Diagnosis of Metabolic Acid–Base Disturbances in Critically Ill Patients

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We compare two commonly used diagnostic approaches, one relying on plasma bicarbonate concentration and "anion gap," the other on "base excess," with a third method based on physicochemical principles, for their value in detecting complex metabolic acid–base disturbances. We analyzed arterial blood samples from 152 patients and nine normal subjects for pH, P_{CO_2}, and concentrations of plasma electrolytes and proteins. Ninety-six percent of the patients had serum albumin concentration ⩽ 3 SD below the mean of the control subjects. In about one-sixth of the patients, base excess and plasma bicarbonate were normal. In a great majority of these apparently normal samples, the third method detected simultaneous presence of acidifying and alkalinizing disturbances, many of them grave. The almost ubiquitous hypoalbuminemia confounded the interpretation of acid–base data when the customary approaches were applied. Base excess missed serious acid–base abnormalities in about one-sixth of the patients; this method fails when the plasma concentrations of the nonbicarbonate buffers (mainly albumin) are abnormal. Anion gap detected a hidden "gap acidosis" in only 31% of those samples with normal plasma bicarbonate in which such acidosis was diagnosed by the third method; when adjusted for hypoalbuminemia, it reliably detected the hidden abnormal anions. The proposed third method identifies and quantifies individual components of complex acid–base abnormalities and provides insights in their pathogenesis.

Two diagnostic systems are commonly used for interpreting acid–base data. One centers on plasma bicarbonate concentration ($[HCO_3^-]$) (1) and "anion gap" (AG) (2), and the other on "base excess/deficit" (BE) (3). These two systems do not ascribe an explicit role to abnormal concentrations of plasma nonbicarbonate buffers in the pathogenesis of nonrespiratory (metabolic) acid–base abnormalities. We posit that, owing to this omission, important metabolic acid–base abnormalities can be missed in the complex disturbances seen in critically ill patients.

The main "nonbicarbonate buffers" in blood plasma are the plasma proteins (4); another (minor) component of this buffer system is inorganic phosphate (Pi) (5). Among the plasma proteins it is the serum albumin that participates in the chemical equilibria that determine the acid–base status of plasma, by carrying a variable net negative charge at pH values compatible with life (6, 7). Because this negative charge figures in the electroneutrality of plasma, the amphiprotic molecule of albumin can be viewed to act as a nonvolatile weak acid in plasma's chemical equilibria. Normal serum globulins do not carry a significant net electric charge at pH values prevailing in plasma (6, 7).

Hypoalbuminemia is a common finding in critically ill patients (8); it may confound the customary interpretation of acid–base data, owing to the contribution of albumin to plasma's acid–base equilibria. In particular, in the diagnostic system relying on plasma $[HCO_3^-]$, hypoalbuminemia is known to cause uncertainty in the interpretation of the AG (2, 9–11); if AG is adjusted for abnormal albumin concentration (12, 13), its usefulness should improve (14). With the BE approach (3), no distinction is made between a deficit/excess of weak or strong nonvolatile acids (11); therefore, the alkalinizing effect of hypoalbuminemia (= deficit of a weak nonvolatile acid) may offset and hide an excess of unmeasured anions (such as lactate or keto acids).

We offer a third system of evaluation of all primary causes of acid–base abnormalities in plasma (7, 15, 16). It applies Stewart's approach to acid–base chemistry (17) and is based on a mathematical model of plasma that has been validated by experiments *in vitro* (6, 7); it is outlined in METHODS and described in detail elsewhere (15). Using clinical data from critically ill patients, we compare the three diagnostic approaches for their ability to detect, characterize, and quantify complex metabolic acid–base abnormalites seen in such patients.

METHODS

The study was approved by the Grant Committee of the Ministry of Health, Czech Republic. Arterial blood samples were drawn from nine healthy subjects in the postprandial state (5 males, 4 females, age 20 to 25 yr); all gave written informed consent. The patient data are single measurements in 152 patients in the intensive care unit (ICU) of the Faculty Hospital Bulovka in Prague (37% with trauma, including craniocerebral trauma; 20% with acute respiratory distress syndrome [ARDS] and related conditions, most of them mechanically ventilated; 18% with cardiovascular failure, including acute myocardial infarction, cardiopulmonary resuscitation; 16% with postoperative complications, including sepsis, renal and multiple organ failure; 9% with metabolic disturbances, including diabetic ketoacidosis and intoxications). Arterial blood gases, serum electrolytes, and proteins were measured in the same blood sample. The raw data are part of a database that served for another study (12).

pH and P_{CO_2} were measured with the ABL300 Blood Gas Analyzer (Radiometer) or with the AVL 990 analyzer. Samples of separated plasma were analyzed for Na and K (FLM3 flame photometer, Radiometer), Ca and Mg (atomic absorption spectrophotometer AAS2, Zeiss), Cl^- (Chloride Titrator CMT10, Radiometer), inorganic phosphate with molybdate, total protein with biuret, and serum albumin with bromcresyl-purple photometries.

