compartment (e.g. the ICF chloride is 1.05 x plasma chloride, and the ICF sodium is 0.95 x the plasma sodium, see Table 1.4).
   d. The osmolality therefore is greater in the compartment with the nondiffusible anions due to:
      i. The nondiffusible anion (i.e. plasma protein), which contributes 17 - 19 mmHg; as albumin exerts an osmotic pressure twice that of globulins and as it is almost twice the concentration in plasma, it is responsible for 70% and globulins 30% of the oncotic effect of plasma proteins
      ii. The diffusible cation, which contributes 8 - 9 mmHg.

The added osmolality generated by the nondiffusible anions is known as the oncotic pressure and accounts for the difference between the plasma and interstitial osmotic pressure of 1.3 mosmol/L (25 - 28 mmHg). The oncotic pressure may be measured directly or calculated reliably from (and thus is reflected reliably by) the total protein concentration.

Active transport mechanisms

These use energy for distribution a substance across a membrane which cannot be achieved by physical forces alone. These mechanisms include ion pumps, facilitated transport, exocytosis and endocytosis.

Ion pumps allow the organism to control the ECF and ICF, ionic composition, osmolality (and thus the ECF and ICF volumes) and potential difference, which accounts for a tissue's excitability, allowing in some cases for signals to be moved rapidly from one part of the body to another. An excess of univalent ions in the order of $10^{-12}$ mmol/L (a concentration difference that is unable to be measured chemically) in one aqueous phase compared to another, can produce a potential difference of 100 mV, which is the approximate magnitude of the potential difference across many biological membranes. Ion pumps are known as 'electrogenic' if they pump ions from one phase to the other, or 'exchange' if they exchange ions of the same charge.

Fluid movement

Fluid moves in response to osmotic and hydrostatic forces.

Osmotic forces

Osmosis is the movement of solvent from a region of higher to one of lower chemical potential across an intervening semipermeable membrane. The osmotic pressure is that hydrostatic pressure which would have to be applied to the membrane to stop the movement of
the solvent. At 37°C, 1 mosmol/kg produces 19.3 mmHg pressure across a semipermeable membrane, thus the osmotic pressure of a solute can be approximated in mmHg by multiplying its concentration in mmol by 19.3.

**Hydrostatic forces**

Filtration is caused by a difference in hydrostatic pressure on either side of a membrane. The movement of fluid and solute depends on the surface area of the membrane, the permeability of the membrane and the hydrostatic pressure difference.

**REFERENCES**


Chapter 2

RENAL PHYSIOLOGY

ANATOMY

The two kidneys lie on either side of the vertebral column in the retroperitoneal space, opposite the L1 - L2 vertebral bodies, the right kidney being approximately 1 cm lower than the left. They are 11.5 - 12.5 cm in length (and no greater than 1 cm difference in length) each weighing 150 g. The kidney is divided into an outer cortex and an inner medulla, the latter is composed of a number of triangular structures known as renal pyramids which are separated by columns of Bertin.

Renal blood supply

The renal artery divides into lobar arteries (one for each pyramid), which divide into interlobar arteries which course between the pyramids. The latter divide into arcuate arteries at the corticomedullary junction, which run parallel to the surface of the kidney at the base of the renal pyramids. Interlobular arteries branch from the arcuate arteries, penetrating the cortex and extending to the surface of the kidney (Figure 2.1). The afferent arteriole of the glomerulus arises from the interlobular artery. After the afferent arteriole breaks up into four to eight parallel glomerular capillaries it rejoins to form the efferent arteriole, which then divides into intertubular vessels that surround and supply the proximal and distal tubules from many nephrons.

Figure 2.1. Sagittal section of the kidney where the upper half shows the overall gross anatomic arrangement and the lower half demonstrates the arterial supply.
Renal Physiology

The vascular supply of the medulla arises from the efferent vessels of the juxta medullary glomeruli as vasa recta, which are vessel loops that dip into the medullary pyramids alongside the loops of Henle. Unlike the cortical circulation there is little autoregulation of the medullary circulation, thus the medullary blood flow is largely pressure-dependent; the juxtamedullary glomeruli also have low renin content. From the peritubular capillaries and the vasa recta, blood drains into interlobular veins, leaving the kidney in veins that flow counter to, and named in accordance with, the adjacent arteries. Sympathetic fibres distribute to the afferent and efferent arterioles.

Figure 2.2. A model of the short and long-looped nephron. 1 = Renal corpuscle, including Bowman’s capsule and glomerulus, 2 = Proximal convoluted tubule, 3 = Pars recta, 4 = Descending thin limb, 5 = Ascending thin limb, 6 = Thick ascending limb, 7 = Macula densa, 8 = Distal convoluted tubule, 9 = Connecting tubule, 10 = Cortical collecting duct, 11 = Outer medullary collecting duct, and 12 = Inner medullary collecting duct.
**RENAL BLOOD FLOW**

The renal blood flow is 1.25 L/min, which is approximately 25% of the resting cardiac output. The renal oxygen consumption is about 18 mL/min, which is approximately 7% of the resting oxygen consumption. As the renal blood flow is large, the arteriovenous oxygen difference is small (approximately 1.4 mL/100 mL of blood). Due to axial streaming, the haematocrit of glomerular blood is about 50% of systemic blood.

**THE NEPHRON**

This is the functional unit of the kidney and consists of the glomerulus and the renal tubule. Morphologically, the renal tubule is divided into the proximal tubule (consisting of the pars convoluta and pars recta), the intermediate tubule (consisting of the descending thin limb and ascending thin limb), distal tubule (consisting of the thick ascending limb which is also known as the pars recta of the distal tubule, macula densa and distal convoluted tubule), the connecting tubule and the collecting duct (consisting of initial collecting tubule and cortical and medullary collecting duct, Figure 2.2). In each kidney there are approximately 1.3 million nephrons. The cortical nephrons have short loops of Henle, whereas the juxtamedullary nephrons have long loops, which extend down to the medullary pyramids. In humans, only 15% of the nephrons have long loops. The total length of the nephron ranges from 45 - 65 mm.

**THE GLOMERULUS**

The glomerulus is formed by the invagination of four to eight parallel capillaries into the dilated blind end of the renal tubule known as Bowman’s capsule (Figure 2.3). The capillary endothelium (which is fenestrated with pores approximately 100 nm in diameter), basement membrane and the tubular epithelium, acts as the filtering surface separating capillary blood from urine. On electron microscopy, the glomerular capillary basement membrane appears to have a central dense layer, which is known as the lamina densa, and two thinner more electron-lucent layers, known as the lamina rara interna and lamina rara externa.

---

**Figure 2.3.** A diagram of the glomerulus.
Renal Physiology

The cells of the visceral epithelial layer have numerous pseudopodia that interdigitate to form slits of approximately 25 nm width along the basement membrane. At the base of the glomerulus are clusters of extraglomerular mesangium cells (because of their similarity to the mesangium cells within the glomerulus) known as the ‘lacis’ or ‘polkissen’.

**Glomerular filtration rate**

The glomerular filtration rate (GFR) is 125 mL/min or 180 L/day, which is 20% of the effective renal plasma flow of 625 mL/min or 900 L/day, and 10% of the renal blood flow. The glomerular filtration rate for each nephron is governed by factors which govern filtration across all capillaries, that is:

\[
GFR = kS[(P_{gc} - P_t) - (O_{gc} - O_t)]
\]

where,

- \(k\) = capillary permeability (glomerular capillaries are about 50 times as permeable as skeletal muscle capillaries. Also as the endothelium is negatively charged, anions are less permeable than cations²)
- \(S\) = size (i.e. area) of the capillary bed
- \(P_{gc}\) = mean hydrostatic pressure within the glomerular capillary
- \(P_t\) = mean hydrostatic pressure within the tubule
- \(O_{gc}\) = plasma osmotic pressure in the glomerular capillary
- \(O_t\) = ultrafiltrate osmotic pressure (i.e. tubular lumen osmotic pressure).

Autoregulation maintains glomerular filtration rate between mean arterial pressures of 60 and 200 mmHg. The afferent arteriole reduces the normal mean arterial pressure of 70 - 105 mmHg to 45 mmHg in the glomerular capillary. As the oncotic pressure increases from 25 mmHg to 35 mmHg throughout the glomerular capillaries, and as the pressure in Bowman’s capsule is 10 mmHg, the effective filtration pressure is 10 mmHg at the afferent end of the glomerular capillary and 0 mmHg at the efferent end of the glomerular capillary. Equalisation pressure (i.e. when no net filtration occurs) is reached two-thirds to three-quarters of the way along the glomerular capillary. The afferent arteriole is fully dilated at a mean arterial pressure of 70 mmHg, and glomerular filtration ceases at a mean arterial pressure of 45 - 50 mmHg. The efferent arteriole reduces the hydrostatic pressure further to 30 mmHg in the peritubular capillaries. At the peritubular capillaries there is a net force of 10 mmHg moving fluid into the capillary.

**Measurement of glomerular filtration rate.** The renal clearance of a substance is the volume of plasma from which that substance is completely cleared by the kidneys per unit time, that is:

\[
Cs = \frac{Us \times \dot{V}}{Ps}
\]

Where

- \(Cs\) = clearance of S (mL/min)
- \(Us\) = concentration of S in urine (mmol/L)
- \(Ps\) = concentration of S in plasma (mmol/L)
- \(\dot{V}\) = volume of urine excreted (mL/min)
If a substance is neither secreted nor absorbed by the nephron, then its clearance is an assessment of the GFR. Substances suitable for measuring GFR must be freely filtered, not protein-bound (i.e. not affected by the Gibbs-Donnan effect), not reabsorbed or secreted by tubules, not metabolised or stored by the kidney, nontoxic, have no effect on the GFR and easily measured in urine and plasma.

Inulin (a fructose polymer, mol. wt 5200) and \[^{51}Cr\]EDTA (ethylenediaminetetraacetic acid) meet the above criteria, and either are regarded as a 'gold standard' when measuring glomerular filtration rate. Recently, \[^{99m}Tc\] DTPA (diethylene triamine pentaacetic acid) was reported to provide an accurate and continuous measure of GFR in critically ill patients. However, these agents are not commonly used in clinical practice, because inulin requires a loading dose and a constant infusion to keep the arterial level constant, and \[^{51}Cr\]EDTA and \[^{99m}Tc\] DTPA require an ability to measure a radiolabelled compound.

Cystatin C (a protease inhibitor a molecular weight of 13,300 which is produced at a constant rate by all nucleated cells and is filtered by the glomerulus without being secreted or taken up into the blood by the nephron) has also recently been used to assess the GFR. As is catabolised by the proximal tubule, the blood level is the only way to estimate the GFR.

Nevertheless, in clinical practice extreme precision is seldom needed, and creatinine clearance is commonly used as an estimate of GFR.

**Creatinine clearance.** Creatinine is formed from the irreversible and constant nonenzymatic degradation of creatine phosphate. The daily creatinine production, which ranges from 8 to 25 mmol/day, varies by only 10% in an individual and depends largely upon the skeletal muscle mass. It is freely filtered by the glomerulus, with a small contribution to the total excretion arising from tubular secretion. The latter causes an error of overestimation of the GFR which becomes larger as the GFR falls. Cimetidine blocks tubular secretion of creatinine and has been used to increase the accuracy of GFR measurements (1200 mg of cimetidine is administered orally; after 3 hr, urine is collected for 3 hr and blood samples are taken at the beginning and end of the urine collection).

As an ICF/ECF concentration gradient for creatinine of 2 - 5 exists, when skeletal muscle damage occurs, a greater amount of creatinine will be liberated into the circulation during the period of muscle damage, which may elevate the serum creatinine (usually only to the upper limit of a normal plasma level) in the absence of a reduction in GFR.

In subjects who have a normal GFR, creatinine has a half-life of 2.4 hr. With a reduction of GFR by 50%, the half-life is doubled, and a period of 4 half-lives (i.e. 20 hr) is required before a new steady plasma level is achieved (i.e. for the plasma level of creatinine to be a useful predictor of the GFR). If the GFR is reduced by 94% (i.e. to approximately 7 mL/min/1.73 m\(^2\)), the half-life of creatinine is increased from 2.4 hr to approximately 40 hr and a period of 160 hr or one week is required before a new steady plasma level is reached. The plasma creatinine doubles with each 50% decrease in functioning nephron mass.

Creatinine is measured using either a colorimetric (i.e. Jaffe picric acid estimation) or an enzymatic method. The results using the Jaffe reaction are greater than that of the enzymatic method, due to the colorimetric method also measuring endogenous chromogens. Acetoacetic acid (but not acetone or beta-hydroxybutyric acid) and cephalosporin antibiotics also interfere with the Jaffe picric acid estimation, causing false elevations of plasma creatinine. Accordingly, plasma creatinine may be falsely elevated during fasting (e.g. after 4 days of fasting the plasma acetoacetic acid can rise up to 1.6 mmol/L, falsely increasing the measured plasma creatinine by up to 70%), in diabetic ketoacidosis or during cephalosporin therapy. High doses of frusemide may also interfere with the Jaffe picric acid estimation, causing the plasma creatinine to be falsely low. Contamination of blood with dobutamine will cause
plasma creatinine to be falsely lowered when creatinine is measured using the enzymatic method.\textsuperscript{11}

The standard creatinine clearance (i.e. measured creatinine clearance x 1.73/patient’s body surface area in m\textsuperscript{2}) 95% reference range is 75 - 185 mL/min/1.73 m\textsuperscript{2} (mean 120 mL/min/1.73 m\textsuperscript{2}) for males, and 70 - 140 mL/min/1.73 m\textsuperscript{2} (mean 100 mL/min/1.73 m\textsuperscript{2}) for females. From day to day, the creatinine clearance may vary by up to 10 - 25% in normal adult males.\textsuperscript{12} The creatinine clearance decreases with age and may be estimated by the formulae,\textsuperscript{13}

\[
\text{Creatinine clearance (mL/min/1.73 m}^2\text{)} = 133 - 0.64 \times \text{age}
\]

**Urea clearance.** The renal handling of urea is by simple diffusion; approximately 50% is reabsorbed by the proximal tubule. The remaining 50% undergoes a recycling characterised by reabsorption from the collecting ducts and secretion into the loop of Henle. Approximately 10% escapes this recycling and is taken by the vasa recta into the systemic circulation. Approximately 40% of urea is cleared with maximum antidiuresis (i.e. when urine flow is low), and 60% of urea is cleared with maximum diuresis (i.e. urine flow is high).

**Glomerular filtration fluid**

Urine formation begins as an ultrafiltrate of plasma into Bowman’s capsule. It differs from plasma by being essentially protein-free (i.e. contains less than 50 mg/L of protein) and the electrolytes have a Gibbs-Donnan distribution (i.e. anions 5% higher and cations 5% lower than plasma water). Renal tubular modifications of the glomerular filtrate are such that it, reabsorbs, Na\textsuperscript{+}, K\textsuperscript{+}, Cl\textsuperscript{-}, HCO\textsubscript{3}\textsuperscript{-}, amino acids, phosphate, glucose and water, adds NH\textsubscript{4}\textsuperscript{+}, H\textsuperscript{+}, K\textsuperscript{+}, inorganic anions (e.g. lactate, penicillin, urate), and concentrates and excretes urea and creatinine.

The 180 L/day of glomerular filtration fluid contains 25,100 mmol of Na\textsuperscript{+}, 5000 mmol of HCO\textsubscript{3}\textsuperscript{-} and 800 mmol of glucose (Table 2.1).

<table>
<thead>
<tr>
<th>Table 2.1 Tubular reabsorption and secretion (mmol per 24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance</td>
</tr>
<tr>
<td>Na\textsuperscript{+}</td>
</tr>
<tr>
<td>K\textsuperscript{+}</td>
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<tr>
<td>Cl\textsuperscript{-}</td>
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<td>HCO\textsubscript{3}\textsuperscript{-}</td>
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<td>Calcium</td>
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<td>Uric acid</td>
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<td>Glucose</td>
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<td>Amino acids</td>
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<tr>
<td>Total solute</td>
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<td>Water (mL)</td>
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Abbreviations: P = proximal tubule, L = loop of Henle, D = distal nephron, C = collecting duct.
The glomerulus allows substances with a molecular weight up to 30,000 to pass freely. If the daily intake of sodium is 200 mmol then 25,000 mmol of the daily glomerular filtration (99.2%) is reabsorbed by the renal tubules. The percentage of sodium reabsorption by the proximal tubule remains the same independent of GFR, which means that the absolute amount of sodium reabsorbed by the proximal tubule varies with GFR. The change in reabsorption (which occurs within seconds after a change in filtration) can be demonstrated with a number of other substances reabsorbed by the proximal tubule. This characteristic is known as glomerulotubular feedback response and should not be confused with tubuloglomerular feedback (i.e. in acute tubular necrosis an increased distal delivery of sodium occurs, which stimulates an increase in renin production at the macula densa which in turn increases local production of angiotensin II, constricting the afferent arteriole and reducing the GFR. It is proposed that this is the mechanism for the tubuloglomerular feedback response, and that this prevents a large loss of ECF and maintains the ECF volume at the expense of extracellular biochemical homeostasis).

THE RENAL TUBULE
A characteristic of the renal tubule epithelial cell is its distribution of plasma membrane proteins into separate apical and basolateral domains so that no transport protein resides in both the apical and basolateral membranes at the same time and within the same cell. The coordinated expression of both segments is responsible for tubular fluid reabsorption. For example, the basolateral membrane Na⁺/K⁺-ATPase acts with apical membrane Na⁺ channel and Na⁺:H⁺ antiporter to provide proximal tubule reabsorption of sodium and water (Figure 2.4).

The proximal tubule
The human proximal tubule is 14 mm long, 60 µm in diameter with a surface area of 2.5 mm². It consists of an initial convoluted portion (i.e. pars convoluta) and a straight portion (i.e. pars recta) which drains into the thin descending limb of the loop of Henle (Figure 2.2). The proximal tubule is made up of a single layer of cells that interdigitate with each other and are united by apical tight junctions. Between the bases of the cells there are extensions of the extracellular space known as lateral intercellular spaces. The luminal edges of the cells have a microvilli ‘brush border’. In the first portion of the proximal tubule the potential difference between the lumen and the ECF is -2 mV (lumen negative) which becomes + 2 mV in the latter portion of the tubule. The proximal tubules absorb 1 L of filtrate every 10 min (i.e. 1 L of water, 140 mmol of Na⁺, 4 mmol of K⁺, 100 mmol of Cl⁻ and 24 mmol of HCO₃⁻). It reabsorbs 70% of the filtered Na⁺ and water, 90% of the filtered HCO₃⁻, 80% of the filtered K⁺, 50% of the filtered chloride, 65% of filtered Ca²⁺, 70% of the filtered PO₄³⁻ and 15% of the filtered Mg²⁺.

The pars convoluta
The pars convoluta absorbs the majority of the filtered Na⁺, K⁺, HCO₃⁻, glucose and amino acids. Sodium reabsorption. Although Na⁺ reabsorption plays a pivotal role in proximal tubular function, the fine tuning of the body’s Na⁺ balance is managed in the distal nephron. Approximately 70% of the filtered Na⁺ is reabsorbed by the proximal tubule (75% with Cl⁻ and 25% with HCO₃⁻), 20% by the loop of Henle, 5% by the distal tubule and 4% by the collecting duct. The mechanisms responsible for sodium reabsorption in the proximal tubule are (Figure 2.4):
1. **Peritubular factors**: Na\(^+\) diffuses passively from the tubular lumen into tubular epithelial cells down its concentration and electrical gradients and is actively transported into the lateral intercellular interstitial space by the basolateral cell surface Na\(^+\)/K\(^+\)-ATPase exchanging 3 Na\(^+\) ions for two K\(^+\) ions. To maintain electrical neutrality, passive movement of chloride accompanies the Na\(^+\) ion. This creates an increase in osmolality which promotes a movement of water into the lateral intercellular space. The rate at which solutes and water move into the capillaries from this space is determined by the Starling forces governing fluid movement across all capillaries. When the capillary hydrostatic pressure is increased or oncotic pressure is decreased, the interstitial fluid is not absorbed, the lateral intercellular spaces expand and fluid leaks back into the lumen.\(^{15}\)

2. **Na/H exchange**. Na\(^+\) is exchanged for intracellular H\(^+\) by a Na\(^+\):H\(^+\) antiporter located in the apical (luminal) membrane and is transported from the cell into the lateral intercellular space accounting for up to 20% of the proximal tubule sodium reabsorption. To maintain electrical neutrality, it is effectively accompanied by HCO\(_3^-\). The operation of the antiporter is dependent on favourable gradients for sodium (lumen to cell, which requires the activity of the basolateral sodium pump) and for H\(^+\) (cell to lumen which requires activity of the brush border and intracellular carbonic anhydrase and a basolateral Na\(^+\):HCO\(_3^-\) symport).\(^{16}\)

3. **Chloride driven sodium transport**: with early H\(^+\) secretion into the tubular fluid (i.e. within the first 1 mm of the proximal tubule), the concentration of HCO\(_3^-\) in the lumen decreases to approximately 8 mmol/L with the concentration of Cl\(^-\) rising to approximately 132 mmol/L. This creates a concentration gradient between the luminal and peritubular chloride (the concentration of the latter is similar to plasma, i.e. 110 mmol/L), causing Cl\(^-\) to move into the peritubular space (i.e. down the gradient), which in turn creates a positive intraluminal charge (the potential difference changes from an early -2 mV lumen negative to 2 mV lumen positive within the first quarter of the proximal tubule) to promote Na\(^+\) movement with the chloride. This effect accounts for up to 50% of the passive proximal tubule sodium reabsorption.

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**Figure 2.4.** A diagram of a cell from the proximal tubule showing its principal membrane transport mechanisms. The dark circle denotes an active transport pump requiring ATP, the open circles denote co- or counter-transport carriers not directly linked to ATP hydrolysis. ‘Organic’ signifies any of a number of organic solutes co-transported into the cell with Na\(^+\) (e.g. glucose). C.a. = carbonic anhydrase.
The energy for all three mechanisms arises from the basolateral Na\(^+\)/K\(^+-\)ATPase. As a large plasma/tubular gradient for glucose, amino acids, organic acids (lactate, keto acids) and phosphate is established within the first quarter of the proximal tubule, a percentage of proximal sodium reabsorption is linked with reabsorption of these compounds due to ‘solvent drag’.

**Glucose reabsorption.** D-glucose is removed from the urine by active transport involving an apical membrane sodium glucose carrier. It is normally filtered at 0.6 mmol/min and may be reabsorbed up to a maximum of 2 mmol/min in men and 1.7 mmol/min in women (although renal threshold occurs at about a venous blood glucose of 10 - 12 mmol/L i.e. at this level glycosuria normally occurs).

**Amino acid reabsorption.** Like glucose, the amino acids are absorbed largely in the proximal portion of the proximal convoluted tubule by an active transport mechanism involving an apical membrane sodium amino acid carrier. There are at least four separate amino acid carriers.

**The pars recta**

The pars recta is responsible for the reabsorption of organic anions (e.g. citrate, acetoacetate, malate, lactate and beta-hydroxybutyrate), organic acids (e.g. bile acids, uric acid and oxalic acid), organic bases (e.g. adrenaline, dopamine, histamine, serotonin and thiamine), and secretion of acidic (e.g. penicillin, cephalothin, chlorothiazide, furosemide and salicylic acid) and basic (e.g. atropine, cimetidine, quinidine and morphine) drugs. The luminal contents at the end of the proximal tubule are isotonic.

**The loop of Henle**

The loop of Henle functions largely for the purpose of altering urine osmolality. The descending portion of the loop is thin, whereas the ascending portion of the loop of Henle has a thin and thick portion (although structurally the loop of Henle consists of three segments: the thick descending limb or the pars recta of the proximal tubule which begins at the corticomedullary junction and ends at the junction of the outer and inner stripe of the outer medulla; the thin segment which consists of the thin descending limb and thin ascending limb; and the thick ascending limb which begins near the border of the inner and outer medulla and extends to the macula densa). The lumen of the loop of Henle is negative to the ECF except in the thick ascending portion, where it is +7 mV. The ascending limb of the loop absorbs 20% of the filtered Na\(^+\) and 20% of the filtered K\(^+\). There are functionally two types of Henle loops, short loops which belonging to the cortical nephrons, in which the bend of the loop is near the junction of the outer and inner medulla, and long loops which arise from the juxtamedullary glomeruli and which bend at varying depths in the inner medulla. In humans 15% of nephrons possess long loops and the other 85% of nephrons have short loops.

The descending thin loop is permeable to water and relatively impermeable to Na\(^+\) and urea, allowing water to move into the interstitium of higher osmolality, thereby increasing the luminal concentration of NaCl. The ascending thin loop is permeable to NaCl, moderately permeable to urea and impermeable to water. Thus Na\(^+\) moves down a concentration gradient reducing the luminal osmolality. In man both the descending thin and the ascending thin portions of the loop are non responsive to ADH. The ascending thin loop joins the thick ascending loop at the junction of the outer and inner zones of the medulla.

The thick ascending loop has been described as the ‘diluting segment’ as NaCl is reabsorbed and trapped in the medullary interstitium and the water is left behind in the tubule to be carried away into the cortex. Sodium chloride reabsorption by the thick ascending loop is mediated by a co-transport mechanism (driven by a basolateral membrane Na\(^+\)/K\(^+-\)ATPase)
which transports two Cl⁻ ions out of the lumen in association with one Na⁺ and one K⁺ ion (Figure 2.5).

The thick segment is impermeable to water, thus the luminal osmolality continues to fall, reducing the Na⁺ concentration to half that of plasma. The thick ascending loop has a medullary and cortical portion. Absorption of sodium chloride is stimulated by ADH and inhibited by prostaglandin E₂ in the medullary segment of the thick ascending loop, whereas in the cortical segment of the thick ascending loop, absorption of NaCl is not stimulated by ADH and the segment is prostaglandin E₂ insensitive. Both segments are responsible for reabsorption of 20% of the filtered Na⁺, although their capacity can increase (up to 40%) if Na⁺ delivery to this segment is increased.

If urea did not exist, then the Na⁺ concentration gradient would not exist in the thin descending limb and the thin ascending limb would not add Na⁺ into the interstitium.

**Figure 2.5.** A diagram of a cell from the thick ascending loop of Henle showing its principal membrane transport mechanisms. The + in the lumen signifies the electrical polarity of the lumen with respect to the interstitium.

**Measurement of renal concentration and diluting capacity**

The renal concentrating ability may be assessed by measuring the urine osmolality after a 24 hr fluid fast, or after an intramuscular dose of 4 µg DDAVP. Normally the maximum urine osmolality achieved should be greater than 800 mosmol/kg. The renal dilution ability may be assessed by reducing the plasma osmolality to 280 mosmol/kg (by imbibing 15 mL of water/kg body weight) at which value maximum suppression of plasma ADH should occur to permit maximum urinary dilution.

The overall assessment of the renal ability to conserve or excrete water may be assessed by measuring the free water clearance which is calculated from the equation:

\[
C_{\text{H₂O}} = \frac{V \times (1 - U_{\text{osm}})}{P_{\text{osm}}}
\]

Where

- \( C_{\text{H₂O}} \) = free water clearance (mL/min)
- \( U_{\text{osm}} \) = urine osmolality (mosmol/kg)
- \( P_{\text{osm}} \) = plasma osmolality (mosmol/kg)
- \( V \) = volume of urine excreted (mL/min)

22
Renal Physiology

While C\textsubscript{H2O} may be useful in defining renal collecting duct function and vasopressin activity, it is an incorrect guide to an assessment of pure water loss or gain by the kidney, as urea is taken into account which does not contribute to the plasma tonicity (and therefore water status).\textsuperscript{23,24} Free water re-absorption or excretion (which is responsible for plasma tonicity and therefore plasma sodium) may be assessed by dividing the urine into two component volumes, for example,\textsuperscript{23,24}

*A component which has the same ion-to-water ratio as the body.* Loss of this component from the body does not change the plasma tonicity. This component can be calculated from the equation:

\[
V \times \frac{(1 - U(Na + K))}{P Na}
\]

*A component which is ion-free water.* Loss or gain of this component will affect the body tonicity. This component may be calculated from the equation:

\[
V \times \frac{(P Na - U(Na + K))}{P Na}
\]

Where
- \( V \) = volume of urine excreted (mL/min)
- \( U(Na + K) \) = urine concentration of sodium and potassium (mmol/L)
- \( P Na \) = plasma concentration of sodium (mmol/L)

**The juxtaglomerular apparatus**

The thick portion of the loop of Henle ascends to the glomerulus of the same nephron and passes close to the afferent arteriole, the wall of which contains the renin-secreting juxtaglomerular cells. The tubular epithelium is modified at this point to form the macula densa. The juxtaglomerular cells, the macula densa and a few granulated cells in the interstitium between them are collectively known as the juxtaglomerular apparatus. The macula densa is defined as the point at which the loop of Henle ends and the distal convoluted tubule begins (Figure 2.3).

