Basic science review

Metabolic Acidosis in Patients with Sepsis: Epiphenomenon or Part of the Pathophysiology?

J. A. KELLUM
Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, UNITED STATES of AMERICA

ABSTRACT

Objective: *To review the mechanisms of metabolic acidosis in sepsis.*

Data sources: *Articles and published reviews on metabolic acidosis in sepsis.*

Summary of review: *Sepsis affects millions of patients each year and efforts to limit mortality have been limited. It is associated with many features one of which is acidosis which may be a result of the underlying pathophysiology (e.g. respiratory failure, shock, renal failure) or may also result from the way in which we manage critically ill patients.*

Lactic acidosis identifies septic patients at risk and aggressive fluid resuscitation (along with inotropes and blood in some patients) to reverse acidosis and improve venous oxygen saturation will improve mortality. However, most patients with severe sepsis or septic shock receive 0.9% saline and therefore may develop hyperchloraemic acidosis as a consequence of their resuscitation. Therefore alterations in acid-base balance are almost always in the background in the management of patients with sepsis. What is unknown is whether acidosis is in the causal pathway for organ dysfunction or whether it is simply an epiphenomenon. Changes in acid-base balance, of the type and magnitude commonly encountered in patients with sepsis, significantly alter the release of inflammatory mediators. Less significant changes in the immune response have already been implicated in influencing outcome for patients with sepsis and a reduction in acidosis in septic patients may have the same effect.

Conclusions: *Understanding the effects of acid-base on the inflammatory response is relevant as all forms of metabolic acidosis appear to be associated with prolonged hospital and ICU length of stay. Since metabolic acidosis is both commonly caused and treated by clinicians, understanding of the physiologic consequences of altered blood pH is imperative.* (**Critical Care and Resuscitation 2004; 6: 197-203**)

Key words: Metabolic acidosis, sepsis, severe sepsis, strong ion difference

Severe sepsis affects millions of patients each year killing between 29-40%. Efforts to limit mortality have been limited in both their absolute success in trials and their subsequent translation into clinical practice. Sepsis is associated with a myriad of clinical features, including acidosis.[1] While acidosis may be a result of the underlying pathophysiology (e.g. respiratory failure, shock, renal failure) it may also result from the way in which we manage critically ill patients. In patients with sepsis-induced organ failure significant improvements in survival have been produced by altering the way in which organ support[2,3] and resuscitation[4] are carried out. Reducing tidal volumes and airway pressures in mechanically ventilated patients with acute lung injury improves survival[2] but may also result in respiratory acidosis, which in turn is managed differently from

Correspondence to: J. A. Kellum, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Scaife Hall, Room 608, 3550 Terrace Street, Pittsburgh, PA 1526, UNITED STATES of AMERICA

clinician to clinician. Delivering higher doses of continuous dialysis to critically ill patients with acute renal failure has been shown to improve survival.[3] Dialysis reduces uraemic toxins and removes fluid but it also removes metabolic acids. A similar improvement in outcome has recently been demonstrated with early resuscitation in patients with severe sepsis.[4] Lactic acidosis was among the criteria used to identify patients at risk and aggressive fluid resuscitation, along with inotropes and blood in some patients, were used to reverse acidosis and improve venous oxygen saturation. Furthermore, most patients received 0.9% saline and therefore may have developed hyperchloraemic acidosis as a consequence of their resuscitation.

Manipulations in acid-base balance are almost always in the background in the management of patients with sepsis. What is unknown is whether acidosis is in the causal pathway for organ dysfunction or whether it is simply an epiphenomenon. We have recently proposed the hypothesis that changes in acid-base balance, of the type and magnitude commonly encountered in patients with sepsis, significantly alter the release of inflammatory mediators.[5] Less significant changes in the immune response have already been implicated in influencing outcome for patients with sepsis. Indeed, two new treatments for sepsis, activated drotrecogin alfa[6] and low-dose corticosteroids[7] appear to work by producing modest changes in the inflammatory response, although the exact mechanisms for their clinical effects are still unknown.