From the measured pH and P_{CO_2} we calculated $[HCO_3^-]$ using the Henderson-Hasselbalch equation, and BE with Siggaard-Andersen's formulas for BE in plasma and in extracellular fluid (18). Anion gap was calculated as $([Na^+]+[K^+]) - ([Cl^-]+[HCO_3^-])$, and adjusted for the effect of abnormal albumin concentration with the formula: $AG_{adjusted}$ (milliequivalents per liter) = $AG_{observed} + 0.25 \times$ ([normal albumin] − [observed albumin]) (in grams per liter) (12, 13).

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Pathophysiologic Evaluation of Acid–Base Balance

Acid–base state in a body fluid is physically determined by several "independent variables" (variables that can change primarily and independently of one another). In blood plasma *in vivo*, the independent variables are: (*1*) P_{CO_2}; (*2*) the "strong ion difference" (SID), i.e., the difference between the sums of all the strong (fully dissociated, chemically nonreacting) cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and all the strong anions ($Cl^-$and other strong anions); and (*3*) concentrations of nonvolatile weak acids (i.e., for each of them, the sum of its dissociated and undissociated forms, Stewart's symbol A_{tot}). Normal acid–base status obtains when the independent variables have normal (empirically established) values. Abnormality of one or more of the independent variables underlies all acid–base disturbances. Adjustment of the independent variables is the essence of all therapeutic interventions, because none of the "dependent variables" (e.g., pH, BE, $[HCO_3^-]$) can be changed primarily or individually: the dependent variables change, all of them simultaneously if, and only if, one or more of the independent variables changes.

A classification of acid–base disturbances based on this approach is shown in Table 1. In this view, metabolic acid–base disturbances can be caused by two types of abnormalities, discussed next: abnormal SID and abnormal concentrations of nonvolatile weak acids.

As for the SID, its value can change in two general ways: first, through excess or deficit of water in plasma, by which the strong cations and the strong anions are equally diluted or concentrated (dilutional acidosis and concentrational alkalosis), detected by abnormal $[Na^+]$; and second, by changing the total concentration of the strong anions only (this is true because concentrations of strong cations other than Na^+ are regulated in extracellular fluids within narrow limits, for purposes unrelated to acid–base balance or osmolarity).

There are two substances that act as nonvolatile weak acids and have concentrations in plasma great enough so that changes in them can produce significant acid–base disturbances: inorganic phosphate ([Pi], millimol per liter or milligrams per deciliter) and serum albumin ([Alb], grams per liter).

One can see from Table 1 that changes in these three independently variable quantities [Alb], [Pi], and SID can have additive or offsetting effects on the metabolic acid–base balance. Such offsetting effects may result in normal values of the dependent variables $[HCO_3^-]$ and BE, while some independent variables are abnormal. Such condition is not considered to be a normal acid–base status. This differs from the diagnostic approach based on BE; there the condition BE = 0 (i.e., pH = 7.40 at P_{CO_2} = 40 mm Hg) is, by definition, normal acid–base status, whatever the values of the independent variables SID and A_{tot} are (14; *see* Appendix in the online web depository of the *Journal*).

The quantities [Alb] (grams per liter) and [Pi] (millimol per liter) can be directly evaluated from routinely available serum analyses. The information necessary for the evaluation of SID and strong anions other than Cl^- ($[XA^-]$ in Table 1) can be derived along the following lines.

Figure 1 shows how it follows from the requirement of electroneutrality that SID in plasma can be derived as the sum of $[HCO_3^-]$ plus the negative electric charges contributed by albumin ($[Alb^-]$) and by inorganic phosphate ($[Pi^-]$) (7, 15, 23):

$$SID = [HCO_3^-] + [Alb^-] + [Pi^-] \quad (1)$$

For this, $[HCO_3^-]$ is available from arterial blood gas measurements, and $[Alb^-]$ and $[Pi^-]$ (milliequivalents per liter) are calculated from the measured [Alb] (grams per liter), [Pi] (millimol per liter), and pH (5,7 Appendix B):

$$[Alb^-] = [Alb] \times (0.123 \times pH - 0.631) \quad (2a)$$

$$[Pi^-] = [Pi] \times (0.309 \times pH - 0.469) \quad (2b)$$

(for clinical determinations of SID simpler estimates are satisfactory; *see* DISCUSSION).

