ORIGINAL ARTICLE

Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap

A Durward, A Mayer, S Skellett, D Taylor, S Hanna, S M Tibby, I A Murdoch

Arch Dis Child 2003;**88**:419–422

See end of article for authors' affiliations

Correspondence to: Dr A Durward, Paediatric Intensive Care Unit, Floor Guy's Tower Block, Guy's Hospital, St Thomas Street, London SE1 9RT, UK; adurward@doctors.org.uk

Accepted 11 October 2002

Aims: Hypoalbuminaemia has significance in adult critical illness as an independent predictor of mortality. In addition, the anion gap is predominantly due to the negative charge of albumin, thus hypoalbuminaemia may lead to its underestimation. We examine this phenomenon in critically ill children, documenting the incidence, early evolution, and prognosis of hypoalbuminaemia (<33 g/l), and quantify its influence on the anion gap.

Methods: Prospective descriptive study of 134 critically ill children in the paediatric intensive care unit (ICU). Paired arterial blood samples were taken at ICU admission and 24 hours later, from which blood gases, electrolytes, and albumin were measured. The anion gap (including potassium) was calculated and then corrected for albumin using Figge's formula.

Results: The incidence of admission hypoalbuminaemia was 57%, increasing to 76% at 24 hours. Neither admission hypoalbuminaemia, nor extreme hypoalbuminaemia (<20 g/l) predicted mortality; however, there was an association with increased median ICU stay (4.9 *v* 3.6 days). After correction for albumin the incidence of a raised anion gap (>18 mEq/l) increased from 28% to 44% in all samples (n = 263); this discrepancy was more pronounced in the 103 samples with metabolic acidosis (38% *v* 73%). Correction produced an average increase in the anion gap of 2.7 mEq/l (mean bias), with limits of agreement of ±3.7 mEq/l.

Conclusion: Admission hypoalbuminaemia is common in critical illness, but is not an independent predictor of mortality. However, failure to correct the anion gap for albumin may underestimate the true anion gap, producing error in the interpretation of acid-base abnormalities. This may have treatment implications.

Abnormally low serum albumin levels (<33 g/l) are a frequent and early biochemical derangement in critically ill adults with a reported incidence of 30–40%, the aetiology of which is complex.[1–3] Hypoalbuminaemia in this setting is a marker of disease severity and has been associated with prolonged ventilatory dependence and length of intensive care stay.[4 5] Furthermore, hypoalbuminaemia may also be an independent predictor of mortality.[3 6] Reinhart *et al* showed a 30 day mortality of 25% with an admission serum albumin concentration below 34 g/l, increasing to 62% with extreme hypoalbuminaemia (<20 g/l).[3]

Serum albumin levels also have a significant influence on acid-base interpretation in critical illness, notably through calculation of the anion gap. In health, the anion gap is predominantly due to the net negative charge of albumin (approximately 12 mEq/l).[7] In patients with metabolic acidosis, the anion gap may increase, reflecting tissue metabolic acid. However, this may be masked by concurrent hypoalbuminaemia, a common occurrence in critical illness.[7] Fortunately the anion gap can be adjusted for albumin concentration in adults using Figge's correction factor.[7 8]

There is, however, a paucity of data on the incidence and significance of hypoalbuminaemia in critically ill children. Thus the aims of this study were twofold: (1) to document the incidence and prognostic value of hypoalbuminaemia in paediatric patients over the 24 hours following admission to the intensive care unit; and (2) to determine the influence of correction for hypoalbuminaemia on the diagnosis of a "raised anion gap" metabolic acidosis.

PATIENTS AND METHODS

Over a six month period, 134 children and infants were studied prospectively following admission to the paediatric intensive care unit (PICU). The median (interquartile) age was 12.5 months (1.5–50.4) and weight 8.1 kg (3.6–15.0). Patients less than 16 years of age with the presence of indwelling arterial lines were eligible for inclusion in the study. Exclusion criteria included postoperative cardiac surgery patients, prior administration of hyperoncotic albumin solution (20%), or concomitant use of total parenteral nutrition. Intravenous use of albumin or fresh frozen plasma as a volume expanding colloid solution was not routine in the PICU and no attempts were made to correct hypoalbuminaemia per se. The diagnostic categories of the 134 patients included respiratory (n = 52), cardiac medical (n = 32), sepsis (n = 17), neurological (n = 12), metabolic (n = 9), trauma (n = 5), and others (n = 7). There were no patients with burns, nephrotic/nephritic syndrome, or protein losing enteropathy. The local ethics committee waived parental consent as all samples were taken as part of routine management.