Metabolic acidosis

Metabolic acidosis is a common problem in patients with sepsis and other forms of critical illness and is associated with poor outcome. Acidosis appears to be common in critically ill patients. However, the exact incidence and prevalence of metabolic acidosis has not been established for patients with sepsis or for critically ill patients in general. Although it remains uncertain whether or not there is a true cause-effect relationship between acidosis and adverse clinical outcomes, acidosis is a powerful marker of poor prognosis in critically ill patients.[8-10] Acidosis may occur as a result of increases in arterial pCO_2, (respiratory acidosis) or from a variety organic or inorganic fixed acids (metabolic acidosis). There appears to be a difference in epidemiology between patients with respiratory and metabolic acidosis[11] leading some investigators to hypothesise that the cause of acidosis rather than the acidosis *per se* is driving the association with clinical outcomes. However, in both respiratory and metabolic acidosis, non-survivors have a lower arterial blood pH. Interestingly, in both groups, non-survivors have blood gases that were further separated from the line of pure respiratory acidosis. In other words, non-survivors had more metabolic acidosis.[11]

Metabolic acidosis results from a variety of common etiologies including lactic acidosis, hyperchloraemic acidosis, renal failure and ketoacidosis. While the underlying disease process associated with each of these sub-types carries its own clinical consequences, acidosis itself might potentially contribute to, or even attenuate, the adverse effects of these conditions. Understanding the mechanisms whereby acid-base disorders occur is paramount in evaluating the clinical consequences and the therapeutic options.

Hyperchloraemic metabolic acidosis

Although common causes of metabolic acidosis such as lactic acidosis and renal failure may be unavoidable, often the source of metabolic acidosis is at least partly iatrogenic. This is because saline resuscitation is often used to treat shock. Large volume saline infusion produces metabolic acidosis by increasing the plasma Cl^- concentration relative to the plasma Na^+ concentration.[12-15] The result is a reduction in the strong ion difference (SID), the difference between positive and negative charged electrolytes, which in turn produces an increase in free H^+ ions to preserve electrical neutrality.[16] The clinical effects of these changes have been documented over the past several years. Comparing starch preparations in saline versus a balanced electrolyte solution for elderly abdominal surgery patients, Wilkes and coworkers recently described a worsening of acid-base balance and more adverse events with the saline-based fluid.[17] Similar findings have been reported with 0.9% saline compared with lactated Ringers solution.[18] Indeed, the side effect profile of saline-induced acidosis, nausea, vomiting, abdominal pain, headache, thirst, hyperventilation and delayed urination is identical to what occurs with ammonium chloride administration.[19,20] Thus, while there is little evidence that treating metabolic acidosis improves clinical outcomes,[21] there is evidence that iatrogenic metabolic acidosis may be harmful. To the extent that acidosis is avoidable and/or treatable, a better understanding of the impact of acidosis on a variety of systems is needed to better balance potential risks and costs with benefits.

Saline resuscitation produces hyperchloraemic acidosis in a predictable fashion.[12] By use of a mathematical model based on a physical-chemical acid-base analysis we have accurately predicted the serum Cl^- concentration and resulting arterial blood pH changes in healthy dogs given large volumes of intravenous 0.9% saline.[12] By applying this model to dogs given bolus intravenous lipopolysaccharide (LPS), 1 mg/kg, and subsequent large-volume saline resuscitation (100

mL/kg over 3 hr) we have quantified the effects on acid-base balance.[12] The total acid load was calculated from the change in standard base excess (SBE) attributable to each source. In LPS-treated animals mean arterial pH decreased from 7.32 to 7.11, $P < 0.01$; pCO_2 and lactate were unchanged. Saline accounted for 38% of the total acid load. Although serum Na^+ did not change, serum Cl^- increased (127.7 ± 5.1 mmol/L vs. 137.0 ± 6.1 mmol/L, $P = 0.016$).

From these experiments we concluded that saline resuscitation alone accounts for more than a third of the acidosis seen in this canine model of acute endotoxaemia, whereas lactate accounts for less than 10%. Furthermore, a large amount of the unexplained acid load in this model appears to be attributable to differential Na^+ and Cl^- shifts presumably from extra-vascular to vascular or intracellular to extra-cellular spaces. This study and work from other groups has lead to the hypothesis that Cl^- (both exogenous and endogenous) plays an important role in the development of acidosis.

