What exactly is the strong ion gap, and does anybody care?

The landscape of critical illness is littered with gradients and gaps. Some enter our consciousness only rarely. Others are discussed every day at the bedside and their trends followed with great interest. Examples include the alveolar-arterial PO$_2$ gradient, the veno-arterial PCO$_2$ gradient, the pulmonary diastolic - PAoP gradient, the arterial to mucosal pH gradient, the lactate gap, the regional-arterial PCO$_2$ gap, the osmolar gap, the plasma anion gap (AG), the corrected anion gap (AGc) and the urinary anion gap. Some gaps can reveal hidden pathophysiology, resetting the diagnostic and therapeutic course. Others are less rewarding. Tracking the arterial to mucosal pH gradient can seem more akin to interrogation of tea leaves or rewardting. Tracking the arterial to mucosal pH gradient, diagnostic and therapeutic course. Others are less anion gap (AGc), lactate gap, plasma are Na and K cannot be disregarded. The principal strong cations in plasma are Na$^+$ and K$^+$, and the principal strong anion is Cl$^-$. Organic acid anions with pKa < 4, such as lactate and ketoacids, also behave as strong anions. SID is [strong cations] - [strong anions]. In plasma there is a surfeit of strong cations, so that plasma SID is approximately 42 mEq/L.

$A_{TOT}$

Body fluid compartments have varying concentrations of non-volatile (i.e. non-CO$_2$) weak acids (HA). In plasma these consist of albumin and inorganic phosphate. Non-volatile weak acids dissociate in body fluids as follows:

$$\text{HA} \leftrightarrow \text{H}^+ + \text{A}^-$$

The total concentration of non-volatile weak acid in any compartment is termed $A_{TOT}$, where $A_{TOT} = [\text{HA}] + [\text{A}^-]$. Although $[\text{A}]$ varies with pH, $A_{TOT}$ does not, and as such is an independent variable. Raising and lowering $A_{TOT}$ while holding SID constant cause a metabolic acidosis and alkalosis respectively. Lowering and raising plasma SID while clamping $A_{TOT}$ cause a metabolic acidosis and alkalosis respectively.

$\text{Weak ions}$

The SID space is filled by weak ions, one of which is $\text{A}^-$. The only other quantitatively important weak ion is HCO$_3^-$, but there are also minute concentrations of CO$_3^{2-}$, OH$^-$, and H$. To preserve electrical neutrality their net charge must always equal SID.

SID can thus be calculated conveniently as $[\text{HCO}_3^-] + [\text{A}^-])$, a value which used to be called the ‘buffer base’, and is now often termed the ‘effective’ SID, or SIDe (Table 1). When SID is calculated more laboriously from measured plasma strong ion concentrations, it is termed the ‘apparent’ SID, or SIDA (Table 1).

$\text{Unmeasured strong anions}$

Accumulations of unmeasured strong anions reduce SID and are important causes of metabolic acidosis. Examples of endogenous strong anions which can accumulate include lactate in sepsis and shock states, acetocetate and beta-hydroxybutyrate in ketoacidosis, and D-lactate in short bowel syndrome. There are many others. Strong anions can arise from exogenous sources. Examples include pyroglyutamate, salicylate, formate, and glycolate. Exogenous strong anions behave similarly from an acid-base perspective, but often have a propensity for direct toxicity.

Early detection of accumulated strong anions would doubtless facilitate diagnostic speed. On occasion it might save lives. Methanol and ethylene glycol poisoning are cases in point, where formate or glycolate/oxalate accumulation can be prevented by prompt administration of 4-methylpyrazole, or institution of haemodialysis. However, Cl$^-$ is still the only directly measured strong anion reported on a routine plasma biochemical profile. Plasma L-lactate
A normalise metabolic acid-base status at the existing represents the change in extracellular SID needed to phosphate). As a result, the AG response to unmeasured the AG is made up of weak anions - the \([A^-]\) component of both strong and weak. The AG would thus normally be quantifies \([\text{unmeasured anions}] - [\text{unmeasured cations}]\), principle of electrical neutrality, the AG really unlikely to do the job well. SBE is the best of these.

Indices of overall metabolic acid-base status seem unlikely to do the job well. SBE is the best of these. It represents the change in extracellular SID needed to normalise metabolic acid-base status at the existing \(A_{TOT}\). However, as a signal for unmeasured anions, SBE suffers from considerable background noise. For example, simple narrowing of the gap between \([\text{Cl}^-]\) and \([\text{Na}^+]\) reduces SID and thus SBE. This is a common phenomenon, particularly with the widespread use of low SID resuscitation fluids. Of note, a low \(A_{TOT}\) or reductions in plasma \([\text{Cl}^-]\) oppose the fall in SBE caused by accumulated strong ions, reducing sensitivity. With all these factors operating, SBE should be an unreliable scanning tool for unmeasured strong anions, unless they are present in high concentrations.

