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Over ten thousand cases and counting: acidbase.org is serving the critical care community

Paul Elbers[1], Niels van Regenmortel[2], Rainer Gatz[3]

[1] *Department of Intensive Care Medicine; Research VUmc Intensive Care; Institute for Cardiovascular Research Vrije Universiteit (ICaR-VU), VU University Medical Center Amsterdam, Amsterdam, Netherlands*
[2] *Department of Intensive Care Medicine and High Care Burn Unit, Ziekenhuis Netwerk Antwerpen, ZNA Stuivenberg, Antwerpen, Belgium*
[3] *Department of Intensive Care Medicine, Herlev Hospital, Herlev, Denmark*

Abstract

Acidbase.org has been serving the critical care community for over a decade. The backbone of this online resource consists of Peter Stewart's original text "How to understand Acid-Base" which is freely available to everyone. In addition, Stewart's Textbook of Acid Base, which puts the theory in today's clinical context is available for purchase from the website. However, many intensivists use acidbase.org on a daily basis for its educational content and in particular for its analysis module. This review provides an overview of the history of the website, a tutorial and descriptive statistics of over 10,000 queries submitted to the analysis module.

Key words: acid base, Stewart approach, strong ion difference, intensive care, critical care

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The Stewart approach to acid base physiology is thought to be especially useful to provide clinical guidance for complex acid base problems. As these are common in the setting of intensive care medicine, it is hardly surprising that the Stewart approach is increasingly being adopted by the critical care community.

Commonly referred to as the quantitative physicochemical approach, the Stewart method disentangles the various components responsible for changes in [H^+], or pH [1]. In addition, it demystifies the relationship between electrolyte balance and acid base physiology. This makes it stand out between the two classical approaches, i.e. the bicarbonate centered and base excess based methods, although it should be noted that all approaches are mathematically compatible.

A disadvantage of the Stewart approach is its perceived complexity. This perception is partly justified, as Stewart proposed a fourth order polynomial equation to calculate pH [1]. However, as shown below, it is much more straightforward to examine the factors that determine a known pH, which is the usual clinical scenario. Still, application of the Stewart approach requires a number of calculations, which may be challenging at the bedside. It is with these considerations in mind and with the aim of helping the critical care community that, back in 2007, we set out to develop our acid base analysis module [2]. Since its integration in the online community acidbase.org, which itself was established in 2003, it has been serving the critical care community worldwide.

As a tribute to the power of the internet and, in particular, that of decision support, this review is focused on the possibilities for acid base analysis and education on acidbase.org. We will first discuss its history, followed by an introduction to the Stewart approach. In addition, we will provide descriptive statistics of over 8 years of online acid base queries and a tutorial on how to best use the decision support module.

HISTORY OF ACIDBASE.ORG

The history of the website starts at the beginning of the new millennium, with a frustrated medical student from the Netherlands, Paul Elbers, struggling to deal with complex

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acid base disorders. He found that the classic approaches suffered from circular reasoning, especially when trying to explain the so-called concept of hyperchloremic acidosis. The internet had only just become widely available, and in search for better explanations he stumbled on Prof. John Kellum's website on quantitative acid base medicine [3]. The website mentioned that Stewart was a genius. Although the website provided helpful information, the concepts of the Stewart approach proved difficult to grasp.

The website also mentioned Stewart's original book "How to understand Acid-Base', which was out of print. Inspired by this, he was disappointed that no copy could be found in the Netherlands. His luck changed while travelling, when he found a copy in the library of Trinity College Dublin, which he eagerly photocopied. As it was indeed true that Stewart's original text [4] was the work of a genius, it was then decided that this work should be made available to the world once and for all. After contacting the original publisher, he learned that their copyright had expired and was returned to the author, who had sadly passed away. Therefore, he contacted his widow, Dr. Babette Stewart. Following discussion with her children, she happily agreed to provide the copyright to acidbase.org on the condition that the work should always be freely available to everyone. This was the moment that the foundations of acidbase.org came into existence. Its core is Stewart's original text, which has been available on the web ever since.