Compared with starch in a balanced electrolyte solution, resuscitation with saline resulted in hyperchloraemic metabolic acidosis and worse short term survival in rats. Normal saline (0.9%) (NS) was compared with other fluids in the resuscitation of Sprague-Dawley rats given bolus intravenous LPS on short-term survival and acid-base balance.[22] An inverse relationship between the change in serum Cl^- and survival time in these animals was demonstrated. We studied 60 rats for 12 hr after intravenous infusion of LPS (20 mg/kg). We volume resuscitated to maintain a MAP > 60 mm Hg using either NS or 6% hetastarch in a balanced electrolyte solution (bHS) or lactated Ringer's (LR). Mean survival time among animals treated with NS or LR was 45% less compared with bHS-treated animals: 391 ± 151 min and 362 ± 94 min vs. 567 ± 140 min, $p < 0.0001$. Overall survival (at 12 hr) was 0% with NS or LR vs. 20% with bHS, $p = 0.05$. After resuscitation with NS, arterial SBE and plasma apparent strong ion difference (SIDa) were both significantly lower (-19.3 ± 5.2 vs. -12.1 ± 5.7 $p < 0.001$ and 23.0 ± 6.2 vs. 30.3 ± 2.9, $p < 0.0001$, respectively) and plasma Cl^- was significantly higher (123 ± 7 vs. 115 ± 3 mmol/L, $p < 0.0001$) compared to bHS. Resuscitation with LR resulted in a SBE, and Cl^- between that of NS and bHS (-15.4 ± 3.1, and 117 ± 3 respectively). These data showed that compared with bHS, volume resuscitation with NS was associated with more metabolic acidosis and shorter survival in this experimental animal model of septic shock.

Metabolic acidosis might reduce survival from sepsis through a variety of mechanisms. First, acidosis has been associated with haemodynamic instability,[23] although the association is not always consistent[24] and the underlying mechanisms are uncertain. Pedoto and colleagues have recently shown that metabolic acidosis may increase inducible nitric oxide synthase (iNOS) expression in animals and this could exacerbate vasodilation and shock.[25] They have also demonstrated that hyperchloraemic acidosis increases lung[25] and intestinal injury[26] in healthy rats. In order to control for other effects of large-volume resuscitation (e.g. cell swelling) we increased serum Cl^- concentration by infusing a dilute HCl solution into Sprague-Dawley rats with CLP-induced sepsis. We showed that hyperchloraemic acidosis induced changes in MAP and NO release in these septic animals.[27] Eighteen hours after inducing lethal sepsis by caecal ligation and puncture (CLP), we randomised 24 rats and divided them into 3 groups. In groups 2 and 3 we began an 8-hour intravenous infusion of 0.1N HCl to reduce the SBE by 5 - 10 and 10 - 15 mEq/L, respectively. We measured mean arterial pressure (MAP), arterial blood gases, electrolytes, plasma nitrate/nitrite levels at 0, 3, 6 and 8 hr. The MAP remained stable in group 1 but decreased in groups 2 and 3 ($p < 0.001$) such that at 8 hr the MAP was much higher in group 1 (94 ± 9.2 mmHg) compared to either group 2 (71.6 ± 20.1 mmHg) or group 3 (49.4 ± 33.2 mmHg), $p = 0.01$. This change in the MAP correlated with the increase in plasma Cl^- ($R^2 = 0.50$; $p < 0.0001$) and less well with the decrease in pH ($R^2 = 0.24$; $p < 0.001$). After 6 hr of acidosis, plasma nitrite levels were significantly higher in group 2 animals compared with either group 1 or group 3 animals, $p < 0.05$. We concluded that moderate acidosis, induced by HCl infusion, worsened blood pressure and increased plasma nitrate/nitrite levels in septic rats. Our results are in general agreement with reports by Pedoto and coworkers that demonstrated that metabolic acidosis increased inducible nitric oxide synthase (iNOS) leading to vasodilatation and shock in healthy rats.[25,26] Studies of non-stimulated resident peritoneal macrophages[28] and LPS-stimulated RAW 264.7 cells[29] have shown increased NO formation at moderately reduced pH (7.0 - 7.2). However, more severely acidic pH reduces NO formation[28,29] and there is an apparent dissociation between the pH effects on iNOS mRNA, protein and final NO release.[29] Thus, HCl seems to affect inflammatory mediators differently at different stages in their synthesis and release.