**The distal nephron**

The distal nephron commences at the macula densa and consists of the distal tubule and collecting duct segments.

**The distal tubule**

Morphologically, the distal tubule includes the thick ascending limb of Henle’s loop, including the macula densa, and the distal convoluted tubule. In micropuncture studies, however, distal tubule refers to the accessible region of the nephron between the macula densa and the confluence with another tubule. The superficial distal tubule is subdivided into an ‘early’ portion corresponding to the distal convoluted tubule, a largely inaccessible connecting tubule and a ‘late’ portion corresponding to the first part of the collecting tubule. The distal convoluted tubule is about 5 mm long, it has an epithelium with a few microvilli and no brush border. It is impermeable to water, and insensitive to aldosterone and ADH. The cells of the distal convoluted tubule give way to principal cells (i.e. collecting duct cells) which line the cortical collecting tubule. Intercalated cells (which have an apical H\textsuperscript{+}-ATPase for proton excretion) are intermingled with the cells of the connecting tubule and cortical collecting duct and progressively reduce in number until none are found in the larger papillary collecting ducts.
In segments beyond the macula densa in the distal convoluted tubule there is active reabsorption of Na\(^+\) due to an apical membrane (thiazide inhibitable) Na\(^+\):Cl\(^-\) cotransporter and in later segments there is a passive movement of Na\(^+\) into cytoplasm of the principal cells (which can be inhibited by amiloride and triamterene) and an active displacement of Na\(^+\) out into the lateral intercellular interstitial space by a basolateral cell surface Na\(^+\)/K\(^+\)-ATPase (Figure 2.6). The latter (at the cortical collecting tubule\(^{25}\)) is mineralocorticoid sensitive (i.e. can be inhibited by spironolactone) and is responsible for reabsorption of 5% of the filtered Na\(^+\). Without aldosterone, only 50% of the distal nephron Na\(^+\) is reabsorbed. Therefore, the maximum excretion of Na\(^+\) (i.e. in the absence of aldosterone) is 750 mmol/day, as 1500 mmol of Na\(^+\) enters the distal nephron (i.e. 20 L/day with a Na\(^+\) concentration of approximately 75 mmol/L).

The early distal tubule has a potential of -10 mV (lumen negative) which changes to a potential of -45 mV (lumen negative) in the late distal tubule due to the influence of aldosterone on Na\(^+\) reabsorption, creating an electrochemical sink into which K\(^+\) and H\(^+\) move.

![Figure 2.6. A diagram of a cell from the early part of the distal tubule showing its principal membrane transport mechanisms.](image)

**The collecting duct system**

The collecting duct system allows urine to pass through the renal cortex and medulla and drain into the renal pelvis at the apex of the renal pyramids. The potential difference in the collecting duct is -35 mV (lumen negative). Functionally, the collecting duct system may be divided into the cortical, medullary and papillary collecting ducts. The cortical collecting duct increases permeability to water in response to plasma ADH, and increases Na\(^+\) reabsorption in response to mineralocorticoids (Figure 2.7). The medullary collecting duct has the same response to ADH; however, the response to mineralocorticoids no longer exists and this segment is relatively impermeable to K\(^+\). Medullary collecting duct Na\(^+\) reabsorption is sensitive to atrial natriuretic hormone. This segment also has a capacity for H\(^+\) secretion which is independent of Na\(^+\) and transported with Cl\(^-\). The papillary collecting duct still has an ADH response, although under the influence of ADH (unlike the cortical collecting duct) this segment is permeable to urea. With maximum ADH secretion 99.7% of total glomerular filtrate is reabsorbed, whereas in the absence of ADH up to 13% of the glomerular filtrate may be excreted. The renal response to ADH is discussed in Ch. 3.
Figure 2.7. A diagram of two cell types from the late part of the distal tubule and the cortical collecting duct showing its principal membrane transport mechanisms.

REFERENCES
Antidiuretic hormone (arginine vasopressin) mechanism

Antidiuretic Hormone (ADH) is a peptide with an 8 amino acid sequence and a molecular weight of 1084. It is synthesised as an inactive prohormone in areas near the nerve bodies of the supraoptic and paraventricular nuclei of the anterior hypothalamus. The prohormone is incorporated along with its carrier protein, neurophysin, into vesicles that are transported along the nerve axons of the supraopticohypophyseal tract to the posterior pituitary. During this migration the prohormone undergoes enzymatic cleavage to form a number of small peptide cleavage products, the neurophysin and ADH. The latter is stored in secretory granules at the neurone terminals. Depolarisation of the nerve increases the nerve-cell membrane permeability to calcium. The increase in ICF ionised calcium causes exocytosis of the secretory granules and release of ADH into the circulation. ADH circulates as a free non-protein-bound peptide, it diffuses readily throughout the ECF and has a plasma half-life of 16 - 20 min. Plasma levels vary from 1 to 10 pg/mL during diuresis and antidiuresis, respectively. Levels of up to 500 pg/mL may occur with severe haemorrhage or vomiting.

ADH secretion

Release of ADH occurs in response to osmoreceptor stimulation, baroreceptor stimulation (i.e. both low-pressure left atrial and high-pressure carotid baroreceptors) and cortical influences (e.g. nausea, pain and anxiety). Other influences (e.g. hormones and drugs) may also cause ADH release.

Osmoreceptor stimulation. ADH release may be stimulated or inhibited by osmoreceptor cells which are located in the hypothalamus, in or near the nuclei where synthesis of ADH takes place. The osmoreceptor cells are thought to be stimulated by a change in cell volume, caused by either water depletion or an impermeant solute (e.g. glucose or sodium chloride) load. Permeant solutes such as urea and ethanol do not stimulate these receptors.

In health, the extremes of plasma osmolality are 280 - 295 mosm/kg or 287 mosm/kg + 2% (although, in a given subject, the normal daily range is much narrower). Plasma osmolalities of about 280 mosmol/kg suppress plasma ADH to levels low enough to permit maximum urinary dilution. Above this value, an increase in ECF tonicity of about 1 - 2%, or a decrease in total body water of 1 - 2 L, causes the posterior pituitary to release ADH, causing urinary osmolality to rise by almost 100 mosm/kg for each 1mosm/kg rise in plasma osmolality. Maximum plasma ADH levels are reached at an osmolality of 295 mosmol/kg (e.g. a loss of 1.1 l of water in a 70 Kg man), and further defence against a reduction in ICF volume depends on the thirst mechanism, which is also stimulated by the hypothalamic osmoreceptors.

In the conscious and ambulant subject, the thirst mechanism is more important in preventing dehydration than the ADH mechanism. Thus, in health, the upper limit of the body osmolality (and therefore plasma sodium) is determined by the osmotic threshold for thirst, whereas the lower limit is determined by the osmotic threshold for ADH release. Normally 1 - 2 units of ADH are released per day in response to body osmolar changes. However, severe hypertonicity or haemorrhage may increase this up to 100 units/day.
Renal Hormones

Baroreceptor stimulation. If the intravascular volume is reduced by greater than 10 - 15%, low-pressure left atrial baroreceptor stimulation causes ADH release. If hypovolaemia leads to hypotension then both low- and high-pressure baroreceptors stimulate ADH release. While osmoreceptors seem more sensitive than volume receptors in initiating an ADH response, severe volume depletion produces a greater release of ADH than hypertonicity. The baroreceptor and osmoreceptor pathways have distinct and anatomically separate inputs into the same population of neurones responsible for ADH synthesis and release. Acute haemodynamic alterations also adjust, upward and downward, the osmoreceptor ADH secretion threshold.

Cortical influences. ADH release may also be stimulated by pain and nausea. These influences are thought to act through the baroreceptor pathways.

Other influences. ADH release may be altered by pharmacological agents (Table 43.2) and by hormones (e.g. angiotensin II and beta-2-adrenergic agonists stimulate ADH release,11,12 and thyroid hormones, alpha adrenergic agonists11,12 and corticosteroids, reduce ADH release12).

ADH receptors

V₂ receptor. ADH acts on the collecting duct of the nephron by binding to the cell membrane V₂ vasopressin receptor, activating an adenylate cyclase present on the basolateral (not luminal) cell membrane and increasing intracellular cAMP. The increase in intracellular cAMP causes an increase in intracellular Ca²⁺ concentration, which in turn causes a calmodulin-dependent increase in permeability of the luminal side of the collecting-duct cell membrane to water and urea due to the insertion of a highly selective water channel (aquaporin 2, one of a family of ten highly selective water channels13) into the apical membrane. While the collecting ducts are impermeable to water in the absence of ADH, if the distal nephron flow is small enough, then the gradient between the hypotonic luminal fluid and the hypertonic medullary interstitium will allow a moderately hypertonic urine to be formed, even in the absence of ADH.

The main function of ADH is to prevent excessive dilution of urine, as the amount of water saved by not excreting a dilute urine, is much greater than the amount of water saved by producing a maximally dilute urine. This may be understood when one compares the renal water excretion during an absence of ADH secretion to that excreted when ADH secretion is enough to produce an isotonic urine. In the absence of ADH and a daily osmolar load of 600 mosmol, the maximal urinary dilution (30 mosmol/kg) is achieved with the excretion of 20 L/day. If enough ADH is secreted to produce an isotonic urine (300 mosmol/kg) then the daily osmolar load of 600 mosmol is excreted in 2 L of urine. Thus, during 24 hr, 18 L of water is saved from excretion by the creation of an isotonic urine. With maximum ADH secretion, the daily osmolar load would be excreted in 0.5 L of urine, saving only an extra 1.5 L of water.

The V₂ receptor is responsible not only for the antidiuretic effects of vasopressin, but also the vasodilator effects of the hormone and its ability to increase factor VIII coagulant activity and the concentration of von Willebrand factor in plasma.15

V₁ receptors. Activation of the V₁ vasopressin receptor activates phospholipase C with intracellular production of inositol 1,4,5-triphosphate (which releases Ca²⁺ from intracellular stores) and diacylglycerol which activates protein kinase C. There are two subclasses of V₁ vasopressin receptors, V₁a and V₁b. V₁a receptor stimulation causes contraction of vascular smooth muscle, activation of hepatic glycogenolysis, stimulation of renal prostaglandin synthesis and inhibition or renal renin secretion5,15. In the brain the V₁a receptors are involved
Renal Hormones

with memory, regulation of blood pressure and the production of CSF.\textsuperscript{15} $V_{1b}$ receptors are found in the pituitary where its activation results in the secretion of ACTH.\textsuperscript{15}

High levels of ADH (e.g. levels observed after severe haemorrhage) exert a pressor effect on arterioles and may contribute significantly to maintaining blood pressure in hypovolaemic shock.\textsuperscript{16,17} Moreover, the pressor effect of catecholamines is enhanced by physiological concentrations of ADH.\textsuperscript{16,18} Antidiuretic hormone also interacts with receptors that mediate uterine contraction and milk ejection, although it is only one-tenth as potent as oxytocin.\textsuperscript{3}

\textit{ADH agonists and antagonists}

\textbf{Pitressin (8-arginine-vasopressin).} This agent has been used to treat diabetes insipidus, bleeding oesophageal varices and postoperative ileus. For abdominal distension and ileus, 5 - 10 u (10 u = 25 µg) intramuscularly 4-hourly may be administered. For bleeding oesophageal varices 20 u in 20 min is infused intravenously, followed by an intravenous infusion at 20 u/h. As ADH clearance is approximately 15 mL/min/kg, an infusion rate of 0.5 u/h/70 kg will give a concentration of 20 pg/mL, and an infusion rate of 0.3 u/min/70 kg (18 - 20 u/hr/70 kg) will give a plasma concentration of approximately 750 pg/mL. The latter level is higher than that observed under extreme stimulations of endogenous ADH release.

\textbf{Desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP).} This agent has virtually no affinity for $V_1$ receptors and so has no pressor activity. By contrast it has a high affinity for $V_2$ receptors and thus a pronounced antidiuretic action. It also has a more prolonged action than ADH, lasting between 8 - 20 hr. Desmopressin 10 - 40 µg daily intranasally has one-tenth the effect of an intravenous dose and in single or divided doses may be used for diabetes insipidus. It has also been used for nocturnal enuresis. An intravenous dose of 0.3 µg/kg over 30 min (20 µg/70 kg) or 300 µg intranasally has been used to decrease postoperative bleeding, which it does by increasing circulating levels of VIII/vWf complex.

\textbf{Ornipressin (8-ornithine-vasopressin).} This agent has a strong vasoconstrictor action with weak antidiuretic activity. It is used largely as a locally administered vasoconstrictive agent.

\textbf{Glypressin (triglycyl-lysine vasopressin).} This agent is slowly broken down in the circulation to lysine-vasopressin, producing a prolonged vasomotor effect. It has been used successfully to control acute variceal haemorrhage.

\textbf{Vasopressin antagonists.} This arginine-vasopressin antagonist (d(CH\textsubscript{2})\textsubscript{5}-D-Tyr(Et)VAVP) has dual activity against $V_1$ and $V_2$ receptors and may have a therapeutic role in patients with cardiac failure and the syndrome of inappropriate antidiuresis (SIAD).\textsuperscript{19,20} The non-peptide arginine-vasopressin $V_2$ receptor antagonist (OPC-31260) has been used to correct the hyponatraemia associated with hypothyroidism.\textsuperscript{21}

\textbf{Renal mechanism}

For the kidney to achieve a maximum water diuresis or antidiuresis normal distal nephron function is required. This means an adequate nephron population, adequate delivery of fluid to the distal diluting segments, reabsorption of solute without water in the diluting segments and, in the case of a diuresis, an escape by distal nephron hypotonic fluid from collecting duct reabsorption (i.e. minimal circulating ADH activity). In the case of an antidiuresis, an hypertonic medullary interstitium and a normal renal response to ADH are also required.

\textbf{Renin-angiotensin-aldosterone system}

The juxtaglomerular apparatus consists of the granular juxtaglomerular cells of the afferent glomerular arteriole and the region of the distal tubule of the same nephron known as the macula densa.\textsuperscript{22} The granular juxtaglomerular cells are modified smooth muscle cells of the
afferent arteriole which synthesise, store and release renin. They are innervated by sympathetic efferent nerves and are in intimate contact with the distal tubular cells known as the macula densa. Activation of the renin-angiotensin-aldosterone system with formation of angiotensin II, causes vasoconstriction, and an increased aldosterone secretion with Na\(^+\) retention and K\(^+\) depletion.

**Renin**

Renin is a proteolytic enzyme with a molecular weight of 40 000 and a half-life of 10 - 15 min when released into the circulation.\(^{22}\) Its release is stimulated by:\(^{23}\)

- A reduction in afferent arteriolar pressure
- Beta-1-adrenoreceptor stimulation (mediated by sympathetic nerve stimulation or circulating sympathomimetic agents and inhibited by beta-blockers)
- A decrease in Cl\(^-\) (or Na\(^+\)) reabsorption across the macula densa
- A decrease in angiotensin II levels
- A decrease in vasopressin levels\(^{24}\)
- Prostaglandins (probably PGE\(_2\). Renin-release can be inhibited by indomethacin\(^{25}\))

Renin acts on an \(\alpha_2\)-globulin (i.e. renin substrate or angiotensinogen, mol. wt 60 000) to liberate the decapeptide angiotensin I from angiotensinogen. Angiotensin I has no haemodynamic effects but serves as the substrate for angiotensin converting enzyme, which rapidly (within one circulation through the lung) removes two amino acids to yield the octapeptide angiotensin II.

Angiotensin converting enzyme (ACE) is found on the surface of all vascular endothelial cells and is responsible for the formation of angiotensin II as well as the inactivation of the vasodilator peptide, bradykinin (ACE is also involved in the degradation of substance P, neurokinins, and luteinising hormone releasing hormone).\(^{26}\) Angiotensin II acts on specific membrane receptors located on target organs and its biological effects are mediated by two receptors, AT\(_1\) and AT\(_2\). The AT\(_1\) receptor is a G-coupled membrane protein which activates phospholipase C and produces the secondary messengers inositol 1,4,5-triphosphate (which releases Ca\(^{2+}\) from the sarcoplasmic reticulum) and diacylglycerol (which activates protein kinase C), causing smooth muscle constriction. AT\(_1\) receptor activation also causes vascular smooth muscle remodelling, catecholamine release (adrenal and presynaptic), vasopressin release, renal tubular sodium reabsorption and aldosterone release, it also inhibits baroreceptor sensitivity.\(^{27,28}\) The function of the AT\(_2\) receptor is not yet clear, although it has been postulated that it may be involved in the differentiation and proliferation of smooth muscle cells as well as being antiproliferative for endothelial cells.\(^{28}\) The enzymes that destroy angiotensin II are collectively called angiotensinas and form a heptapeptide called angiotensin III. While angiotensin III has only about 40\% of the pressor activity of angiotensin II, it has 100\% of the aldosterone-stimulating activity.

The renin-angiotensin-aldosterone system may be inhibited at several levels: inhibition of renin release by the juxtaglomerular apparatus (e.g. beta adrenergic blockade, indomethacin), inhibition of the angiotensinogen-renin step by using monoclonal renin antibodies or angiotensinogen analogues (e.g. renin inhibitory peptides) which compete with angiotensinogen for renin binding sites, conversion of angiotensin I to angiotensin II by angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor blockade (e.g. losartan) and aldosterone receptor blockade (e.g. spironolactone).\(^{29}\)
Angiotensin II

Angiotensin II has a half-life of 1 - 2 min and it:

- Is a potent arterial vasoconstrictor (e.g. 4 - 8 times as active as noradrenaline on a weight basis).
- Stimulates intrarenal PGE$_2$ synthesis (reducing the intrarenal vasoconstrictive effects$^{25}$)
- Is the principal stimulus for aldosterone secretion from the zona glomerulosa of the adrenal cortex
- Acts on peripheral noradrenergic neurones to facilitate catecholamine synthesis and release
- Preferentially constricts the efferent arteriole to maintain GFR$^{22,30}$ (explaining the reversible increase in creatinine when ACE inhibitors are used in patients in whom renal perfusion pressure is low$^{30}$)
- Produces CNS effects of ADH and ACTH release and thirst stimulation$^{31}$
- Directly suppresses renin release$^{32}$
- Stimulates arterial wall growth and ventricular hypertrophy$^{33}$

ACE inhibitors.$^{32}$

ACE inhibitors cause:

1. A reduction in blood pressure due to a reduction in angiotensin II levels, a decrease in prejunctional release of noradrenaline in response to sympathetic nerve stimulation (caused by the reduction in angiotensin II levels) and an increase in bradykinin levels. The latter causes peripheral vasodilation (due to endothelial NO and prostacyclin release) and may be responsible for the hypotensive effect of captopril observed in anephric patients$^{34}$ and the reduction in myocardial oxygen consumption (due to bradykinin induced release of NO which in turn inhibits cytochrome oxidase) observed with ACE inhibitors.$^{35}$

2. A reduction in aldosterone secretion from the zona glomerulosa which results in a mild natriuresis and a tendency towards $K^+$ retention. In patients with Na$^+$ depletion and high renin levels (i.e. renal artery stenosis, renovascular hypertension, hypovolaemia or diuretic therapy) a large reduction in blood pressure, and natriuretic and antikaliuretic effects may occur. In patients with low renin hypertension (which is usually associated with an increase in intravascular volume), the fall in blood pressure, natriuretic and antikaliuretic effects may be mild.

3. Renal vasodilation with a fall in filtration fraction due to a fall in post glomerular (efferent) arteriolar tone, which may lead to a reduction in GFR.$^{36}$ The rise in creatinine, with ACE inhibitors, may be a valuable clue of an undetected bilateral renal artery stenosis or renal artery stenosis in a single kidney (e.g. renal allograft).$^{37,38,39}$ Endogenous prostaglandins serve to maintain renal blood flow in low cardiac output states by dilating the afferent arteriole, and maintain GFR by increasing efferent vasoconstriction by stimulating the intrarenal release of renin. Therefore, prostaglandin inhibition with ACE inhibition leads to both afferent arteriole vasoconstriction and efferent arteriole vasodilation and reduction in GFR.$^{38}$ Proteinuria may decrease with ACE inhibition.$^{40}$ In patients with diabetic nephropathy, captopril reduces the risk of the combined endpoints of dialysis, transplantation and death by 50%.$^{41}$

4. A decrease in renin substrate levels.

5. An increase in renin and angiotensin I levels (which so far has not been reported to be associated with any abnormality).
Captopril and lisinopril are active compounds whereas enalapril, alacepril (prodrug of captopril), pentopril, fosinopril, perindopril, quinapril, trandolapril, cilazapril, benazepril and ramipril are prodrugs (i.e. remain inactive until converted by the liver into an active compound). The active form of the drug reach peak levels later with the prodrug (e.g. peak levels of captopril occur 90 min after captopril ingestion and 4 h after alacepril ingestion). The commonly used ACE inhibitors and their oral dosages are listed in Table 21.4.

In comparison with the beta-blocking drugs, ACE inhibitors are not associated with drowsiness, sexual dysfunction, or Raynaud's phenomenon, and the autonomic reflexes are intact (i.e. heart rate and cardiac output response to exercise and the Valsalva manoeuvre are not altered). In comparison to the direct vasodilators, ACE inhibitors are not associated with postural hypotensive effects or reflex tachycardia (i.e. reduction in cardiac work due to afterload reduction is not negated by tachycardia). Also the hypotensive effects of diuretics are enhanced without inducing hypokalaemia because the secondary hyperaldosterone effects of diuretics are inhibited. However, as ACE inhibitors are competitive inhibitors, high levels of angiotensin I resulting from ACE inhibition may drive continued production of angiotensin II, and suppression of Angiotensin II might upregulate the angiotensin receptor, increasing its sensitivity to angiotensin II.

ACE inhibitors are indicated for hypertension, cardiac failure, to reduce the progression to symptomatic heart disease in patients with asymptomatic left ventricular dysfunction, to reduce remodelling in patients with myocardial infarction and reduced ejection fraction (particularly when therapy delayed for 2 days following the myocardial infarct), reduction of cardiovascular mortality in patients with evidence of cardiovascular disease as well as nephropathy in diabetic patients and decrease the progression of renal insufficiency in patients with chronic renal failure (particularly diabetic and IgA nephropathy - an effect which is independent of their blood-pressure-lowering effect).

ACE inhibitors are contraindicated during pregnancy (as they increase the incidence of foetal death, oligohydramnios and neonatal renal failure) and in patients who have angio-oedema (causing oedema, hypotension, dyspnoea, or visceral pain), collagen vascular disease and bilateral renal artery or diffuse intrarenal vascular stenosis.

**Natriuretic-peptide family**

**Atrial natriuretic peptide (ANP):** The discovery of granules in the atrial myocyte (more granules are found in the right atrium than the left atrium), and their variation in number according to Na⁺ and water balance, led to the discovery of human proatrial natriuretic factor that has a 152 amino acid sequence. This is cleaved to a 126 amino acid sequence proatrial natriuretic factor (i.e. atriopeptigen), which is converted to a number of smaller biologically active peptides varying from 19 to 28 amino acids in length. The predominant circulating peptide is a 28 amino acid peptide (i.e. atriopeptin 28 or ANP, which has a half life of 2.5 minutes). Atrial natriuretic peptide release occurs in response to stretch of the atrial myocyte and increase in atrial rate as well as increase in circulating endothelin, ADH and catecholamines.

**Brain natriuretic peptide (BNP):** Brain natriuretic peptide (initially isolated from porcine brain) is a 32-amino acid peptide that is structurally similar to ANP and shares the same guanylate cyclase receptors on endothelial cells. It is secreted predominantly from the ventricular myocytes in response to stretch.

**C-type natriuretic peptide (CNP):** This is predominantly found in the brain although it can be synthesised by vascular endothelial cells. Its plasma concentration however is very low.
Three natriuretic peptide receptors have also been described (NPR-A, NPR-B and NPR-C). Two receptors (i.e. NPR-A and NPR-B) are guanylate cyclases that have an extracellular, single transmembrane and an intracellular portion. They have been identified in vascular, renal and adrenal tissue which, when stimulated, increase intracellular cyclic guanosine monophosphate.\(^{53,54}\) NPR-C is less clearly linked to a second messenger system and appears to be involved in the clearance of the peptides. ANP has the highest affinity for NPR-A and least for NPR-B whereas CNP has the highest affinity for NPR-B and least for NPR-A. Atrial natriuretic peptide does not inhibit NaK-ATPase and is not inhibited by indomethacin (i.e. its effects are not prostaglandin mediated).\(^{53,54}\)

In physiological doses ANP causes a natriuresis and moderate kaliuresis, vasodilation with reduction in mean arterial pressure, a decrease in sympathetic tone, an increase in glomerular filtration rate (by dilating the afferent and constricting the efferent arteriole) and inhibition of renin release, ADH release, aldosterone release and aldosterone biosynthesis.\(^{55,56,57,58}\) While BNP shares some of the same actions of ANP (i.e. vasodilation, natriuresis, reduction in aldosterone secretion), it does not reduce noradrenaline levels (unlike ANP), and may even increase noradrenaline levels via a baroreceptor-mediated sympathetic response.\(^{59}\) CNP, like ANP has antitropic effects and inhibits structural remodelling of blood vessels.\(^{60}\)

In healthy individuals, plasma levels of ANP are increased by increasing dietary Na\(^+\) intake, intravenous saline and by other manoeuvres that increase the intravascular volume (i.e. head-out body immersion). In disease, high plasma levels of ANP have been observed in hypervolaemic disorders of hyperaldosteronism, cardiac failure and chronic renal failure, as well as in essential hypertension, paroxysmal atrial tachycardia, pre-eclampsia, SIADH, hyperthyroidism and cirrhosis.\(^{61}\)

A renal natriuretic peptide (urodilatin) containing an extension of four amino acids at the N terminus of the ANP, is synthesised within the kidney and acts on luminal receptors of the distal segment of the nephron, causing a reduction in sodium and water reabsorption. The mechanism regulating urodilatin is unclear.\(^{62}\)

### Prostaglandins

The major site of renal prostaglandin synthesis occurs in the medulla and the papilla and the major prostaglandin produced is PGE\(_2\). Sodium depletion and ADH increases PGE\(_2\) production and Na\(^-\) excess diminishes PGE\(_2\) production. Lesser amounts of PGI\(_2\), PGD\(_2\) and thromboxane A\(_2\) are also formed, although during injury the thromboxane pathway may increase.\(^{63}\) Inhibition of prostaglandin synthesis does not depress renal blood flow or the GFR in normal animals or humans.\(^{64}\) By contrast, inhibition of prostaglandin synthesis does reduce renal blood flow and the GFR when superimposed on a preceding haemodynamic insult such as hypotension, salt depletion, or heart failure. Prostaglandins, therefore, probably contribute more to the maintenance of renal haemodynamics under adverse conditions (e.g. PGE\(_2\), PGD\(_2\) and PGI\(_2\) are powerful dilators and maintain renal blood flow when elevated levels of angiotensin II, noradrenaline and ADH exist) rather than under normal circumstances. The renal effects of prostaglandin inhibitors include:

1. **Acute renal failure:** cyclooxygenase inhibitors (particularly indomethacin) in circumstances with elevated levels of angiotensin II, noradrenaline and ADH, allow the vasoconstrictive effects of these agents to continue uninhibited, leading in some cases to acute renal failure.\(^{65}\)

2. **Papillary necrosis and chronic renal failure:** papillary necrosis and chronic renal failure can occur with prolonged use of NSAIDs in susceptible patients (e.g. salt depleted, cardiac failure, and diuretic users)
3. **Hyporeninaemic hypoaldosteronism:** prostaglandins directly stimulate the release of renin, thus NSAIDs can lead to hyporeninaemic hypoaldosteronism, with hyperkalaemia and RTA.