The website became immediately popular, and by popular demand, a pdf version was made available. In addition, following extensive discussions with Prof. John Kellum, it was decided to publish a new edition of the textbook. The main reason for this step was to put Stewart's ideas in today's clinical context. This led to the publication of "Stewart's Textbook of Acid-Base", published by AcidBase.org in 2009 [1] (Fig. 1). As a tribute to Peter Stewart and his heirs, the first nine chapters were left unaltered from Stewart's original writings. These were complemented by chapters by over 20 modern day experts on clinical acid-base. Since then, over 2,000 copies have found their way into the critical care community. The book remains available at acidbase.org

In the meantime, and again by means of the internet, Paul Elbers had met Rainer Gatz. He is a German anesthesiologist and intensivist with a keen interest both in intensive care ultrasound and programming. Their collaboration led to the development of the analysis module at acidbase.org in 2007, which is extensively discussed below.

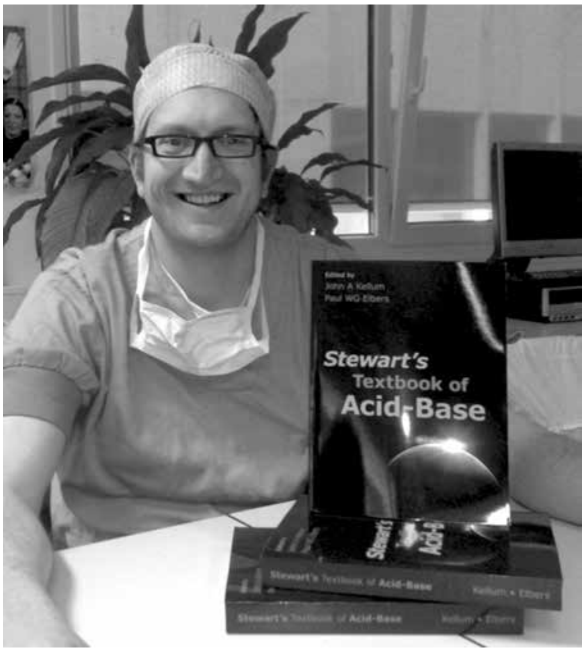

Figure 1. In 2009 Stewart's Textbook of Acid-Base edited by Prof. John Kellum and Dr. Paul Elbers, was published by acidbase.org. A young Paul Elbers, a resident in anesthesiology at St. Antonius Hospital Nieuwegein at the time, is showing the first copies

Table 1. The Stewart equations, all of which need to be satisfied simultaneously

Water dissociation equilibrium	$[H^+] \times [OH^-] = K'_W$
Weak acid dissociation equilibrium	$K_A \times [HA] = [H^+] \times [A^-]$
Conservation of mass for "A"	$A_{TOT} = [A^-] + [HA]$
Bicarbonate ion formation equilibrium	$[PCO_2] \times K_C = [H^+] \times [HCO_3^-]$
Carbonate ion formation equilibrium	$[K_3] \times [HCO_3^-] = [H^+] \times [CO_3^{2-}]$
Electrical neutrality equation	$SID + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

THE STEWART APPROACH

As recently reviewed by ourselves [5], from a Stewartian perspective, bicarbonate (HCO_3^-) does not play a causal role in acid base balance. Instead, acid-base and electrolyte balance are described by a number of physicochemical equations, derived from basic principles of physics and chemistry (Table 1). These must be satisfied simultaneously.

Two important concepts thus emerge. First, water is abundantly present in the body and is a virtually inexhaustible source of $[H^+]$ formation or reuptake. This is described by the water equilibrium equation. Second, as all equations must be simultaneously satisfied, it follows that only three independent parameters will ultimately determine the final equilibrium of water dissociation, and therefore also $[H^+]$ or pH, but also