Effects of acidosis on inflammatory mediator release

If acidosis alters the release of NO, might is also affect the release of other inflammatory mediators? There are now several studies documenting the effects of decreased pH on the synthesis and release of inflammatory mediators, especially tumour necrosis

factor (TNF) and interleukin 6 (IL-6). Most of these studies have been conducted in resident macrophages or macrophage-like cell lines and have found conflicting results. However, studies using HCl have consistently shown pro-inflammatory effects at the level of nuclear factor kappa-B (NF-κB) DNA-binding or TNF synthesis, provided pH was not less than 6.0;[28,30,31] although TNF secretion was reduced even at pH as high as 7.0.[30-32] Little is known about the effects of HCl on other cytokines or on the kinetics of pH mediated effects.

Lactic acid has been studied in an even more limited way than HCl. Lactic acid (pH 6.75) has been shown in one study[33] to result in increased TNF release in LPS-stimulated peritoneal macrophages. This finding is surprising in light of the growing evidence of a protective effect of lactic acid in neuronal injury.[34-36] Several studies have sought to explore the effect of dialysis solutions on the immune response.[37,38] These acidic, lactate-based, solutions have been shown to decrease various aspects of the immune response including TNF synthesis and release.[37,38] Douvdevani also demonstrated a decrease in LPS-induced NF-κB DNA-binding in human blood-derived macrophages when incubated with dialysis solution.[38] Although these solutions are also hyper-osmolar and have excessive glucose concentrations, variables known to influence immune function,[37,39] they provide additional evidence of a potential anti-inflammatory role of lactate and highlight potential differences between various acids and their effects on the immune response.

We have conducted a series of experiments in LPS-stimulated RAW 264.7 murine macrophage-like cells in which we have decreased the pH of the medium using different acids. Remarkably, dramatically different patterns of inflammatory mediator expression occurred with different acids despite normalisation to the same pH. In our first set of experiments[40] we acidified the cell culture medium using HCl and stimulated the cells with 10 ng/mL of LPS (*E. coli* 0111:B4) for 24 hours. Acidic medium itself barely affected the release of inflammatory mediators, including NO, IL-6 and IL-10. However, compared with a pH 7.4, acidosis (pH 7.0) was associated with a significantly increased NO release in response to LPS stimulation. Interestingly, under more extreme acidic conditions (pH 6.5), NO release decreased in response to LPS and was again similar to pH 7.4 (Table 1). At pH 6.5 both IL-6 and IL-10 release was significantly less compared with either pH 7.0 or 7.4. However, IL-10 release was reduced far greater than IL-6 and thus the ratio of IL-6 to IL-10 increased significantly from 5:1 at pH 7.4 to 55:1 at pH 6.5. These results suggest a pro-inflammatory effect of HCl, consistent with the existing literature on the effects of HCl on TNF synthesis.[38,30,31]

Table 1. Affects of lactic acid vs. HCl on LPS-stimulated RAW 264.7 cells

	HCl pH 7.0	*HCl pH 6.5*	*Lactate pH 7.0*	*Lactate pH 6.5*
NF-κB	↑	↓	↓	↓↓
NO	↑	--	↓	↓↓
iNOS mRNA	↑	↑↑	↓	↓↓
IL-6	--	↓	↓	↓↓
IL-6 mRNA	--	↓	↓	↓↓
IL-10	↓	↓↓↓	↓	↓↓
IL-10 mRNA	--	--	↓↓	↓↓
IL-6 : IL-10	--	↑↑	--	--

Adapted from Kellum et al.[40]

To clarify the mechanism by which HCl influenced the release of cytokines from LPS-stimulated cells, we measured NF-κB DNA binding using electrophoretic mobility shift assay (EMSA) after exposure to different concentration of HCl.[40] Again, acidosis (pH 7.0) significantly increased LPS-induced NF-κB activation, compared with a pH 7.4, whereas more extreme acidosis (pH 6.5) actually attenuated NF-κB activation. Thus, different degrees of hyperchloraemic acidosis have differing effects on inflammatory mediator release as well as NF-κB activation. Overall, the effects of HCl appear to be pro-inflammatory. These results agree with studies in resident peritoneal macrophages in which Bellocq and colleagues found that these cells produced more NO when incubated in medium at pH 7.0 compared to pH 7.4 and this effect was associated with up-regulation of iNOS mRNA as well as the activation of NF-κB.[28]