**SBE**

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**AG**

The AG looks to be a step forward. It is normally calculated as \([\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]\), although \([\text{K}^+]\) is omitted in many laboratories (Table 1). By the principle of electrical neutrality, the AG really quantifies [unmeasured anions] - [unmeasured cations], both strong and weak. The AG would thus normally be elevated in the presence of unmeasured anions and reduced by unmeasured cations. Although there can be a wide variety of unmeasured ions, in health the bulk of the AG is made up of weak anions - the \([A^-]\) component of \(A_{TOT}\) (i.e. the negative charge on albumin and phosphate). As a result, the AG response to unmeasured strong anions can easily be blurred by \(A_{TOT}\) fluctuations, which alter \([A^-]\) directly, and severe pH disturbances, which alter the \([A^-]\) component of \(A_{TOT}\) (Table 2).

However, as also shown in Table 2, the AG is sensitive to altered \([\text{Ca}^{++}]\) and \([\text{Mg}^{++}]\), lithium carbonate administration, THAM administration and high concentrations of anionic and cationic globulins. Unfortunately, these all erode AG sensitivity and specificity when scanning for unmeasured strong anions. Despite these deficiencies the AG should still perform better than SBE. Which makes it surprising that in the best available comparison (scanning for plasma L-lactate > 5 mmol/L), it was no better than base excess. Areas under the ROC curve for both were approximately 0.85.

**AGc**

The AGc was devised to overcome just one AG deficiency, albeit a major one, namely susceptibility to variations in plasma \(A_{TOT}\) (Table 1). However, for a few reasons the correction is fairly rough. First, it adjusts for albumin fluctuations only, not allowing for phosphate offsets at all. Except in severe hyperphosphataemia this makes little difference. Second, it attributes a fixed negative charge to albumin, making no adjustment for pH effects on imidazole groups. Again this can be shown to be a minor source of error, except in severe alkalaeemia.

Finally, there is a theoretical objection. Although ‘correcting’ derived variables such as the AG has intuitive merit, the usual laboratory reference ranges (derived from ‘uncorrected’ AG values) are still applied. Ideally ‘corrected’ values should be used to derive ‘corrected’ reference ranges. Because the reference population is healthy, this difference should also be small.

Despite all this, the AGc should be an advance on its uncorrected version, particularly in critical illness when plasma [albumin] varies widely and is often greatly reduced. It would be good to prove this. For reasons that are unclear, an opportunity was lost in the recent study by Rocktaeschel and co-workers.
Table 2. Comparison of anion gap (AG), corrected anion gap (AGc) and strong ion gap (SIG)

<table>
<thead>
<tr>
<th>Component</th>
<th>AG</th>
<th>AGc</th>
<th>SIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmeasured strong anions (e.g. lactate, keto-acids)</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Unmeasured weak anions (e.g. polygelinate, IgA myeloma)</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Unmeasured strong cations (e.g. lithium)</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Unmeasured weak cations (e.g. THAMH(+)), IgG myeloma</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Bromism, hyperlipidemia (Positive [Cl(-)] measurement bias)</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Hypernatraemia (Negative [Na(+)] measurement bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Pi]</td>
<td>(\uparrow) raises</td>
<td>(\uparrow) raises</td>
<td>No effect</td>
</tr>
<tr>
<td>pH</td>
<td>(\downarrow) lowers</td>
<td>(\downarrow) lowers</td>
<td></td>
</tr>
<tr>
<td>[Ca(^{++})] and [Mg(^{++})]</td>
<td>(\downarrow) lowers</td>
<td>(\downarrow) lowers</td>
<td>No effect</td>
</tr>
<tr>
<td>[Albumin]</td>
<td>(\uparrow) raises</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>(\downarrow) lowers</td>
<td></td>
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</tr>
</tbody>
</table>

**SIG**

The SIG concept, first hit upon by Figge and colleagues,\(^{37}\) exploits the fact that there are two ways to determine SID, namely SIDa, calculated by summation of individual strong anion and cation concentrations, and SIDc, calculated as ([A\(-\)] + [HCO\(_3\)-]) (Table 1). In healthy individuals inhabiting an error-free world, SIG, which is the difference between the two, would be zero. Unmeasured strong anions would reveal their presence by increasing SIDa, giving SIG a positive value.