4. **Acute interstitial nephritis and nephrotic syndrome:** these disorders may occur after 6 - 8 months of NSAIDs (particularly with fenoprofen) administration, and is thought to be due to an allergy to the drug, mediated through cytotoxic T cells.

**REFERENCES**


Renal Hormones

Diuretics are compounds that increase the urinary excretion of solute and water, and are commonly used for the treatment of fluid retaining states. A natriuretic produces a diuresis by interfering with the tubular reabsorption of sodium, an aquaretic produces a diuresis by interfering with vasopressin-mediated water reabsorption.

Apart from the osmotic diuretics, they are extensively protein bound (e.g. frusemide 95 - 98%; bumetanide 94 - 97%; thiazides 40 - 95%; spironolactone 98%; amiloride 23%; triamterene 50 - 67%), and except for spironolactone, they are secreted by the pars recta (via the organic acid transport system) to act from within the lumen. Loop and thiazide diuretics and acetazolamide are secreted through the organic-acid pathway, and amiloride and triamterene through the organic base pathway. The dose, onset and duration of the commonly used diuretics are listed in Table 4.1 and the sites of action are shown in Figure 4.1.

### Table 4.1  Dose, onset and duration of the commonly used diuretics

<table>
<thead>
<tr>
<th>Site of Action</th>
<th>Agent</th>
<th>Daily dose (mg)</th>
<th>Onset (hr)</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal nephron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium sparing</td>
<td>Spironolactone</td>
<td>25-400</td>
<td>24-48</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>5-15</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Triamterene</td>
<td>100-200</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Diluting segment</td>
<td>Chlorothiazide</td>
<td>500-2000</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>50-100</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Bendrofluazide</td>
<td>2.5-10</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>25-100</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Metolazone</td>
<td>2.5-20</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Frusemide</td>
<td>20-1000</td>
<td>5-15 min</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>Bumetanide</td>
<td>1-15</td>
<td>30 min</td>
<td>6</td>
</tr>
<tr>
<td>Proximal tubule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonic anhydrase</td>
<td>Acetazolamide</td>
<td>250-500</td>
<td>30 min</td>
<td>6-12</td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuretics</td>
<td>Mannitol</td>
<td>12.5-50 g</td>
<td>5 min</td>
<td>2</td>
</tr>
</tbody>
</table>

39
Diuretics

*Figure 4.1* A diagram of the nephron showing the four main tubular sites where diuretics interfere with sodium reabsorption.

**DILUTING-SEGMENT DIURETICS (THIAZIDES, METOLAZONE, INDAPAMIDE)**

*Action*

The thiazides, metolazone and indapamide inhibit an apical distal convoluted tubule epithelium Na\(^+\):Cl\(^-\) cotransporter (i.e. Site III, where up to 10% of the filtered load of sodium is reabsorbed).\(^5\) While metolazone shares the pharmacologic actions of thiazide diuretics, in contrast to the thiazides it also reduces proximal tubule sodium reabsorption and therefore has a greater diuretic effect. While indapamide has a mild diuretic action, it has a pronounced antihypertensive effect, largely by inhibiting the vascular smooth muscle slow component of delayed rectifier potassium current, and thereby reducing the inward Ca\(^{2+}\) current.\(^6\)

Up to 10% of the filtered load of sodium may be excreted with maximal thiazide doses. They work in hypertension by causing peripheral vasodilation (an effect which is maximum at the lowest dose, e.g. 2.5 mg of bendrofluazide daily) rather than by their diuretic effect, and in this regard they are superior to loop diuretics.\(^7\) Thiazides reduce urinary excretion of calcium by directly stimulating calcium uptake in the distal tubule and, through volume contraction, indirectly stimulating calcium uptake in the proximal tubule.

*Side-effects*

The side-effects include hypokalaemia (by increasing sodium delivery to the mineralocorticoid sensitive segment), azotaemia, hypomagnesaemia, hypercalcaemia, metabolic alkalosis, hyperglycaemia, hyperuricaemia (due to inhibition of renal urate excretion in the pars recta), pancreatitis, and, rarely, allergic reactions (e.g. erythema multiforme, photosensitivity, interstitial nephritis, thrombocytopenia and neutropenia) and male impotence.
Diuretics

LOOP DIURETICS (FRUSEMIDE, ETHACRINIC ACID, BUMETANIDE)

Action
Frusemide, ethacrinic acid and bumetanide inhibit the sodium-potassium-chloride transporter in the medullary thick ascending limb (i.e. site II), where up to 20% of the filtered load of sodium is absorbed. Frusemide (but not ethacrinic acid) also has a carbonic anhydrase inhibition activity. Frusemide also increases venous capacitance, causing a rapid reduction in PAoP, and enhances interstitial to intravascular fluid movement, thereby reducing pulmonary oedema and maintaining blood volume during the diuresis.

In controlled studies, prevention of acute renal failure or reduction in duration or mortality of acute renal failure has not been shown in patients treated with frusemide.

The ‘historical’ mercurial diuretics acted at sites II and III, although as they inhibited K⁺ secretion, potassium depletion was not as marked as that commonly observed with the loop diuretics.

Side-effects
The side-effects of frusemide, ethacrinic acid and bumetanide include hypokalaemia (40 mg of frusemide increases the urinary potassium secretion by 13 - 18 mmol/24 h in normal individuals; in patients with secondary hyperaldosteronism the potassium loss may be increased by 25 - 50 mmol/24 h), hyperglycaemia (not with ethacrinic acid or bumetanide), hyperuricaemia (not with bumetanide), hypernatraemia, hypocalcaemia, hypomagnesaemia, hypertriglyceridaemia, hypotension (due to salt loss), azotaemia, pancreatitis, rarely allergic reactions (i.e. bullous skin lesions, fever, photosensitivity, thrombocytopenia, interstitial nephritis and urticaria) and neural deafness (not with bumetanide) particularly with ethacrinic acid (or frusemide in doses exceeding 500 mg/day) and if used in association with aminoglycosides.

POTASSIUM-SPARING DIURETICS (SPIRONOLACTONE, TRIAMTERENE, AMILORIDE)

These drugs act at the distal nephron (i.e. Site IV, where less than 5% of the filtered load of sodium may be excreted). They are often used to inhibit the kaliuria and magnesiuria associated with thiazide and loop diuretics. These agents may cause significant hyperkalaemia, particularly if used in patients with renal failure, non insulin-dependent diabetes mellitus or treated with ACE inhibitors or NSAIDs. Spironolactone does not increase the plasma urate, whereas triamterene and amiloride may.

Spironolactone

Action
Spironolactone decreases potassium excretion by blocking the effect of mineralocorticoids on the distal tubule. It is converted to canrenone which also has mineralocorticoid antagonism and may account for up to 75% of the antimineralocorticoid activity during chronic spironolactone therapy. Both spironolactone and canrenone are 98% protein bound and act from the vascular side of the tubular cell. Maximum inhibition occurs with 800 mg/day, although 25 mg/day may be quite effective.
Diuretics

Side effects
The side effects of spironolactone include, headaches, nausea, vomiting, oestrogen effects (e.g. decreased libido, impotence, and gynaecomastia in men, and menstrual irregularity and painful breast enlargement in women), induction of the cytochrome P450 system and reduction in the positive inotropic effect of digoxin.17

Amiloride
Amiloride inhibits renal potassium secretion at the distal nephron by a mineralocorticoid-independent mechanism. It acts at the luminal side by blocking sodium entry at the luminal membrane, thereby decreasing the transmembrane potential difference, inhibiting hydrogen ion as well as potassium excretion.18 The maximum effect occurs at 40 mg, although doses greater than 20 mg/day are likely to cause nausea, vomiting and diarrhoea.

Triamterene
Triamterene acts from the luminal side of the distal nephron, inhibiting renal potassium secretion by a mineralocorticoid-independent mechanism. The dose usually ranges from 100 to 200 mg/day, although the maximum effect occurs at 400 mg/day.

Triamterene's side-effects include diarrhoea, nausea and vomiting, and, because the agent is a folic acid antagonist, megaloblastosis.19 Metabolites of the drug may cause nephrolithiasis.20

CARBONIC ANHYDRASE INHIBITORS (ACETAZOLAMIDE)
Acetazolamide inhibits carbonic anhydrase, with its major effect occurring in the proximal tubule (i.e. site I). The reduction in pulmonary carbon dioxide excretion associated with carbonic anhydrase inhibition is transient and clinically unimportant.21 Acetazolamide’s diuretic action is usually relatively weak because the distal sodium reabsorptive mechanisms commonly override the proximal effect. It increases the urinary excretion of sodium, potassium, and bicarbonate, without altering the excretion of chloride.

OSMOTIC DIURETICS (MANNITOL)
Osmotic diuretics are low molecular weight substances that are freely filtered by the glomeruli and remain in the tubular lumen because of a limitation of their reabsorption. By virtue of their size and high concentration, they contribute notably to the osmolality of the filtrate, which is responsible for their diuretic effect. Mannitol is a non-absorbable, non-metabolisable carbohydrate with a molecular weight of 182. It is the most commonly used osmotic diuretic. It is most often used intravenously to treat cerebral oedema, although oral administration has been used for preoperative bowel preparation and in the evacuation of ingested toxins. In controlled studies, prevention of acute renal failure or reduction in duration or mortality of acute renal failure, has not been shown in patients treated with mannitol.2,3

If 100 g of mannitol is administered intravenously, the urinary sodium increases to 50-70 mmol/l. Most of the diuretic action of mannitol is due to an inhibition of sodium and water transport in the ascending loop of Henle, with less than 50% of its action due to inhibition of sodium and water reabsorption in the proximal tubule.22 Initially the ECF is increased due to a fluid shift from the ICF to ECF.

The side-effects of mannitol include exacerbation of cardiac failure,14,23 hypotension (due to a peripheral vasodilating effect associated with the hypertonicity)24, factitious hyponatraemia,25 hyperosmolality26,27,28 and acute renal failure.
METHYLXANTHINES

Methylxanthines (e.g. theophylline) inhibit the adenosine A<sub>1</sub> receptor mediated vasoconstriction of interlobular and afferent arterioles and A<sub>2</sub> receptor mediated vasodilation of efferent arterioles, causing renal vasodilation, reducing the medullary concentration gradient, which in turn inhibits sodium and water reabsorption and causes a diuresis.

REFERENCES

Diuretics

Chapter 5

PRINCIPLES OF FLUID AND ELECTROLYTE THERAPY

The basic steps of fluid and electrolyte therapy are:

1. Correct previous losses or excesses (i.e. resuscitate)
2. Administer baseline requirements
3. Replace current losses
4. Consider nutrition

1. RESUSCITATE

The principles and practice of resuscitation for hypovolaemia involves management of intravascular fluid loss and replacement of intravascular fluid volume. Operative control of blood loss is the major consideration in patients who have continuing haemorrhage. In one study, an improvement in outcome was reported in hypotensive patients with penetrating torso injuries, when aggressive fluid resuscitation was delayed until operative intervention had occurred, suggesting that with uncontrolled haemorrhage temporary or definitive haemostasis (even in the presence of hypotension) should be performed first followed by intravascular fluid replacement. In the severely hypotensive trauma patient in whom haemostasis will be delayed, initial administration of intravenous fluids will still be required.

Intravenous fluids including blood, colloid and saline solutions are administered until blood pressure and peripheral perfusion are satisfactory or until the pulmonary wedge pressure is between 12 - 18 mmHg. Replacement of blood loss in an adult with colloid or crystalloid solutions (e.g. fresh frozen plasma, 5% albumin, polygeline, 0.9% saline) will cause a reduction in the haemoglobin by approximately 1 g/100mL per 500 mL of colloid or crystalloid solution remaining in the vascular compartment. While passive leg raising is sometimes used as a method to increase central blood volume during resuscitation, only 100 - 150 mL are transferred to the intravascular space by this method.

Recently, some have proposed the use of hypertonic saline or hypertonic and hyperoncotic solutions as a resuscitation fluid for the treatment of haemorrhagic and hypovolaemic shock, particularly in burns patients and trauma patients who sustain simultaneous head trauma with high intracranial pressures. While these solutions may have specific indications, they should not be used as the sole resuscitation fluid in patients with hypovolaemic shock. Furthermore, with uncontrolled haemorrhage, hypertonic saline, in comparison to 0.9% saline, may increase mortality.

Lower body positive pressure apparatus (e.g. inflatable trousers or military anti-shock trouser - MAST) have been recommended in the management of traumatic shock, despite the lack of data supporting their efficacy. Nevertheless, if they are to be used it should be during patient transport, to splint and control haemorrhage for pelvic and lower limb fractures, to tamponade haemorrhage in soft tissue, and to stabilise and maintain the upper torso circulation, when intravenous therapy cannot be administered or when volume replacement is inadequate.
Treatment of hypovolaemia with catecholamines is only used in patients in whom cardiac arrest is imminent to divert flow from the splanchnic circulation to serve the cerebral and coronary circulation as it can cause left ventricular outflow obstruction.\textsuperscript{12}

2. BASELINE REQUIREMENTS

\textit{Water}

Insensible water loss in the apyrexial adult patient in an environmental temperature of 25\textdegree{}C and 70\% humidity will rarely vary outside 500 - 1000 mL/24 hr.\textsuperscript{13,14} Also, in the postoperative patient, catabolism of body glycogen, fat and protein will produce from 500 to 1000 mL of water daily.\textsuperscript{15} Accordingly, 1500 - 2000 mL of water is considered to be the average requirement for the postoperative adult surgical patient when balancing the:
- Insensible skin and respiratory losses and faecal losses
- Water of metabolism
- Obligatory 500 - 1000 mL of water for urine solute excretion

\textit{Electrolytes}

The minimum daily adult requirements for electrolytes are shown in Table 5.1, also shown is the daily dose often administered to a standard post operative patient.

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Minimal requirement (mmol/24 hr)</th>
<th>Standard dose (mmol/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na\textsuperscript{+}</td>
<td>0 - 50</td>
<td>75 - 150</td>
</tr>
<tr>
<td>K\textsuperscript{+}</td>
<td>20 - 40</td>
<td>0 - 40</td>
</tr>
<tr>
<td>PO\textsubscript{4}\textsuperscript{3-}</td>
<td>15 - 20</td>
<td>-</td>
</tr>
<tr>
<td>Mg\textsuperscript{2+}</td>
<td>0 - 2</td>
<td>-</td>
</tr>
<tr>
<td>Ca\textsuperscript{2+}</td>
<td>3 - 5</td>
<td>-</td>
</tr>
</tbody>
</table>

The composition of the commonly used intravenous fluids are shown in Table 5.2, and the distribution of the commonly used intravenous fluids\textsuperscript{16,17,18,19,20} (assuming no losses and metabolism of all the dextrose - which occurs at a rate of 150 - 300 mmol or 30 - 50 g/hr/70 kg\textsuperscript{21}), is shown in Table 5.3. The lactate contained in some intravenous fluids (e.g. Hartmann’s solution, dialysate solutions) may exist in two forms (D-lactate and L-lactate) and while it is generally assumed that these solutions have a true racemic (1:1) mixture of each isomer, the composition varies widely, depending on the method of preparation.\textsuperscript{22} In a normal 70 kg individual the maximum rate of L-lactate metabolism is approximately 300 mmol/hr\textsuperscript{23} and the maximum rate of D-lactate metabolism is approximately 100 mmol/hr (8\% of D-lactate is excreted in the urine),\textsuperscript{24} lactic acid generates CO\textsubscript{2} and H\textsubscript{2}O as end products whereas sodium lactate changes to sodium bicarbonate. However, during acute illness, shock and liver failure lactate metabolism is often reduced, and endogenous lactate production increased, leading to an increase in plasma lactate and an anion gap in some patients in whom lactate solutions are infused.
Table 5.2 Composition of Commonly Used Solutions

<table>
<thead>
<tr>
<th></th>
<th>Na⁺ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Cl⁻ (mmol/L)</th>
<th>Ca²⁺ (mmol/L)</th>
<th>Lactate</th>
<th>Dextrose</th>
<th>Osmolality mosmol/kg</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Albumin 4%</td>
<td>140</td>
<td>128</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>280</td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>140</td>
<td>128</td>
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<td>Albumin 20%</td>
<td>60</td>
<td>60</td>
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<td>80</td>
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<td>Gelatin solutions</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Haemaccel 3.5%</td>
<td>145</td>
<td>5.1</td>
<td>145</td>
<td>6.25</td>
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<tr>
<td>Gelofusine 4%</td>
<td>154</td>
<td>&lt;0.4</td>
<td>120</td>
<td>&lt;0.4</td>
<td></td>
<td></td>
<td>274</td>
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<tr>
<td>Dextran 70</td>
<td>154</td>
<td>154</td>
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<td></td>
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<td>Dextran 40</td>
<td>154</td>
<td>154</td>
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<td></td>
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<tr>
<td>Rheomacrodex</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
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<td>290</td>
</tr>
<tr>
<td>Saline 0.9%</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>287</td>
</tr>
<tr>
<td>Saline 0.45%</td>
<td>77</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
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<td>Hartmann's solution</td>
<td>131</td>
<td>5</td>
<td>112</td>
<td>1.8</td>
<td>28</td>
<td></td>
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<tr>
<td>Dextrose 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>278</td>
<td>278</td>
</tr>
<tr>
<td>Dextrose 4%</td>
<td>31</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>222</td>
</tr>
<tr>
<td>in saline 0.18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>284</td>
</tr>
</tbody>
</table>

3. REPLACE CURRENT LOSSES

**Gastrointestinal losses**

The daily volumes and composition of gastrointestinal secretions in mmol/L are shown in Table 5.4. The clinical effects of fluid loss from the gastrointestinal tract (GIT) are largely determined by the volume and composition of the fluid, and therapy is usually directed at replacing, volume for volume and millimole for millimole, the fluid and electrolyte losses. In gastrointestinal disorders some fluid may be sequestered within the gut lumen (e.g. ileus), outside the lumen (e.g. ascites) or within the interstitial spaces (e.g., retroperitoneal oedema in pancreatitis), thus an assessment of the fluid status must be made on an assessment of the ECF and ICF volumes, rather than on the fluid balance chart.

Characteristic biochemical profiles of GIT fluid losses are:

1. *Gastric fluid loss* (e.g. vomiting, nasogastric suction) may result in metabolic alkalosis, hypokalaemia, hypotension and dehydration, if the saline and potassium chloride losses are not replaced.

2. *Pancreatic and biliary fluid losses* (e.g. pancreatic or biliary fistula and occasionally severe diarrhoea) may result in hyperchloraemic acidosis with hypokalaemia, hypotension and dehydration, if the losses of bicarbonate, potassium and saline are not replaced.

3. *Small and large bowel fluid losses* (e.g. fistula or ileostomy losses, diarrhoea and ileus) may result in hypokalaemia, hypotension and dehydration if the saline and potassium losses are not replaced.
Table 5.3  Body compartment change/litre of fluid/70 kg man
(1 hour after infusion)

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Plasma</th>
<th>Interstitium</th>
<th>Intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Albumin (in 0.9% saline)</td>
<td>980</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4% Albumin (in 0.9% saline)</td>
<td>950</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Succinylated gelatin 4%</td>
<td>600</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Polypegline 3.5%</td>
<td>500</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Rheomacrodex 10% (in 0.9% saline)</td>
<td>1600</td>
<td>-260</td>
<td>-340</td>
</tr>
<tr>
<td>Macrodex 6% (in 0.9% saline)</td>
<td>1100</td>
<td>-43</td>
<td>-57</td>
</tr>
<tr>
<td>1.8% Saline</td>
<td>320</td>
<td>1280</td>
<td>-600</td>
</tr>
<tr>
<td>Isotonic (0.9%) saline</td>
<td>200</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>1/2 isotonic (0.45%) saline</td>
<td>141</td>
<td>567</td>
<td>292</td>
</tr>
<tr>
<td>4% dextrose 1/5 isotonic (0.18%) saline</td>
<td>106</td>
<td>427</td>
<td>467</td>
</tr>
<tr>
<td>5% dextrose</td>
<td>83</td>
<td>333</td>
<td>584</td>
</tr>
</tbody>
</table>

Table 5.4  Daily volume and electrolyte composition of GIT secretions

<table>
<thead>
<tr>
<th></th>
<th>Electrolytes (mmol/L)</th>
<th>Vol (L)</th>
<th>H⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td></td>
<td>0.5-1.0</td>
<td>0</td>
<td>30</td>
<td>20</td>
<td>10-35</td>
<td>0-15</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>1.0-2.5</td>
<td>0-120</td>
<td>60</td>
<td>10</td>
<td>100-120</td>
<td>0</td>
</tr>
<tr>
<td>Bile</td>
<td></td>
<td>0.5</td>
<td>0</td>
<td>140</td>
<td>5-10</td>
<td>100</td>
<td>40-70</td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>0.75</td>
<td>0</td>
<td>140</td>
<td>5-10</td>
<td>70</td>
<td>40-70</td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
<td>2.0-4.0</td>
<td>0</td>
<td>110</td>
<td>5-10</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Renal losses
These are only required to be replaced in unusual circumstances where there is an unwanted diuresis, usually associated with neurogenic or nephrogenic diabetes insipidus, of greater than 250 mL/hr (6 L/day). Replacement fluids consisting of water (e.g. 5% dextrose) are usually all that is required, unless renal sodium loss also coexists.

4. NUTRITION

The principles and practice of enteral and parenteral nutrition will be described in a future handbook.

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).

1. Discuss the diagnosis and management of diastolic heart failure. Dr. K. Deshpande 53
2. Discuss the ECG features and treatment of hyperkalaemia. Dr. S. Perrin 58
3. Discuss the clinical features and management of methanol poisoning. Dr. R. Plant 60
4. Discuss the management of a patient with severe hypotherma. Dr. M. Daley 63
5. Discuss the causes of high cardiac output lactic acidosis. Dr. A. Delaney 65
6. Discuss the use of helical computed tomography and the diagnosis of pulmonary embolism. Dr. M. Gillham 66
7. Discuss the reasons why low tidal volumes are thought to reduce mortality in patients with ARDS. Dr. S. Baker 68
8. Discuss the causes and how you would confirm the sign of ‘fixed dilated pupils’. Dr. J. Field 70
9. Discuss the indications and use of epsilon aminocaproic acid. Dr. R. Fabian 72
10. Discuss the management of a child with severe croup. Dr. J. Berkahn 74
11. Discuss the risks and benefits of intravenous pralidoxime in a patient with acetylcholinesterase poisoning. Dr. B. Curran 77
12. Discuss the management of a patient with anaemia (Hb 70g/L) and congestive cardiac failure. Dr. K. Vidhani 80
13. Discuss the diagnosis and management of the acute coronary syndrome. Dr. B. Turner 82
14. Discuss the management of a patient with MRSA aortic valve endocarditis. Dr. K. Lui 85
15. Discuss the reasons for ‘daily dose’ gentamicin. Dr. P. Lane 91
16. Discuss the indications and complications of an intra aortic balloon pump. Dr. C. Schneider 93
17. Define and discuss the diagnosis and management of ventilator associated pneumonia. Dr. S. Nolan 95
18. Discuss the diagnosis and management of amniotic fluid embolism. Dr. P. Whyte 100
19. Discuss the management of a patient with closed head injury and an intracranial pressure > 25 mmHg. Dr. T. Browne 103
20. Discuss the indications and complications of muscle relaxants, sedative and analgesic agents used to settle a mechanically ventilated patient. Dr. C. Fagan 106
21. Discuss the clinical features of bacterial endocarditis and what investigations you would use to confirm it. Dr. N. McNeillis 110
22. Discuss the clinical features and management of salicilate poisoning.  Dr. D. Lowe 113
23. Discuss the indications for intravenous potassium acetate.  Dr. E. Hughes 114
24. Discuss the indications for and complications of non-invasive ventilation in acute respiratory failure.  Dr. S. Sviri 115
25. Discuss the diagnosis and emergency management of a patient with a high spinal fracture.  Dr. D. Evans 117
26. Discuss the clinical features and management of the serotonin syndrome.  Dr. D. Murphy 120
27. Discuss the management of a cardiac tamponade and how you would perform a pericardial tap.  Dr. D. Collins 122
28. Discuss the management of a large broncho-pleural leak in a trauma patient who requires mechanical ventilation.  Dr. R. Hegde 128
29. Discuss the emergency management of a patient who has severe upper airway obstruction.  Dr. R. Holland
30. Discuss the indications for intravenous magnesium sulphate.  Dr. S. Valandy Koottayi
31. Discuss the diagnosis and management of a patient with a closed head injury and elevated intracranial pressure.  Dr. P. Garrett
32. Discuss the clinical features and management of common brown snake envenomation.  Dr. L. Ware
33. Compare and contrast the effects of inhaled NO and nebulised prostacyclin (PGI₂) in a patient with ARDS.  Dr. J. Shen
34. Discuss the management of a patient with a serum sodium of 119 mmol/l who has status epilepticus.  Dr. K. O’Connor
35. Discuss the management of a patient who has acute iron poisoning.  Dr. S. DeSilva
36. Discuss the clinical features and management of a patient with an acute left ventricular aneurysm.  Dr. A. Warmington
37. Discuss the management of a patient with Wegner’s granulomatosis and respiratory failure.  Dr. R. Purcell
DISCUSS THE DIAGNOSIS AND MANAGEMENT OF DIASTOLIC HEART FAILURE

Dr. K. Deshpande, Intensive Care Unit, Repatriation General Hospital, SA

Definition: A condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of congestion due to an inappropriate upward shift of the diastolic pressure-volume relation (that is, during the terminal phase of the cardiac cycle).

Risk factors: Advancing age, hypertension, diabetes, LVH, CAD

More common: women, black race

Incidence: 30-50% of patients with heart failure.

Mortality: 9-28% per year.

Four times that among persons without heart failure
Half of that among patients with systolic heart failure.