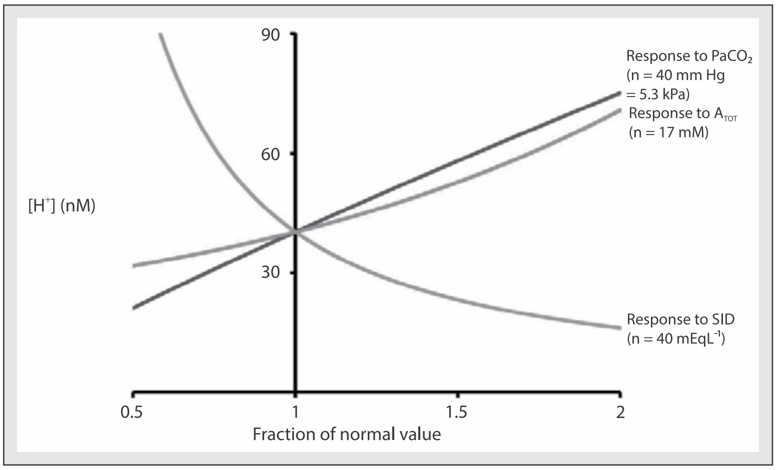

Figure 2. The relative influence of the three independent parameters, SID, A_{TOT} and P_aCO_2 on H+. pH 7.4 corresponds to $[H^+]$ = 40 nM, whereas pH = 7 and pH =8 correspond to $[H^+]$ of 100 and 10 nM respectively; SID — strong ion difference

for other dependent parameters, including HCO_3^-, which also follows the equilibrium set by SID, A_{TOT} and P_aCO_2:

$$[H^+] = f\,(P_aCO_2, \text{SID}, A_{TOT}).$$

THE PARTIAL PRESSURE OF CO_2 — P_aCO_2

It follows from the Stewart equations that if $PaCO_2$ increases, $[H^+]$ must increase as well. This is not different from other approaches to acid base physiology.

THE STRONG ION DIFFERENCE (SID)

Strong ions are completely dissociated in body fluids and thus exist in a charged form only. The relevant ones are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, lactate and ketoacids. The SID is the sum of strong cations minus the sum of strong anions. In plasma, this is mainly determined by $[Na^+]$ and $[Cl^-]$ and its normal value is about 40 mEq L^{-1}, but this may vary slightly due to differences in local normal laboratory values.

It follows from the Stewart equations, that if SID decreases, $[H^+]$ must increase and vice versa. Any pathological process that disturbs the balance between strong cations and strong anions will thus directly affect pH. This includes lactic acidosis, ketoacidosis, renal acidosis, vomiting induced alkalosis, contraction alkalosis and, most importantly, iatrogenic fluid administration [1].

Therefore, it is a misconception that hyperchloremia causes acidosis. It is in fact a low strong ion difference that causes this phenomenon. Of course, at normal sodium levels, raised chloride levels will lower SID. However, low SID acidosis can also exist at normal or decreased chloride levels, provided that kation concentration, such as Na is relatively even more decreased. Thus, hyperchloremic acidosis is a misnomer [6].

The SID concept also makes it easy to understand how fluid therapy may influence acid base balance. If SID is lower than that of plasma, plasma SID will decrease and thus directly cause acidosis. Therefore, it is prudent to know the SID of commonly used infusion fluids. For example, an SID of glucose 5% and NaCl 0.9% are both 0 mEq L^{-1}, whereas that of a balanced solution such as Ringer's Acetate is higher, usually around 27 mEq L^{-1} depending on the manufacturer. An SID of $NaHCO_3$ 8.3% is of course much higher: 1000 mEq L^{-1}.

SID can be estimated by adding all cations and subtracting all anions. This is called the apparent SID, or SIDa. Of course, only ions that have been measured can be taken into account for this estimate. SID can also be determined by calculating it from the electroneutrality equation. This yields the so-called effective SID, or SIDe. The difference is called the strong ion gap, or SIG, which represents the sum of unmeasured strong cations minus the sum of unmeasured strong anions. The SIG is very useful for narrowing down the differential diagnosis of complex acid base disorders.

THE TOTAL AMOUNT OF WEAK ACIDS (A_{TOT})

These are grouped as A_{TOT}, the total amount of weak acids, and consist mainly of plasma proteins that are partially dissociated. From an acid-base perspective, albumin and to a lesser extent phosphate are the most important contributors. It follows from the Stewart equations that if A_{TOT} increases, $[H^+]$ must also increase. This implies that hypoalbuminemia of any cause contributes to alkalosis. Similarly, hyperphosphatemia, as seen in renal failure, causes acidosis.