However, a number of realities conspire against this ideal. Firstly, like the AG, the SIG is a quantification of [unmeasured anions] - [unmeasured cations], both strong and weak. Its advantage over AG and AGc is that the unmeasured list is shorter (Table 1). This theoretically insulates SIG from variations in A\(_{TOT}\), pH, [L-lactate], [Ca\(^{++}\)] and [Mg\(^{++}\)] (Table 2). However, it still leaves SIG vulnerable to unmeasured strong cations like lithium, and unmeasured weak anions such as polygelinate (from gelatin-based colloid preparations), weak cations such as THAMH\(^+\), and the anionic and cationic bands of multiple myeloma (Table 2). A further disadvantage is that each extra analyte brings with it its own imprecision. As a result, the confidence intervals around SIG values due to measurement variability alone are likely to be quite wide and should exceed \(\pm 7\) mEq/L.\(^{38}\) By comparison, the confidence intervals for AG, when incorporating *both* measurement and population variability, are generally only \(\pm 5\) mEq/L.

Systematic bias has also been noticed. In other words it should not be assumed that the normal reference range for SIG is centred on zero. The ‘normal’ SIG at this author’s hospital, calculated by inserting local mid reference-range values in the SIG equation, comes to around 3.7 mEq/L. Small concentrations of keto-acids and other metabolic anions no doubt can contribute to some extent, but do not explain a positive SIG of this size. (Readers are invited to perform this exercise, using published values from their own hospital laboratories). Similar positive SIG bias has cropped up in other parts of the world,\(^{38,39}\) but not everywhere.\(^{40}\)

This does not mean that regions where the mean SIG is strongly positive are populated by individuals harbouring exotic anions. More likely there is systematic bias in one or more components of the SIG determination, due to locally adopted measurement technologies and variations in analytic reference standards. It is widely recognised that when different technologies measure the same thing they produce different reference values. Unless this is taken into account, results can be misinterpreted and diagnostic conclusions skewed.\(^{40}\) If SIG is to find clinical application, individual laboratories will need to calibrate on site against a local population. The good news is that systematic bias, unlike imprecision, can be factored out, once recognised.

The main question, given the likely imprecision and residual background noise, is whether the SIG is really any better at detecting unmeasured ions. Unfortunately, there are no published data to provide the answer. In Rocktaeschel’s study\(^{35}\) the base excess gap,\(^{41}\) a close cousin of SIG in which L-lactate remains an unmeasured anion, was no more useful than the AG at detecting plasma [L-lactate] > 5 mmol/L. The area under the ROC curve for each was around 0.85.\(^{35}\) For what it is worth, this editorialist has unpublished data which may shed further light. Using 296 paired data-sets from one ICU, an [L-lactate] threshold of 2.5 mmol/L, and SIG values calculated without L-lactate, there was little difference in the hyperlactaemia scanning power of the AG, SIG and base excess gap. Areas under the ROC curve were 0.82, 0.85, and 0.84 respectively. Interestingly, the area...
under the ROC curve for SBE was only 0.36, more in line with the background noise transmitted through SBE in sick patients.

The main danger with highly processed indices like the SIG and the base excess gap is over-interpretation. There has been speculation about unsuspected anions and even unidentified cations in critical illness, based on positive and negative deviations or significant differences in base excess gap or SIG values. Although these possibilities cannot be ruled out, particularly in the Kaplan study, both SIG and the base excess gap are inherently imprecise. Note also that both indices contain pH-based calculations of weak acid behaviour. Small systematic inaccuracies if present will be magnified in sicker patients with prominent acid-base disturbances. It is wise to remember the tidal wave that grew out of apparent delivery-dependent oxygen consumption and presumed covert oxygen debt until someone thought of mathematical coupling.

Similar comments apply to prognostic power. A couple of studies have produced data suggesting that the SIG or the base excess gap are more predictive of mortality, perhaps because hidden ions are reflected in their values. However, two other well-conducted studies do not support that contention. Rocktaeschel and colleagues conclude that indices for unmeasured anions are too closely correlated for any one to outshine the rest. This editorialist concurs with that view.

So where does that leave us? Will SIG fill a unique and valuable niche? Can it give us information than its rivals cannot? The jury is still out, but I think their answer will probably be ‘no’. Watch this space.