By contrast, our data using lactic acid demonstrates that this acid is anti-inflammatory to RAW 264.7 cells as assessed by decreased cytokine expression and NF-κB activation.[40] In these experiments increasing concentrations of lactic acid (0 - 30 mM) caused increasing acidification of the media; and trypan blue exclusion and LDH release demonstrated that lactic acid did not reduce cell viability. However, lactic acid inhibited LPS-induced NF-kB DNA binding. Lactic acid also significantly decreased LPS-induced NO, IL-6, and IL-10 expression, both RNA and protein, in a dose-dependent manner. These effects may be partially mediated through NFκB since DNA-binding of this transcription factor is generally consistent with the effects on NO and IL-6 (table 1). However, extracellular acids also have effects on IL-10, which is outside the

NFκB pathway. What is apparent is that the effects of extracellular acids are not limited to the effects on pH since different acids produce different effects despite similar pH. Whether different effects can be explained by differences in pH_i are, as yet, unknown, although the patterns of response (table 1) do not make this likely.

Management of metabolic acidosis

Despite the association between metabolic acidosis and adverse clinical outcomes and evidence of injury from metabolic acidosis in animals, clinical evidence that treating metabolic acidosis is beneficial has not been forthcoming. In their systematic review, Forsythe and Schmidt[21] could not find evidence to support the routine use of sodium bicarbonate ($NaHCO_3$) in the treatment of lactic acidosis. A similar absence of evidence has characterised the literature on diabetic ketoacidosis where no proof exists that treating acidosis improves clinical outcomes[41] and prevailing opinion is against treatment, at least when the arterial pH is > 7.0.[42] However, many of the patients in studies of ketoacidosis have been young, otherwise healthy patients with type I diabetes mellitus and such patients may bare little resemblance to patients with sepsis. Furthermore, low-level ketosis is a physiologic condition and one might envision that endogenous defense mechanisms have evolved for this kind of acidosis. In a similar way, even severe lactic acidosis commonly occurs as a result exercise and it would seem unlikely that short-term lactic acidosis would be harmful. However these conditions may be quite distinct from hyperchloraemia or organic acidoses of renal failure or even prolonged lactic acidosis. Indeed, chronic acidaemia, even when mild (pH < 7.35), may produce a variety of adverse effects including metabolic bone disease[43] and protein catabolism.[44]

There has been a long-standing debate in the literature over whether administration of sodium bicarbonate can help reverse shock, possibly through improving the function of exogenous and endogenous catacholamines.[45] This debate has not been resolved but the weight of existing evidence does not support the use of sodium bicarbonate. Animal experiments using hypoxic lactic acidosis have yielded conflicting results.[46,47] Two clinical trials have been conducted to determine the effectiveness of $NaHCO_3$ therapy in reversing acidosis and improving haemodynamics in patients with lactic acidosis.[48,49] The results of both studies were the same; $NaHCO_3$ neither improved nor worsened systemic haemodynamics despite improving arterial pH. There was also no evidence that $NaHCO_3$ treatment worsened tissue hypoxia. Adding to this debate is the evidence that metabolic acidosis might produce beneficial effects on oxygen delivery or metabolism[50] and that correcting it might therefore be harmful. Indeed some authors have argued that some forms of acidosis such as respiratory[51] or lactic[50] acidosis may even have beneficial effects. In support of this point of view are data from experimental models of ischaemia/reperfusion injury in animals suggesting that correcting respiratory acidosis with $NaHCO_3$ may worsen inflammation and organ injury.[52] Although experimental evidence is emerging to suggest an effect of acidosis on the immune response, it has been difficult to establish a clear link between metabolic acidosis in humans and alterations in immune function. Data from clinical studies have been extremely limited and confounded by numerous other physiologic and pharmacologic variables known influence the immune response. For example studies of ketoacidosis fail to disentangle the effects of glucose and insulin.[53] Similarly, patients with chronic renal failure are also exposed to the effects of uraemic toxins, nutritional deficiencies, plasma volume and tonicity changes and treatments such as haemodialysis. Finally, lactic acidosis, while being a common clinical condition, frequently occurs as a result of other "immunologically" active conditions such a shock and sepsis. Even exercise presumably has effects on the immune response mediated by catacholamines[54] and perhaps other hormonal responses. Clinical studies of acid infusion (e.g. HCl) have not generally focused on the immune response and therefore it is difficult know what effects correcting hyperchloraemic acidosis would produce. Thus, it is impossible to discern from the existing clinical or basic science literature whether acidosis should be treated and if so under what conditions and using which therapies. This lack of evidence has lead to ambiguity in clinical recommendations in textbooks and review articles and further highlights the need for basic research in this area.