"Unidentified strong anions" (XA^- in Figure 1) are strong anions other than Cl^- (lactate, keto acids and other organic anions, sulfate); in certain disease states, their concentrations increase (*see* Table 1). Total $[XA^-]$ cannot be direcly measured in plasma; Figure 1 shows that they can be derived as follows:

$$[XA^-] = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - [Cl^-] - SID \quad (3)$$

Water excess/deficit is detected as abnormal $[Na^+]$ (Table 1). To appreciate and quantitate a Cl^- excess or deficit when abnormalities of plasma water are present, the observed $[Cl^-]$ has to be corrected for the resulting dilution/concentration. This can be done by multiplying the observed $[Cl^-]$ by a correcting factor, e.g.:

$$[Cl^-]_{corrected} = [Cl^-]_{observed} \times ([Na^+]_{normal} / [Na^+]_{observed}), \quad (4)$$

and chloride excess/deficit (millimols per liter) $\approx [Cl^-]_{normal} - [Cl^-]_{corrected}$. Similar considerations apply to the evaluation of $[XA^-]$.

If [Alb], [Pi], and SID with $[XA^-]$, $[Cl^-]$, and $[Na^+]$ are known, all the information necessary for a detailed pathophysiologic interpretation of the metabolic acid–base data is available (Table 1).

TABLE 1

CLASSIFICATION OF PRIMARY ACID–BASE DISTURBANCES

	Acidosis	Alkalosis
I. Respiratory	↑ P_{CO_2}	↓ P_{CO_2}
II. Nonrespiratory (metabolic)		
1. Abnormal SID		
a. Water excess/deficit*	↓ SID, ↓ $[Na^+]$	↑ SID, ↑ Na^+]
b. Imbalance of strong anions		
i. Chloride excess/ deficit†	↓ SID, ↑ $[Cl^-]$	↑ SID, ↓ $[Cl^-]$
ii. Unidentified anion excess‡	↓ SID, ↑ $[XA^-]$	—
2. Nonvolatile weak acids		
a. Serum albumin	↑ [Alb]§	↓ [Alb]
b. Inorganic phosphate	↑ [Pi]	↓ [Pi]‖

Definition of abbreviations: [Alb] = concentration of serum albumin; [Pi] = concentration of inorganic phosphate; SID = strong ion difference (Σ[strong cations] − Σ[strong anions]); $[XA^-]$ = concentration of unidentified strong anions.

* Dilutional acidosis and concentrational alkalosis: when there is a deficit or excess of water in plasma (by the criterion of an abnormal $[Na^+]$), the strong cations and anions are concentrated or diluted equally; this increases or reduces the SID by the same degree: if C − A = D, then a × C − a × A = a × D; concentrational alkalosis and dilutional acidosis as used here are not to be confused with "contraction alkalosis" and "dilution acidosis" (19). The latter terms have been used in reference to supposed acid–base effects of decrease and increase in extracellular fluid volume, respectively. However, changes in volume do not, by themselves, change any of the variables that determine acid–base state. If the extracellular volume is expanded by infusion of NaCl saline, hyperchloremic acidosis results (20, 21).

† Hyperchloremic acidosis and hypochloremic alkalosis.

‡ Includes organic acids (lactate, keto acids in "metabolic acidosis" *sensu strictiori*; formate or salicylate in intoxications), and sulfate and other anions in chronic renal failure (the pK values of all these organic acids are at least three orders of magnitude lower than the plasma pH compatible with life; therefore, they are always > 99.9% dissociated in plasma and their anions can be included in the definition of the SID); unlike "anion gap," [XA] does not include inorganic phosphate (which here is evaluated separately and directly, as one of the nonvolatile weak acids).

§ Component of acidosis in severe extracellular volume loss, such as in cholera (22).

‖ This source of alkalosis is clinically insignificant: the normal value of [Pi] (∼ 1 mmol/L) cannot decrease enough to have an appreciable acid–base effect.

Adapted from (15).