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**Oxygen therapy for acute illness: reasoned or ritual?**

Oxygen therapy is often used in the acutely ill patient based on a belief that individuals at risk of hypoxia are benefited by oxygen and that oxygen is without adverse effects. However, while life cannot be sustained without oxygen, there is surprisingly little evidence to support its routine use in the critically ill patient outside its role in cardiopulmonary resuscitation where both an urgent increase in haemoglobin saturation as well as cardiac output are required to deliver oxygen rapidly to the brain and heart.

Normal human arterial oxygen tension at sea level varies between 80 - 100 mmHg and corresponds to a saturation of 96 - 97%.¹ The oxyhaemoglobin dissociation curve reveals a haemoglobin saturation that is
altered little while the oxygen tension falls from 100 mmHg to 60 mmHg, thereby maintaining the arterial oxygen content in the presence of a low ambient pressures or pulmonary disease. At low oxygen pressures the curve demonstrates an oxygen tension which is maintained while the saturation falls, thereby sustaining a pressure gradient necessary to diffuse oxygen from blood to mitochondria. As long as there is an effective pressure gradient, oxygen will diffuse into tissues with mitochondrial cytochrome c oxidase reducing oxygen to water at oxygen levels as low as 2.25 mmHg. At mitochondrial oxygen tensions above 7.5 mmHg oxygen uptake is increased, an effect which is most likely due to an increase in oxygen radical production. When a progressive reduction in inhaled oxygen is applied, anaerobic metabolism with increasing blood lactate levels appears to occur in the human at an arterial blood haemoglobin oxygen saturation (SaO_2) of 40% or PaO_2 of 23 mmHg, a value which is rarely achieved with lung injury.

Tissue oxygen delivery depends on cardiac output, haemoglobin concentration and haemoglobin oxygen saturation and a reduction of up to 50% in haemoglobin concentration in the critically ill patient has been reported to be beneficial, although many clinicians do not tolerate a saturation reduction in any patient of more than 10%. When pulmonary shunt produces an SaO_2 of 85% with an inspired oxygen concentration (FIO_2) of 0.3, an increase in FIO_2 to 1 will increase the SaO_2 by 8% and oxygen content by 9%. The resultant increase in oxygen delivery could easily be accomplished by a similar percentage increase in cardiac output or haemoglobin with no change in FIO_2.

Of the pulmonary disorders that cause a low SaO_2 (e.g. hypoventilation, low ventilation/perfusion ratio, intrapulmonary shunt, diffusion defect) some increase in SaO_2 occurs with an increase in inhaled oxygen, although none are cured. Oxygen therapy may even delay diagnosis and corrective therapy.

On the other hand, high inspired oxygen levels have been repeatedly identified as a source of acute lung injury, atelectasis, and adverse central nervous system effects. In one prospective, randomised double-blind controlled study of patients with uncomplicated myocardial infarction, oxygen, at 6 L/min for 24 hours, was not associated with any reduction in mortality and may have been detrimental. In a study of patients with acute stroke, oxygen administration at 3 L/min through nasal cannulae was not associated with any benefit. Postoperative increase in ventilation/perfusion mismatch is increased if extubation is preceded by a short period of 100% oxygen and while one prospective, randomised study of patients undergoing colorectal surgery reported a reduction in the incidence of surgical wound infections from 11.2% to 5.2%, using 80% oxygen compared with 30% oxygen interoperatively and two hours postoperatively, another study of patients undergoing major intraabdominal surgery found that this therapy was associated with an increase in the incidence of surgical site infections (e.g. 11.3% vs 25%).

A lack of correlation between arterial oxygen levels and long term outcome has also been demonstrated in the ARDS network study where low and traditional tidal volumes were compared. Those who received the 6 mL/kg of predicted body weight tidal volume during mechanical ventilation had a lower mean PaO_2 than those randomised to receive a higher tidal volume, yet had a statistically lower mortality rate. The absence of a relationship between arterial oxygen level and mortality was also found in a multicentre, randomised, placebo-controlled study of non-sepsis ARDS patients where nitric oxide at 5 ppm up to 28 days was not associated with any significant effect on duration of ventilatory support or mortality, although there was a significant increase in PaO_2. Even in the two recent multicentre, double-blind, randomised trials in ARDS patients treated with recombinant surfactant protein C-based surfactant, the arterial oxygenation was higher in the treated patients compared with the untreated patients without any change in mortality.

Nonetheless, in COPD patients whose disease is stable with maximum medical therapy and who have a PaO_2 < 55 mmHg (< 7.4 kPa), long-term oxygen therapy (LTOT) for more than 15 hours per day prolongs life expectancy, improves sleep, cognitive functions and prevents progression of hypoxic pulmonary hypertension, although LTOT appears not to improve mortality in patients with COPD and a PaO_2 between 56 - 65 mmHg.