Clinical measurements and definitions

Paired arterial samples for electrolytes, serum albumin concentration, blood lactate, and blood gas determination, were analysed within two hours of admission to PICU and again at 24 hours. After collection in standard lithium heparin bottles, concentrations of Na, K, and Cl were measured by automated ion specific electrodes and albumin assayed using the bromocresol green dye binding technique. Both pH and blood gases were measured with an automated blood gas analyser (Radiometer ABL-30, Copenhagen, Denmark) and corrected to a temperature of 37°C. Hypoalbuminaemia was defined as a serum albumin of <33 g/l[9] and extreme hypoalbuminaemia as ≤20 g/l.[3]

Metabolic acidaemia was defined by a standard bicarbonate less than 22 mmol/l.[10] The anion gap (AG) was calculated using

Abbreviations: AG, anion gap; ICU, intensive care unit; PICU, paediatric intensive care unit; PIM, paediatric index of mortality score; ROC, receiver operating characteristic

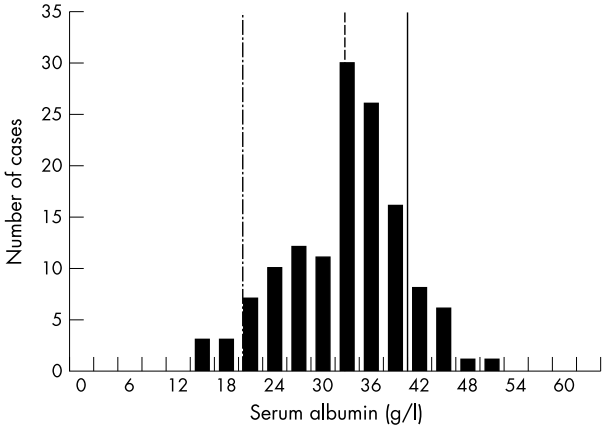

Figure 1 Histogram of admission serum albumin concentration for all patients (n = 134). Lines indicate cut off values for normal albumin concentration (solid line), hypoalbuminaemia (dashed line), and extreme hypoalbuminaemia (dashed-dotted line).

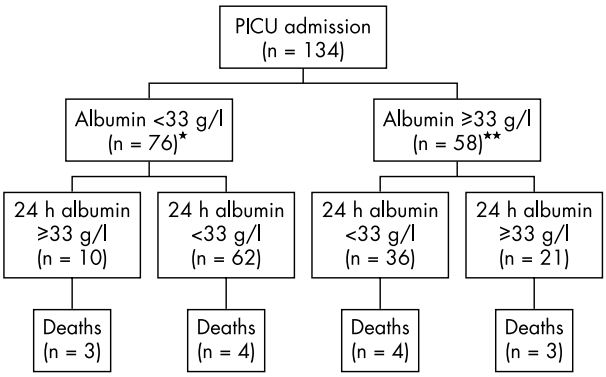

Figure 2 Temporal profile of patients with (n = 76) and without admission hypoalbuminaemia (n = 58). *One death and three discharges from PICU before 24 hours; **one discharge from PICU before 24 hours.

the formula AG = plasma (Na + K) − (Cl + TCO_2), where TCO_2 is the total content of carbon dioxide of whole blood derived from the Hendersen-Hasselbalch equation (TCO_2 = pCO_2 (mmHg) × 0.03 + standard bicarbonate).[11] A raised anion gap was defined as greater than 18 mEq/l.[10] Correction of anion gap for albumin (AG_{corr}) was obtained by assuming each g/l of albumin contributes a charge of 0.25 mEq/l, as suggested by Figge using the formula AG_{corr} = AG + 0.25 × (normal serum albumin (40 g/l) − observed albumin). Validation of Figge's formula in children using our sample population was performed (see appendix) and found to be accurate.

Risk of mortality was calculated using the paediatric index of mortality score.[12] Outcome parameters were length of ventilation, length of PICU stay, and survival to discharge from PICU. Paired samples were not obtained in five patients (four discharges from PICU and one death before 24 hours).

Statistical analysis

Continuous variables are reported as mean (SD) or as median (interquartile range) when appropriate. Fisher's exact test was used for categorical data and Student's *t* test for continuous data. The Mann-Whitney test was used when appropriate for non-normal data. Discrimination was quantified by the area under the receiver operating characteristic (ROC) curve. Serum albumin values were normally distributed (Shapiro-Wilke coefficient 0.99, p = 0.22). Bland Altman analysis was used to determine sample bias. A p value of <0.05 was considered significant.