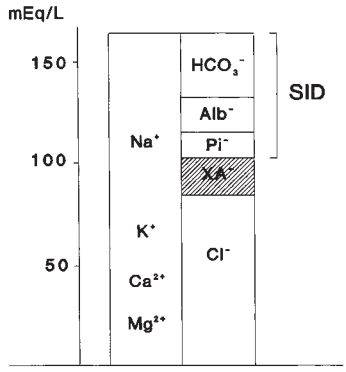

Figure 1. Electroneutrality in blood plasma: sum of positive charges equals the sum of negative charges, as indicated by equal heights of the columns representing cations and anions. Omitted (as insignificant on the scale shown) are ions having micromolar or nanomolar concentrations in plasma (OH^-, CO_3^{2-}, and H^+). Alb^- and Pi^- are negative electric charges displayed by serum albumin and inorganic phosphate, respectively. XA^- = unidentified strong anions; SID = strong ion difference.

TABLE 2

ACID–BASE VARIABLES IN ARTERIAL BLOOD PLASMA

	Number Subjects* ($n = 9$)	Patients† ($n = 152$)
Measured quantities		
$[Na^+]$, mEq/L	142 ± 2	117–159
$[K^+]$, mEq/L	4.1 ± 0.3	2.3–6.8
[Ca], mmol/L‡	2.3 ± 0.1	1.1–2.6
[Mg, mmol/L‡	0.8 ± 0.05	0.4–1.3
$[Cl^-]$, mEq/L	106 ± 2	80–121
[Pi], mmol/L	1.0 ± 0.2	0.2–3.4
[TP], g/L	77 ± 4	28–94
[Serum albumin], g/L	44 ± 3	4–43
pH	7.422 ± 0.015	7.11–7.58
P_{CO_2}, mm Hg	38 ± 1.5	16–90
Derived quantities, mEq/L		
$[HCO_3]$	24.5 ± 0.5	12–39
$AG_{observed}$	16 ± 2	4–38
$AG_{adjusted}$	15 ± 2	5–42
BE_{pl}	+0.3 ± 0.5	−15–+14
BE_{ecf}	+0.3 ± 0.5	−18–+14
SID	39 ± 1	18–47
$[Cl^-]_{corrected}$§	106 ± 2	90–123
$[XA^-]$	8 ± 2	2–35
$[XA^-]_{corrected}$§	8 ± 2	2–37

Definition of abbreviations: $AG_{adjusted}$ = anion gap adjusted for abnormal albumin concentration = $AG_{observed}$ + 0.25 × ([normal albumin] − [observed albumin]) (12); $AG_{observed}$ = observed anion gap = ($[Na^+]$ + $[K^+]$) − ($[Cl^-]$ + $[HCO_3^-]$); BE = base excess/deficit for plasma or extracellular fluid (18); Pi = inorganic phosphate (mg/dL = 3.09 mmol/L); SID = strong ion difference (*see* Methods, Equation 1); TP = total plasma proteins; $[XA^-]$ = concentration of unidentified strong anions (Equation 3).

* Means ± S.D.

† Ranges.

‡ mEq/L = 2 × mmol/L.

§ Corrected for water excess/deficit (Equation 4). SID = $[HCO_3^-]$ + $[Alb^{x-}]$ + $[Pi^{y-}]$.

RESULTS

Table 2 shows the measured and some derived acid–base variables. In the normal subjects, the measured quantities as well as the customary derived quantities BE, $[HCO_3^-]$, and anion gap were within the range of established normal values (2, 3, 24). SID was 39 ± 1 and $[XA^-]$ 8 ± 2 (mEq/L; means ± SD).

In the patients, pH indicated severe acidemia to pronounced alkalemia, as a result of extensive respiratory or metabolic abnormalities. Metabolic acid–base abnormalities recognized by the traditional diagnostic approaches—BE or $[HCO_3^-]$ with AG—varied widely in magnitude. Hypoalbuminemia ([Alb] ⩽ 3 SD below the mean of the normals) was present in 96% of the patients. The classification proposed here in Table 1 and previously (15) would identify and quantify various individual metabolic alkalinizing and acidifying abnormalities. Among the alkalinizing deviations from normal are hypoalbuminemia (lowest observed [Alb] 4 g/L), hypophosphatemia (lowest [Pi] 0.2 mmol/L or 0.6 mg/dl), and increased SID (highest 47 mEq/L). The acidifying nonrespiratory deviations are hyperphosphatemia (highest [Pi] 3.4 mmol/L or 10.5 mg/dl), and reduced SID (lowest 18 mEq/L). Among the abnormalities that change the value of SID the following are found: (*1*) abnormalities in water content in plasma, producing dilutional acidosis (lowest $[Na^+]$ 117 mEq/L) or concentrational alkalosis (highest $[Na^+]$ 159 mEq/L); (*2*) abnormal $[Cl^-]$, producing hypochloremic alkalosis (lowest $[Cl^-]_{corrected}$ 90 mEq/L) or hyperchloremic acidosis (highest $[Cl^-]_{corrected}$ 123 mEq/L); (*3*) presence of excess "strong anions other than Cl^-": highest $[XA^-]_{corrected}$ 37 mEq/L (corrected for water excess/deficit in plasma, Equation 4).