Diagnosis: difficult to establish because

1. Routine use of cardiac catheterization, the gold standard for demonstrating LV diastolic dysfunction is not feasible in all cases.
2. Noninvasive imaging techniques (principally Doppler imaging studies of mitral inflow) have been problematic as the results must be interpreted in the context of loading conditions, heart rate, and systolic function.
3. Accuracy and usefulness of newer load-independent measures is yet to be proved.
4. Detailed Echocardiographic study is required which is technically demanding, time consuming and difficult to interpret. (See the complex nature of the criteria by European Study Group)

Criteria for definite Diastolic Heart Failure

Definitive evidence of CHF

Includes clinical symptoms and signs, supporting lab tests (such as CXR), and a typical clinical response to treatment with diuretics, with or without documentation of elevated LV filling pressure (at rest, on exercise, or in response to a volume load) or a low cardiac index

AND

Objective evidence of normal LV systolic function in proximity to the CHF event

LV EF ≥ 0.50 within 72 hours of CHF event

AND

Objective evidence of LV diastolic dysfunction

Abnormal LV relaxation / filling / distensibility indices on cardiac catheterization

Criteria for probable Diastolic Heart Failure

Definitive evidence of CHF

Includes clinical symptoms and signs, supporting lab tests (such as CXR), and a typical clinical response to treatment with diuretics, with or without documentation of elevated LV filling pressure (at rest, on exercise, or in response to a volume load) or a low cardiac index

AND

Objective evidence of normal LV systolic function, but not at the time of the CHF event

LV EF ≥ 0.50 within 72 hours of CHF event

AND

Objective evidence of LV diastolic dysfunction is lacking

No conclusive information on LV diastolic function
Criteria for possible Diastolic Heart Failure

Definitive evidence of CHF

Includes clinical symptoms and signs, supporting lab tests (such as CXR), and a typical clinical response to treatment with diuretics, with or without documentation of elevated LV filling pressure (at rest, on exercise, or in response to a volume load) or a low cardiac index

AND

Objective evidence of normal LV systolic function, but not at the time of the CHF event

LV EF ≥ 0.50

AND

Objective evidence of LV diastolic dysfunction is lacking

No conclusive information on LV diastolic function

Reasons to Upgrade Diagnosis from Possible DHF to Probable DHF

• Markedly elevated BP during the episode of heart failure (systolic >160 or diastolic >100 mm Hg)
• Echo: concentric LV hypertrophy without wall motion abnormalities
• A tachyarrhythmia with a shortened diastolic filling period
• Precipitation of event by the infusion of a small amount of i.v. fluid
• Clinical improvement in response to therapy directed at the cause of diastolic dysfunction (such as reducing BP, heart rate, or restoring atrial booster mechanism)

Diagnostic Criteria: European Study Group on Diastolic Heart Failure

Signs or symptoms of congestive heart failure

Exertional dyspnoea [eventually objective evidence by reduced peak exercise oxygen consumption (< 25 mL. kg⁻¹. min⁻¹), orthopnoea, gallop sounds, lung crepitations, pulmonary oedema.

and

Normal or mildly reduced LV systolic function:

LVEF ≥ 45% and LVEDVI < 3.2 cm² or LVEDVI < 102 mL. m²

and

Evidence of abnormal LV relaxation, filling, diastolic distensibility and stiffness:

Slow isovolumetric LV relaxation:

LVdP/dtₘᵢₘₖ < 1 100 mmHg. s⁻¹

and/or IVRT₃₀ < 92 ms, IVRT₃₀-₅₀ > 100 ms, IVRT₅₀ > 105 ms

and/or τ > 48 ms

and/or slow early LV filling:

PFR < 160 mL. s⁻¹. m²⁻¹

and/or PFR₃₀ < 2.0 EDV. s⁻¹, PFR₃₀-₅₀ < 1.8 EDV. s⁻¹, PFR₅₀ < 1.6 EDV. s⁻¹

and/or E/A₃₀ < 1.0 and DT₃₀ > 220 ms, E/A₅₀ > 2.5 and DT₅₀ > 280 ms

and/or S/D₅₀ > 1.5, S/D₅₀ > 2.5

and/or reduced LV diastolic distensibility:

LVEDP > 16 mm Hg or mean PCW > 12 mm Hg

and/or PV A Flow > 35 cm. S⁻¹

and/or PV A t > MV A t + 30 ms

and/or A / H > 0.20

and/or increased LV chamber or muscle stiffness:

b > 0.27

and/or b’ > 16
LVEF=left ventricular ejection fraction; LVEDIDI=left ventricular end-diastolic internal dimension index; LVEDVI=left ventricular end-diastolic volume index; \( \text{LVDp/dt}_{\text{min}} = \) peak negative left ventricular \( \text{dP/dt} \); IVRT=iso Chimelotic relaxation time indexed for age groups; \( \tau = \) time constant of LV pressure decay; PFR=peak LV filling rate indexed for age groups; EDV=end diastolic volume; \( E/A = \) ratio of peak early to peak atrial Doppler flow velocity indexed for age groups; \( S/D = \) ratio of pulmonary vein systolic and diastolic flow velocities indexed for age groups; \( \text{PCW} = \) left ventricular end-diastolic pressure; \( \text{PV A} = \) pulmonary capillary wedge pressure; \( \text{PV A flow} = \) pulmonary venous flow velocity; \( \text{PV A t} = \) pulmonary venous atrial flow velocity duration; \( \text{MV A t} = \) mitral atrial flow velocity duration; \( A/H = \) ratio of atrial wave to total signal excursion on the apex- cardiogram; \( b = \) constant of LV chamber stiffness; \( b' = \) constant of muscle stiffness

(Bicycle ergometer exercise test, Doppler Echocardiography, Radionuclide LV angiogram, PA catheter etc. are needed to measure above parameters)

<table>
<thead>
<tr>
<th>Treatment of diastolic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
</tr>
<tr>
<td>1. Acute ischaemia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2. Postinfarction scar or ventricular aneurysm</td>
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<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>1. Hypertensive urgency or emergency</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>2. Hypertensive heart disease</td>
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<td></td>
</tr>
</tbody>
</table>
Hypertrophic Cardiomyopathy  
- *Impaired relaxation*  
  - ↑ contraction load in obstructive disease, reduced relaxation load, non uniform relaxation due to fibrosis, cellular disarray and regional variation in hypertrophy, diminished coronary reserve  
  - ↑ *chamber stiffness*  
  - (altered geometry, increased myocardial stiffness)  
- Negative inotropic drugs, dual chamber pacing and surgical myomectomy for refractory symptoms.

Restrictive or infiltrative Cardiomyopathies  
- *Impaired relaxation*  
- ↑ *chamber stiffness*  
- (↑ myocardial stiffness, fibrosis)  
- Treat any reversible factors. Cardiac transplantation for end-stage cardiac failure; Avoid digitalis and beta blockers in amyloidosis.

Valvular heart disease  
1. Stenotic lesions (AS / MS)  
- *Pressure overload*  
- *Impaired relaxation*  
- ↑ *chamber stiffness* due to concentric hypertrophy  
- Surgery, valvuloplasty commissurotomy
2. Regurgitant lesions (AR / MR)  
- *Volume overload*  
- *Impaired relaxation*  
- ↓ *chamber stiffness* due to eccentric hypertrophy, which is offset by ↑ *myocardial stiffness*  
- *Pericardial restraint* plays an important role in acute volume overload  
- Surgery, diuretics, and afterload reduction

General Principles  
- Reduce venous pressure: cautious use of diuretics and other preload reducing agents.  
- Treat precipitating factors; control of tachycardia; restore sinus rhythm and atrioventricular synchrony.  
- Avoid positive inotropes in the absence of systolic dysfunction (an exception is the use of digoxin for control of ventricular rate in AF)  
- Identify and treat the underlying etiology.  
- Treatment remains empirical and there are currently few clinical data to support the efficacy of any particular class of drugs.  
- From a public health perspective, best treatment is prevention (e.g. early detection and optimal control of elevated BP).
Cardiac cycle showing etiology and treatment of DHF

S = systole, D = diastole, F = flow, IC = isovolumetric contraction, IR = isovolumetric relaxation, RFP = rapid filling phase, 1 = aortic valve closure, 2 = mitral valve opening, 3 = end of early rapid filling, 4 = end-diastole

References
DISCUSS THE ECG FEATURES AND TREATMENT OF HYPERKALAEMIA

Dr. S. Perrin. Intensive Care Unit, The Bendigo Hospital, Victoria

Definition of Hyperkalaemia (HK)

Laboratory - Serum [K+] > 5.1 (Mean + 2S.D.’s (well non drug taking popn) + 3 X laboratory imprecision (ie.0 04mmol/L)

Clinical - Serum [K+] > 6.0

Life-threatening - Serum [K+] > 7.0mmol/L OR > 5.5mmol/L + ECG changes

Overview of potassium homeostasis

Total body Potassium 3500 mmol
Intracellular Potassium 3400 mmol
ECF Potassium 75 mmol

Factors promoting intracellular shift of K⁺:
Alkalosis
Increasing Osmolality
Na+/K+ ATPase pump B2 receptor stimulation
Aldosterone
Insulin (independent of glucose uptake)

Clinical features of Hyperkalaemia

Typical situations - Major trauma
- Release aortic cross clamp
- I.V. K⁺ replacement
- Renal failure with or without dialysis
- Burn victim

Hyperkalaemia raises resting membrane potential in excitable tissues increasing irritability and simultaneously inhibits the fast Na channel impairing the action potential explaining the clinical phenomenon of;

Gastro-intestinal paresis
Parasthesias
Flaccid tetraparesis
Hypotension

E.C.G. changes - 6 to 7mmol/L Tall peaked T waves (>5mm) esp. precordial leads
- 7 to 8mmol/L prolonged PR interval
- p wave flattenning progressing to atrial asystole
- junctional rhythms
- 8 to 9 mmol/L Broadened QRST to sine wave complexes
- >9.0mmol/L Asystole/Ventricular Fibrillation/Tachycardia

Treatment of Hyperkalaemia

This was recently reviewed by by Ahee and Crowe. They provide an excellent literature review of the topic with emphasis on effectiveness of methods to stimulate intracellular movement of K⁺.
1. Repeat Potassium assay to exclude artefact eg haemolysis, delayed processing, thrombocytosis, leukocytosis
2. If ECG changes present, Stabilise Myocardium with
   – Ca Gluconate 10% 10 to 30 mls under ECG guidance
3. Avoid / Treat Acidosis by instituting simple measures eg hyperventilation, NaHCO₃
4. Stimulate intracellular movement of Potassium
<table>
<thead>
<tr>
<th>Onset</th>
<th>Duration</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin with Dextrose – 50gms Dextrose + 20u insulin</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>OR</td>
<td>Salbutamol 4ug/Kg IV. or 0.3mg/Kg Nebulised</td>
<td>30</td>
</tr>
</tbody>
</table>
   **Problems**
   Insulin – hypoglycaemic effect extends beyond hypokalaemic effect
   Salbutamol – 10 to 40% fail to respond, tachycardia, nausea etc
5. Determine cause of HK
   Inadequate secretion
   - Drugs K⁺ sparing diuretics, NSAID’s, ACE inhibitors esp. in combination
   - Renal failure
   - Addison’s disease
   - Hypoaldosteronism
   Exogenous sources of K⁺ - beware antibiotics especially Co-trimoxazole
   Endogenous sources of K⁺ - rhabdomyolysis
   - other tissue damage burns, trauma, haemolysis
   - succinylcholine.in burns, neurological disease
   - 1 Kg muscle contains 80 mmol K⁺
   Compartmental shift – Acidosis, Insulin deficiency, Digoxin O/D, Arginine infusion, B₂ adrenergic blockade, HK periodic paralysis
6. NaHCO₃ is commonly recommended for treatment of HK. Has failed to show any reduction in K⁺ when tested. May be useful in controlling acidosis.
7. Remove Potassium
   Polystyrene Resin (ResoniumA) 30gms po/pr
   - ea gram exchanges 1mmol Na for 1mmol K
   Dialysis - definitive therapy but above temporizing measures required while waiting
   - Potassium free dialysate will reduce [K⁺] 1.0 to 1.5 mmol/hr

References
DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF METHANOL POISONING

Dr. R. Plant. Intensive Care Unit, The Alfred Hospital, Victoria

Methanol (CH$_3$OH, Wood alcohol) is a component of shellac, varnish, de-icing solutions and other commercial preparations.

Ingestion is suspected in the patient with a presentation suggestive of inebriation but without blood or breath levels supportive of same, though co-ingestion may be a confusing issue. Inhalation exposure or absorption through the skin are other routes of poisoning. The finding of an elevated anion gap acidosis with an osmolal gap is typical, though not inevitable and not diagnostic alone.

Toxicity is due to toxic metabolites rather than methanol itself (methanol is metabolized to formaldahyde (via alcohol dehydrogenase), then formic acid(via aldehyde dehydrogenase)).

The approach to the suspected methanol poisoning must have a similar ordered approach as for any poisoning$^1$:

Evaluation, including recognition that poisoning has occurred, identification of the agent responsible, assessment severity and prediction of toxicity

Management, consisting of supportive care with urgent attention to the ABC’s, efforts to reduce further absorption, and the administration of an antidote and measures to increase elimination where appropriate.

EVALUATION

Recognition of poisoning, and identification of methanol as the agent responsible, is from the clinical and laboratory features:

CNS: Initial effects as per alcohol with ataxia, confusion, drowsiness, nausea, vomiting…later effects due to acidosis and/or toxic metabolites include seizures and coma

Optic: Visual loss/blurring, photophobia, optic nerve oedema, retinal ‘sheen’ (2$^\circ$ to retinal oedema)

CVS: Tachycardia, tachypnoea, hypertension 2$^\circ$ to acidosis…cardiogenic shock with ARF possible with severe toxicity

Labs: Metabolic acidosis, elevated anion gap

(Osmolal Gap (ie measured – calculated osmolality)

(Upper limit normal: 10mosm/kg; > 25 significant)

Must be measured by freezing point depression.

But metabolism of all ingested methanol may bring gap back to normal!

Differentials: DKA, Alcoholic KA, Lactic acidosis, CRF not ARF, Ethylene glycol

Essentially anion gap acidosis is the metabolites, osmolal gap the parent compound!

Hyperkalaemia, hypocalcaemia may occur (frequent reassessment during treatment)

Assessment of severity/Prediction of toxicity:

Clinical features: Mortality >80% if coma/seizures or pH <7.0

< 6% if theses features absent

Minimal lethal dose 50-100ml (less can cause permanent blindness)
Lethal serum level 80-100mg/dl
T1/2 is dose dependent: Mild intoxication 14 - 20 hrs
   Severe intoxication 24-30hrs
   With ethanol 30 - 35 hrs
   (Ethanol + HD 2.5 hrs)$^3$

MANAGEMENT

Supportive care:
As in any poisoning the initial priority is stabilization of the ABC’s, especially wrt protection
of the airway in the obtunded patient. IV access, hydration (+/- glucose/thiamine) Attention to
the possibility of trauma with c/spine injury or intracranial event must be included with an
unconscious patient.
Sodium bicarbonate should be administered if there is significant metabolic acidosis, and
massive dosage may be required in the face of severe and ongoing acidosis.
Continued monitoring for and correction of hypocalcaemia/hyperkalaemia, other electrolyte
abnormalities

Decrease further absorption:
Administration of activated charcoal within 1-2 hrs of the ingestion…methanol is rapidly
absorbed and not very well adsorbed by charcoal, therefore of only limited usefulness
(Induced emesis/ gastric lavage may be potentially harmful in the patient with impaired
consciousness)

Antidote:
Ethanol: Alcohol dehydrogenase, responsible for the metabolism of methanol to its toxic
metabolites, has a 10x affinity for ethanol.
Administration of ethanol aims for a level of 100-200mg/dl (22-23mmol/l)
   Dose: Loading: 0.6g/kg (as 5 or 10% IV solution)
   Hourly IVI 66/154/240mg/kg (non-drinker/drinker/haemodialysis)$^4$
Folate: 50-70mg IV Q 4hrly x 1day
Promotes catalase mediated metabolism of folic acid to CO$_2$/H$_2$O
Fomepizole: (4-methyl-pyazole) competitively inhibits alcohol dehydrogenase more effectively
than ethanol and is used as an alternative to ethanol. Used widely in Europe.

Enhanced elimination:
Haemodialysis should be performed in severe intoxications to remove both the parent
compound and the toxic metabolites, and continued until level < 20mg/dl
Indications for dialysis:
   Level > 50mg/dl
   Visual symptoms
   Change in mental status
       > 30ml ingested
       Refractory metabolic acidosis

Key points:
   High index of suspicion; Primarily visual/CNS symptoms; High anion gap metabolic acidosis
   and osmolal gap typical, but neither is inevitable; Mgt consists of usual supportive care, sodium
   bicarbonate, ethanol, folate, +/- dialysis$^5$
References
1. Micromedex Healthcare Series; Poisonindex @ Electronic Health Library @ clinicians.vic.gov.au
2. UpToDate Clinical reference on CDROM and online
5. Mc Coy HG et al, Severe methanol poisoning: application of a pharmacokinetic model for ethanol therapy and dialysis
DISCUSS THE MANAGEMENT OF A PATIENT WITH SEVERE HYPOTHERMIA

Dr. M. Daley. Intensive Care Unit, St George Hospital, New South Wales

Severe hypothermia stated as < 28°C.

Airway – Secure and maintain airway with jaw thrust. Intubate if unconscious/unable to maintain airway – preoxygenate, minimal laryngeal manipulation (→ VF).

Breathing – assess ventilation. Supplemental oxygen warmed, humidified to maintain O₂ Sat 100%. Avoid hyperventilation (→ VF).

Circulation – controversial

One approach:

**IS THERE A PERFUSING RHYTHM PRESENT?**

**NO** → Extracorporeal rewarming to >32°C – treatment of choice. If not available → CPR + all available methods of active core rewarming + active external rewarming.

For VF, 3 x DC shocks should be delivered – if VF persists, give no further shocks until >30°C. VF usually refractory to anti-arrhythmic agents. Cardiac pacing has been used for asystole - ? effectiveness.

Decision to cease unsuccessful resuscitation should not be made until core temp. exceeds 32-35°C + efforts futile.

**YES** → Active core rewarming alone or with active external truncal rewarming (active limb rewarming → increased complications). If hypotensive, treat with IV fluids (patients intravascularly dry), possibly dopamine (other catechols → dysrhythmias).

Controversy surrounds “perfusing rhythm.” Sinus rhythm regarded by many as perfusing rhythm even with impalpable pulses (ie. cardiac compressions not indicated). Others argue CPR should be given if pulses impalpable. Problem is that pulse can be very difficult to detect.

If in doubt – CPR; or consider confirming blood flow - emergency ECHO if available in ED, femoral art. line (difficult insertion).

If ECG not available - pulseless hypothermic patient → chest compressions. Any palpable pulse even extreme bradycardia → no chest compressions (risk of VF).

**Continued management:**

- Prevent further heat loss
- Rewarming – Active Central (see below)
- Supportive care. Arrhythmias are usually refractory to therapy at < 30°C
- Warm all IV fluids
- Prevent complications – esp. aspiration, infection
- Find and treat cause – commonest exposure, hypoglycaemia, alcohol abuse. Also CVA, head injury, quadriplegia, mental illness, hypothyroidism, Addison’s, drugs.
- Prevent recurrence

**Active Central Rewarming** (fast, invasive):

- humidified warmed inspired gases 40°C (1.0-1.5°C/hr)
- warm intragastric irrigation – risk of VF and aspiration
- peritoneal lavage – 1 catheter exchange q15min, 2 catheters continuous infusion + drainage (2-4°C/hr)
- haemodialysis with blood warmer
- intrapleural lavage described
- cardiopulmonary bypass – femoral-femoral, median sternotomy.

Active External Rewarming:
- Electric pads or hot water mattresses/blankets,
- circulating/convection hot air
- warm water immersion
- radiant heat
? higher mortality due to less controlled temp. increase, paradoxical core temp. drop due to increased peripheral perfusion, rewarming shock, rewarming acidosis.

Passive Rewarming (0.4°C/hr):
- keep dry
- warm blanket
- radiation reflective sheet

References
1. Danzl DF, Pozos RS, Current concepts – accidental hypothermia NEJM 331(26) 1756-60
**DISCUSS THE CAUSES OF HIGH OUTPUT LACTIC ACIDOSIS**

**Dr. A. Delaney.** Intensive Care Unit, Royal North Shore Hospital, **New South Wales**

Lactic acidosis is the consequence of an imbalance between lactate production and lactate metabolism.

![Chemical Reaction](image)

### Causes of High Cardiac Output Lactic Acidosis

* Increased Production.
  • Impaired Oxygen Delivery. (increased C.O. as compensation)
    - severe anaemia
    - low oxygen saturation
  • Impaired Oxygen Utilisation. (increased C.O. as compensation)
    - Poisoning; cyanide, carbon monoxide, salicylate
    - Thiamine deficiency (impaired pyruvate DH activity)
    - Biguanides
    - Inherited enzyme defects.
  • Increased metabolic production. (increased C.O. proportional to increased demand)
    - Extreme muscular exertion; exercise, status epilepticus
    - Malignant hyperpyrexia syndromes; malignant hypertension,
    - serotonin syndrome, neuroleptic malignant syndrome, heat stroke.
    - Beta agonists
    - Acute lung injury

* Impaired Lactate Clearance.
  • Systemic Inflammatory response syndromes; sepsis, pancreatitis, burns
  • Liver failure
  • Renal failure.

### References

DISCUSS THE USE OF HELICAL COMPUTED TOMOGRAPHY AND THE DIAGNOSIS OF PULMONARY EMBOLISM

Dr. M. Gillham. Intensive Care Unit, Liverpool Hospital, New South Wales

Pulmonary thromboembolism (PTE) is a common and potentially life threatening disease. Crude three month mortality for patients with PTE has been shown to be approximately 17.4%. This mortality is higher in patients with hypotension (mortality odds ratio 2.9 [1.7-5.0]) and with in patients with right ventricular dysfunction (mortality odds ratio 2.0 [1.3 – 1.9]) at time of diagnosis.¹

Ventilation perfusion scans (V/Q scans) have long been recognised to have limited utility in the diagnosis of PTE. They have limited sensitivity and specificity, and this is further reduced when cardiorespiratory disease is known to be present. From PIOPED data, 90% of patients with chronic obstructive lung disease and 80% of patients with any cardiorespiratory disease had non diagnostic scan results.²³ When we consider that for these best results the ventilation scan is best done in the upright position and that a scan can take two hours or more, its utility (particularly in intensive care patients) becomes questionable.

Use of helical computed tomography (hCT) in suspected PTE should be governed by the clinical condition of the patient and whether treatment (and if so which treatment) is likely to be instituted. In haemodynamically unstable patients, transoesophageal echocardiography (which is easily portable to the patient’s bed side) should be used first, as it has a sensitivity for PTE (with haemodynamic instability) of approximately 80%,⁴ and may include or exclude other diagnoses. If this is non diagnostic, then hCT is indicated if management is likely to be changed by the diagnosis. For instance presence of a large clot and haemodynamic compromise may warrant thrombolysis or pulmonary embolectomy.

If the patient is haemodynamically normal and suspicion is low then a D-dimer assay may be indicated. Some D-dimer assays may be used to rule out PTE if the clinical suspicion for the disease is low, and the negative predictive value for the assay is high. However these D-dimer tests are expensive and frequently not available. Following this Duplex scanning of the legs is warranted before hCT. If this test proves positive, then anticoagulation is warranted and transfer to the hCT is not required. However, because the prevalence of deep venous thrombosis (DVT) in patients with suspected PTE is only 18%, and in those with proven PTE is 36 - 45%,⁵ then a negative duplex of the legs must be followed up with a hCT.

Reported studies of the diagnostic accuracy of hCT for PTE are of variable methodological quality. A recent review of these studies suggests a sensitivity between 64 and 93% and a specificity between 89 and 100%, when compared to pulmonary angiography (PA) in a population where the prevalence of PTE was approximately 35%.⁶ Problems with the interpretation of this data begin with the fact that PA is not a perfect gold standard test, with a false positive rate of 2%, and an appreciable false negative rate. Important advantages of hCT over PA include the lesser required dye load (an average of 120 ml of contrast required for a hCT v 300 mL for bilateral PA), the speed of the examination, ability to pick up alternative diagnoses, wider availability and the lesser morbidity/mortality of the test. PA has a reported morbidity of 6% and mortality of 0.5% in experienced hands and these rates are operator experience dependent. When using hCT, it is necessary to use a suitable protocol⁷ and have suitably trained radiologists interpreting the scans,⁸ in order for the quoted sensitivities and specificities to be achieved. This involves the use of a timing injection of contrast prior to administration of the main contrast bolus, and a 20 - 25 second breath hold in order to minimise movement artefact. Even in the trials published there is a rate of inconclusive, technically inadequate or incomplete procedures of approximately 8%. Pick up rate for sub segmental
embolus is poor (5/17) and inter observer agreement for this defect is also poor. The clinical significance of these PTE is not yet clear.

In summary, hCT has a high sensitivity and specificity for PTE when compared to PA, and overall performs as well if not better than vq scanning. It has several important advantages over both vq scanning and PA, but should not necessarily be the first test when evaluating the patient with suspected PTE. A negative hCT is not as negatively predictive as a normal vq scan, and if clinical suspicion is high, PA may still be warranted after negative hCT.8

References
DISCUSS WHY LOW TIDAL VOLUMES ARE THOUGHT TO REDUCE MORTALITY IN PATIENTS WITH ARDS

Dr. S. Baker. Department of Critical Care Medicine, Flinders Medical Centre, SA

1. Perpetuate Inflammation and MOSF
   ▪ in ARDS lungs are highly asymmetrical along the vertical axis with 3 distinct zones
     i. small, non dependent lung region continuously open to ventilation
     ii. a dependent, consolidated, atelectatic region
     iii. in between a region that can be recruited or derecruited depending on ventilator strategy
   ▪ use of large tidal volumes can cause
     i. repetitive opening and closing of collapsed alveoli leading to shear stress which can be prevented by increasing PEEP
     ii. overdistention of the reduced number of alveoli able to receive ventilation
   ▪ both these effects can initiate a cascade of proinflammatory cytokines
   ▪ disrupted alveolar epithelial endothelial barrier allows cytokines produced in the lung to enter the systemic circulation
   ▪ protective lung ventilation has been shown to reduce pulmonary neutrophil infiltration, reduce pulmonary production of cytokines and reduce subsequent transfer of these cytokines into the pulmonary circulation
   ▪ the reduced levels of systemic cytokines (IL-6, TNF-α, IL-1β, IL-6) is associated with reduced occurrence of MSOF
     i. systemic cytokines are thought to cause MSOF
     ii. most deaths in ARDS are due to MSOF not respiratory failure

2. Barotrauma
   ▪ alveolar overdistention (rather than high pressure) is associated with barotrauma (pneumothorax, bronchopleural fistula)
   ▪ animal studies suggest lung volume should not exceed TLC of ventilated region of the lung
     i. usually represented by an inspiratory plateau pressure of 30 –35 cmH₂O
   ▪ protective lung ventilation did not decrease barotrauma in a recent trial

3. Ventilator Induced Lung Injury
   ▪ VILI has been shown to be due to lung overdistention rather than high airway pressures
   ▪ diseased lungs with patchy distribution of lesions are subjected to greater regional stress than homogenously inflated lungs
   ▪ characteristics of ventilator induced pulmonary oedema
     i. Surfactant inactivation resulting in increased alveolar surface tension causing more negative pressures surrounding alveolar vessels enhancing fluid filtration
     ii. “pulmonary interdependence” causes pressure in perivascular space surrounding extra-alveolar vessels to decrease enhancing fluid filtration
     iii. increased epithelial and endothelial permeability
     iv. combined effect of increased filtration pressure and increased permeability are much greater than either alone
     v. intravascular leukocyte and intra-alveolar macrophage accumulation
4. **Hypercapnia**
   - animal studies have shown that hypercapnia compared with normocapnia in a model of ALI is associated with
     - preservation of lung mechanics
     - attenuation of protein leakage
     - reduction in pulmonary oedema
     - improved oxygenation
     - attenuation of inflammation including
       - neutrophil and macrophage sequestration
       - cytokine release
       - lipid peroxidation and peroxynitrite induced tissue injury
     - reduced apoptosis

5. **Bacterial Translocation**
   - high peak airway pressures and absence of PEEP increased bacterial translocation from the lung in an animal model
   - this has been suggested as possible mediator of systemic manifestations in ARDS

**References**
DISCUSS THE CAUSES AND HOW YOU WOULD CONFIRM THE SIGN OF FIXED DILATED PUPILS

Dr. J. Field, Intensive Care Unit, Royal Perth Hospital, Western Australia

Examination of the pupils

Look ahead (to avoid accommodation reflex)
Compare pupils for size, shape, equality, and regularity
Light from side – direct and consensual on both sides
Swinging light test – relative afferent pupillary defect (reduced afferent impulses)

Parasympathetic constrictor pathway

Sympathetic dilator pathway
Causes
1. Dorsal midbrain damage
   - Primary injury - CVA, tumours, degenerative or infectious disease
   - Secondary (ischaemia, anoxia)
   - Dorsal (Edinger – Westphal nucleus or connections)
   - Ventral (IIIrd nerve) – Weber syndrome –

2. IIIrd nerve damage
   - Basal aneurysms
   - Supratentorial space occupying masses
     - Central brainstem displacement
     - Transtentorial herniation medial uncal herniation
   - Basal meningitis
   - Ischaemic oculomotor palsy
   - Parasellar tumour – pituitary adenoma, meningioma, craniopharyngioma, nasopharyngeal carcinoma, distal metastases.
   - Parasellar inflammation – temporal arteritis, herpes zoster

3. Damage to ciliary ganglion or short ciliary nerves
   - Viral infection – herpes zoster
   - Orbital trauma, tumour or surgery
   - Retrobulbar injections

4. Damage to the Iris
   - Iritis
   - Acute glaucoma
   - Blunt trauma to globe – traumatic iridoplegia
   - Cataract surgery
   - Anticholinergics

5. Total blindness - retina, optic nerves or cortex
   (Anterior ischaemic optic neuropathy, optic neuritis, C. retinal V or A occlusion

Drugs – pupils dilated and sluggish but not usually fixed
Anticholinergics (TCAs, phenothiazines), sympathomimetics (cocaine, amphetamines, clonidine, bronchodilators), barbiturates, benzodiazepines

References
DISCUSS THE INDICATIONS AND USE OF EPSILON AMINOCAPROIC ACID

Dr. R. Fabian, Intensive Care Unit, St George Hospital, New South Wales

Lysine analogue antifibrinolytic. Reduces bleeding by preventing clot lysis by inhibiting plasmin formation.