Conclusion

Understanding the effects of acid-base on the inflammatory response is highly relevant to clinical medicine for a variety of reasons. First, current deficiencies in our understanding of the effects of acidosis on a wide range of cellular processes have lead to controversy in way in which patients are managed in a variety of clinical settings. Most clinicians tend to ignore the effects of exogenous Cl^- on blood pH, yet many will treat even mild forms of acidaemia. In addition, all forms of metabolic acidosis appear to be associated with prolonged hospital and ICU length of stay. Since metabolic acidosis is both commonly caused and treated by clinicians, understanding of the physiologic consequences of altered blood pH is imperative.

Second, our ability to alter acid-base balance as a

tool to manipulate cellular processes is dependent on an improved understand of the relationship between blood pH and the synthesis and release of inflammatory molecules. Investigators continue to seek for means to modulate the inflammatory response as primary therapy for sepsis and related conditions. These efforts have been focused not only on reducing pro-inflammatory mediators in an effort to reduce tissue injury but also on the converse, augmenting the inflammatory response to infection. These interests also extend into other fields including autoimmune disease and cancer therapy.

Third, even when it is not practical or desirable to manipulate blood pH as a primary means of altering the inflammatory response, an understanding of how pH affects this response is necessary to 1) interpret data from studies of immunomodulation; 2) avoid unintended immunomodulation in clinical and laboratory settings; 3) explore the capacity of pH to improve the effectiveness of existing treatments. Finally understanding how blood pH is involved in the regulation of inflammation by intracellular signaling pathways or other mechanisms might ultimately lead to other strategies for immunomodulation.

REFERENCES

1. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-710.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-1308.
3. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356:26-30.
4. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-1377.
5. Gunnerson KJ, Song M, Kellum JA. Influence of Acid-Base Balance in Patients with Sepsis. In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag, Berlin, p 58-67, 2004.
6. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
7. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283:1038-1045.
8. Hickling KG, Walsh TJ, Henderson SJ, Jackson R. Low mortality rate in adult respiratory distress syndrome using low volume pressure limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994;22:1568-1578.
9. Broder G, Weil MH. Excess lactate: an index of reversibility of shock in human patients. Science 1964;143:1457.
10. Stacpoole PW, Lorenz AC, Thomas RG, Harman EM. Dichloroacetate in the treatment of lactic acidosis. Ann Intern Med 1998;108:58-63.
11. Kellum JA, Song M, Subramanian S. Acidemia: good, bad or inconsequential? In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin, p 510-516, 2002.
12. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock 1998;9:364-368.
13. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265-1270.
14. Waters JH, Bernstein CA. Dilutional Acidosis following Hetastarch or Albumin in Healthy Volunteers. Anesthesiology 2000;93:1184-1187.
15. Rehm M, Orth V, Scheingraber S, Kreimeier U, Brechtelsbauer H, Finsterer U. Acid-Base Changes Caused by 5% Albumin versus 6% Hydroxyethyl Starch Solution in Patients Undergoing Acute Normovolemic Hemodilution: A Randomized Prospective Study. Anesthesiology 2000;93:1174-1183.
16. Stewart P. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-1461.
17. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001;93:811-816.
18. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 1999;88:999-1003.
19. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest 1983;71:726-735.
20. Bushinsky DA, Coe FL. Hyperkalemia during acute ammonium chloride acidosis in man. Nephron 1985;40:38.
21. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. Chest 2000;117:260-267.
22. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: Improved survival and acid-base balance with a synthetic colloid in a balanced electrolyte solution compared to saline. Crit Care Med 2002;30:300-305.
23. Opie L. Effect of extracellular pH on function and metabolism of isolated perfused rat heart. J Appl Physiol 1965;209:1975-1980.
24. Cooper D, Herbertson M, Werner H, Walley K. Bicarbonate does not increase left ventricular contractility during L-lactic acidemia in pigs. Am Rev Resp Dis 1993;148:317-322.