Hypoxia is a feature that requires a clinical diagnosis and specific treatment which may include antibiotics, anticoagulation, corticosteroids, bronchodilators, diuretics, ACE inhibitors, etc, rather than just an increase in inhaled oxygen. As there are no human data that define the optimal FIO_2 and SaO_2 in critically ill patients, a wide variation of SaO_2 and FIO_2 prescription is often found in clinical practice. Perhaps, oxygen should be thought of in the same light as any resuscitation manoeuvre (e.g. external cardiac massage, mechanical ventilation) and prescribed to achieve a PaO_2 > 55 mmHg but < 80 mmHg (SaO_2 between 85% and 95%) while the disorder causing the hypoxia is diagnosed and definitive therapy takes effect.

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Defining emerging evidence for osmotherapy in traumatic brain injury

Three years ago, an editorial appeared in Critical Care and Resuscitation that suggested that “the role of routine osmotherapy remained questionable in neurological emergencies, and that mannitol in particular, should be used with circumspection.” Despite
theoretical physiological effects that primarily relate to transient hypervolaemia rather than an osmotic challenge. This negative opinion was based on the narrow therapeutic index of mannitol (particularly when administered to intoxicated patients), the potential to cause hyperosmolarity and diuresis-induced hypovolaemia and hypotension. Furthermore, the paucity of high-level evidence identified by the Brain Trauma Foundation resulted in the recommendation that mannitol be used as an option only in resuscitated patients with unequivocal signs of raised intracranial pressure prior to imaging or evacuation of a mass lesion. Nevertheless, mannitol remains an established drug in the armamentarium of emergency physicians, anaesthetists, intensivists and, in particular, neurosurgeons. It is often administered in variable doses to patients with a myriad of neurological emergencies, ranging from stroke, hypoxic encephalopathy and traumatic brain injury. Its use is usually justified by anecdotal experience and habit, often with the caveat that in the modern resuscitatorist era, hypotension and hypovolaemia are promptly recognised and treated, so that the potential side effects of mannitol are minimised so that the theoretical benefit may exert some effect in patients with life-threatening neurological emergencies.

This latter perception is likely to be encouraged with the recent publication of a study of the effects of “new high-dose” mannitol by Cruz and colleagues. The aim of the study was to target a specific population of severely head-injured patients primarily based on the “presence of recent clinical signs of impending brain death on the first emergency room evaluation.” These signs were defined as a Glasgow Coma Score of 3 (or motor score of 1) and bilateral abnormal pupillary dilatation (> 4 mm). Patient selection was further refined to exclude patients with penetrating trauma, systolic hypotension associated with major extracranial trauma and to include only those patients with severe diffuse brain swelling as the predominant intracranial lesion on head CT scan. Over a three-year period, 44 such patients were randomised to receive “ultra-fast intravenous mannitol” in two doses described as “~1.4g/kg and ~0.7g/kg”. The doses were based on a 70 kg person, but the actual doses administered were 500 mL (“high dose”) and 250 mL (“conventional dose”) of 20% mannitol, respectively. During emergency room resuscitation and following admission to the intensive care unit, patients were closely monitored with assiduous attention to oxygenation and haemodynamics. Patients were entered into a “cumulative treatment protocol” that Cruz has previously published, and includes aggressive defence of cerebral perfusion pressure, “optimised” hyperventilation titrated to derived cerebral oxygen extraction ratios, and decompressive craniectomy for refractory intracranial hypertension.

The primary outcome measurement for this study was 6-month dichotomised Glasgow Outcome Score. Not surprisingly, the overall mortality for the patient cohort was high (52%) with 9/23 (39.1%) deaths occurring in the “high dose” mannitol group and 14/21 (66.7%) deaths occurring in the “conventional dose” group. Expressed as dichotomised Glasgow Outcome Score, 10/23 (43%) patients in the “high dose” mannitol group had a favourable outcome compared to 2/21 (9.5%) patients in the “conventional dose” group. This difference achieved statistical significance (p < 0.02). Furthermore, Cruz demonstrated that a statistically significant improvement in pupillary diameter occurred in patients who received “high dose” mannitol (14/23; 60%) compared with those who received “conventional dose” mannitol (5/21; 23%). However, there was no difference in the numbers of patients who subsequently developed refractory intracranial hypertension in the intensive care unit (43.5 vs. 47.6%).