Actual examples of metabolic acid–base abnormalities detected with this approach, some of them complex, are shown in Table 3 (*see* Table 2 for reference normal values of the variables). In Patient 18 (chronic obstructive pulmonary disease [COPD], bronchopneumonia, congestive heart failure), hypoalbuminemia is the only source of the severe metabolic alkalosis. The traditional methods report a very high $[HCO_3^-]$ and BE of +9 mEq/L; however, SID, $[Na^+]$, $[Cl^-]$, and $[XA^-]$ are all normal (as is $AG_{adjusted}$). This is a case of simple hypoalbuminemic alkalosis. In patient 59 (postoperative multiple organ failure), SID is reduced by ∼ 20 mEq/L, which is caused by the combination of plasma water excess

TABLE 3

EXAMPLES OF COMPLEX ACID–BASE DISTURBANCES

	Patient No.								
	18	59	63	81	29	51	88	41	53
Measured quantities									
Na^+, mEq/L	140	117	159	131	130	133	137	143	125
K^+, mEq/L	4.8	3.9	3.6	4.2	3.5	3.9	4.9	4.5	5.2
Ca^{2+}, mEq/L	3.4	3.0	4.2	3.6	4.0	4.2	3.2	4.0	3.2
Mg^{2+}, mEq/L	1.6	1.4	2.2	2.2	1.6	1.6	1.6	1.6	1.0
Cl^-, mEq/L	103	92	121	86	90	96	102	111	98
Pi, mmol/L	0.9	0.6	0.5	2.3	0.9	0.4	0.3	1.2	0.9
Albumin, g/L	15	6	9	8	20	10	6	18	13
pH	7.45	7.33	7.55	7.32	7.50	7.36	7.40	7.40	7.40
P_{CO_2}, mm Hg	48	30	29	41	30	45	39	41	39
Derived quantities									
HCO_3^-, mEq/L	33	15	25.5	21	23.5	25.5	24	25	24
$AG_{observed}$, mEq/L	7	13	16	28	20	15	16	11	8
$AG_{adjusted}$, mEq/L	15	23	25	37	26	24	25	18	16
BE_{pl}, mEq/L	+9	−10	+2	−4	0	+1	0	0	0
BE_{ecf}, mEq/L	+10	−10	+3.5	−4.5	+1	+1	0	0	0
SID, mEq/L	39	18	29	27	31	29	26	32	29
$Cl^-_{corrected}$, mEq/L	105	112	108	93	98	103	106	110	111
$XA^-_{corrected}$, mEq/L	9	18	17	30	20	19	19	9	8

Definition of abbreviations: $AG_{observed}$ and $AG_{adjusted}$ = anion gap observed and adjusted -abnormal albumin, respectively; BE_{pl} and BE_{ecf} = base excess in plasma and in extracellular fluid, respectively (18); $Cl^-_{corrected}$ and $XA^-_{corrected}$ = chloride and unidentified anions, corrected for water excess/deficit, respectively; Pi = inorganic phosphate; .

($[Na^+]$ = 117 mEq/L), chloride excess (appreciated only with $[Cl^-]_{corrected}$), and by increased $[XA^-]$; the alkalinizing hypoalbuminemia mitigates the SID acidosis: BE_{pl}, which is claimed to be a measure of the change in plasma SID (25, 26), is − 10 mEq/L, i.e., it detects only one-half of the change in SID. $AG_{observed}$ is low normal (but abnormal anions are shown by the high $[XA^-]$.) The acidemia is mitigated by hypocapnia.

In patient 63 (cardiac arrest, cardiopulmonary resuscitation, hypoxic encephalopathy), reduction of SID by ∼ 10 mEq/L results from the offsetting effects of high $[XA^-]$ (lowering SID), and plasma water deficit ($[Na^+$ = 159 mEq/L, increasing SID). The resulting low-SID acidosis is hidden by the alkalinizing hypoalbuminemia. BE misses the high-$[XA^-]$ acidosis and interprets the acid–base status as a mild metabolic alkalosis. $[HCO_3^-]$ is high-normal and $AG_{observed}$ misses the high abnormal anions. No large chloride excess is present, although the measured $[Cl^-]$ would suggest it. The alkalemia is the result of severe hypocapnia.