RESULTS

Incidence and prognostic value of hypoalbuminaemia

On admission to PICU (n = 134), the mean serum albumin was 29.6 (8) g/l (fig 1). Seventy six patients (56.7%) had an admission serum albumin concentration below 33 g/l, of which 10 (7.5%) had extreme hypoalbuminaemia. At 24 hours hypoalbuminaemia persisted in 62/72 cases (86%) where paired data were available and had developed in a further 36 patients (63%) (fig 2). Consequently hypoalbuminaemia was more frequent at 24 hours: 76.0% *v* 56.7% (p = 0.001, odds ratio 2.4, 95% CI 1.4 to 4.0).

Patients admitted with and without admission hypoalbuminaemia were similar for age, weight, mechanical ventilation, and risk of mortality (table 1). However, length of PICU stay (p = 0.006) was prolonged in the hypoalbuminaemic group. Table 2 shows biochemical and acid-base profiles of the two groups. Adjusting for case mix, length of stay was similar between disease categories (Kruskal-Wallis, p = 0.14), with shortest and longest length of stay occurring in the group with sepsis at 3.2 days (IQR 1.9–6.4) and neurological disease at 5.0 days (IQR 3.7–7.5) respectively.

The crude mortality rate was 11.1% (15/134). Survival to PICU discharge was similar between patient groups (68/76 *v* 51/58, p = 0.7) as was survival in patients with extreme hypoalbuminaemia when compared to those with albumin levels greater than 20 g/l (7/10 *v* 112/124, p = 0.12). Mean albumin concentration was also similar between survivors and non-survivors (31.8 (6.8) *v* 31.0 (9.5) g/l, p = 0.69). The discriminatory ability of admission serum albumin concentration for detecting PICU non-survival was poor with an area under the ROC curve of 0.50 (95% CI 0.32 to 0.62).

Influence of correction for hypoalbuminaemia on the diagnosis of a "raised anion gap" metabolic acidosis

A raised anion gap (>18 mEq/l) was detected in 28.1% (39/263) of all samples, which increased to 44.4% (117/263) following correction for hypoalbuminaemia using Figge's formula

Table 1 Demographic characteristics for patients with and without admission hypoalbuminaemia

Variable	Albumin <33 g/l (n=76)	Albumin ≥33 g/l (n=58)	p value (Mann-Whitney)
Age (months)	7.4 (1.2 to 144.6)	14.8 (3.9 to 70.4)	0.13
Weight (kg)	6.2 (3.5 to 15.0)	9.0 (4.6 to 16.0)	0.19
Mechanical ventilation (no. cases)	65 (85.5%)	46 (79.3%)	0.36*
Length of ventilation (days)	3.9 (2.5-6.9)	2.8 (1.9 to 4.0)	0.16
Length of stay (days)	4.9 (2.8 –11.5)	3.6 (1.9 to 5.7)	0.006
PIM derived mortality risk (%)	9.0 (4.7 to 20.3)	8.1 (6.1 to 14.3)	0.67
Deaths (no. cases)	7 (12.5%)	8 (13.7%)	0.98

Results expressed as median (interquartile range).
PIM, paediatric index of mortality.
*Fisher's exact test.

Table 2 Blood chemistry and acid-base data for patients with and without hypoalbuminaemia on admission and at 24 hours

	Admission		24 hours	
	Albumin <33 g/l (n=76)	Albumin ⩾33 g/l (n=58)	Albumin <33 g/l (n=101)	Albumin ⩾33 g/l (n=33)
Blood chemistry				
Na (mEq/l)	138 (5)	140 (5)†	141 (5)*	144 (6)†
K (mEq/l)	3.9 (0.7)	3.7 (0.8)	3.7 (0.8)	3.7 (0.6)
Cl (mEq/l)	103 (6)	104 (8)	106 (7)	108 (7)
Albumin (g/l)	27 (5.3)	37.9 (3.5)‡	26.6 (4.9)	38.1 (4.4)‡
Lactate (mmol/l)	1.6 (2.0)	2.1 (2.7)	1.5 (2.1)	2.0 (3.6)
Acid-base data				
pH	7.35 (0.12)	7.32 (0.16)	7.38 (0.08)	7.35 (0.09)
pCO_2 (kPa)	5.3 (1.7)	5.6 (2.4)	5.4 (1.5)	5.3 (1.8)
SB (mmol/l)	22.7 (5.8)	22.2 (7)	24.5 (5.5)	22.5 (4.3)
Base excess	–2.1 (7.0)	–3.1 (7.8)	0 (5.7)†	–2.7 (5.2)
AG (mEq/l)	16 (6.2)	17.9 (7.3)	14.7 (5.1)*	17.8 (7.6)
Corrected AG (mEq/l)	19.2 (6.4)	18.5 (7.3)	18 (5.3)	18.2 (8)