The discussion of the results is remarkably long and there is much detail about the justification of neuromonitoring and purported physiological rationale of the relationship between derived cerebral oxygenation measurements and cerebral perfusion pressure. There is no discussion about the statistical design of the study, limitations of sample size or external validity of the results. The study concludes with the statement “…this prospective controlled trial of high dose mannitol…in (patients) with impending brain death, (demonstrated) statistically significant clinical benefits with respect to long term clinical outcomes.” This study received an editorial which acknowledging the provocative nature of Cruz’s study, highlighted some limitations. These included concerns about the external validity of the results of this single-centre study (despite the international authorship), and questions about the utility of “optimised hyperventilation” (for which Cruz has been a highly vocal and long-term advocate). The editorial concluded with the comment that a multicentred study should be considered to address the efficacy of “high dose” mannitol. Intriguingly, the journal editor permitted a rapid response letter by Cruz to this editorial in the same issue. Dr Cruz’s response is extraordinary and categorically states that, on the basis of his results, “…there is no need for further studies involving our novel high-dose mannitol treatment proposition…” He dismisses any suggestion of inadequacy of power due to close matching of a highly specified study population, and claims that the favourable outcomes he has demonstrated in his patients when compared with historical controls, are primarily a reflection of the quality of overall care that his unit provides.

Whilst it is acknowledged that Cruz went to great
lengths to ensure baseline imbalance and parity of severity of injury to minimise “background noise”, there are a number of methodological and interpretative flaws in Cruz’s study. Firstly, to confirm the observed reduction in mortality of 27.6% between “high dose” and “conventional dose” mannitol, a sample of 120 patients would be required (80% power, α = 0.05). However, accepting that mortality in this patient population is invariably very high and that functional survival is considered to be a more appropriate outcome measure, confirmation of the reduction in unfavourable outcomes from 90.5% to 56.5% would require a sample of 24 patients (80% power, α = 0.05). It may be assumed that this is the statistical basis of Cruz’s justification for his sample size. However, this is fallacious given the use of composite endpoints such as Glasgow Outcome Score where dramatic changes in one domain may not represent overall changes in the composite score. Secondly, the distinction between “high” and “conventional” dose mannitol is questionable, as the prescribed doses, whilst based on body weight and which Cruz confirms approximated 70 kg in the study population, are such that statistical separation of delivered dose is improbable. Thirdly, it is difficult to attribute such a profound impact on mortality and functional survival by a single intervention. The reliance of “magic bullets” to turn around the devastating pathophysiological process that occur following high-lethality traumatic brain injury is implausible. This has been demonstrated by the inexorable failure of validated neuroprotective agents in improving outcomes in head-injured patients. Finally, if such a profound effect were indeed true, then an adequately powered, concealed, randomised trial is required. The feasibility that such trials are possible has been demonstrated by the recent hypertonic saline and saline vs. albumin fluid evaluation (SAFE) studies. Although these two important studies produced “negative” results, they provide clinicians with unequivocal evidence about the efficacy of two fluid resuscitation strategies.

Such an initiative is required for mannitol, before it is accepted as a “proven” therapy. The jury is still very much out on this issue.

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Where have all the donors gone?

Australia is one of the world leaders in transplantation with excellent survival rates. Liver and heart recipient five-year survival in Australia is 80% and improving. However, in Australia, as in all other countries, there are insufficient organs to meet the needs of people with end-stage organ failure who require a transplant. Rates of organ donation in Australia are consistently lower than other Western countries, averaging 9 donors per million population compared with 20 in the United States of America, 19 in France and 12 in the United Kingdom in 2003. Spain has the highest rate of more than 30 donors per million. So why is the rate in Australia comparatively low and is it possible to increase the number of organs available for transplantation?

We have been examining this question since 1997. The potential for cadaveric organ donation in Victoria was estimated in a pilot study undertaken in 1998/1999. This audit aimed to determine the potential for heart-beating (death from brain death) organ donation. All deaths in 12 Victorian hospitals were
reviewed over a 12-month period to identify patients with confirmed or imminent brain death who were medically suitable for organ donation.

This audit estimated the maximal potential donor pool in Victoria to be 30 donors per million. Although a substantial increase from the current rate, this estimate is not practically achievable, as its calculation assumes that all identified patients would proceed to brain death and is based on the family consenting to organ donation all of the time. When these factors are taken into consideration, our realistic maximal rate falls short of the actual rate of organ donation in Spain. Some studies have speculated that there may be as many as 50 potential donors per million in some communities.\(^5\)\(^6\) We clearly have a lower number. Why is there such a disparity?