In patient 81 (multiple trauma, ARDS, sepsis), SID is reduced by ∼ 12 mEq/L (owing to plasma water excess and very high $[XA^-]$) and [Pi] is elevated. These acidoses are mitigated by alkaloses of chloride deficit and hypoalbuminemia: $[HCO_3^-]$ is only slightly lowered; $AG_{observed}$ is elevated; base deficit is only − 4 mEq/L; i.e., the severity of the acidosis is greatly underestimated.

In patient 29 (diabetic ketoacidosis), SID is reduced to 31 mEq/L, owing to the offsetting effects of high $[XA^-]$ with plasma water excess (lowering SID), and Cl^- deficit (increasing SID). The low-SID acidosis is almost exactly balanced by alkalosis of hypoalbuminemia, so that BE and $[HCO_3^-]$ are within normal limits; $AG_{observed}$ is high normal. Both traditional diagnostic approaches miss the high-$[XA^-]$ acidosis and interpret the data as a simple respiratory alkalosis, with no metabolic abnormalities.

In patient 51 (head trauma, coma, acute renal failure), SID is reduced by ∼ 10 mEq/L. This is caused by increased $[XA^-]$ and by plasma water excess ($[Na^+]$ = 133 mEq/L). No chloride deficit is present, although the measured $[Cl^-]$ would suggest it. The low-SID acidosis is balanced by hypoalbuminemic alkalosis, so that both BE and $[HCO_3^-]$ with $AG_{observed}$ appear normal. BE misses the elevated $[XA^-]$ and interprets the data as simple respiratory acidosis, with no metabolic abnormalities.

In patient 88 (postoperative multiple organ failure), SID is reduced by ∼ 13 mEq/L owing to very high $[XA^-]$. This acidosis is exactly matched by the alkalinizing hypoalbuminemia, so that both BE and $[HCO_3^-]$ (and $AG_{observed}$) are within normal limits; a severe metabolic acidosis is missed. However, in all samples where $[XA^-]$ or [Pi] were elevated, adjusting AG for hypoalbuminemia (12)—as expected—did allow detection of this abnormality.

In patient 41 (multiple trauma), SID is reduced to 32 mEq/L by chloride excess. The hyperchloremic acidosis is exactly matched by alkalosis of hypoalbuminemia, so that both BE and $[HCO_3^-]$ are normal.

In patient 53 (liver cirrhosis, bleeding varices), SID is reduced by ∼ 10 mEq/L, as a result of excess of plasma water ($[Na^+]$ = 125 mEq/L) and Cl^- (the latter appreciated only with $[Cl^-]_{corrected}$). This mixed low-SID acidosis is exactly matched by hypoalbuminemic alkalosis. BE and $[HCO_3^-]$ are normal; both traditional diagnostic approaches miss this mixed metabolic acidosis.

In Table 4 we selected those patients in whom the values of BE and $[HCO_3^-]$ were within the range of their normal values (within ± 2 SD of control in Table 2). In these samples with apparently normal customary indices of the metabolic acid–base status, the approach outlined in Table 1 detected abnormalities with surprising frequency, some of them severe and grave. The acidifying effect of low SID (present in 95% of these samples with normal BE and $[HCO_3^-]$, and caused by excess of Cl^- or XA^-, or by plasma dilution) was offset and thus hidden by the alkalinizing effect of hypoalbuminemia (seen in 100% of these apparently normal samples). Hypochloremic alkalosis (present in 40% and 32%, respectively) was offset by elevated $[XA^-]$, or by dilutional or hyperphosphatemic acidoses. In 14% of the samples with normal $[HCO_3^-]$, the observed anion gap was elevated (⩾ 3 SD above the means of normals); adjusting the anion gap for hypoalbuminemia (12) increased the detection of abnormal "gap anions" fourfold.