Fluid therapy using solutions without albumin or phosphate will reduce A_{TOT}, thus partially offsetting any SID effect. Therefore, to avoid pH change by fluid therapy, the SID of the solution has to equal the patient's bicarbonate concentration [7–9].

The effect of the different parameters on acidity is summarized in Figure 2. It is easily appreciated that a decrease in SID exerts the strongest effect.

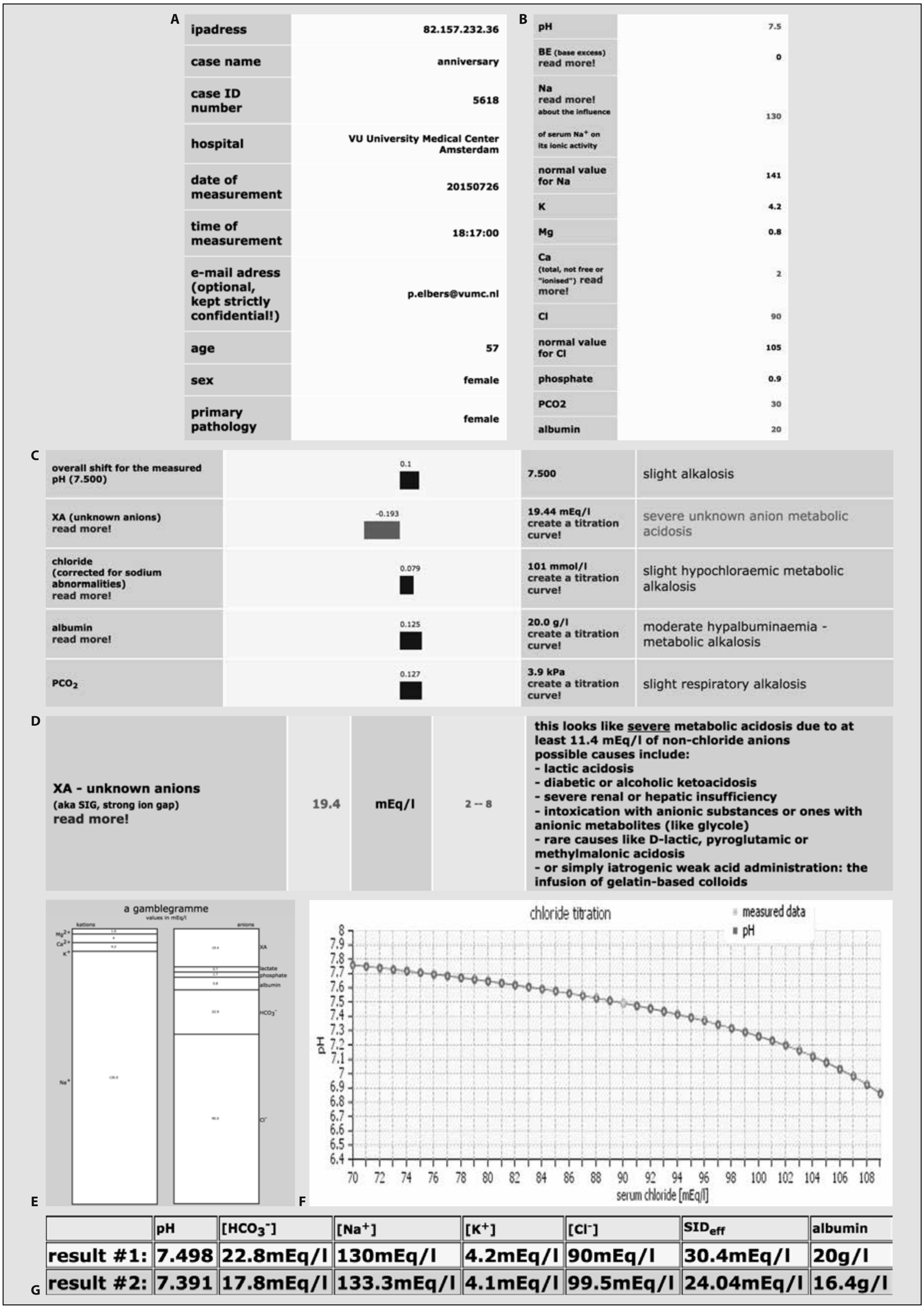

Figure 3. Screenshots accompanying the tutorial for acidbase.org. See text for details. **Panel F** shows the effect of changing chloride values for pH, provided that other parameters remain unchanged. **Panel G** shows the effect of providing 3 liters of NaCl 0.9% to the patient, again assuming that other parameters remain unchanged

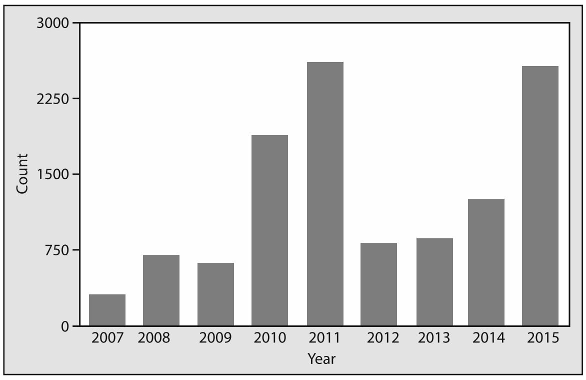

Figure 4. Number of user-submitted cases to acidbase.org grouped by year

A TUTORIAL FOR THE ANALYSIS MODULE

Acidbase.org allows for easy analysis of complex acid base disorders. Let us illustrate this by considering an example patient based on published acid base data [10]. This particular patient was a 57 year old female who was brought to the emergency department of a university hospital, at about 11 pm, after a fall. She was slightly drowsy. Her vital signs included a pulse rate of 97 bpm, a blood pressure level of 110/70 mm Hg and peripheral oxygen saturation of 96% on room air. Communication was not easy, probably as her right leg was obviously in pain. An X-ray confirmed the diagnosis of a femoral fracture and the orthopedic surgeon asked the registrar in anesthesia to clear her for immediate surgery quickly so everyone could finally go home.