It is often speculated that the low and falling donation rate in Australia is due to the success of initiatives to lower road trauma, resulting in a smaller donor pool. However, the proportion of donors who arise from individuals dying of trauma in Australia is similar to other countries, so this alone does not explain our lower rate. The audit of hospital records in Victoria provides information about whether missed opportunities for organ donation occur and where efforts might be focused in order to increase the rate of donation. Four possible ways to increase the organ donation rate have been identified.

1. Increasing the consent rate.
2. Increasing the identification of potential organ donors, support to brain death and request for organ donation.
3. Ensuring adequate provision of physiological support to brain dead potential donors.
4. Enlarging the potential donor pool with, for example, marginal donors, living donors or non-heart beating organ donors.

We address each in turn.

*Increasing the consent rate*

In Victoria, non-consent to organ donation by families, as determined by the 1998/1999 pilot study and our ongoing audit, is 40%. There is an increasing political interest in maximising the organ donation rate with the focus being on the consent process and intensive care practice. An Australian Health Ministers Advisory Committee Working Group is currently considering recommendations, which include:

- If the deceased has enlisted on the Register, informing the family of the deceased’s known wishes after they have been advised that brain death has been confirmed, and advising them that the deceased’s known wishes to donate fulfil the requirement for informed consent.
- To not proceed with organ donation if the family raises a sincerely held objection that cannot be reversed by explanation and assurance.

In Australia it is Intensivists who almost exclusively raise the option of organ donation with the family. Intensivists understand the practical issues involved and are best placed to advise on what strategies are feasible and have a moral responsibility to care for the deceased patient’s family. We do not support any coercive strategy. Our involvement in the development of any recommendations is critical to the success of their implementation. A survey of families, identified during the 1998/1999 pilot study as having been approached regarding organ donation, found that the family’s knowledge of their deceased family member’s wishes was the most important factor in influencing their decision whether or not to donate. There was no instance of the family going against the patient’s wishes. However, when families did not know their relative’s wishes regarding organ donation there was a 50% rate of non-consent. Families also felt burdened in having to make a decision.

As families uncommonly overturn a deceased’s wish to donate, focusing on this area may do little to increase the organ donation rate. It is certainly important for the family to take account of the patient’s wishes to donate. However, if there is family distress or objection, it is not appropriate to continue with the donation. Proceeding in these circumstances may complicate family members’ bereavement and, secondarily, can result in adverse publicity for organ donation if the family make their grievances public.

The importance of individuals informing their family members of their wishes is emphasised in recent organ donation promotions such as the “think, talk, tell - Think about it, Talk about it, Tell your family” campaign. A useful function of the Organ Donor Registry may be to stimulate this type of communication amongst family members.

Family consent rates of up to 80% occur in Spain. This may reflect high societal support of organ donation but may be partly due to the use of repeated requests and persuasive discussions by full-time medical donor coordinators, which would be unacceptable in Australia.\(^7\) Another strategy used in some countries is the adoption of presumed consent legislation. The rationale behind this approach is to promote a culture where organ donation is the norm by changing the default position to one of donation. This removes the
decision-making burden from the family although most countries with such a system still obtain the family’s assent prior to proceeding with donation. The attempt to introduce such legislation may be perceived, however, as coercive and impinging on individual freedoms and for these reasons it may not be embraced by the Australian public.

Increasing the identification of potential organ donors, support to brain death and request for organ donation

The second area identified as having an impact on the organ donation rate is the failure, on occasions, to identify potential organ donors or to physiologically support them to brain death and request for organ donation. Auditing of hospital records, in order to identify deceased patients who may have been potential donors, has been undertaken for 2 to 3 years in Victoria, New South Wales, Queensland, Australian Capital Territory and Northern Territory and is about to be implemented in Western Australia. One of the most useful outcomes of the audit has been to confirm, with data, that for greater than 98% of patients with confirmed brain death, organ donation has been discussed with the patient’s family. This has enabled us to refute claims that “Intensivists are missing donors”.

This ongoing audit review process has the purpose of identifying, and creating a forum for discussion amongst intensivists, a more contentious group of potential donors. These are patients with severe brain injury in whom brain death may have been present, but not formally diagnosed, or in whom brain death has not occurred but is imminent. A typical scenario is the older patient who presents to hospital comatose from a large intracranial bleed and who has a deteriorating neurological state with the absence of some, but not all, brainstem reflexes. Frequently, once the family have been informed of the hopeless prognosis, treatment is withdrawn without informing the family of the possibility of brain death and organ donation. In considering the potential for organ donation, such patients should be viewed as potential donors. Whereas it is the common practice in some hospital emergency departments to withdraw treatment in these patients without referral to intensive care, others routinely admit such patients to the intensive care unit. In the latter scenario it is more likely that brain death will ensue. In addition, in the intensive care unit there are appropriately skilled staff who can raise the possibility of organ donation with the family.