TABLE 4

HIDDEN METABOLIC ACID–BASE DISTURBANCES IN PATIENTS WITH NORMAL* BASE EXCESS OR PLASMA BICARBONATE CONCENTRATION

	B_{ecf}† −0.7 to +1.3 mEq/L (*n = 20*)	$[HCO_3]$ 23.5 to 25.5 mEq/L (*n = 22*)
SID ⩽ 36 mEq/L‡	19 (95%) [26]**	21 (95%) [26]
Hyperchloremic acidosis;		
[Cl] ⩾ 112 mEq/L§‖	2 (10%) [114]	4 (18%) [121]
[XA] ⩾ 14 mEq/L§‖	7 (35%) [25]	12 (55%) [22]
Dilutional acidosis;		
$[Na^+]$ ⩽ 136 mEq/L‡	11 (55%) [125]	11 (50%) [125]
Hyperphosphatemic acidosis;		
[Pi] ⩾ 2.0 mmol/L¶	2 (10%) [2.7]	2 (9%) [2.7]
Concentrational alkalosis;		
$[Na^+]$ ⩾ 148 mEq/L§	2 (10%) [153]	2 (9%) [159]
Hypochloremic alkalosis;		
$[Cl^-]$ ⩽ 100 mEq/L‡‖	8 (40%) [90]	7 (32%) [90]
Hypoalbuminemic alkalosis;		
[Serum albumin] ⩽ 35 g/L‡	20 (100%) [6]	22 (100%) [3]
$AG_{observed}$ ⩾ 22 mEq/L§	3 (14%) [25]	
AGadjusted ⩾ 21 mEq/L§	13 (59%) [30]	

Definition of abbreviations: $AG_{adjusted}$ (milliequivalents per liter) = anion gap adjusted for abnormal albumin concentration = $AG_{observed}$ + 0.25 × ([normal albumin] − [observed albumin]) (grams per liter) (12); $AG_{observed}$ = observed anion gap = $([Na^+] + [K^+]) - ([Cl^-]+[HCO_3^+])$; [Pi] = inorganic phosphate concentration; SID = strong ion difference (*see* METHODS, Equation 1); $[XA^-]$ = concentration of unmeasured strong anions (Equation 3).

* Within ± 2 SD of mean control value (*see* Table 2).

† Base excess/deficit for extracellular fluid (15).

‡ ⩽ 3 SD below the mean of controls (*see* Table 2).

§ ⩾ 3 SD above the mean of controls.

‖ Corrected for water excess/deficit (Equation 4).

¶ Arbitrary cutoff.

** Data in brackets are extreme values in the groups.

DISCUSSION

All the acid–base disturbances seen here could be easily interpreted, and evaluated directly and quantitatively, as abnormalities of the independent variables P_{CO_2}, [Alb], [Pi], and SID. The data required for such comprehensive evaluation (P_{CO_2} and pH, [Alb], [Pi], and the concentrations of the electrolytes Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-) are available from blood gas measurements and serum chemistry profiles.

Though determination of $[Mg^{2+}]$ is not included in routine chemistry profiles, its changes are usually so small that they can be neglected and a constant value for $[Mg^{2+}]$ can be assumed in the calculation of $[XA^-]$ (Equation 3). In our data from very ill patients, $[Mg^{2+}]$ varied from 0.8 to 2.6 mEq/L; when the measured $[Mg^{2+}]$ was replaced by a constant of 1.7, the effect on the calculated values of $[XA^-]$ was negligible: the mean difference was 0.1 mEq/L (±0.3, SD; range −0.9 to +0.9 mEq/L). This simplification is not applicable if large doses of Mg salts are administered parenterally (e.g., in treatment of preeclamp-

sia) (25). For bedside evalutation of data the formula for SID (Equations 1, 2a, and 2b) can also be simplified to

$$SID \approx [HCO_3^-] + 0.28 \times [Alb]\ (g/L) + 1.8 \times [Pi]\ (mmol/L) \quad (5)$$

The factors 0.28 and 1.8 are negative electric charges (in milliequivalents) displayed by 1 g of albumin and 1 mmol of phosphate, respectively, in plasma at pH = 7.40 (7); if the units of [Pi] are milligrams per deciliter, the factor for $[Pi^-]$ is 0.6. The variation of these factors with the actual pH or with ion binding is negligible for the purpose of these calculations. The agreement between SID values computed with Equations 1, 2a, and 2b, and those estimated with Equation 5 was satisfactory in our data: the mean difference was 0.0 ± 0.2 mEq/L (± SD; range − 1.2 to +0.8 mEq/L).

In uncomplicated clinical situations the customary approaches based on BE, or on $[HCO_3^-]$ supplemented with anion gap, may be satisfactory. In the complex disturbances of critically ill patients, however, alkalinizing and acidifying disturbances may both be present; they may escape detection because of their offsetting effects on the customary indices of the metabolic acid–base status (Tables 3 and 4).

With the $[HCO_3^-]$ approach, calculation of $AG_{observed}$ should suggest that the apparent normalcy in the measurements with normal $[HCO_3^-]$ was false, but this would have helped in only two of the 13 patients with hidden acidoses from elevated $[XA^-]$ or [Pi], or both. When AG was adjusted to take account of the effects of hypoalbuminemia (12), as expected, it was elevated in all of the samples with normal $[HCO_3^-]$ that had elevated $[XA^-]$ and [Pi].