For some reason, unknown to the anesthesia registrar, a blood glass had already been drawn by the ER attending. The results included a pH of 7.50, pCO_2 of 30 mm Hg (4 kPa), $[HCO_3^-]$ of 22 mM and a base excess of 0 mM. According to the classic approaches, this seemed consistent with simple respiratory alkalosis, for example because of pain or anxiety, especially given the normal S_pO_2. However, as the electronic patient record of the hospital was directly linked to acidbase.org, obviating the need for manual data entry, it was no trouble to check the analysis module (Fig. 3).

Table 2. Top 20 identifiable hospitals using acidbase.org, grouped by country

Australia	The Royal Melbourne Hospital
Australia	Queensland Health
Belgium	Ziekenhuis Netwerk Antwerpen
Belgium	Universitair Ziekenhuis Gent
Denmark	Herlev Hospital
Germany	Katholisches Hospitalgesellschaft mbH
Germany	Eberhard Karls Universitaet Tuebingen
Greece	University of Crete
Italy	Fondazione IRCCS Ospedale Maggiore Policlinico
Italy	Politecnico di Torino
Netherlands	UMCU
Netherlands	Radboud UMC
Netherlands	OLVG
Russia	Baranova Hospital Petrozavodsk
Sweden	University Hospital of Linkoping
Switzerland	Universitatsspital Zurich
UK	Royal Brompton Hospital
USA	Memorial Medical Center
USA	The Johns Hopkins Medical Institutions
USA	Mayo Foundation for Medical Education and Research
USA	Sisters of Mercy Health System
USA	Adventist Health
USA	The Connecticut Hospital and Affiliates

To his surprise, a severely decreased SID was identified by acidbase.org, mainly due to an increased SIG. This was

Figure 5. Heatmaps of the world and Europe showing using acidbase.org. Darker shading means more intense use