Statistical comparisons are between the low and normal albumin groups at the same time point.
Results expressed as mean (SD).
SB, standard bicarbonate; AG, anion gap.
*p=0.01, †p=0.02, ‡p<0.001 (Student's *t* test).

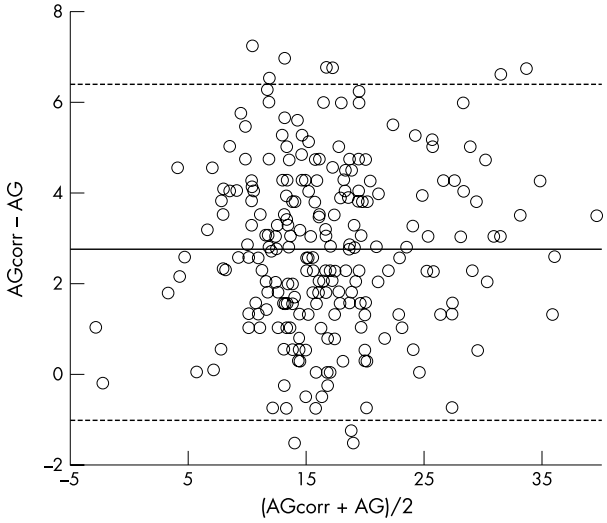

Figure 3 Bland Altman plot for all samples (n = 263) comparing the corrected (AG_{corr}) and uncorrected anion gap (AG). Solid line represents the mean bias (2.7 mEq/l), dotted lines represent limits of agreement (–1.0 to 6.4 mEq/l).

(p = 0.0001, odds ratio 2.0, 95% CI 1.4 to 2.9). In the subgroup with metabolic acidosis (standard bicarbonate concentration <22 mmol/l, n = 103) the incidence of a raised anion gap was 37.9% (39/103), which effectively doubled to 72.8% (75/103) following correction (p = 0.0001, odds ratio 2.3, 95% CI 1.4 to 3.5). Failure to correct for hypoalbuminaemia consistently underestimated the anion gap, producing a mean bias 2.7 mEq/l (95% CI 2.4 to 2.9) with limits of agreement of (3.7) mEq/l (fig 3).

DISCUSSION

Hypoalbuminaemia is a frequent occurrence in critically ill adults, with spontaneous normalisation of values often only occurring late in the recovery phase of the disease.[13] The aetiology of hypoalbuminaemia in critical illness is complex and may involve a number of mechanisms such as an imbalance between albumin synthesis and degradation, increased capillary leakage, and altered intravascular and tissue albumin distribution.[13] A low serum albumin concentration may be associated with a poor outcome independent of the underlying disease process[13]; furthermore, correction by administration of intravenous albumin does not decrease mortality.[5 14]

Surprisingly, the incidence and outcome associated with hypoalbuminaemia in critically ill children has not been documented to date. The 56.7% shown in our study is higher than that reported in adult series (30–40%).[13] This may be partly explained by inconsistencies in defining hypoalbuminaemia and varying case mix. Certainly, the adult study comprising a "general" ICU population most comparable to our own showed a similar mean albumin concentration (28.1 (8.1) *v* 29.6 (8) g/l respectively).[15]

The major finding in this study is that almost half (36/75) of the episodes of metabolic acidosis associated with a raised anion gap would be missed without correction for albumin. Indeed, the margin of error from traditional calculation of the anion gap shown by Bland-Altman analysis is as high as 7.4 mEq/l (limits of agreement −1.0 to 6.4). This apparent weakness of the anion gap has been highlighted recently.[7 8 11]

Although of interest, it was beyond the scope of this study to determine the compensatory physiological responses to hypoalbuminaemia concerning the regulation of acid-base variables, particularly with reference to Stewart's physicochemical theory of acid-base. Wilkes observed a tendency towards compensatory hyperchloraemia in patients with hypoalbuminaemia in critically ill adults.[15] In our study plasma chloride was similar between the groups with and without hypoalbuminaemia. However, support for Wilkes' observation is gained as plasma sodium concentration was lower at both time points in the hypoalbuminaemic group (p < 0.05) resulting in a "relative" hyperchloraemia.[19] We made no attempt to analyse primary acid-base disturbances due to abnormalities in albumin concentration alone.