**Indications**
In Australia mainly used for complicated cardiac surgery such as redo, valves and coronary bypass grafting, long cardiopulmonary bypass on aspirin, impaired clotting, Jehovah's witness. Also used for systemic hyperfibrinolysis associated with portacaval shunt; haematological disorders such as aplastic anaemia, *abruptio placentae*, hepatic cirrhosis, neoplastic disease such as carcinoma of the prostate, lung, stomach and cervix and bleeding after tPA.

**Contraindications**
Evidence of an active intravascular clotting process. Platelet count is usually decreased in DIC but normal in primary fibrinolysis. Protamine paracoagulation test is positive in DIC; a precipitate forms when protamine sulphate is dropped into citrated plasma. The test is negative in the presence of primary fibrinolysis. The euglobulin clot lysis test is abnormal in primary fibrinolysis, but normal in DIC. Amicar must not be used in the presence of DIC without concomitant heparin.

**Side effects**
Muscle necrosis, Clots anywhere, but no increase in CVA or AMI

**Dosage**
Plasma levels of 0.13 mg/mL apparently necessary for the inhibition of systemic hyperfibrinolysis. 16 to 20 mL (4 to 5 g) of Amicar iv infusion during first hour, followed by a continuing infusion at the rate of 4 mL (1 g/hour for eight hours or until the bleeding as been controlled). Administration of more than 30 g in any 24 hour period is not recommended. Can be given as repeat slow boli.

**Presentation**
Vial (aqueous solution), 5 g/20 mL

**COMPARE TO OTHER ANTIFIBRINOLYTICS:**
*Trasylol - Aprotinin* Serine protease inhibitor - inhibits free plasmin and other enzymes which cause inflammatory reaction. Protein extracted from bovine lung. Manufacturer claims it is Prion -save. Anaphylaxis on second use. Scavenges free plasmin rather than inhibiting the activation of plasminogen. Used for CBP surgery with increased risk of bleeding. More expensive than Amincaproic act

*Tranexamic acid - Cyclokapron* is another lysine analogue antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin. used as adjunctive therapy in haemophilia and some other bleeding disorders.

**Physiology:**
Plasmin is a proteolytic enzyme. It lyses fibrin and other proteins. Normally plasmin is generated by the action of tissue plasminogen activator (tPA) on the fibrin strand. Plasmin easily escapes from its fibrin binding site. $\alpha_2$ antiplasmin = $\alpha_2$ plasmin inhibitor ($\alpha_2$PI) is the natural plasmin inhibitor. The time-constant of the plasmin neutralization is 5 min for bound plasmin, and 0.01 second for free plasmin - the fastest enzyme in the universe. This results in little inhibition of tPA induced thrombolysis, but also little inhibition of physiological clotting (as measured by little increase of blood loss in induced bleeding).
Trials:
Meta analysis by Munoz compares aprotinin with aminocaproic acid in bypass surgery: Both drugs found to:
- reduce blood loss -35% High dose aprotinin 53% reduction blood loss.
- reduce units transfused -61%, and number of transfused patients
- less take backs (significant reduction for aprotinin only due to numbers of patients enrolled in trials)
  No effect on periop infarct or mortality.

References
1. http://mims.hcn.net.au
3. Goodman and Gillman The pharmacologic basis of therapeutics sixth ed.
DISCUSS THE MANAGEMENT OF A CHILD WITH SEVERE CROUP

Dr. J. Berkahn. Intensive Care Unit, Waikato Hospital, New Zealand

INTRODUCTION
Croup describes a clinical syndrome characterised by a coryzal prodrome, followed by inspiratory stridor, barking cough, hoarseness, respiratory distress & low grade fever. It is responsible for ~ 90% of cases of stridor outside the neonatal period & 0.5-3% of cases require ICU admission. It is usually self-limiting, is frequently caused by para-influenza viruses, and it affects children aged two months to three years, with a peak incidence in those aged 1-2 years. Although generalised upper airway inflammation occurs, the subglottic region, which is completely surrounded by cartilage and has the smallest diameter, is responsible for airway obstruction.

DIAGNOSIS
It is important to exclude other causes of stridor. Diagnosis is primarily clinical. Radiological studies occasionally demonstrate early epiglottis. In 50% of croup, PA and lateral films of the neck are characterised by symmetrical tapered narrowing of the subglottic tracheal air column (steeple or pencil sign), but this does not correlate with severity. The epiglottis and retropharynx are normal. A PA chest film will exclude a radio-opaque foreign body. In selected cases a CT scan of the neck or endoscopy may be helpful. Semi-objective scales (eg. Westley & Associates), may be useful to gauge severity, response to treatment, and also as a comparative tool for research.

MANAGEMENT OF UNCOMPLICATED CROUP
1. Laboratory tests, (incl. blood cultures & nasopharyngeal washings) are unnecessary.
2. Antibiotics are of no benefit.
3. Sedatives and narcotics should be avoided (suppress the cough reflex).
4. Nurse upright, with minimal disturbance.
5. Ensure adequate hydration & analgesia (sore throat).
6. Antipyretics (reduce fever, minute ventilation and work of breathing).
7. Pulse oximetry. (NB. hypoxaemia is a late indicator of airway obstruction, as gas exchange is normal until obstruction is severe).
8. Humidified oxygen, if required.
9. Cool nebulised mist - commonly used, but no proven benefit.
10. Corticosteroids – Have produced a 70% reduction in rates of ICU admission and intubation, they are thought to act by reducing vascular permeability and swelling with early effects apparent within ½ -2hours.

Dexamethasone:
- Most benefit was demonstrated after a single IV dose 0.06 mg/kg (maximum dose 10mg).
- Nebulised dexamethasone is not recommended, it has no benefit & may cause bacterial tracheitis & neutropenia.
- In severe croup, further 6 hourly doses of 0.15mg/kg may be given.
- Prednisolone 1mg/kg p.o. or prednisone 1mg/kg p.o. may be used.
- Nebulised Budesonide (2mg=4ml of 5%) produces improvement within two hours. It is as effective as 4 mg nebulised racemic adrenaline or 0.6 mg/kg oral dexamethasone . However as yet, nebulised corticosteroids do not constitute standard care.
11. Nebulsed Adrenaline
- Of proven benefit, reduces exudation into the tissues by stimulating alpha-adrenergic receptors to produce capillary constriction.
- There are two forms:
  i) Racemic – composed of equimolar amounts L- and D-isomers
  ii) L isomer – possesses ~3x activity of the D-isomer.
- Effective within 10 minutes, with maximum effect at 1-1½ hours and duration of action ~30 mins-2 hrs.
- Recurrence of symptoms or rebound can occur in 38% of patients 2-3 hrs after nebulisation. A minimum 3-hour period of observation is recommended. It is relatively contraindicated in heart conditions, particularly ventricular outlet obstruction.
- Dosage (up to q20mins)
  * L-adrenaline           Accurate         Approx. Quick dose
  1:1,000         0.5 ml/kg (max. 5 ml)   2.5 ml <1 year
  1 ml = 1 mg                        5 ml >1 year
  *Racemic adrenaline:
  2.25% (1.125%L) 0.05 ml/kg (max. 0.5 ml) 0.25 ml <6 months
  0.5 ml >6 months

12. Heliox:
- 60-80% helium in O2, by reducing density and viscosity reduces work of breathing. However it is of no use when > 40% O2 is required.
- Indications are controversial, but it may make intubation unnecessary by allowing corticosteroids and adrenaline time to work.

13. Laryngoscopy (under general anaesthesia with a skilled anaesthetist & in a controlled setting), should be considered where the illness is not resolving, where episodes are frequent or progressive, where there is noisy breathing between episodes, and in those with ongoing stridor who have been intubated in the neonatal period. It should be performed immediately where a foreign body (history of gagging, choking), or early epiglottitis is suspected.

14. Tracheal intubation:
- The decision to intubate is clinical. It is indicated in severe obstruction and respiratory failure. Other factors (eg. age <1yr, coexisting neonatal disease, and where transport is required), are also considered.
- With aggressive medical treatment less than 1% will require intubation.
- The endotracheal tube should be ~ two sizes (0.5 – 1.5 mm) smaller than normal.
- Deep inhalational induction, avoiding the use of muscle relaxants is preferred. In the presence of airway obstruction, inhalational induction may be prolonged.
- The endotracheal tube is prone to obstruction from secretions.
- Muscle relaxants and high dose sedation are seldom necessary, but low dose sedation may be helpful.
- Extubation is considered when there is clinical improvement, an increasing leak, and decreasing secretions.

15. Complications of croup include: otitis media, pneumonia, bacterial tracheitis, measles pneumonitis, bronchospasm, difficult intubation, pulmocardiac arrest.

References
DISCUSS THE RISKS AND BENEFITS OF INTRAVENOUS PRALIDOXIME IN A PATIENT WITH ACETYLCHOLINESTERASE POISONING

Dr. B. Curran. Intensive Care Unit, Waikato Hospital, New Zealand

Introduction
Pralidoxime is a cholinesterase reactivator.
Organophosphate (OP) compounds that are inhibitors of acetylcholinesterase (AchE) are used as insecticides and agents of chemical warfare.
Inhibition of AchE by an OP is due to phosphorylation of the esteretic site of the enzyme. After inhibition the OP-enzyme complex may simultaneously undergo several reactions:
1. Spontaneous reactivation: Velocity and degree depend on poison type
2. Ageing: Speed depends on type of poison.
3. Oxime induced reactivation: Velocity dependent on concentration of both the inhibited enzyme and the oxime, and also influenced by the oxime type.

Chemistry
Pralidoxime has been administered as the chloride, iodide, lactate, mesylate and methylsulphate salts.
Pralidoxime Iodide (PAM) Injection 500mg/20mL
Molecular weight: 264.1
Pka: 8.0
Octanol/water partition coefficient: very low

Pharmacokinetics
Poorly soluble in water, so the usual route of administration is by parenteral injection.
Not bound to plasma proteins, a quaternary ammonium compound, with poor blood-brain barrier penetration.
Volume of distribution = 0.6 l/kg
Has a half-life of 1.2 h when administered intravenously.
Excreted in urine unchanged. A small fraction of dose is metabolised to an aldehyde.

Dosage
Adults: Slow IV dose of 1-2 grams followed by infusion of 0.5 grams per hour
Children: 20-50 mg/kg as intermittent doses. An infusion 10-20 mg/kg/hr can be used after initial dose.

Benefits of Pralidoxime
Three actions have been attributed to Pralidoxime:
1. Reactivation of cholinesterase by cleavage of phosphorylated active sites.
2. Direct reaction and detoxification of un-bonded OP molecules.
3. Endogenous anticholinergic effect in normal doses.

When effective concentrations of oxime are achieved the balance between ageing and reactivation rates for the inhibited acetylcholinesterase is altered in favour of the latter. Thus benefit may continue even if oxime therapy is commenced or continued several days after poisoning.

The reactivation action of pralidoxime is most marked at the neuromuscular junction. It does not reverse the muscarinic manifestations of OP poisoning.
Oximes being ionised compounds do not cross the blood-brain-barrier easily. However limited passage of the oxime to the brain may have a small but significant clinical effect.

**Risks of Pralidoxime**

Well tolerated in healthy volunteers. Administration of loading dose over 30 min to minimize side effects such as tachycardia, laryngospasm, and muscle rigidity. Other reported adverse effects include dizziness, blurred vision, diplopia, and impaired accommodation, headache, drowsiness, nausea, tachycardia, hyperventilation, and muscular weakness (but it is very difficult to differentiate the toxic effects produced by atropine or poison from those of pralidoxime).

In large doses, pralidoxime can produce neuromuscular block and even inhibition of acetylcholinesterase.

No information is available on the safety of Pralidoxime in Pregnancy and Lactation.

Repeated dosages should be lowered for patients with renal failure.

Caution in treating overdose in cases with myasthenia gravis since it may precipitate a myasthenic crisis.

Pralidoxime is not useful in carbamate poisoning.

**Discussion**

There exists some controversy regarding the use of pralidoxime in OP poisoning, and the timing and sequence of the administration of atropine and pralidoxime.

1. **Does Pralidoxime administration improve outcome?**

   De Silva et al⁴ in a controlled trial compared atropine for treatment of OP poisoning vs. atropine and pralidoxime. No benefit from pralidoxime was found however dose of pralidoxime given was small.

   Johnson and Vale⁵ have argued that insufficient doses were used. They recommend therapeutic concentration of 4mg/L and that in severely poisoned patients an infusion of 500 mg/hr be continued until clear, irreversible, clinical improvement is achieved; this may take many days while residual poison is cleared from body stores.

   A prospective study in Iran by Balai-Mood and Shariat,⁶ compared atropine, obidoxime + atropine, and pralidoxime + atropine for OP pesticide poisoning. AchE reactivation was only observed in the pralidoxime group, although it was not statistically significant. There were no deaths in the pralidoxime group, and doses of pralidoxime used were well tolerated. (8 mg/kg followed by 2 mg/kg/hr). A high rate of hepatotoxicity was observed in the obidoxime group.

2. **What dose and target concentration of Pralidoxime?**

   Dosage depends on both the type of OP and the oxime used.

   A recommended target concentration of 4 mg/L has been shown to be effective only when using pralidoxime mesylate. This concentration was subsequently regarded as the reference value for all oximes.

   Extrapolation of dosage to other oximes may not be valid.

   Altered pharmacokinetics in poisoned patients may result in higher levels due to changes in haemodynamics, particularly the reduction in renal blood flow produced by intoxication with organophosphorous esters.

3. **What is the optimal duration of pralidoxime treatment?**

   Optimal duration of Pralidoxime therapy is influenced by the ageing rates of various poisons. In daily practice, however the poison involved is often unknown and the respective kinetic data
are usually not available, while immediate treatment is mandatory. Serial measurements of RBC AchE can be used as a guide for the continuation of oxime treatment.

References
2. Schexnayder S, James L et al. The Pharmacokinetics of Continuous Infusion Pralidoxime in Children with Organophosphate Poisoning Clinical Toxicology, 36, 6,549-555, 1998
DISCUSS THE MANAGEMENT OF A PATIENT WITH ANAEMIA (Hb 70g/L) AND CONGESTIVE CARDIAC FAILURE

Dr K. Vidhani. Intensive Care Unit, Liverpool Hospital, New South Wales

Introduction
Anaemia causes well-described physiological responses of the cardiovascular system: these will be modified in the presence of congestive cardiac failure. The presence of hypo through to hypervolaemia according to cause and the level of haemoglobin (Hb) which provides optimal oxygen delivery will govern the management of these patients. A haemoglobin level of 100g/L has been previously accepted as the trigger for transfusion, however recent work suggests that a lower level may be acceptable in the critically ill and hence lead to a reduction in transfusions and their well documented associated risks. The sub-population of patients with cardiopulmonary limitations has less well described evidence and may exhibit increased risk.

There exists a spectrum of scenarios in which the patients may present including the patients with congestive cardiac failure who develop anaemia and those, whose anaemia leads to cardiac failure. Identification and management of the acutely ill deteriorating patient requiring a rapid assessment of the airway, breathing and circulation with concurrent resuscitation takes priority before less urgent interventions are made in the stable patient.

Oxygen delivery is defined by the equation:
\[
D_{O_2} = \text{Cardiac Output (C.O) x (SaO}_2\text{xHb x 1.34)}
\]
The consequences of a reduction in Hb are as listed:
Sympathetic stimulation causing ↑ Heart Rate and ↑ contractility
- ↑ Oxygen extraction
- ↑ Vascular tone
- ↓ Viscosity leading to pre-load and after-load changes.

All these effects will be less well tolerated in the patient with cardiac failure.
The consequences of reduced cardiac output are:
- Myocardial ischaemia
- ↑ Oxygen consumption
- Activation of Neuro-humeral response
  - Renin angiotensin system
  - A.D.H

These effects will be exacerbated by anaemia.

Management

Unstable patient
A. Secure the airway-intubation may be necessary.
B. Invasive or non-invasive ventilation if patient unable to maintain oxygen saturation > 95% or becoming hypercarbic.
C. Achieve a mean arterial pressure normal for that patient-inotropes after assessment of volume status may be necessary.

Stable patient
Assessment of volaemic status
1. Hypervolaemia eg. Chronic renal failure
These patients usually have a dilutional normochromic, normocytic anaemia due to excessive free water not cleared by the kidneys as well as poor production from lack of erythropoietin. Ultrafiltration of fluid and use of erythropoietin is the management of choice. Blood transfusion would exacerbate the fluid overload and reduce oxygen delivery.

2. Normovolaemia eg. valve disruption and myocardial ischaemia
The anaemia maybe haemolytic in nature as a consequence of turbulent blood flow. The volume status of the patient would be unchanged and treatment would be directed at valve repair or replacement. Transfusion of red cells in this situation would cause hypervolaemia and exacerbate the ongoing process.

3. Hypovolaemia eg. Acute bleed leading to ischaemia
Blood transfusion is the treatment of choice in this group of patients where cardiac failure is a result of ischaemia through lack of filling and oxygen delivery and may result from blood loss of any source or gross fluid loss eg. burns victims. In this patient I would transfuse them sufficient units of packed cells to achieve treatment endpoints which would include a normal mean arterial pressure sufficient to provide end-organ perfusion judged by indices such as urine output and acid base status along with myocardial ischaemia (E.C.G changes.)

Conclusion
Clear evidence does not exist for the level of Hb in patients with cardiovascular compromise. Management must be guided by underlying diagnosis, duration of onset of the conditions and treatment endpoints of organ perfusion.

References
DISCUSS THE DIAGNOSIS AND MANAGEMENT OF THE ACUTE CORONARY SYNDROME

Dr. B. Turner. Intensive Care Unit, The Alfred Hospital, Victoria

Definition
Unstable angina and non ST elevation myocardial infarction are acute coronary syndromes that form a spectrum with stable angina and ST elevation myocardial infarction.

Early Risk Stratification

<table>
<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td><strong>Prior IHD / CVD</strong></td>
<td><strong>New onset angina in past 2 weeks</strong></td>
</tr>
<tr>
<td>• accelerating tempo of symptoms in past 48 hours</td>
<td>• prior aspirin use</td>
<td></td>
</tr>
<tr>
<td>• &gt; 20 mins of rest pain</td>
<td>• &gt; 20 mins of rest pain now resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &lt; 20 mins rest angina, or resolved with GTN</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Examination</strong></th>
<th><strong>Age &gt; 70 years</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• pulmonary oedema / rales</td>
<td>• Age &gt; 70 years</td>
<td></td>
</tr>
<tr>
<td>• changed MR murmur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• S3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• hypotension, bradycardia, tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• age &gt; 75 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ECG</strong></th>
<th><strong>T wave inversion &gt; 0.2mV</strong></th>
<th><strong>Normal / unchanged ECG</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• angina at rest with transient &gt; 0.05mV ST deviation</td>
<td>• T wave inversion &gt; 0.2mV</td>
<td></td>
</tr>
<tr>
<td>• new BBB</td>
<td></td>
<td></td>
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<tr>
<td>• VT</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiac Markers</strong></th>
<th><strong>Slightly elevated CKMB, troponin I or T</strong></th>
<th><strong>Normal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• markedly elevated CKMB, troponin I or T</td>
<td>• Slightly elevated CKMB, troponin I or T</td>
<td></td>
</tr>
</tbody>
</table>

**Note**
- 33% of patients may not have chest pain on presentation
- Examination may be normal
- If presentation is < 6 hours after symptom onset, myoglobin or CKMB subforms should be measured
- Troponin remains elevated for 7-10 days; CKMB for 72 hours
In-Hospital Treatment

**Oxygen**

*Nitroglycerin* - sublingual then intravenous
- symptom relief
- no evidence for reduced MI or mortality

*Morphine* - for symptom control, pulmonary congestion or agitation

*β-blockers* - intravenously then orally if tolerated and no contraindications
- 13% reduction in MI

**Calcium channel antagonists** - for symptom control if maximum β-blockade and GTN
- non-dihydropyridines if β-blockers contraindicated
- dihydropyridines increase mortality without β-blockers

**ACE Inhibitors** - for patients with acute MI, recent MI, LV systolic dysfunction and high risk CAD
- if hypertension is not controlled with β-blockers and GTN

**Antiplatelet therapy**
- Aspirin - first choice
  - > 50% reduction in mortality in unstable angina
- Clopidogrel - first alternative to aspirin
  - takes days for maximum effect
- Ticlopidine - alternative to aspirin
  - 2.4% incidence of neutropaenia
- Gp IIb / IIIa receptor antagonists
  - antibody (abciximab), synthetic peptide (eptifibatide), non-synthetic peptides (tirofiban, lamifiban)
  - role in refractory ischaemia despite aspirin and heparin
  - prevent complications with percutaneous interventions
  - relative efficacy unclear

**Anticoagulants**
- Unfractionated heparin - decrease rate of death and MI by 50-60% with aspirin
  - after 48 hours risk : benefit profile less favourable
- LMW heparin - ease of use
  - enoxaparin superior to unfractionated heparin
  - lower incidence of thrombocytopaenia

**Antithrombolytics**
- no role without ST elevation, true posterior MI or new LBBB

**Risk Stratification**
- non-invasive stress testing in - low risk patients free of ischaemia and CHF at rest for ≥ 12 hours, or
  - intermediate risk without symptoms for 2-3 days
- exercise stress testing if patient can exercise, else pharmacological stress required
- ECG monitoring if changes in ST segment are interpretable, else require imaging
- angiography without non-invasive investigation for failure of medical therapy
- investigation of LV function with echocardiogram or left ventriculogram
Early Conservative versus Invasive Strategies

Early invasive strategy for

- patients with recurrent or refractory symptoms, CHF, high risk findings on non-invasive stress testing, reduced LV function, haemodynamic instability, VT, percutaneous intervention within 6 months, prior CABG
- patients > 65 years of age with ST depression or elevated cardiac markers without contraindication to revascularisation

Revascularisation

- **CABG** for - left main disease
  - 3 vessel disease
  - 2 vessel disease including LAD, and either abnormal LV function or positive stress test
  - 1-2 vessel disease (not including LAD) with viable myocardium and positive stress test (PCI is alternative management)

- **PCI** - suitable coronary anatomy and normal LV function without diabetes

In low risk patients with failed medical therapy, consider revascularisation.

References

DISCUSS THE MANAGEMENT OF A PATIENT WITH MRSA AORTIC VALVE ENDOCARDITIS

Dr. K. Lui. Intensive Care Unit, Queen Elizabeth Hospital, Hong Kong

MRSA aortic valve endocarditis
• can occur in patients with native or prosthetic aortic valve (early or late infection)
• can be acquired either from community or from hospital.

The management of patient with MRSA aortic valve endocarditis includes:
1. establishment of the diagnosis
2. supportive therapy and antibiotic treatment
3. surgical intervention if indicated

Diagnosis
Diagnosis of MRSA aortic valve endocarditis is based on careful history and physical examination, blood culture and laboratory results as well as other appropriate diagnostic investigations.

History:
Risk factors should be sought including:
♦ previous history of structural heart disease (degenerative aortic valve)
♦ history of rheumatic carditis involving aortic valve
♦ presence of prosthetic aortic valve
♦ intravenous drug abuse
♦ previous history of infective endocarditis
♦ history of central venous catheter insertion
♦ cellulitis or skin abscess
♦ historical clues pointing towards a recent source of bacteremia

Clinical symptoms include:
♦ fever
♦ malaise/weakness
♦ anorexia
♦ weight loss
♦ arthralgia
♦ cardiac or neurological symptoms
The duration and tempo of the illness should also be noted. Acute endocarditis usually presented with acute onset of symptoms, chills and fever, while subacute endocarditis characterized by vague illness occurring over a period of several weeks and months.

Physical examination:
The physical examination should look for:
♦ new aortic regurgitant murmur
♦ changing aortic murmur
♦ petechiae over conjunctiva, buccal mucosa, toes and fingertips
♦ splinter haemorrhage
♦ Janeway lesion
Osler nodes
♦ Roth spots
♦ splenomegaly
♦ congestive heart failure
♦ focal neurological impairment

Fingertip, subungal, conjunctival and retinal lesions all developed in acute staphylococcal endocarditis.

Prosthetic valve endocarditis has higher rate of congestive heart failure and conduction disturbances than patients with native valve do.

Complications:
Particular attention should be made to look for complications associated with MRSA aortic valve endocarditis. These include:

♦ Congestive heart failure due to aortic insufficiency, vegetation-induced stenosis of coronary ostia causing myocardial infarction.
♦ Abscess and paravalvular extension of infection causing conduction blockade, aneurysm/pseudoaneurysm, aortic valve dissection
♦ Neurological complications include acute encephalopathy, meningocerebralitis, purulent or aseptic meningitis, embolic stroke, cerebral haemorrhage or brain abscess
♦ Higher risk of systemic embolization of vegetation causing stroke, blindness, painful ischaemic/frankly gangrenous extremities
♦ Metastatic abscess
♦ Septic arthritis and osteomyelitis

Positive blood culture result:
A minimum of three blood cultures should be obtained over a time period based on the severity of illness. Each set of cultures should be obtained from separate venipuncture sites.

Additional laboratory tests:
Other laboratory tests include
♦ raised ESR or elevated C-reactive protein
♦ normochromic normocytic anaemia
♦ leukocytosis: commonly occur in patients with staphylococcal endocarditis
♦ abnormal urinalysis like microscopic or gross haematuria, proteinuria or pyuria.

However, these findings are relatively nonspecific

ECG:
ECG rarely showed diagnostic finding but should be performed as initial evaluation. The presence of changes suggestive of ischaemia or infarction may provide clues to the presence of emboli in the coronary circulation.

In aortic valve disease, especially on prosthetic valve, serial ECG should be used to monitor for abscess development. Changes such as persistent prolongation of PR interval, new or persistent bundle branch block or complete heart block are quite specific for predicting extension to myocardial or aortic root tissue.

Echocardiogram:
Echocardiogram is performed to:
1. characterize the underlying valvular lesions
2. clarify the destructive nature of endocarditis
3. assess for evidence the perivalvular extension of infection
4. assess valvular function in prosthetic valve endocarditis

Transthoracic echocardiograph (TTE) (two-dimensional) has an overall sensitivity of 70% for detecting vegetation. Limitations include obesity, chronic lung disease, thoracic deformity and artifacts from prosthetic valves.

Transoesophageal echocardiograph (TEE) has a higher sensitivity of detecting vegetation (overall 87%) and detecting complication such as extravalvular extension of infection.