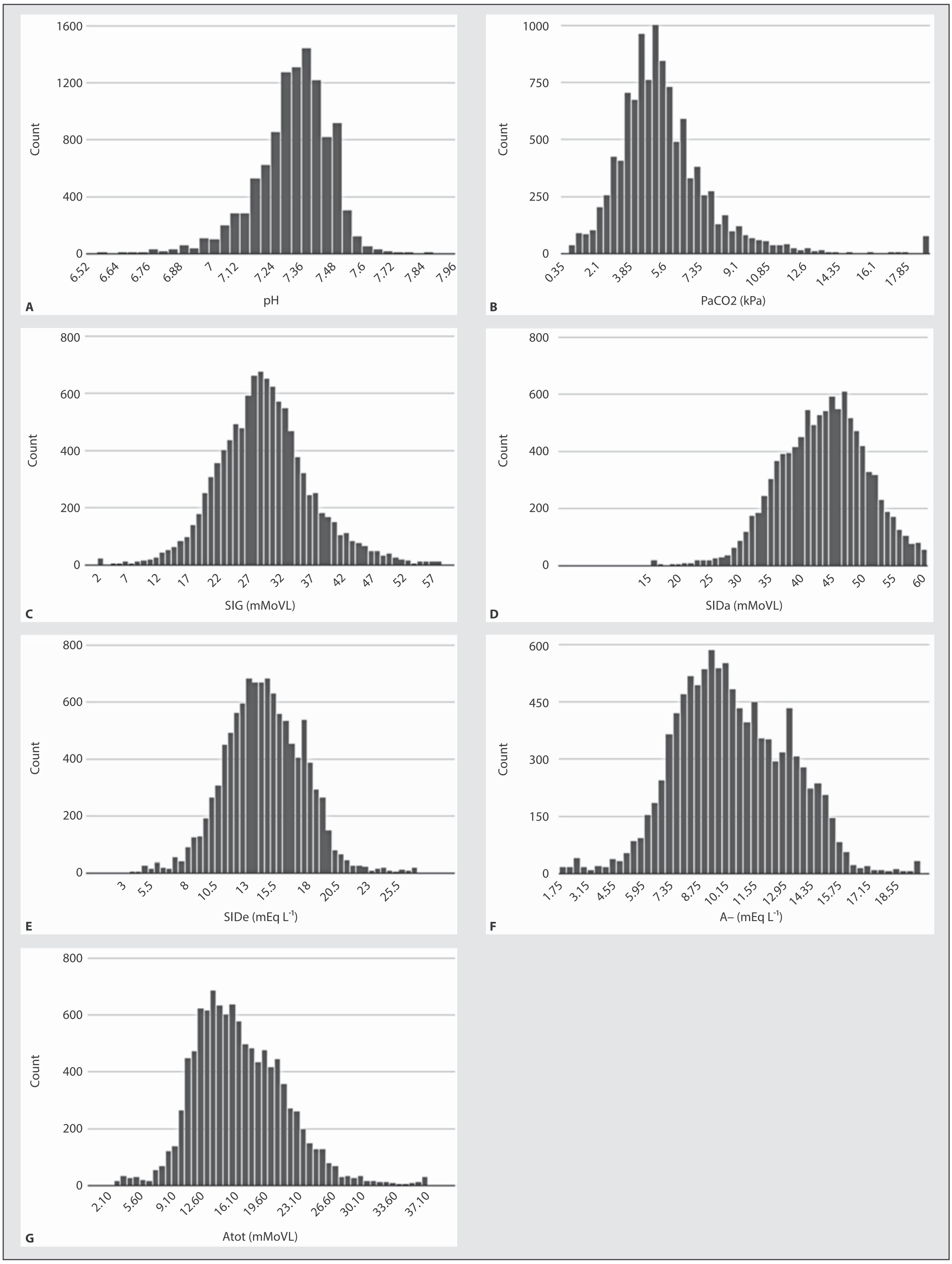

Figure 6. Histograms of pH, $PaCO_2$, SIG, SIDa, SIDe, A- and A_{TOT} for the more than 10,000 cases submitted to acidbase.org. For calculations, normal values for parameters were assumed if not reported by the user

offset by the alkalinising influence of a low A_{TOT}, obviously caused by severe hypoalbuminemia. Figure 3 shows the differential diagnosis provided by acidbase.org. As lactate was in the normal range (1.5 mM), a urine sample was taken confirming 3+ ketones, consistent with diabetic ketoacidosis.