Very few studies have followed the progression of hypoalbuminaemia in the critically ill. We showed that the increased incidence at 24 hours (57–76%) was due both to its development in patients with normal admission albumin concentrations (36/58) and lack of resolution in patients admitted with hypoalbuminaemia (62/76, fig 2). The aetiology of this may be multifactorial, including: disease progression, a reduced capacity to synthesise albumin with acute disease,[16] or minimal use of intravenous albumin as a volume expanding solution in our PICU.

In contrast to adult studies we were unable to document a higher disease severity at admission in the hyopalbuminaemic patients as demographic data, number of ventilated cases, length of ventilation, and PIM scores were similar between both groups. Admission acid-base data (pH, base excess, anion gap, and blood lactate), which are often used as surrogate markers of disease severity,[17 18] were also similar between

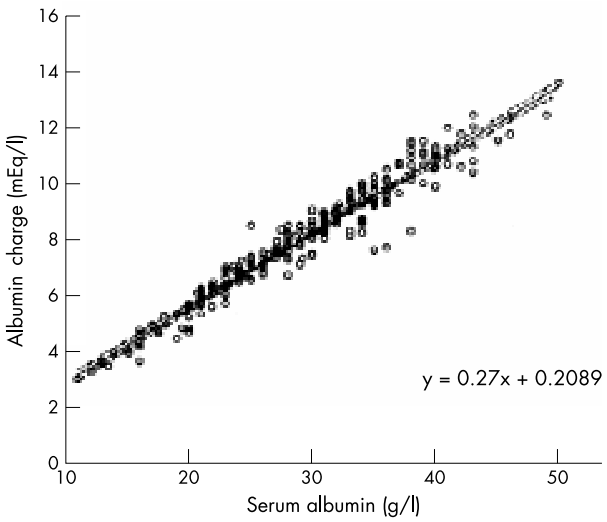

Figure 4 Regression plot for the serum albumin concentration and albumin charge derived from Stewart's strong ion theory. The slope of the line is 0.27. Dotted lines represent 95% confidence intervals.

groups. However, length of stay in the PICU, reflecting a longer ventilator free period, was significantly prolonged in patients with hypoalbuminaemia. The explanation for this is not clear but may be related to an increase in complications and morbidity, factors which were not specifically addressed in this study.

Finally, we did not find a relation between hypoalbuminaemia and mortality as the mean serum albumin concentrations between survivors and non-survivors did not differ (31.8 (6.8) *v* 31.0 (9.5) g/l, p = 0.96). Furthermore, this held true in the small group of patients with extreme hypoalbuminaemia (≤20 g/l), in contract to the study by Reinhart and colleagues.[3] We, however, recognise the limited predictive value of single biochemical parameters such as serum albumin in predicting mortality.

Two potential limitations of this study exist. First, we made no attempt to define the aetiology of a raised anion gap metabolic acidosis, nor were the clinical consequences of its underreporting examined. This is partly due to the ongoing controversies in how best to treat acidosis and wide variability in personal clinician preferences. Second, we do not know whether lack of use of intravenous albumin or other albumin containing solutions, such as fresh frozen plasma for volume expansion or correction of coagulopathies influenced our results, specifically in those who went on to develop hypoalbuminaemia at 24 hours.

In conclusion we have shown a high incidence of hypoalbuminaemia in critically ill children requiring admission for intensive care. Contrary to the adult population, hypoalbuminaemia did not appear to be a risk factor for mortality. However, its presence produces a gross underestimation of the true anion gap, which can be corrected using Figge's formula. The clinical consequences of underestimating the anion gap in hypoalbuminaemic patients and its impact on the treatment of metabolic acidosis warrant further investigation.

APPENDIX: VALIDATION OF THE FORMULA OF FIGGE FOR PAEDIATRIC PATIENTS

The anion gap is the difference between measured cations (Na, K) and anions (HCO_3, Cl). The major contributor to a normal anion gap is albumin, by value of its net negative charge (for example, an albumin concentration of 40 g/l typically has a net negative charge of 12 mEq/l). This net negative charge is dependent on two factors: the absolute concentration of albumin and pH. The relevance of pH stems from the molecular structure of albumin which has 16 negatively charged histidine residues. These have a pK within the physiological pH range (7.2–7.3), accounting for its buffering effect.