In patients with prosthetic valve in aortic position, TEE should be either directly proceeded or performed after TTE because:
1. acoustic shadowing frequently present
2. superior spatial resolution of TEE
3. increase risk of endocarditis in these patients with bacteremia

Supportive therapy
Supportive therapy should be given to patient who develops respiratory or cardiac failure. These include:
♦ oxygen therapy ± ventilatory support
♦ inotropic support & diuretic therapy
♦ fluid replacement
♦ nutritional supplement.
Complications should also be treated accordingly.

Antibiotic treatment
The effective antibiotic treatment of MRSA aortic valve endocarditis is vancomycin. Regimen depends on the presence of native or prosthetic aortic valve.

Patient with native aortic valve:
♦ monotherapy with vancomycin for four to six weeks is usually adequate
♦ dosage is 30 mg/kg per 24 hours intravenously in equally divided doses not to exceed 2 g/24h unless serum level is monitored

Patients with prosthetic aortic valve:
♦ combination therapy with intravenous vancomycin and oral rifampin for six to eight weeks is usually employed
♦ Gentamicin is also recommended for the first two weeks of this therapeutic regimen
♦ Rifampin is recommended because of the greater nephrotoxicity of vancomycin-aminoglycoside combination, but emergence of rifampin resistance has been documented.
♦ dosage of vancomycin is similar to that for patients with native valve.
♦ dosage of rifampin is 300 mg orally every eight hours.
♦ dosage of gentamicin is 1 mg/kg intramuscularly or intravenously every 8 hours.

Assessment of treatment efficacy:
♦ Vancomycin level should be monitored during treatment
♦ Minimal bactericidal concentration has been used to guide therapy
**Surgical intervention**

Surgical interventions include debridement of vegetation, aortic valve repair or replacement. Surgery should be considered when:

1. Progressive or significant heart failure due to aortic insufficiency
2. Echocardiographic evidence of premature closure of mitral valves
3. Persistent bacteremia after one week despite appropriate antibiotics
4. Persistent fever after one week despite appropriate antibiotics and exclusion of other causes of fever
5. Extravalvular extension of infection
6. Resistant microorganisms (to vancomycin)
7. Prosthetic valve dehiscence or obstruction
8. More than one emboli events

**References**

2. UpToDate, Vol. 8, No. 3, [www.uptodate.com](http://www.uptodate.com)
SUMMARY: DISCUSS THE MANAGEMENT OF A PATIENT WITH MRSA AORTIC VALVE ENDOCARDITIS

MRSA aortic valve endocarditis:
♦ native valves or prosthetic valve
♦ community or hospital acquired

Ask for:
Risk factors:
♦ Structural heart disease
♦ Rheumatic carditis
♦ Prosthetic aortic valve
♦ IV drug abuse
♦ Central line insertion
♦ Cellulitis or skin abscess
♦ Recent bacteremia

Symptoms:
♦ Fever
♦ Malaise/weakness
♦ Anorexia
♦ Weight loss
♦ Arthralgia
♦ Cardiac/neurological symptoms
♦ Duration

Look for:
Signs:
♦ New/changing aortic murmur
♦ Petechiae: conjunctiva, buccal mucosa, toes & fingertips
♦ Splinter haemorrhage
♦ Janeway lesion
♦ Roth spots
♦ Osler nodes
♦ Splenomegaly
♦ Congestive heart failure
♦ Focal neurological signs

Complications
♦ CNS infection, stroke, haemorrhage
♦ Systemic embolisation
♦ Metastatic abscess
♦ Septic arthritis, osteomyelitis
♦ Aortic insufficiency, AMI
♦ Paravalvular extension
Positive blood culture:
♦ 3 cultures, different time, different sites

Additional tests:
♦ ↑ ESR, ↑ C-reactive protein
♦ NCNC anaemia
♦ Leukocytosis
♦ Haematuria, proteinuria, pyuria
♦ ECG
♦ Echocardiograph
  (TTE, TEE)

Treatment:
♦ Supportive
♦ Antibiotic:
  Native valve: Vancomycin 4-6 wks
  Prosthetic: Vanco + Rifampin + Gentamicin
♦ Surgery
  Indications:
  1. Structure failure
  2. Persistent infection
  3. Extension of infection
  4. Resistant organism
  5. Multi-emboli
DISCUSS THE REASONS FOR ‘DAILY DOSE’ GENTAMICIN

Dr. P. Lane, Intensive Care Unit, Townsville General Hospital, Queensland

Aminoglycosides are well established antibiotics in the treatment of serious gram negative infections. They have become increasingly important in the treatment of gram positive infections through synergistic activity with the beta-lactam agents. To maximise anti-bacterial efficacy and to minimise toxicity, various drug regimens and methods of monitoring serum concentration have been proposed. In recent times, through the results of meta-analyses of important clinical trials, once-daily dosing for aminoglycosides has become increasingly prescribed.

The results of recent trials in immunocompetent and immunocompromised patients indicate that once-daily dosing is at least as efficacious as multiple daily administration, with no increase in nephrotoxicity or ototoxicity. Aminoglycoside toxicity is related to cumulative systemic exposure as well as underlying risk factors such as renal impairment. Nephrotoxicity is due to accumulation of high doses in the renal cortex, with direct toxicity to proximal renal tubule cells. It is apparent that saturable receptors are present, such that saturation with a high peak serum level, followed by a prolonged trough of aminoglycoside to obtain a very low trough level, results in less nephrotoxicity in the once-daily regimen. The risk of nephrotoxicity is not eliminated with the once-daily regimen. Ototoxicity is also dependent on the concentration of accumulating aminoglycoside or a metabolite in the cochlear hair cells and vestibular apparatus. Whilst renal impairment is an important factor in the acute management of patients there does tend to be recovery, however permanent loss of hearing and vestibular function can occur.

For Gentamicin, an adult once-daily dose of 4-7mg/kg (to maximum 360mg) is recommended in the ‘normal’ patient, with a trough of less than 1mg/L. A continuous infusion of a relatively low dose aminoglycoside induces the most nephrotoxicity.

Aminoglycosides display concentration dependent killing, have a ribosomal site of action and a significant post antibiotic effect. The bactericidal profile of the aminoglycosides is biphasic. The first peak involves interaction of the positively charged antibiotic and the negatively charged lipopolysaccharide cell membrane, the efficacy proportional to the concentration of the antibiotic. The slower second peak involves internalisation and binding to bacterial ribosomes with subsequent inhibition of protein synthesis. The post antibiotic effect is a laboratory phenomena which describes ongoing bacterial killing after a culture of bacteria is exposed to an aminoglycoside then washed to remove the antibiotic. This is due to internalisation and may explain the safety of allowing the concentration of aminoglycoside to fall below the MIC of the organism.

Gram negative bacteria, especially pseudomonas, develop adaptive resistance to aminoglycosides. Following the post antibiotic effect, there is a period of resistance to aminoglycoside killing. Barclay et al using a dynamic in vitro model, found that the development of adaptive resistance was directly proportional to the concentration of the drug the bacteria was exposed to, with partial return of sensitivity by 24 hours and fully reversed by 36-43 hours. Adaptive resistance becomes evident 3-6 hours after administration of aminoglycosides, and doses given during this period have no antibacterial effect. Therefore, dosing should allow sufficient area under the curve for optimal killing and subsequent sufficiently low trough levels for the adaptive resistance to reverse. Currently there are no aminoglycosides in clinical use with a very short half life which would ideally suit this proposed model.
Synergy with the beta-lactam agents in the treatment of serious gram positive infections such as enterococcal endocarditis is becoming increasingly important. The aminoglycosides also display synergism with the beta-lactams against pseudomonal species. Whilst there are minimal human studies, animal studies reveal that multiple daily doses of aminoglycoside are superior for this clinical indication. Current clinical regimens reflect this.

There are a number of patient populations for which the data on once-daily dosing of aminoglycosides is lacking. They include pregnant women, sepsis, burns, ascites, renal failure, and patients with meningitis, endocarditis and osteomyelitis. If once-daily dosing is used for these patients then additional monitoring and observation of efficacy and toxicity is required. Patients with altered pharmacokinetics of drug clearance such as renal impairment and/or increased volume of distribution as in sepsis, require individualised monitoring and dose determination. The clinician must establish the best peak aminoglycoside level to MIC ratio for the pathogen in the particular clinical setting. The administration of safe drug therapy must not be overshadowed by the practical and economic incentives of once-daily dosing.

A greater understanding of the pharmacokinetics and pharmacodynamics of the aminoglycoside antibiotics has lead to the once-daily treatment regimens that are widely used by clinicians. This regimen improves efficacy without increasing toxicity and has practical and economic advantages over multiple daily dosing. There remains a group of patients with conditions including sepsis, burns, renal impairment and meningitis where the clinician must establish individualised regimens for administration and monitoring of efficacy and toxicity to ensure safe drug therapy.

References
LIST THE INDICATIONS AND COMPLICATIONS OF INTRA-AORTIC BALLOON PUMP

Dr. C. Schneider. Intensive Care Unit, Middlemore Hospital, New Zealand

1. Physiology: counterpulsation improves LV performance through a favourable influence on myocardial oxygen balance. Myocardial oxygen supply is improved by diastolic augmentation of coronary perfusion. Systolic deflation of the balloon reduces the impedance to left ventricular ejection thereby leading to a reduction in oxygen requirement for contraction. Improved cardiac output leads to better endorgan perfusion.

2. Indications
   2.1 Ischaemic heart disease
      - unstable angina refractory to medical therapy as support during balloon angioplasty or while awaiting CABG
      - myocardial infarction associated with cardiogenic shock, if amenable to revascularization. Massive infarction with loss of > 40 % of myocardium is usually associated with poor prognosis, therefore IABP is not beneficial.
      - myocardial infarction associated with rupture of papillary muscle or septum in preparation for surgery
      - critical left main coronary artery stenosis: insertion of IABP preoperatively may reduce frequency of ischaemic events in immediate pre-bypass period or as support during angioplasty
      - failed angioplasty as support prior to emergency CABG
      - refractory ventricular arrhythmia’s associated with ischaemia
   2.2 Post cardiopulmonary bypass pump failure
      - expected or unexpected difficulties in weaning from CPB (prolonged clamp/bypass time, inadequate myocardial protection, graft failure)
   2.3 Cardiac transplant recipients
      - ventricular dysfunction associated with prolonged ischaemia times
   2.4. Any other potentially reversible cause of cardiogenic shock
      - myocardial contusion
      - acute viral myocarditis
      - acute mitral incompetence associated with endocarditis
      - severe poisoning with negative inotropic substances

3. Contraindications
   3.1 Absolute: aortic regurgitation/ dissection
   3.2 Relative: coagulopathy, occlusive peripheral vascular disease extreme tachycardia/arrhythmia where timing is difficult irreversible ventricular dysfunction untrained staff

4. Complications
   4.1 Arterial cannulation; haematoma/haemorrhage, damage to surrounding structures, false aneurysm, a-v fistula
   4.2 Passage of wire/dilator/IABP: arterial perforation, dissection
   4.3 Presence of IABP:
      - limb ischaemia (diabetes, females, PVD, sheathed insertion)
      - infection (rare but high mortality)
- thrombosis/embolism from balloon or aorta
- thrombocytopenia/haemolysis (rare)
- balloon rupture and gas embolism (rare)
- incorrect timing/positioning

References
DEFINE AND DISCUSS THE DIAGNOSIS AND MANAGEMENT OF VENTILATOR-ASSOCIATED PNEUMONIA

Dr. S. Nolan, Intensive Care Unit, Royal Prince Alfred Hospital. New South Wales

Definition
Ventilator-associated pneumonia (VAP) is defined as parenchymal lung infection occurring more than 48 hours after initiation of mechanical ventilation. This definition can be further refined to include early onset and late onset VAP which carries prognostic information.

Epidemiology of VAP
- Accounts for almost half of the ICU infections
- Incidence of VAP ranges from 6 to 52 cases per hundred patients
- Crude rate of VAP is 1-3%/day of intubation and mechanical ventilation
- Overall rate of 10-15 cases per 1000 ventilator days
- Extends ICU stay by approximately 4 days
- Is the most common infection acquired in the intensive care unit and has a mortality of 24-71%

Pathogenesis
The pathogenesis of ventilator-associated pneumonia usually requires that 2 important processes take place: bacterial colonisation of the aerodigestive tract and the aspiration of contaminated secretions.

Risk factors for developing VAP
- Fixed (1st impaired mucociliary clearance of lungs)
  - Underlying cardiorespiratory disease
  - Neurologic injury (head injury)
  - Burn patients
  - Trauma
  - Duration of ventilation
- Modifiable
  - Supine body position
  - Witnessed aspiration
  - Paralytic agents
  - Antibiotic exposure
  - Failed extubation and re-intubation
  - Frequent ventilator circuit changes
  - Overuse of sedative drugs

Diagnosis
Despite extensive studies diagnosis of VAP remains a subject of controversy. The diagnosis of VAP is usually made by a combination of clinical and microbiological criteria using a variety of sampling techniques such as: Transbronchial aspirates, protected specimen brush and bronchoalveolar lavage.

Clinical
CXR: New, progressive or persistent (>24 hrs) infiltrate (necessary)
1. Fever > 38.3°C or hypothermia < 36°C
2. Purulent endotracheal aspirate
3. Leukocyte count >10 000/mm$^3$ or < 4 000/mm$^3$

NB: Need CXR changes and 2 or more of the above criteria to make a clinical diagnosis of VAP$^3$,$^6$,$^7$

- If one needs all four criteria to be present for the diagnosis of VAP specificity improves but sensitivity drops to below 50%$^4$
- Clinical diagnosis is inaccurate in up to 33% of cases so microbiological confirmation is needed$^7$,$^{10}$
- Clinical manifestations can be used for initial screening for VAP but clinical suspicion is as sensitive and specific as any fixed objective set of criteria$^4$

Microbiological

*Histological pneumonia* is said to be present when >10$^3$ cfu/g of lung tissue associated with an intense accumulation of neutrophils (Often used as the gold standard)

**Methodology used to diagnose VAP on microbiological grounds**

1. Transbronchial aspirate (10$^5$ cfu/ml)
2. Bronchoalveolar lavage (10$^4$ cfu/ml)
3. Protected specimen brush (10$^3$ cfu/ml)

**Transbronchial Aspirate**

Usually identifies organisms found by more invasive tests
Often recover multiple organisms (including non-pathogens)
If negative unlikely to have VAP unless prior antibiotic therapy
Studies have shown sensitivity (38-100%) and specificity (14-100%)

**Bronchoalveolar Lavage**

BAL technique has not been standardized within the literature
Sensitivity (22-100%; mean=73%), Specificity (45-100%; mean=82±19%)
Not diagnostic in 25% or wrong in 20% of cases
Detecting intracellular organisms has a high positive predictive value

**Protected-Specimen Brush**

Gram stain may provide an early guide to therapy
Sensitivity (33->95%; median 67%), Specificity (50-100%; median 95%)

Invasive procedures will result in the isolation of a pathogen in approximately 50% of cases
No evidence to suggest more invasive procedures result in an improved rate of diagnosis or mortality in VAP

**Microbiology Of VAP**

The pathogens associated with VAP can be conceptually divided into early-onset (up to day 4) and late-onset (after day 4).
**Early Onset Pathogens** (Community-Acquired pathogens)
- Streptococcus pneumoniae
- Haemophilus influenzae
- Moraxella catarrhalis
- Anaerobes (less common)

**Late Onset Pathogens** (Hospital-acquired, Inducible gram negatives)
- Pseudomonas aeruginosa
- Acinetobacter spp
- Staphylococcus aureus (MRSA)
- Multiple organisms (1st gram –ve: E Coli, Serratia, Enterobacter etc)
- Often have multi-drug resistance (MDR) profiles

**Management of VAP**

**Selection of Antibiotic** (Fig 1)
- Antibiotic cover should be given early after infection is suspected
- Antibiotics chosen should address all reasonably suspected pathogens
- Studies have shown that a need to change antibiotics after culture data identifies a subgroup of patients with a higher mortality\(^2\,^8\)
- Single most important decision is whether antibiotic cover should include antimicrobials against resistant organisms (Pseudomonas spp, Acinetobacter spp etc). Such organisms usually occur late and in the presence of previous antibiotic therapy\(^3\,^7\)
- Important to use multiple drugs as monotherapy has been associated with a 15-30% clinical failure rate\(^3\,^7\)
- Empirical antibiotic selection should be cognizant of local bacterial resistance patterns and the heightened risk of inadequate therapy in the more severely ill patient\(^7\)

![Figure 1. Selection of Antibiotic](image-url)
Avoiding Antibiotic Resistance

- Should encourage judicious use of antibiotics
- Extended-spectrum lactam drugs are particularly likely to induce resistance
- Should use narrowest spectrum drugs after culture and sensitivity and cease drugs when infection has been excluded
- Crop rotation of antibiotics used for empirical therapy

Table 1 Proposed strategies to prevent pulmonary nosocomial infections

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Relative importance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hygiene</td>
<td>++</td>
<td>Antimicrobial soaps may be more effective than unmedicated (prospective multiple crossover trial)</td>
</tr>
<tr>
<td>Heat and moisture exchangers</td>
<td>++</td>
<td>Reduced incidence of nosocomial pneumonia (randomised trials, meta-analysis) but caution as increased endotracheal secretions (randomised risk)</td>
</tr>
<tr>
<td>Selective digestive decontamination</td>
<td>++ (especially in trauma patients)</td>
<td>Reduced respiratory tract infections (meta-analysis) but risk of bacterial resistance remains a problem (prospective survey)</td>
</tr>
<tr>
<td>Subglottic drainage</td>
<td>++</td>
<td>Reduced incidence of nosocomial pneumonia (randomised trial, meta-analysis)</td>
</tr>
<tr>
<td>Single-recumbent position</td>
<td>++</td>
<td>Reduces aspiration of gastric contents (randomised crossover trial)</td>
</tr>
<tr>
<td>Avoidance of H₂ blockers</td>
<td>+</td>
<td>May be of some benefit in reducing nosocomial pneumonia (meta-analysis) but increased risk of gastrointestinal bleeding</td>
</tr>
<tr>
<td>Kinetic beds</td>
<td>+</td>
<td>Reduced incidence of nosocomial pneumonia (randomised controlled trial) but not well tolerated by some patients</td>
</tr>
<tr>
<td>Exchanging lung response</td>
<td>++</td>
<td>Reduces risk of infection (meta-analysis); jejunal feeding may be preferable (randomised trial); immune supplements foods may provide more protection (randomised trial)</td>
</tr>
<tr>
<td>Early enteral nutrition</td>
<td>++</td>
<td>Remains experimental</td>
</tr>
</tbody>
</table>

Prevention Of VAP (See Table 1)

Strategies aimed at preventing ventilator-associated pneumonia usually focus on reducing the burden of bacterial colonisation in the aerodigestive tract, decreasing incidence of aspiration or both

- Simple measures such as hand-washing with antimicrobial soap and use of disposable gowns and aprons during patient contact
- Kinetic beds (recumbent instead of supine position)
- Decreased use of sedatives and antibiotics
- Initiation of early nutrition (malnutrition is immunosuppressive)
- Greater use of non-invasive ventilation techniques
- Changing ventilator circuits every seven days
- Use of H&H as opposed to humidifying circuits (definitive trials lacking)
- Selective digestive decontamination
  - Benefit in trauma patients/liver transplantation/oesophagectomy
    - Marginal benefit
    - Risk of inducing bacterial resistance
- Minimize the systematic use of H₂-receptor antagonists
- Use of ETT allowing sub-glottic suctioning (Evac tube)
• Orotracheal instead of nasotracheal intubation
• Role of jejunal feeding tube as opposed to naso-gastric tube?
• Role of cytokines (interferon-gamma, G-CSF, IL-12), await further research.

References
DISCUSS THE DIAGNOSIS AND MANAGEMENT OF AMNIOTIC FLUID EMBOLISM

Dr. P. Whyte. Department of Critical Care Medicine, Flinders Medical Centre, SA

Incidence

Amniotic fluid embolism (AFE) was first described in 1926 and remains one of the most lethal and unpredictable complications of pregnancy occurring in the setting of a disrupted barrier between the amniotic fluid and the maternal circulation. It is responsible for approximately 10% of maternal deaths in the USA with a reported incidence of 1:8,000-1:80,000 deliveries. Fifty percent of patients die within the first hour and the overall maternal mortality is approximately 85%, secondary to cardiopulmonary collapse or uncontrolled haemorrhage related to disseminated intravascular coagulation (DIC).

Clinical Presentation

The clinical presentation is characteristically abrupt. It occurs during labour, in the immediate postpartum period and during second trimester evacuation procedures. The syndrome is characterized by dyspnoea, cyanosis and hypotension, followed by DIC in 40% of cases. However, bleeding may be the initial presentation in 10-15%. An altered neurological state may progress to coma. Grand mal seizures occur in 10-20%. Pulmonary oedema is observed in 24-70% of cases.

Differential Diagnosis

The differential diagnosis includes haemorrhagic shock, thromboembolism, air embolism, aspiration pneumonitis, eclamptic convulsions, local anaesthetic toxicity, anaphylaxis and acute heart failure.

Risk Factors

Risk factors were believed to include age, parity and augmented labour. These have not been confirmed in subsequent studies. Strong contractions are associated with decreased communication between maternal and placental circulations and the uterine tetany, commonly associated with AFE and thought to be responsible for transfer of fetal material, is more likely a response to profound hypoxia.

A consistent factor in the development of AFE is a tear in the fetal membranes. This may follow spontaneous or artificial membrane rupture or insertion of intrauterine pressure catheters. The three most common sites of entry into the maternal circulation are the endocervical veins, the placental bed, and a uterine trauma site.

Pathophysiology

Traditionally AFE was believed to result from an abnormal volume of amniotic fluid entering the maternal circulation or the physical blockage of the maternal pulmonary circulation by fetal debris. It has more recently been suggested that disruption of the fetomaternal barrier allows transfer of amniotic fluid derived humoral substances leading to an anaphylactic type reaction to fetal antigens. The roles of endothelin, arachidonic acid and leukotrienes are being investigated. It has been suggested that the syndrome be renamed anaphylactoid syndrome of pregnancy.
Detection

Fetal Squames

Detection of fetal squames in the maternal pulmonary circulation either at autopsy or from a pulmonary artery catheter is not pathognomonic. The amount of particulate matter found in the pulmonary vasculature has not been consistently related to clinical findings, fetal squamous cells may routinely enter the venous circulation of pregnant women and differentiation of maternal and fetal squames is problematic.4,6

Monoclonal Antibody

TKH-2 is a monoclonal antibody directed against mucin derived from amniotic fluid and although normally found in maternal serum during pregnancy, it can be markedly elevated in cases of AFE.6 Its accuracy and usefulness in the acute setting have not been evaluated.

Clinical

In the absence of a rapid and reliable test, the diagnosis of AFE must be made on the basis of clinical signs and laboratory findings. The national registry devised by Clarke4 required four of the following:

1. Acute hypotension or cardiac arrest
2. Acute hypoxia
3. Coagulopathy
4. Absence of other explanations
5. Onset during labour or within 30mins of delivery or surgical abortion.

Management (ABC)

Inotropes

Acute left ventricular dysfunction is the primary haemodynamic insult. Therefore inotropes are commonly required and where medical management has failed, intraaortic balloon pumps and extracorporeal membrane oxygenation have been used successfully.8 Overhydration must be avoided in these patients who are predisposed to pulmonary oedema.

Coagulopathy

Platelets, fresh-frozen plasma, cryoprecipitate, and red cell transfusion may all be required.

Steroids

In a review of AFE, 41% of patients had a history of atopy and the authors suggest the use of IV hydrocortisone.4

Outcome

Outcome is universally poor. In Clarke's registry maternal mortality was 61%, with an intact survival in 15%. Seventy-nine percent of the fetuses in utero at the time of the collapse survived but only 50% were neurologically intact. In the presence of meconium or a dead fetus no patient survived neurologically intact suggesting that an associated substance may provoke a more severe reaction. Uncomplicated second pregnancies have been reported.2

References


101
DISCUSS THE MANAGEMENT OF A PATIENT WITH CLOSED HEAD INJURY AND AN INTRACRANIAL PRESSURE > 25 MMHG

Dr. T. S. Browne. Intensive Care Unit, Queen Elizabeth Hospital, SA

Introduction
Closed head injuries cause brain ischaemia when raised intracranial pressure decreases cerebral perfusion pressure.

\[ CPP = MAP - ICP \] (or CVP, if CVP > ICP)

The lesions caused by ischaemic events are only partially redeemable as there is little forewarning to the disease and the process is usually well established when clinicians intervene. It is unlikely that a single line of treatment is going to prevent cellular death or restore cell function.

The continuous monitoring of ICP is of great value. Prolonged levels of ICP greater than 25 mmHg are associated with a very poor prognosis. The outcome in head injury is better if ICP greater than 15 – 20 mmHg is managed aggressively.

MONITORING

Initial assessment
The initial resuscitation (ABC) of the head injured patient is vital to ensure adequate oxygen delivery to the brain. Following this a secondary survey is carried out to ascertain other injuries and to decide on the priorities of treatment.

Further history relating to mechanism of injury, seizures, drugs/alcohol, medication and pre-existing medical conditions should be sought. A baseline neurological examination consisting of assessment of GCS, pupils, motor function, airway protection and cardiac rhythm is vital as a head injury is a dynamic process, which evolves with time. All patients with a GCS < 8 will need intubation and urgent neurosurgical assessment. A head CT scan is the most informative radiological technique. Intracranial mass lesions occur in 40 – 60 % of severe head injuries.

Monitoring
Routine monitoring includes ECG, MAP, SaO\(_2\), ETCO\(_2\) and ABG. Once intracranial mass lesions are excluded, then raised ICP in head injuries is due to vasodilatation, cerebral oedema, or a combination of both. Measurements of ICP (to calculate CPP) are essential to try to maintain CPP. SjO\(_2\) (via retrograde jugular vein catheterization) and CBF velocity (using transcranial Doppler) can assist in optimizing therapy.

MANAGEMENT
Once immediate and surgically amenable intracranial problems have been rectified the aims of management becomes:

Constant observation
If GCS decreases or pupil signs change then causes must be sought.

Patient position
The patient must be nursed in a 30 – 40 degrees head-up position with the head in a neutral plain to allow venous drainage. This will facilitate a decrease in ICP.
Cerebral oxygen delivery
This is achieved by ensuring adequate PaO₂ (>80mmHg), Hb (>100 G/l) and normal cardiac output. The critical CPP is about 70 mmHg.

Reduction in ICP
The plan here is to rapidly reduce ICP. These techniques are only effective for up to about 48 hours. During this time the stabilizing treatments should have been commenced and become effective.

Rapid onset treatments
**Hyperventilation:** This is very effective and rapid. The patient must be intubated and ventilated with increased minute volumes. A target PaCO₂ of 25 mmHg is optimal. Removing too much CO₂ can cause cerebral vasoconstriction and worsen ischaemia.

**Bolus osmotic treatments:** This can be initiated with mannitol (0.25 – 1.0 g/kg), glycerol, urea, hypertonic saline or THAM buffer. For this treatment to be effective the blood brain barrier must be intact. By causing an osmotic diuresis fluid is drawn from the brain tissue resulting in shrinkage of the brain and reduction in ICP.

Stabilizing treatments
**Osmotherapy:** The above treatment can be repeated 6 hourly and is usually effective for 3 – 5 days before tachyphylaxis occurs. Once stabilized, Osmotherapy should be withdrawn gradually to avoid rebound cerebral oedema.

**Other:** Dexamethasone 4 – 10 mg 4 – 6 hourly is unlikely to be of any benefit in ischaemic or traumatic cerebral oedema. Barbiturate coma and mild early hypothermia may be beneficial.

Surgical treatments
**Cerebral masses:** Any intracranial haematoma must be drained.

**Removal of CSF:** CSF can be withdrawn from an intraventricular catheter to reduce ICP. This is more useful for obstructive hydrocephalus than traumatic raised ICP.