Should all patients with severe brain injury, irrespective of prognosis, be admitted to the intensive care unit? Some Intensivists consider that it is appropriate to admit such patients until the prognosis and response to full supportive therapy is established. The added benefit is the time provided to the family to gather at the bedside, understand the patient’s condition and accept the poor prognosis. Other Intensivists consider it unethical to admit patients to the intensive care unit solely for the purpose of facilitating organ donation, unless it is with the family’s informed consent and in keeping with the individual’s wishes.

Should the option of continuing support in patients who have a hopeless prognosis and the potential to progress to brain death be presented to the family? Who should conduct these discussions? Some Intensivists regularly discuss the option of organ donation prior to brain death confirmation once the family have accepted that their relative’s prognosis is hopeless and that they will die. The important principles are to respect the previously expressed wishes of the deceased and the wishes of the grieving family and to fully inform them of the possibility of organ donation. It is essential that such family discussions be conducted with tact and sensitivity by skilled Intensivists to ensure that families do not misunderstand the situation. The various possible outcomes, including failure to progress to brain death in a reasonable time frame, would need to be conveyed. The ability to admit these patients to intensive care units that are already under pressure and under resourced is an important issue.

Ensuring adequate physiological support of the brain dead potential donor

Intensivists perform well in providing adequate physiological support to the potential donor. Less than 5% of consented brain dead potential donors do not proceed to organ procurement because of failed physiological support. This compares well with other reported rates.

Marginal donors, living donors and non-heart beating organ donors

Criteria for donor suitability are constantly being broadened. Marginal donors are older and have more co-morbidities and relative contraindications to organ donation than conventional donors. Factors such as a history of intravenous drug use or cancer are no longer automatic exclusions. Each case should be carefully assessed and the risks weighed against the urgency of transplantation for a potential recipient.

Cautious expansion of criteria, which has occurred with lung donation in Victoria, can result in similar outcomes to conventional donors. Successful kidney and liver transplantations from donors as old as 90 years have been performed in Spain. A recent comparison of donor databases of the United States of America and Spain, however, found a much higher proportion of older donors in Spain but also a higher non-utilisation of procured organs due to organ unsuitability.

Living donation is another source of organs. The
proportion of kidneys transplanted from living donors has increased in Australia, from 24% of all kidneys transplanted in 1996 to 38% in 2002.\textsuperscript{13,14} Living donation of liver (partial hepatectomy) and a lung are also possible, although these are associated with a substantial morbidity and mortality risk for the donor. Non-heart beating donation (donation after cardiac death) contributes to very few transplanted organs in Australia (only one donor in 2003).\textsuperscript{3} Some centres report that up to 10% of transplanted livers arise from non-heart beating donors.\textsuperscript{15} In Japan almost all transplanted kidneys are from non-heart beating donors due to poor public acceptance of recently introduced brain death legislation.\textsuperscript{16} Carefully developed protocols are required to guide practice in identifying suitable patients, mode of withdrawal of therapy and timing of declaration of death, managing the logistics of organ retrieval and balancing ethical concerns with the practical issues of minimising warm ischaemia. Non-heart beating donation of lungs has great potential due to a peculiar resilience of the lungs to warm ischaemia, and centres have reported successful results in humans. The feasibility of such a program in Victoria is currently being explored. More important than the logistic concerns are the ethical issues, which are only resolvable by widespread consultation and debate and careful development of safe protocols.

It is clear that the solution to the low organ donation rate in Australia is not simple. The focus of intensivists, however, should not be on increasing the donation rate \textit{per se} but on improving the whole process around potential donation and advocating for the deceased patient and their family. Any valid attempt to increase the rate would require a change in practice that may have resource, clinical and ethical implications. The key role of Intensivists, as the gatekeepers to organ donation, makes it imperative for us to, a) consider whether a patient with a severe brain injury has a potential to progress to brain death and, therefore, be a donor, and b) ensure that we are adequately skilled to talk clearly and compassionately to grieving families about brain death and organ donation.

\textit{We wish to thank Professor David Tuxen and Dr. Ray Raper for their helpful comments in preparing this manuscript.}

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