The influence of both concentration and pH on albumin charge has recently been described by Figge and others.[7] They showed that 94% of the variability in albumin charge was explained by albumin concentration alone in critically ill adults, observing a 0.25 change in albumin charge per g/l of albumin. This was incorporated into a correction factor to improve the accuracy of the anion gap as follows: corrected anion gap = anion gap + 0.25 × (40 g/l – patient albumin concentration).

We repeated this analysis in critically ill children. Here measured albumin concentration was plotted against albumin charge (fig 4). Albumin charge was calculated using the formula proposed by Fencl: albumin charge (mEq/l) = serum albumin (g/l) × (0.123 × pH − 0.631).[8 20 21] As with Figge, we found the majority of *change* in albumin charge was explained by *change* in albumin concentration ($r^2 = 0.9$). However the rate of change (slope) was slightly different (0.27 *v* 0.25). Substituting 0.27 for Figge's "adult" value of 0.25 in the anion gap correction formula resulted in little clinical impact, only diagnosing one extra case of a raised anion gap in all samples. Hence we retained Figge's original correction factor in this study.

Authors' affiliations

A Durward, A Mayer, S Skellett, D Taylor, S Hanna, S M Tibby, I A Murdoch, Paediatric Intensive Care Unit, Guy's Hospital, London, UK

REFERENCES

1 **Blunt MC**, Nicholson JP, Park GR. Serum albumin and colloid osmotic pressure in survivors and nonsurvivors of prolonged critical illness. *Anaesthesia* 1998;**53**:755–61.
2 **Fleck A**, Raines G, Hawker F, *et al*. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985;(8432):781–4.
3 **Reinhardt GF**, Myscofski JW, Wilkens DB, *et al*. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. *J Parenter Enteral Nutr* 1980;**4**:357–9.
4 **Rady MY**, Ryan T. Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. *Crit Care Med* 1999;**27**:340–7.
5 **Foley EF**, Borlase BC, Dzik WH, *et al*. Albumin supplementation in the critically ill. A prospective, randomized trial. *Arch Surg* 1990;**125**:739–42.
6 **Klonoff-Cohen H**, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the healthy elderly. *J Clin Epidemiol* 1992;**45**:207–12.
7 **Figge J**, Jabor A, Kazda A, *et al*. Anion gap and hypoalbuminaemia. *Crit Care Med* 1998;**26**:1807–10.
8 **Fencl V**, Jabor A, Kazda A, *et al*. Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Med* 2000;**162**:2246–51.
9 **Shann F**. *Drug doses*, 8th edn. Melbourne: Collective Pty Ltd, 1994.
10 **Anonymous**. Normal reference values. *N Engl J Med* 1992;**327**:718–24.
11 **Reilly RF**, Anderson RJ. Interpreting the anion gap. *Crit Care Med* 1998;**26**:1771–2.
12 **Shann F**, Pearson G, Slater A, *et al*. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med* 1997;**23**:201–7.
13 **Nicholson JP**, Wolmarans MR, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000;**85**:599–610.
14 **Golub R**, Sorrento JJ Jr, Cantu R Jr, *et al*. Efficacy of albumin supplementation in the surgical intensive care unit: a prospective, randomized study. *Crit Care Med* 1994;**22**:613–19.
15 **Wilkes P**. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. *J Appl Physiol* 1998;**84**:1740–8.
16 **Cogo PE**, Carnielli VP, Rosso F, *et al*. Protein turnover, lipolysis, and endogenous hormonal secretion in critically ill children. *Crit Care Med* 2002;**30**:65–70.
17 **Hatherill M**, Sajjanhar T, Tibby SM, *et al*. Serum lactate as a predictor of mortality after paediatric cardiac surgery. *Arch Dis Child* 1997;**77**:235–8.
18 **Moomey CB Jr**, Melton SM, Croce MA, *et al*. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med* 1999;**27**:154–61.
19 **Durward A**, Skellett S, Mayer A, *et al*. The value of the chloride: sodium ratio in differentiating the aetiology of metabolic acidosis. *Intensive Care Med* 2001;**27**:828–35.
20 **Stewart PA**. Independent and dependent variables of acid-base control. *Respir Physiol* 1978;**33**:9–26.
21 **Stewart PA**. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983;**61**:1444–61.