**Bony decompression:** Alteration of the cranial vault will reduce ICP, but this is not widely advocated.

Other experimental therapies to protect brain
Aims to prevent secondary brain injury by NMDA receptor blockers or by blocking free radical production (allopurinol, superoxide dismutase inhibitors) or by scavenging free radicals (dimethyl sulfoxide, mannitol, deferoxamine) have not been promising.

Antibiotics
Prophylactic antibiotics are not recommended for skull fractures. Anti-tetanus toxoid should be administered.

Treatment of epileptic seizures
Seizures lead to increase in cerebral oxygen demand, and uncontrolled jerking will raise ICP. The seizure should be stopped with a barbiturate or benzodiazepine, and then the patient loaded with phenytoin (15 mg/kg).
Stress ulcer prophylaxis
Should be considered while feeding is pending.

Nutrition
Early feeding is recommended.

Other aspects
Temperature control
- Mild hypothermia is neuroprotective.
- Fever should be aggressively diagnosed and treated, as it will increase cerebral oxygen demand.
SIADH or Diabetes insipidus
- may follow head injury.
Coagulopathy
- Should be treated aggressively to prevent further intracranial bleeds.

Physiotherapy
Chest physiotherapy and pressure care may have to be withheld to avoid unnecessary increases in ICP. The patient should be given a muscle relaxant to prevent coughing before suctioning.

Family
Keep family well informed of patient’s condition and likely prognosis. They often need explanation of the therapy to feel reassured that everything is being done to ensure the best outcome.

References
DISCUSS THE INDICATIONS AND COMPLICATIONS OF MUSCLE RELAXANTS, SEDATIVE AND ANALGESIC AGENTS USED TO SETTLE A MECHANICALLY VENTILATED PATIENT

Dr. C. Fagan. Intensive Care Unit, Royal Perth Hospital, WA

Introduction
Critical illness is often associated with a combination of pain and anxiety associated with both the illness itself and its treatment. Pain and anxiety commonly exist in combination in such patients and the effect of drugs used to treat them frequently overlap. Sedatives and analgesics are almost always used to settle a patient requiring mechanical ventilation during a critical illness and less commonly a muscleparalysing agent is required. The role of muscle relaxants will be discussed first.

Muscle Relaxants
Indications:
Muscle relaxants or neuromuscular blocking agents (NMBAs) paralyse skeletal muscles by blocking the transmission of nerve impulses at the myoneural junction. NMBAs have no sedative, amnestic or analgesic properties. NMBAs are indicated as an adjunct to sedation and analgesic agents in the following circumstances:

1) To improve patient-ventilator synchrony (increase chest wall compliance, prevent poorly co-ordinated respiratory movements, reduce peak airway pressures, and facilitate permissive hypercapnia) despite adequate sedation and analgesia, therefore enhancing gas exchange and diminishing the risk of barotrauma.¹
2) NDMAs have a specific role in reducing peak airway pressures in severe bronchospasm due to either acute asthma or chronic obstructive airways disease where sedative agents alone are inadequate.
3) To reduce muscle oxygen consumption and the work of breathing (this has the added advantage of reducing patient temperature if this is desirable).
4) To prevent respiratory or other movements, and coughing on tracheal suction in patients with increased intracranial pressure.
5) To facilitate treatment and mechanical ventilation (by reducing muscle tone) in medical conditions such as tetanus, neuroleptic malignant syndrome, status epilepticus and malignant hyperthermia.
6) In combination with sedatives and analgesics to facilitate ventilation in the prone position where patient movement is particularly undesirable and potentially hazardous.
7) Sedatives and analgesics may result in hypotension in critically ill patients and the use of muscle relaxants can reduce the amount of these agents required. (i.e. allow patient synchrony with a ventilator at a light level of sedation)

Complications:
The NMBAs are used to settle a patient receiving mechanical ventilation. Atracurium, cisatracurium, vecuronium, rocuronium and pancuronium are commonly used agents. Of these vecuronium, rocuronium and cisatracurium are associated with a minimal risk of hypotension, atracurium with a moderate risk and pancuronium is associated with a moderate risk of tachycardia, hypertension and increased cardiac output due to vagal blockade. Intensive Care Unit (ICU) staff must be trained in the administration and monitoring of NMBAs. Patients require an endotracheal tube (or tracheostomy) and a mechanical ventilator. Adequate sedation
and analgesia are essential prior to the initiation of NMBA therapy as patients are unable to indicate they are distressed or in pain. The following list summarises these complications and how they may be avoided:

1) Death. Patients cannot be left unsupervised because interruption of the ventilator circuit can be fatal.
2) Ventilator associated pneumonia. All NMBAs inhibit the cough reflex, suctioning of the endotracheal tube to remove accumulated secretions should be performed as needed based on the amount of secretions present.
3) Corneal abrasions due to absent eyelash reflex. Apply artificial tears 2-hourly to cornea and tape shut.
4) Skin breakdown and decubitus ulcers. Patients require frequent turning and drying, ensure wrinkle free bedding. Peripheral nerve damage can occur.
5) Deep venous thrombosis. (Prophylaxis)
6) Pulmonary aspiration. (Raise the head of the bed to reduce risk)
7) Impaired assessment of neurological status. Pupillary reflexes should be closely monitored.
8) Prolonged weaning from ventilatory support. (see below)

Prolonged paralysis following drug discontinuation results from accumulation of drug and/or active metabolises, or an acute myopathy. With the exception of atracurium and cisatracurium most of these drugs rely on renal clearance and their effect can be prolonged in renal disease. NMBAs with active metabolises include pancuronium, vecuronium and atracurium. Prolonged paralysis may result from an NMBA-associated syndrome of acute myopathy with selective loss of myosin filaments. Most reported cases have occurred after combined treatment with corticosteroids and NMDAs, suggesting the myopathy is the result of an interaction between the two drugs. The risk of this complication can be minimised by limiting the administration of NMDAs to 48-hours or less. In addition, corticosteroids should not be administered for uncertain or unproven indications during administration of an NMBA.

**Sedation and Analgesia**

**Indications**

Critical illness alone is associated with a high level of patient distress which manifests itself as agitation, defined as excessive motor activity associated with internal tension and anxiety, defined as a sustained state of apprehension and autonomic arousal in response to real or perceived threats. Sedatives are often given to such patients in the (ICU) receiving mechanical ventilation to alleviate their anxiety, and when necessary combined with an opioid analgesic to provide adequate analgesia in the setting of a noxious insult such as trauma or surgery. It is worth noting that the presence of an endotracheal tube in itself is a noxious stimulant and unpleasant. In critically ill and ventilated patients poorly treated anxiety and pain will result in untoward physiological responses such as increased sympathetic tone, protein catabolism, increased plasma catecholamines, prostaglandins, growth hormone, prolactin, anti-diuretic hormone, cortisol and glucagon. Theses physiological responses may contribute to organ ischaemia, fluid and electrolyte imbalance and decreased wound healing. Grimacing, withdrawal, combativeness, diaphoresis, hyperventilation and tachycardia are all clinical manifestations but are often difficult to assess with accuracy.

Benzodiazepines and opioid analgesics have formed the mainstay of sedative and analgesic agents in ICU in recent years. Propofol has an established role but it is expensive without any proven advantage. All provide sedation, amnesia, anxiolysis, some reduction in muscle tone
(facilitating mechanical ventilation) and a reduction in agitation, opiates also provide analgesia. Analgesics and sedatives like muscle relaxants facilitate mechanical ventilation by improving patient-ventilator synchrony by improving chest compliance and inhibiting the patients respiratory centre. They contribute to a reduction in muscle oxygen consumption and reduce respiratory or other movements such as coughing on tracheal suction in patients with increased intracranial pressure. By inhibiting the respiratory centre they facilitate novel therapies such as permissive hypercapnia. The level of sedation should be recorded for example using the Ramsay scale and a level of 2-3 is desirable to settle a patient on mechanical ventilation (calm, slightly sleepy and easily awakened and responds to commands). Deeper levels of sedation maybe required in severe pulmonary disease or haemodynamic instability and the addition of a muscle relaxant is a clinical decision. In severe pulmonary disease a deep level of sedation will minimise oxygen consumption, maximise chest compliance and reduce peak airway pressures which have been associated with a poorer outcome in patients with Adult Respiratory Distress Syndrome (ARDS).5

Complications
Sedatives have been have been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital.7 Sedation to facilitate mechanical ventilation limits the physicians ability to interpret clinical signs, this is of particular importance in patients with neurological/neurosurgical disease. A recent study where daily sedative infusions were interrupted decreased the duration of mechanical ventilation and stay in ICU.8 Benzodiazepines cause respiratory and cardiac depression and those that undergo oxidative reduction (diazepam, midazolam) are particularly influenced by aging, hepatic dysfunction and drug-drug interactions. Tolerance (increased dosage requirement with continued administration) is a problem with all benzodiazepines.

All opiates share common side effects. These include depression of brainstem control of respiratory drive, hypotension, nausea and vomiting. Histamine release with morphine may produce flushing, tachycardia, hypotension, and bronchospasm. Gastrointestinal transit time slows with prolonged administration, resulting in constipation and ileus in many patients, making the establishment of enteral feeding more difficult. This effect is thought to reflect binding to local opiate receptors in the gut.9 Morphine may have a prolonged effect in patients with renal impairment due to the accumulation of morphine-6-glucuronide, an active metabolite.

Patients receiving receiving sedatives and analgesics must be closely observed for symptoms of withdrawal when these drugs are discontinued or reduced. Symptoms include increased agitation, confusion and anxiety. In a study involving 28 mechanically ventilated patients requiring greater than one week of intensive care found that 9 (32%) developed acute withdrawal symptoms.10 Small doses of lorazepam or clonidine may facilitate gradual withdrawal.

References
DISCUSS THE CLINICAL FEATURES OF BACTERIA ENDOCARDITIS AND WHAT INVESTIGATIONS YOU WOULD USE TO CONFIRM IT

Dr. N. McNeillis. Intensive Care Unit, The Canberra Hospital, ACT

Introduction
Infective endocarditis is a disease that produces vegetations on the endocardium. It is due to any microorganism infecting the endocardium of the heart. It usually affects the heart valves but can affect other parts of the endocardium. It is fatal if left untreated. There are various classifications that can be used. The first has three categories: native valve, prosthetic valve and intravenous drug abuse (IVDA) infective endocarditis. The second classification is into acute and subacute infective endocarditis. They are useful as in general they have different infecting organisms and different clinical courses. The most important classification is based on organism because this has implications for treatment and clinical course.

Acute endocarditis
More virulent organisms usually cause acute endocarditis, often affecting normal valves (Staphylococcus aureus, Streptococcus pneumoniae, β-haemolytic streptococcus and Neisseria gonorrhoeae). The clinical course is short and rapidly destructive and produces metastatic foci with a high mortality rate. If untreated it is fatal within six weeks. It needs early aggressive treatment.

Subacute endocarditis
This is usually caused by less virulent, commensal organisms on damaged valves and runs a more indolent course (staphylococcus epidermis or streptococcus viridans). It does not produce metastatic foci and if left untreated takes longer to be fatal.

Aetiology
Normal cardiac valves are resistant to colonization by microorganisms. Damage to the endocardium due to scarring secondary to, for example rheumatic fever, or direct trauma due to turbulent flow, leads to platelet and fibrin deposition (nonbacterial thrombotic endocarditis). This renders the tissue venerable to colonization by circulating microorganisms.

Clinical features
The principle features of infective endocarditis are temperature and cardiac murmur. It can present in a variety of ways depending on the effect on the valve, arterial embolisation by vegetations, bacteremia with metastatic infection, the virulence of the organism and whether it left or right sided heart lesion.

The infecting organism largely determines clinical presentation. With pyogenic organisms such as S.aureus the disease is acute and fulminant, with a high fever, multiple metastatic abscesses, peripheral embolic events, rapid valve destruction and a high mortality.

The subacute form accounts for two thirds of cases and usually either viridans streptococci (oropharyngeal commensal) or enterococci (genitourinary commensal), which can commonly occur after an invasive procedure causing a transient bacteraemia, affecting susceptible valves. Symptoms are usually insidious with anorexia, weakness, weight loss, night sweats and arthralgia and so may be incorrectly diagnosed as a malignancy or connective tissue disease. Acute and subacute presentations represent the extremes of a continuum. There is considerable overlap.
The physical findings can provide important diagnostic clues. Nearly all patients have a fever. Heart murmurs are common especially left sided (easier to hear). A new or changing murmur has particular significance. Cutaneous manifestations are more commonly found in more indolent presentations of infective endocarditis and include petechiae, which appear on the conjunctiva, palate, buccal mucosa and extremities. Osler nodes are pea sized painful nodular lesions in the pads of the fingers and toes. Janeway lesions are haemorrhagic, macular, flat, painless plaques on the palms and soles usually found in acute staphylococcal infections. Roth spots are pale, oval retinal lesions with a peripheral area of haemorrhage found near the optic disc. Splinter hemorrhages are subungual, linear, reddish brown streaks in the fingers and toes. If the disease is prolonged then clubbing is a feature. Splenomegaly occurs the longer the duration of the illness.

Musculoskeletal symptoms are common and appear early in the disease and may be the presenting symptom. Neurological symptoms are relatively common and may dominate the clinical picture. They range from transient ischaemic attacks (due to embolic events), subarachnoid hemorrhages (due to rupture of mycotic aneurysms), and symptoms due to space occupying lesions, seizures, visual changes, choreoathetoid movement, mononeuropathy, cranial nerve palsies and toxic encephalopathy.

Major embolic events occur more commonly with acute endocarditis due to virulent organisms or fungal infective endocarditis (due to large vegetations). Splenic infarcts cause left upper quadrant pain, pleural rub and left pleural effusion. Embolic can lodge in mesenteric artery causing an acute abdomen, or distal artery causing acute limb ischaemia. Pulmonary emboli arise from right heart endocarditis in IVDA leading to haemoptysis, pleural rub and shortness of breath.

Coronary emboli occur leading to myocardial infarction. Congestive cardiac failure may be the predominant presentation secondary to valve dysfunction, myocarditis or myocardial infarction.

Uraemia was a common presenting feature but is rarely seen now. Glomerulonephritis is common and secondary to immune complex deposition.

**Diagnosis**

A high index of suspicion is an important prerequisite, especially in the fulminant acute endocarditis, as a missed diagnosis can be fatal. The pyrexial IVDA is another important subgroup.

The detection of bacteremia with blood culture is the single most important investigation. Bacteremia is usually continuous and low grade in the subacute form and high grade in the acute form. In patients who eventually have a positive culture the first is positive 80% of the time, the second 89% and the third 99% of the time. Therefore three culture, drawn at three separate sites and on three different occasions.

The next most important investigation is echocardiography, particularly transoesophageal echocardiography (TOE). TOE is particularly powerful at diagnosing valve ring abscesses, mycotic aneurysms, prosthetic valve abnormalities and small vegetations. It allows for haemodynamic assessment of cardiac function and valve dysfunction. It is particularly important in the intensive care and intraoperatively. It provides prognostic information related to the risk of embolisation, congestive cardiac failure, the need for surgery and the risk of death.

Minor laboratory finding suggestive of infective endocarditis include the presence of normochromic, normocytic anemia, a leucocytosis in acute disease and a leucopenia in the subacute presentation. The erythrocyte sedimentation rate is nearly always raised. Rheumatoid
factor is present in the majority, which have symptoms over six weeks. Finally, examination of
the urine may reveal proteinuria, microscopic haematuria and red cell castes.

References
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DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF SALICYLATE POISONING

Dr. D. Lowe. Intensive Care Unit, StVincent’s Hospital, New South Wales

Clinical Features

CNS       Agitation, tremor, confusion, obtundation, seizures
RESP      Tachypnoea
GI        Nausea, vomiting, epigastric pain
HAEM      ↑ PT
            Platelet dysfunction
METABOLIC Respiratory alkalosis - initially
            - often masked by CNS depression and respiratory
              acidosis in mixed overdose / noncardiogenic
              pulmonary oedema / fatigue from hyperventilation
Metabolic acidosis - uncoupling of oxidative phosphorylation
Fever
Electrolyte abnormalities - ↑ or ↓ K+, ↑ or ↓ glucose
Dehydration - secondary to fever, tachypnoea, vomiting

Management

Airway
Breathing
Circulation
Repeat Charcoal
Salicylate Levels
- < 3.5 mmol/L    mild
- 3.5 - 5 mmol/L  moderate
- > 5 mmol/L      severe
Rehydration
Cooling
Alkalisation
- ↑ blood pH → more ionised therefore less lipid soluble
- ↑ urine pH → more ionised therefore more water soluble and hence ↑ urinary
  excretion
- requires hyperventilation or iv bicarbonate
- acetazolamide produces metabolic acidosis therefore more salicylate enters
  tissues i.e counter productive
- aim urine pH 7.5 - 8.0
- blood pH < 7.55 (to avoid left shift O2-Hb dissociation curve)
Haemodialysis - small molecule therefore effective
- indications: level > 5 mmol/L
  renal failure (cant eliminate - avoid bicarbonate)
  CCF - avoid excess volume i.e i.v. bicarbonate.
DISCUSS THE INDICATIONS FOR INTRAVENOUS POTASSIUM ACETATE

Dr. E. Hughes. Intensive Care Unit, North Shore Hospital, New Zealand

Potassium acetate (KAc) is a solution made up of potassium ions with an acetate buffer base. The main indication for intravenous (IV) KAc replacement is hypokalemia with renal tubular acidosis (RTA). RTA is a disorder characterised by excessive urinary loss of bicarbonate, a normal anion gap, and an elevation of serum chloride. Essentially KAc in RTA provides replacement potassium without aggravating the renal tubular acidosis or the hyperchloremia. In RTA up to 100 - 200 mM of K⁺ may need to be given in 24 hours to correct hypokalemia. If KCl was given as replacement instead of KAc this amount of Cl⁻ ion would worsen RTA but if renal function deteriorates further then the hypokalemia usually is self correcting.

In ICU practice RTA is usually seen in the setting of generalised proximal tubular dysfunction due to drug toxicity e.g. immunosuppressants and antifungals (cyclosporine, amphotericin). Distal tubular RTA can occur with systemic illness such as sjogrens syndrome, lupus or multiple myeloma. The RTA of renal transplantation can occur with proximal or distal tubular dysfunction.

RTA is classified into the three types depending upon the site of the defect in the renal tubule. Both type 1 and type 2 can cause severe hypokalemia but type 4 causes hyperkalemia.

In type 1 RTA, the distal tubule fails to acidify the urine. Failure of urinary acidification is diagnosed if the urine pH fails to drop below 5.4 following an oral load of ammonium chloride (0.1 mg/Kg NH₄Cl) in a fasted subject. Calcium phosphate stones, osteomalacia and rickets are associated with type 1 RTA. Inherited disorders such as galactosemia, medullary sponge kidney and Ehler-Danlos syndrome are also associations, as are some systemic disorders such as lupus, multiple myeloma and sjogrens syndrome.

In type 2 RTA, the proximal tubule reabsorption of bicarbonate (HCO₃⁻) is defective so that large amounts of HCO₃⁻ overwhelm the absorbptive capacity of the distal tubule. Type 2 RTA is often seen as a result of drug induced renal toxicity. In children growth may be impaired if alkali is not given to correct the metabolic acidosis.

In type 4 RTA, also called hyperkalemic distal RTA, distal tubule secretion of both potassium and hydrogen ions is abnormal, resulting in a hyperchloremic acidosis with hyperkalemia. Type 4 RTA can be caused by Addison’s disease, urinary tract obstruction, diabetes, interstitial nephritis, spironolactone, triamterene, amiloride, non-steroidal anti-inflammatory drugs and cyclosporin.
DISCUSS THE INDICATIONS FOR AND COMPLICATIONS OF NON-INVASIVE VENTILATION IN ACUTE RESPIRATORY FAILURE

Dr. S. Sviri. Intensive Care Unit, The Sir Charles Gairdner Hospital, WA

<table>
<thead>
<tr>
<th><strong>Indications</strong></th>
<th><strong>Selection Guidelines</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstructive lung disease</strong></td>
<td><strong>Symptoms and signs of ARF</strong></td>
</tr>
<tr>
<td>- COAD</td>
<td>- moderate to severe dyspnoea</td>
</tr>
<tr>
<td>- Asthma</td>
<td>- RR&gt;24, accessory muscles</td>
</tr>
<tr>
<td>- Cystic Fibrosis</td>
<td>paradoxical breathing.</td>
</tr>
<tr>
<td>- Upper airway obstruction</td>
<td></td>
</tr>
<tr>
<td>- Sleep apnea</td>
<td></td>
</tr>
<tr>
<td><strong>Restrictive lung disease</strong></td>
<td><strong>Abnormal gas exchange</strong></td>
</tr>
<tr>
<td>- Chest wall deformity</td>
<td>- PaO2/FiO2 &lt; 200</td>
</tr>
<tr>
<td>- Neuromuscular disease</td>
<td>- PaCO2 &gt; 45 mmHg, pH &lt; 7.35</td>
</tr>
<tr>
<td>- Obesity hypoventilation</td>
<td></td>
</tr>
<tr>
<td><strong>Parenchymal</strong></td>
<td><strong>Modes</strong></td>
</tr>
<tr>
<td>- Pneumonia</td>
<td>CPAP, PSV+PEEP, BiPAP</td>
</tr>
<tr>
<td>- ARDS</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiogenic</strong></td>
<td><strong>Masks</strong></td>
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<tr>
<td>- Pulmonary edema</td>
<td>Nasal, oronasal (full-face)</td>
</tr>
</tbody>
</table>

**Contraindications**
- Cardiac or respiratory arrest
- Medically unstable (hypotension, cardiac ischaemia, arrhythmia)
- GI bleeding, vomiting
- Severe upper airway obstruction
- Unable to protect airway, risk of aspiration
- Excessive secretions
- Uncooperative or agitated
- Facial trauma, burns or surgery
- Anatomical abnormalities interfering with mask fit

**Complications**

<table>
<thead>
<tr>
<th><strong>Mask related</strong></th>
<th><strong>Possible remedy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- discomfort 30-50%,</td>
<td>- Check fit, new mask</td>
</tr>
<tr>
<td>- skin erythema 20-34%,</td>
<td>- Loosen strap, artificial skin</td>
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<tr>
<td>- claustrophobia 5-10%, nasal bridge ulceration 5-10%</td>
<td>- Smaller mask, artificial skin</td>
</tr>
<tr>
<td><strong>Air pressure or flow related</strong></td>
<td></td>
</tr>
<tr>
<td>- nasal congestion 20-50%, sinus/ear pain 10-30%</td>
<td>- Nasal steroids &amp; decongestants</td>
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<tr>
<td>- nasal/oral dryness 10-20%</td>
<td>- Add humidification</td>
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<tr>
<td>- eye irritation 10-20%</td>
<td>- Check mask, readjust straps</td>
</tr>
<tr>
<td>- gastric insufflation 5-10%</td>
<td>- Reduce pressure if possible</td>
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</tbody>
</table>
Air Leak 80-100%

Major complications
- Aspiration pneumonia <5%
- Hypotension <5%
- Pneumothorax <5%

- Encourage mouth closure, Oronasal mask, chin straps
- Careful patient selection
- Reduce pressures
- Thoracostomy tube if required
DISCUSS THE DIAGNOSIS AND EMERGENCY MANAGEMENT OF A PATIENT WITH A HIGH SPINAL FRACTURE

Dr. D. Evans. Intensive Care Unit, The Women’s and Children’s Hospital, SA

Aetiology of Spinal Injury (USA data)

- 45% Automobile Accidents
- 20% Falls
- 15% Diving/Sports Injury
- 15% Violence
- 5-10% Paediatric

Cervical Spine is the most mobile section of the spine and the most commonly injured (about 2/3 of injuries)

- Cervical spine injury (CSI) occurs primarily at two levels 1/3 at C2 and ½ at CC6 or C7

In major trauma 1.9 to 5% of patients will have CSI

Patients with Cranial or facial fracture are not at increased risk of CSI

Diagnosis

Should be suspected in patients with major trauma or patients with minor trauma with spinal pain or motor or sensory symptoms or in patients with distracting injuries or altered mental state

Guidelines

1. Alert, awake, not intoxicated, neurologically normal, no midline neck pain or tenderness even with full range of motion of neck and palpation of cervical spine
   a. Cervical spine X-rays not necessary
2. Awake alert and complains of neck pain
   a. 3-view cervical spine X-rays (lateral, AP and odontoid) are obtained
   b. 3mm axial CT of suspicious areas
   c. If above are normal voluntary lateral flexion/extension c-spine X-rays
   d. If unable to voluntary flex/extend greater than 30 degrees replace cervical spine collar and repeat X-rays in 2 weeks.
3. Neurologogic deficits referable to a spinal injury.
   a. Plain films and CT as above
   b. MRI of cervical spine
4. Altered level of consciousness or other causes which leave the patient unable to complain of neck injury or neurological defecits
   a. 3-view X-rays and supplementary CT as above
   b. Fine cut CT trough C1 and C2
   c. If above normal can consider patient has a stable cervical spine

A subsequent review by the same authors suggested in group 4 an incidence of 5/227 (2.2%) of occult CSI missed by the above method. These injuries were detected by flexion extension radiography. No spinal cord injury was documented during these studies. They concluded that flexion extension fluoroscopy with neck movement done an appropriate senior medical officer

In paediatrics clearance of the spine is complicated by Spinal Cord Injury Without Radiological Abnormality SCIWORA this accounts for 20-60% of spinal injury 30 – 50% of children with SCIWORA will have complete neurological loss
Management

Prevent Further Neurological injury

Spinal Immobilization
Indicated in trauma patients who have an injury mechanism that could potentially cause spinal injury and one of the following:
- Complains of neck pain
- Altered mental state or evidence of intoxication
- A distracting painful injury (e.g. long bone fracture)
- Neuroligical deficits
- Palpation tenderness

A hard cervical collar does provide some restriction decreasing movement by only about one third and is poor at controlling rotational movement. The best method was use of a short spinal board, Philadelphia collar and sandbags.

Steroids
Intravenous high dose methylprednisolone given within 8 hours of injury has been advocated since the publication of NASICS 2.
This study has been criticized as differences were only found on post hoc analysis of subgroups on non-clinical criteria and improvements in neurological score were not borne out in functional improvement.
A systematic review of 3 clinical trials and 6 cohort studies concluded that the use of high dose methylprednisolone could not be supported and a deleterious effect on early mortality and morbidity could not be excluded.

Prevention of complications from neurological deficits

Airway
Airway management is complicated by need to maintain neutral position and prevertebral swelling making intubation technically more difficult.
Indications include
- Apnoea
- Hypoventilation
- GCS <9
- Uncontrollable patient

The technique used is dependent on the skills and experience of the operator. Nasal techniques e.g. awake fibreoptic or blind nasal may be contraindicated by the suspicion of base of skull or midface fractures. They also can result in significant coughing and bucking. Standard rapid sequence induction may be more appropriate.

The use of manual in line stabilization, not traction, using a two-person technique appears to be the best way to minimize iatrogenic injury during intubation.

Respiratory
Anoxia/hypoxia is the commonest and pneumonia the second most common cause of death in acute spinal cord injury.
Degree of respiratory embarrassment is dependent on the injury level (this may be higher than the level of the fracture)
Phrenic paralysis C3,4,5 leaves only accessory muscles and causes severe hypoventilation
Lesions above T7 are associated with intercostal and abdominal muscle paralysis and significant reduction in pulmonary function
Pulmonary oedema is common in CSI patients presumably contributed to by over enthusiastic volume resuscitation
Pulmonary embolism is also a significant cause mortality and morbidity

**Cardiovascular**

Experimental models suggest an initial phase of abrupt increase in MAP possibly due to increased sympathoadrenal outflow. This is associated with increases in cerebral blood flow intracranial pressure and blood-brain barrier permeability and increased extra vascular lung water. This may explain the observation that pulmonary and cerebral oedema occurs more commonly in these patients.
Loss of systemic sympathetic vasomotor tone may result in vasodilatation, increased venous capacity and hypotension.
Loss of the cardio accelerator fibers (T1-4) produces bradycardia
Treatment is with judicious fluid loading and vasopressors and inotropes as required.