BE missed important metabolic acid–base abnormalities in the complex disturbances in our patients. Among the 20 patients with normal BE (Table 4), 19 had very low SID values. These acidotic abnormalities resulted from increased $[XA^-]$, plasma dilution, or hyperchloremia (or their combinations). This was not detected by BE because the low-SID acidosis was masked by the alkalinizing effect of hypoalbuminemia, present in all these patients. The reasons for this failure of BE to detect metabolic acidosis in the presence of hypoalbuminemia are as follows.

BE is claimed to be equal to the deviation of SID from its normal value (26, 27). However, this is true only if the plasma concentrations of the nonbicarbonate buffers (albumin and phosphate) are normal. When this condition is not met, the reference state for "normal SID" must be adjusted (14; *see also* Appendix in the online supplement to this article). This is what the BE method indeed does (3, 26): for the condition of BE = 0, when hypoalbuminemia is present, an adjusted SID is considered normal; it has to be lower than what obtains when serum albumin concentration is normal, to satisfy the condition of pH = 7.40 at P_{CO_2} = 40 mm Hg, which is the sole definition of BE = 0; changes in albumin concentration are not considered acid–base abnormalities (26). However, such adjusted (lowered) SID may result from three different mechanisms: hyperchloremia, elevated $[XA^-]$, or plasma dilution (*see* Table 1).* Wilkes (28) claims that, with hypoalbuminemia SID is lowered by increasing plasma $[Cl^-]$, by a renal compensation for hypoalbuminemia; his conclusion is based on 223 measurements of acid–base variables in 91 ICU patients. In our single measurements in critically ill patients we find no correlation between serum albumin concentration and $[Cl^-]_{observed}$ or $[Cl^-]_{corrected}$. This is not surprising, because in most ICU patients many routine interventions change the plasma $[Cl^-]$ to a degree that can overwhelm the scope of regulation of this anion by the kidneys (e.g., diuretics, nasogastric suction, transfusions of citrated blood products, intravenous hyperalimentation, large infusions of NaCl solutions). On the other hand, high $[XA^-]$ (≥ 3 SD above the mean of the control subjects) were present in more than half of all of our patients with hypoalbuminemia, and in one-third of those with normal BE (Table 4).

In four of the 152 patients, $[XA^-]$ (corrected for water excess/deficit) was apparently less than 4 mEq/L (> 2 SD below the mean of the control data). Because this is improbable, one has to suspect that some unidentified cations were present in plasma, such as cationic paraproteins (29) or cationic drugs in millimolar (toxic) concentrations (30, 31). When such cations are present, the value of $[XA^-]$ calculated with Equation 3 is not a valid measure of "all strong anions other than Cl^-." Instead, it solves for ($[XA^-]$ − unidentified cations), i.e., it underestimates the true value of $[XA^-]$. Fortunately, high concentrations of unidentified cations are rare, even in ICU settings; and when suspected, methods exist by which they can be identified.

Conclusions

Hypoalbuminemia, an almost ubiquitous abnormality in critically ill patients, can confound the interpretation of acid–base data when the customary diagnostic approaches based on BE or plasma $[HCO_3^-]$ with AG are applied.

BE fails as a measure of metabolic acidosis when the concentration of serum albumin, the main nonbicarbonate buffer in plasma, is low.

The method that relies on plasma $[HCO_3^-]$ and $AG_{observed}$ can miss or underestimate "gap acidoses" when serum albumin is low. However, when adjusted for abnormal albumin concentration (12), AG is reliable in detecting such hidden "gap" acidoses. The usefulness of this approach was recently questioned (32).

The third approach to analysis of acid–base data presented here allows one to detect and quantify all the various individual components of even the most complex acid–base disturbances seen in critically ill patients. In addition, it gives insights into the pathogenesis of metabolic acid–base disturbances, which clarifies the choice of appropriate specific therapeutic interventions. All the calculations necessary for the proposed system of evaluation can be done easily at bedside, with a simple hand-held calculator. The system lends itself to an automated comprehensive evaluation of complex acid–base data. A simple computer program for this can be obtained from the authors.

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*The arguments developed in the Appendix (in the online supplement to this article) apply to BE for separated plasma, BE_{pl} (i.e., plasma not interacting with red blood cells or extravascular space); however, the widely used "BE for the extracellular space" (BE_{ecf}) (26) is affected by the changes in plasma nonbicarbonate buffers as much as BE_{pl}, as the data in Table 3 show.

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