Table 3. Top 20 countries using acidbase.org and their number of submitted cases

Rank	Country	Cases (n)
1	Sweden	1,839
2	Netherlands	1,322
3	Egypt	1,011
4	United States	881
5	Belgium	654
6	United Kingdom	611
7	Turkey	526
8	Spain	490
9	Italy	356
10	Switzerland	332
11	Portugal	289
12	Denmark	283
13	Colombia	232
14	Australia	215
15	Indonesia	169
16	Poland	153
17	Germany	150
18	Czech Republic	133
19	Brazil	120
20	France	79

Surgery was postponed at this point to allow for metabolic correction, needing insulin, fluids and probably potassium. Not too sure of which fluid to administer, the resident examined the acid-base effects of administering 3 L of normal saline (NaCl 0.9%), using the acidbase.org fluid therapy modeling section. The results are given in Figure 3.

8 YEARS OF ANALYSIS AT ACIDBASE.ORG

In real life, many doctors continue to find their way to acidbase.org to provide them with real time advice on acid base disorders, just as our imaginary resident did. In fact, as of July 2015, 10,620 cases had been submitted to acidbase.org. This number has been steadily increasing over the years (Fig. 4), at least if ignoring the peak years 2010 and 2011. The 2010 peak may be explained by the publication of Stewart's Textbook of Acid-Base in 2009 (Fig. 1). For 2011, we have no obvious explanation. It was mainly due to a surge in activity in April, November and December 2011. For the current year, there are over 200 consultations per month on average. Tables 2 and 3 provide an overview of the top 20 countries and the top 20 identifiable hospitals using acidbase.org. In addition, the maps in Figure 5 give an overview of its worldwide use.

The histograms in Figure 6 provide an insight into the type of patients and acid base disturbances for which they sought advice. These histograms are skewed in the direction of very low pHs, very low SIDs, very high CO_2s; and very low A_{TOT}s. Of course, this is easy to explain, as it is probably for such complex patients that the Stewart approach is most helpful. Of course these data should be interpreted with caution, as there is no formal check by acidbase.org on whether submitted cases are real. In fact, users are encouraged to play with acid base data, by providing a so-called test case id.

The analysis tools also include functionality in order to draw so-called gamblegrams, in which anions and cations are represented as two bars immediately identifying all relevant gaps (Fig. 3). In addition, users may explore real time graphical modelling of effects caused by changes in the dependent parameters (Fig. 3). While the analysis module is the most popular aspect of the site, other frequently used parts of acidbase.org are include reading Stewart's classic text "How to understand acid-base" [4] and browsing the educational section which provides onsite and linked tutorials on all approaches to acid base medicine. In addition, an extensive glossary and help function is provided. This includes instruction for those hospitals that also wish to connect their electronic patient record directly to acidbase.org.

CONCLUSIONS

Acidbase.org has been serving the critical care community for years and continues to do so. As the Stewart approach continues to gain ground, the online community grows equally stronger. Using the power of the internet and computers, acidbase.org circumvents the need for complex bedside calculations. Many physicians in many countries throughout the world use acidbase.org on a daily basis. By providing integration with patient data management systems, true bedside evaluation of the crossroads between electrolyte and acid base physiology becomes a reality.

ACKNOWLEDGEMENTS

1. The authors declare no financial disclosure.
2. Paul Elbers is editor and publisher of Stewart's Textbook of Acid Base and founder of www.acidbase.org. Rainer Gatz has developed the analysis module at www.acidbase.org.

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Adres do korespondencji:
Paul Elbers, MD, PhD, EDIC
Department of Intensive Care Medicine
ZH.7D.167
VU University Medical Center Amsterdam
De Boelelaan 1117
1081 HV, Amsterdam, Netherlands
e-mail: p.elbers@vumc.nl