**Other Systems**

Abdominal trauma is difficult to diagnose clinically
25–65% have significant associated trauma
Loss of sympathetic tone and loss of shivering results in impaired temperature regulation and a tendency to become poikilothermic.

**References**

DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF THE SEROTONIN SYNDROME

Dr. D. Murphy. Intensive Care Unit, St Vincent’s Hospital, Victoria

The serotonin syndrome is a disorder caused by the use of drugs or combinations of drugs that increase serotonin availability. It is thought to be due to drug induced excess of intrasynaptic 5-hydroxytryptamine. It most often occurs when two or more drugs that increase serotonin availability are used in conjunction. It can occur following therapeutic usage or overdose.

The following classes of drug may be implicated:
1. Drugs increasing serotonin synthesis- L -tryptophan
2. Drugs inhibiting serotonin metabolism- meclobemide, MAOIs, isocarbazide, selegeline
3. Drugs increasing serotonin release-amphetamine, cocaine, fenfluramine, MDMA, reserpine
4. Drugs inhibiting serotonin re-uptake
   a) SSRIs
   b) TCADs
   c) Other serotonin reuptake inhibitors- NMDA, pethidine, cocaine.
5. Direct serotonin agonists – busperidone, LSD, sumatriptan
6. Non-specific increase in serotonin – ECT, lithium
7. Dopamine agonists – amantadine, bromocriptine, bupropion, levodopa.
8. Other drugs implicated include fentanyl, tramadol, carbamazepine

CLINICAL FEATURES

Clinically, it shares many features with the neuroleptic malignant syndrome (NMS). Unlike NMS it is due to a direct toxic effect and not an idiosyncratic reaction. It typically presents with
1. CNS disturbance- confusion, agitation
2. Autonomic features- diaphoresis, tachycardia
3. Neuromuscular dysfunction- myoclonus, hyperreflexia.
Severe cases can develop disseminated intravascular coagulation, acidosis, respiratory failure, rhabdomyolysis, renal failure and ARDs.
The diagnostic criteria described by Sternbach include at least three of the following features: mental state changes (hypomania, confusion), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.
Other aetiologies must be ruled out and the patient must not have started or increased the dose of a neuroleptic prior to the onset of effects.
There is no laboratory test to confirm the diagnosis.

TREATMENT

Treatment is predominantly supportive. The offending drug or drugs should, of course, be discontinued. The management includes general supportive measures including intubation, circulatory support, sedation and paralysis as necessary, aggressive active cooling measures and organ support as indicated. Benzodiazepines (diazepam, lorazepam) may be used to control seizures. Parenteral antihypertensive therapy may be necessary. If the serotonin syndrome occurs in the setting of a recent overdose gastric decontamination and activated charcoal may be useful.

Animal studies and case reports detailing the use of specific serotonin antagonists have been described but these are controversial. To date there is no effective drug treatment established.
Cyproheptadine is an antihistamine with both antiserotonergic and anticholinergic properties. Case reports of the use of cyproheptadine have detailed varying efficacy possibly because the dose used (4-8 mg 4 hourly) was not sufficient to ensure blockade of brain 5-HT receptors for which dose of up to 20-30 mg would be necessary. There is some evidence from case reports for the use of chlorpromazine. Dantrolene can increase brain serotonin as can bromocriptine and both these agents are contraindicated.

References
DISCUSS THE MANAGEMENT OF A CARDIAC TAMPOONADE AND HOW YOU WOULD PERFORM A PERICARDIAL TAP

Dr. D. Collins. Department of Critical Care Medicine, Flinders Medical Centre, SA

Cardiac Tamponade is defined as compression of the heart by fluid within the pericardial sac, so that it impairs filling of the ventricles;¹ Alternatively it has been defined as hemodynamic abnormalities induced by the accumulation of pericardial fluid with compression of the heart throughout diastole.² Echocardiographically the most common definition is compression of the right atrium during diastole.³

Pathophysiology

The normal pericardium has two layers; the visceral and parietal layers which envelope the heart, they are fibrous structures with limited elastic capabilities whose function in normal circumstances is to limit ventricular distension. Between the two layers there is approximately 20 to 35 ml of serous fluid whose function is to minimise friction.

The pressure-volume relationship of the pericardial sac is curvilinear, initially when additional fluid accumulates in the space, pressure rises slowly, however, additional fluid beyond a certain point will result in a rapid rise in pressure. In acute situations tamponade can be precipitated by as little as 200 ml of fluid. However in chronic situations such as a slowly accumulating pericardial effusion, the parietal layer is stretched gradually and thereby accommodating much larger volumes and may not reach its critical point on the pericardial pressure-volume curve until 2000 ml or even more fluid has accumulated.

According to Spodick 3 prerequisites must be met for clinically significant cardiac compression to evolve. The pericardial contents must:
• fill the relative small pericardial reserve volume,
• thereafter increase at a rate exceeding the stretch rate of the parietal pericardium; and
• exceed the rate at which the venous blood volume expands to support the small normal pressure gradient for right heart filling.⁴

Therefore in tamponade as fluid enters the pericardial space, the pericardial pressure which is normally 0 mmHg and less than the right ventricular end diastolic pressure (RVEDP), rises steadily to equilibrate with the right ventricular pressure. Up to this point, cardiac output and pressures do not change. With further accumulation of fluid in the pericardial space, pericardial and right ventricular pressures rise in equal increments to equilibrate with the left ventricular end diastolic pressure (LVEDP), which is normally higher than the right side.

Aetiology

Many processes may result in the accumulation of pericardial effusions, they can roughly divided into two major categories however;

Traumatic: This refers to situations where there is a rapid accumulation of blood. Tamponade evolves rapidly because as the bleeding does not stop spontaneously and the pericardial space cannot expand acutely to accommodate the extra volume. Most traumatic tamponade is the result of stab wounds to the heart, in this case the pericardial perforation seals itself and decompression is consequently prevented. About 80% to 90% of stab wounds to the heart demonstrate tamponade, compared with only 20% of gunshot wounds. Gunshots produce larger pericardial perforations that often do not seal themselves off and generally drain into the pleural space producing a hemothorax.

Nontraumatic: This refers to the accumulation of an exudate or transudate in the pericardial space. These nontraumatic effusions are frequently large as their gradual development permits
the pericardium to stretch, preventing rapid rises in intrapericardial pressure. When tamponade does occur, it develops more slowly, medical patients most frequently develop this type of effusion and there are a multitude of causes. The medical causes of pericardial effusion with potential tamponade are common and may be summarised under the following headings:

- Neoplastic.
- Uremic.
- Connective tissue disease.
- Infective.
- Haemorrhagic
- Idiopathic

**Clinical features**

Patients with cardiac tamponade are generally acutely ill and appear distressed and dyspnoeic with a rapid pulse and respiration. Symptoms most commonly described are listed below and are manifestations of the low output state which occurs in tamponade:\(^5\)

- General malaise
- Shortness of breath and fatigue
- Dizziness and light-headedness
- Palpitations
- Chest pain

The classic picture of cardiac tamponade was described by Beck in 1935 and consisted of a triad of hypotension, raised jugular venous pressure and muffled heart sounds.\(^6\) This became known as Beck’s triad, however this triad referred to acute situations of intrapericardial bleeding from cardiac trauma or aorto-cardiac rupture. Unfortunately only about a third of patients with traumatic tamponade demonstrate the complete triad. These signs if seen at all are very late manifestations of tamponade and are usually seen shortly before cardiac arrest. Beck also described a triad of raised jugular venous pressure, ascites and a small quiet heart in chronic cardiac compression.

The physical signs of cardiac tamponade reflect a combination of variable cardiac compression and the compensatory cardiovascular responses to counter this compressive low output state, they include:

- tachycardia
- hypotension
- pulsus paradoxus
- raised jugular venous pressure (with accentuated ‘x’ descent and attenuated ‘y’descent)
- muffled heart sounds
- atrial arrhythmia
- low grade fever

Pulsus paradoxus is defined as an exaggeration of the normal inspiratory fall in blood pressure, (> 10mmHg). Most patients with tamponade will have a drop of 20-30 mmHg or more, but this sign may not occur. Also, Kussmaul’s sign, defined as an inspiratory increase in mean venous pressure, is never present in tamponade.\(^7\) In addition to paradoxical pulse, tachycardia is the next most common sign in cardiac tamponade.

In a study involving 56 medical patients with cardiac tamponade, Guberman et al found that Beck’s triad was not present in most patients. The majority of patients in that study had well-preserved blood pressure and heart sounds.\(^8\) There is no physical sign or symptom that conclusively points to the diagnosis. The only arbitrator may be the clinical suspicion of the
diagnosis and the decision to proceed to echocardiography. Fowler has listed the clinical suspicious features as:

- Unexplained elevation of systemic venous pressure, unexplained low or falling blood pressure, pulsus paradoxus, unexplained tachycardia, unexplained dyspnoea or tachypnoea.
- Patients with evidence of pericarditis
- Unexplained cardiac enlargement on chest x-ray
- Echocardiographic evidence of pericardial effusion
- History of a possible aetiological factor e.g. recent cardiac surgery, history of anticoagulation, chronic dialysis, malignancy (especially breast or lung), connective tissue disease, recent cardiac procedures such as cardiac catheterisation or central venous access.

**Investigations**

The relevant investigations include:

**Electrocardiography:** The electrocardiogram (ECG) is frequently not helpful in making the diagnosis. A number of ECG changes are associated with cardiac tamponade, such as diffuse low voltage, especially when serial tracings show decreasing voltage indicative of an accumulating effusion. However, electrical alternans of both the P wave and the QRS complex together (total electrical alternans), although a rare finding, is pathognomonic of tamponade. It is caused by the pendular swinging motion of the heart in the pericardial sac and may be most noticeable in one lead. Additional ECG changes such as altered ST segments, T-wave inversion and alternans of the P-wave and the QRS complex alone are non-specific. In patients in the terminal phase of cardiac tamponade profound bradycardia and electromechanical dissociation may be seen.

**Radiography:** There are no signs on the standard chest radiograph that conclusively demonstrates the presence of cardiac tamponade. However, features that are suggestive of pericardial effusion include:

- Considerable enlargement of the heart shadow with a normal pulmonary vascular pattern – which is the most suggestive of pericardial effusion, often in combination with a pleural effusion.
- Prominence of the superior vena cava, reflecting elevation of the central venous pressure.
- Pleural effusions reflecting the formation of transudates in the pleural space due to the raised central venous pressure.
- The epicardial fat pad sign which is best seen on lateral chest radiographs, this is a radiolucent line between the epicardial fat and the mediastinal fat, it represents the pericardium and it contents and should be 2 mm or less. An increase suggests fluid or thickening in the pericardium.

Allegedly specific shapes of the heart shadow in the chest radiograph such as ‘water bottle’ or ‘globular’ have little specificity for the presence of pericardial effusion.

**Hemodynamic findings:** Ameli et al have summarised the haemodynamic findings as:

- Elevated right atrial and right ventricular end-diastolic pressures.
- Equilibration of right atrial and right ventricular-end diastolic pressures with pericardial pressure, left atrial, left ventricular end-diastolic and pulmonary capillary wedge pressure.
- Attenuation of right atrial Y descent with preservation of X descent.
- Absence of Kussmaul’s sign.
- Absence of “dip and plateau” in ventricular pressure waveform.
- Pulsus paradoxus in: systemic arterial pressure and pulmonary artery pressure (out of phase with systemic).
The measurement of intrapericardial pressure via pericardiocentesis, however, provides the definitive diagnosis of cardiac tamponade, being elevated to within 3-4 mmHg of right atrial pressure.

Echocardiography: Echocardiography has become the gold standard for assessing pericardial effusion and cardiac tamponade. Studies have shown that echocardiographic signs of tamponade may be identified at a time when there are no clinical signs of tamponade present and minimal impairment of cardiac output. In addition to visualizing the effusion, it can also assess the distribution of the effusion i.e. concentric or loculated. If trans-thoracic echocardiography is inadequate for visualization of a pericardial effusion, trans-oesophageal echocardiography may be considered. This may be of particular value in postoperative patients who develop regional tamponade (localized tamponade) from a loculated pericardial effusion or an intrapericardial clot.

The echocardiographic doppler features of cardiac tamponade described by Fowler include:

- Right atrial compression (late diastole)
- Right ventricular collapse (early diastole)
- Abnormal respiratory changes in ventricular dimensions
- Exaggerated inspiratory augmentation of flow velocity integral across tricuspid and pulmonary valves with a reciprocal decrease across aortic and mitral valves.
- Dilated inferior vena cava with lack of inspiratory collapse
- Left atrial compression
- Left ventricular diastolic compression
- Swinging heart

Treatment
The treatment of pericardial tamponade involves relieving compression of the heart by removing the effusion either by pericardiocentesis or by surgical means. The net effect of this is the reduction of intrapericardial pressure and alleviation of cardiac chamber compression. This can occur with the removal of as little as 50mL of fluid due to the curvilinear nature of the pressure-volume curve of the pericardium. Surgical options include sub-xiphoid pericardial drainage, video-assisted thoracoscopy, pericardial-peritoneal drainage, pericardial window surgery, or pericardiectomy (partial or complete) by sternotomy or thoracotomy.

Blind pericardiocentesis cannot be recommended as a routine procedure, due to its unacceptably high complication rate of 7 to 50%. The only circumstance where this approach may be advocated is when the patient is in extremis and the diagnosis is highly likely on clinical grounds and no echocardiographic facilities are readily available. Complications of pericardiocentesis are chamber puncture, vessel injury, pneumothorax, infection, ventricular arrhythmias and death. Blind pericardiocentesis is associated with a mortality rate of up to 6%. Echocardiographically guided pericardiocentesis is now becoming the treatment of choice as it has a complication rate of only 4.4%. This method is contraindicated in situations such as type A aortic dissection or myocardial rupture, as relief of the tamponade may extend the dissection or rupture. Drainage is also contraindicated in posteriorly loculated collections, thrombosis and infection, in these circumstances open surgical drainage is a more rational approach.
Echocardiographically guided pericardiocentesis

Using both 2-D and Doppler studies, the size, distribution, and haemodynamic impact of the effusion is assessed. The ideal entry point is that of maximum proximity between the transducer and the maximal fluid accumulation. This may be facilitated by elevating the head of the bed approximately 45 degrees, which favours movement of the effusion towards the anterior chest wall. The needle trajectory is dictated by the angulation of the handheld transducer, a trajectory is chosen which avoids vital structures such as the liver, lung and myocardium. The skin is widely prepared with standard sterile technique and anaesthetized with 1% or 2% lignocaine solution using a 20-25-gauge needle. An incision is then made with a scalpel and a 18-gauge, 8cm, thin walled needle with a short bevel (to decrease the risk of laceration) is introduced through the skin and advanced directly into the fluid space. Entry into the pericardium is normally accompanied by a distinct ‘popping’ sensation. Initial intrapericardial fluid pressure should be measured immediately, because pressure may fall considerably with removal of small amounts of fluid. The fluid which is removed should be sent for the following investigations:

- Haemoglobin, haematocrit
- White blood cell count and differential
- Microbiology: Gram stain, acid-fast bacillus smear, aerobic and anaerobic cultures, viral cultures and parasite studies
- Biochemistry: Glucose, protein, lactic dehydrogenase, amylase, cholesterol, thyroid-stimulating hormone
- Serology: Antibody to nuclear antigen, Rheumatoid factor, complement levels

References
Broncho-pleural fistula (BPF) is a serious complication of chest trauma particularly in presence of mechanical ventilation. It can lead to persistent pneumothorax, poor lung expansion, ventilation/perfusion mismatch & failure to maintain adequate alveolar ventilation resulting in respiratory acidosis. The common causes are given below:

- Direct blunt or penetrating chest trauma
- Post partial or complete lobectomy
- Barotrauma in Mechanically ventilated severe ARDS patients
- Accidental lung injury during thoracocentesis or CVC insertion

Persistent leak occurs in 4 to 23% of chest trauma victims (1). In mechanically ventilated patients combination of negative pleural pressure from chest tube ( - 20 to -25 cm water) & positive pressure from ventilation (30 to 35 cm water) creates a very high pressure gradient resulting in persistence of a broncho-pleural fistula (BPF).

**MANAGEMENT**

1. Mechanical ventilatory support
   - The indications for mechanical ventilation in patients with BPF are as follows…..
     - Persistent hypoxia (PaO\(_2\) < 60 mm Hg) on maximum O\(_2\) therapy.
     - Hypercapnia CO\(_2\) > 55 to 60 mmHg.
     - Respiratory arrest
     - Airway protection e.g severe head injury.

   The aim of ventilation is to minimise pressure gradient across the lung while maintaining acceptable gas exchange (PaO\(_2\) 55 to 60, PaCO\(_2\) 50 to 70). Pressure preset mode is preferred. Peak airway pressure is maintained less than 30 - 35 cm water. Rate is adjusted to ensure adequate minute ventilation. Permissive hypercapnia is acceptable (CO\(_2\) 50 - 70mmHg). This may need heavy sedation & paralysis. High FiO\(_2\) is more desirable than more pressure so that ideal settings would be 0 PEEP & F\(_{\text{IO2}}\) adjusted to PaO\(_2\) of 55 - 60 mmHg. However in patients with associated severe ARDS higher levels of PEEP may be necessary to combat severe hypoxia despite 100% F\(_{\text{IO2}}\).

   Independent Lung Ventilation - Independent lung ventilation using double lumen tube is recommended if there is large airway rupture or if acceptable gas exchange is not possible with traditional ventilation. Each lung is ventilated with two separate ventilators using CPAP only or much lower pressure to the affected lung. The major complications are ulceration of the trachea & main bronchi, difficulty with sputum clearance and difficulty in maintaining proper position of the tube. This strategy can be used for short time awaiting surgical intervention like lobectomy.

   High frequency jet ventilation has been used in this setting with degree of success but there is no favourable outcome data to support it.
2) Chest tube management

Chest tube with an adequate diameter (32-36F) to convey potentially large airflow of BPF is a must. A chest tube of too small a diameter can lead to tension pneumothorax & lung collapse with dire consequences. A second chest tube may at times be necessary. Various drainage devices are available with maximum airflow achievable is 35 L /minute with 20 cm H2O vacuum. This provides optimum drainage with further increase in vacuum does not alter flow through the chest tube but may impede healing of BPF. Adverse effects with chest tube in BPF patients are:

- a) loss of gas making maintenance of effective tidal volume difficult though some CO2 excretion does occur through the fistula.
- b) Negative pressure applied may be transmitted to the airways with inappropriate cycling of the ventilator.
- c) Interference with closure of the fistula.
- d) Chest tube is a potential source of infection.

Different protocols are used for the timing of removal of chest tube but majority would remove it if there is no air leak for 24 hrs.

3) Bronchoscopic applications

The location of the BPF can be defined. A balloon can be passed & inflated to block the fistula. Various agents have been placed in the pleural space bronchoscopically to seal the leak with degree of success. e.g silver nitrate, gelfoam, autologous blood with tetracyclin, cyanoacrylate. These agents reduce the leak by plugging it & subsequently induce inflammatory response causing fibrosis thereby sealing the leak.

4) Supportive treatment

Many patients with BPF may be debilitated due to primary disease process. Supportive therapy includes adequate sedation & reassurance, Maintenance of hemodynamics & organ perfusion, adequate nutrition, appropriate antibiotic therapy against pleural space infection and/or ventilator associated pneumonia, stress ulcer prophylaxis, DVT prophylaxis.

5) Surgical management

Indicated if BPF does not close with adequate chest tube drainage in 7 to 10 days, a large leak from BPF making it impossible to ventilate & maintain gas exchange, where leak has been temporarily sealed with a balloon. The options available are direct closure of the fistula which can be done using video-assisted thoracoscopy, segmental resection or lobectomy.

References
INDEX

ACE, 30
ACE inhibitors
actions of, 31
contraindications, 32
indications for, 32
Acetazolamide, 42
Active transport, 9
ADH, 24
baroreceptor stimulation, 28
cortical stimulation, 28
osmoreceptor stimulation, 27
prohormone, 27
V1 receptors, 29
V2 receptors, 28
Afferent arteriole, 13
Alacepril, 32
Aldosterone, 31
Amiloride, 42
Amino acid reabsorption, 21
Amniotic fluid embolism, 100
Anaemia, 80
Angiotensin converting enzyme. See ACE
Angiotensin converting enzyme inhibitors. See ACE inhibitors
Angiotensin I, 30
Angiotensin II, 30
actions, 31
receptors, 30
Angiotensinogen, 30
Anion gap
decrease, 4
definition, 3
increase, 3
Anions
nondiffusible, 9
Anterior hypothalamus, 27
Antidiuretic hormone, 27
agonists, 29
antagonists, 29
receptors, 28
release, 27
ARDS
Low tidal volumes in, 68
Atrial natriuretic peptide, 33
actions of, 33
Bacterial endocarditis, 110
Benazepril, 32
Biologic membranes, 10
Bowman’s capsule, 15
Bradykinin, 30
Brain natriuretic peptide, 33
Bromism, 4
Broncho-pleural fistula, 128
Bumetanide, 41
Canrenone, 41
Captopril, 32
Cardiac tamponade, 122
Carotid baroreceptors, 27
Cations
diffusible, 9
Clazapril, 32
Collecting duct, 15, 25
Compartment wall, 8
Congestive cardiac failure, 80
Coronary syndrome
acute, 82
Cortical nephrons, 15
Creatinine
daily production of, 17
false depression of, 18
false elevation of, 18
half life, 17
measurement of, 17
Creatinine clearance, 17
normal range, 18
Croup
management of, 74
C-type natriuretic peptide, 33
Cystatin C
clearance of, 17
DDAVP, 22
Desmopressin. See DDAVP
Diastolic heart failure, 53
Diffusion
definition, 9
nonionic, 9
Distal nephron, 23
Distal tubule, 15, 24
Diuretics, 39
actions of, 39
<table>
<thead>
<tr>
<th>Term</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol poisoning</td>
<td>60</td>
</tr>
<tr>
<td>Metolazone</td>
<td>40</td>
</tr>
<tr>
<td>Military anti-shock trousers. See MAST</td>
<td></td>
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<tr>
<td>Molality</td>
<td></td>
</tr>
<tr>
<td>definition, 1</td>
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<tr>
<td>Mole</td>
<td></td>
</tr>
<tr>
<td>definition, 1</td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>85</td>
</tr>
<tr>
<td>Natriuretic peptide family</td>
<td>33</td>
</tr>
<tr>
<td>Natriuretic peptide receptors</td>
<td>33</td>
</tr>
<tr>
<td>Nephron</td>
<td></td>
</tr>
<tr>
<td>morphology of, 15</td>
<td></td>
</tr>
<tr>
<td>Neurophysin</td>
<td>27</td>
</tr>
<tr>
<td>Noninvasive ventilation, 115</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>49</td>
</tr>
<tr>
<td>Organic anions</td>
<td></td>
</tr>
<tr>
<td>reabsorption of, 21</td>
<td></td>
</tr>
<tr>
<td>Organic bases</td>
<td></td>
</tr>
<tr>
<td>reabsorption of, 21</td>
<td></td>
</tr>
<tr>
<td>Ornipressin</td>
<td>29</td>
</tr>
<tr>
<td>Osmolality</td>
<td></td>
</tr>
<tr>
<td>definition, 1</td>
<td></td>
</tr>
<tr>
<td>Osmolar gap</td>
<td></td>
</tr>
<tr>
<td>definition, 1</td>
<td></td>
</tr>
<tr>
<td>increases in, 3</td>
<td></td>
</tr>
<tr>
<td>Osmolarity</td>
<td></td>
</tr>
<tr>
<td>definition, 2</td>
<td></td>
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<tr>
<td>Osmole</td>
<td></td>
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<tr>
<td>definition, 1</td>
<td></td>
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<tr>
<td>Osmosis</td>
<td></td>
</tr>
<tr>
<td>definition, 10</td>
<td></td>
</tr>
<tr>
<td>Osmotic forces</td>
<td>10</td>
</tr>
<tr>
<td>Pars convoluta, 15, 20</td>
<td></td>
</tr>
<tr>
<td>Pars recta, 15, 21</td>
<td></td>
</tr>
<tr>
<td>Pentopril</td>
<td>32</td>
</tr>
<tr>
<td>Pericardial tap, 122</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>32</td>
</tr>
<tr>
<td>Pitressin</td>
<td>29</td>
</tr>
<tr>
<td>Plasma volume</td>
<td></td>
</tr>
<tr>
<td>measurement, 7</td>
<td></td>
</tr>
<tr>
<td>Posterior pituitary, 27</td>
<td>27</td>
</tr>
<tr>
<td>Potassium acetate, 114</td>
<td></td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>77</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td></td>
</tr>
<tr>
<td>renal action of, 34</td>
<td></td>
</tr>
<tr>
<td>Proximal tubule, 15, 19</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism, 66</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>32</td>
</tr>
<tr>
<td>Ramipril</td>
<td>32</td>
</tr>
<tr>
<td>Red blood cell volume</td>
<td></td>
</tr>
<tr>
<td>measurement, 7</td>
<td></td>
</tr>
<tr>
<td>Renal blood flow, 15</td>
<td></td>
</tr>
<tr>
<td>Renal concentrating capacity, 22</td>
<td></td>
</tr>
<tr>
<td>Renal diluting capacity, 22</td>
<td></td>
</tr>
<tr>
<td>Renal natriuretic peptide. See Urodilantin</td>
<td></td>
</tr>
<tr>
<td>Renal pyramids, 13</td>
<td></td>
</tr>
<tr>
<td>Renin, 30</td>
<td></td>
</tr>
<tr>
<td>actions of, 30</td>
<td></td>
</tr>
<tr>
<td>Renin-angiotensin system, 30</td>
<td></td>
</tr>
<tr>
<td>Salicylate poisoning, 113</td>
<td></td>
</tr>
<tr>
<td>Sedatives and muscle relaxants, 106</td>
<td></td>
</tr>
<tr>
<td>Serotonin syndrome, 120</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>plasma, calculation of, 2</td>
<td></td>
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<tr>
<td>Sodium reabsorption</td>
<td></td>
</tr>
<tr>
<td>factors governing, 20</td>
<td></td>
</tr>
<tr>
<td>peritubular factors, 20</td>
<td></td>
</tr>
<tr>
<td>Solute movement, 9</td>
<td></td>
</tr>
<tr>
<td>Solutes</td>
<td></td>
</tr>
<tr>
<td>impermeant, 2</td>
<td></td>
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<tr>
<td>permeant, 2</td>
<td></td>
</tr>
<tr>
<td>Spinal fracture, 117</td>
<td></td>
</tr>
<tr>
<td>Spironolactone, 41</td>
<td></td>
</tr>
<tr>
<td>action of, 41</td>
<td></td>
</tr>
<tr>
<td>side effects, 42</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>43</td>
</tr>
<tr>
<td>Thiazides</td>
<td>40</td>
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<tr>
<td>Tonicity</td>
<td></td>
</tr>
<tr>
<td>definition, 2</td>
<td></td>
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<tr>
<td>Total body water, 4</td>
<td></td>
</tr>
<tr>
<td>measurement of, 4</td>
<td></td>
</tr>
<tr>
<td>Trandolapril, 32</td>
<td></td>
</tr>
<tr>
<td>Transport mechanisms</td>
<td></td>
</tr>
<tr>
<td>active, 9</td>
<td></td>
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<tr>
<td>passive, 9</td>
<td></td>
</tr>
<tr>
<td>Triamterene, 42</td>
<td></td>
</tr>
<tr>
<td>Urea clearance, 18</td>
<td></td>
</tr>
<tr>
<td>Urodilantin, 34</td>
<td></td>
</tr>
<tr>
<td>Vasa recta, 14</td>
<td></td>
</tr>
</tbody>
</table>
Ventilator associated pneumonia, 95

Zona glomerulosa, 31