25. Pedoto A, Caruso JE, Nandi J. Acidosis Stimulates Nitric Oxide Production and Lung Damage In Rats. Am J Respir Crit Care Med 1999;159:397-402.
26. Pedoto A, Nandi J, Oler A, Camporesi EM, Hakim TS, Levine RA. Role of nitric oxide in acidosis-induced intestinal injury in anesthetized rats. J Lab Clin Med 2001;138:270-276.
27. Kellum JA, Song M, Venkataraman R. Effects of Hyperchloremic Acidosis on Arterial Pressure and Circulating Inflammatory Molecules in Experimental Sepsis. Chest 2004;125:243-248.
28. Bellocq A, Suberville S, Philippe C, et al. Low environmental pH is responsible for the induction of nitric-oxide synthase in macrophages. Evidence for involvement of nuclear factor-kappaB activation. J Biol Chem 1998;273:5086-5092.
29. Huang CJ, Haque IC, Slovin PN, Nielsen RB, Fang X, Skimming JW. Environmental pH regulates LPS-induced nitric oxide formation in murine macrophages. Nitric Oxide 2002;6:73-78.
30. Heming TA, Dave SK, Tuazon DM, Chopra AK, Peterson JW, Bidani A. Effects of extracellular pH on tumour necrosis factor-alpha production by resident alveolar macrophages. Clin Sci (Colch) 2001;101:267-274.
31. Heming TA, Tuazon DM, Dave SK, Chopra AK, Peterson JW, Bidani A. Post-transcriptional effects of extracellular pH on tumour necrosis factor-alpha production in RAW 246.7 and J774 A.1 cells. Clin Sci (Colch) 2001;100:259-266.
32. Bidani A, Wang CZ, Saggi SJ, Heming TA. Evidence for pH sensitivity of tumor necrosis factor-alpha release by alveolar macrophages. Lung 1998;176:111-121.
33. Jensen JC, Buresh C, Norton JA. Lactic acidosis increases tumor necrosis factor secretion and transcription in vitro. J Surg Res 1990;49:350-353.
34. Himmelseher S, Pfenninger E, Georgieff M. Basic fibroblast growth factor reduces lactic acid-induced neuronal injury in rat hippocampal neurons. Crit Care Med 1998;26:2029-2036.
35. Schurr A, Payne RS, Miller JJ, Rigor BM. Brain lactate is an obligatory aerobic energy substrate for functional recovery after hypoxia: further in vitro validation. J Neurochem 1997;69:423-426.
36. Schurr A, Payne RS, Miller JJ, Rigor BM. Brain lactate, not glucose, fuels the recovery of synaptic function from hypoxia upon reoxygenation: an in vitro study. Brain Res 1997;744:105-111.
37. Jorres A, Gahl GM, Frei U. In vitro studies on the effect of dialysis solutions on peritoneal leukocytes. Perit Dial Int 1995;15:S41-S45.
38. Douvdevani A, Abramson O, Tamir A, Konforty A, Isakov N, Chaimovitz C. Commercial dialysate inhibits TNF alpha mRNA expression and NF-kappa B DNA-binding activity in LPS-stimulated macrophages. Kidney Int 1995;47:1537-1545.
39. ALKharfy KM, Kellum JA, Matzke G. Unintended Immunomodulation: Part I. Effect of Common Clinical Conditions on Cytokine Biosynthesis. Shock 2000;13:333-345.
40. Kellum JA, Song M, Li J. Lactic, and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. Am J Physiol Regul Inegr Comp Phsyiol 2004;286:R686-R692.
41. Viallon A, Zeni F, Lafond P, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med 1999;27:2690-2693.
42. Androque HJ, Tannen RL. Ketoacidosis, hyperosmolar states, and lactic acidosis. In: Kokko JP, Tannen RL (eds) Fluids and Electrolytes. W.B. Saunders, Philadelphia, p 643-674, 1996.
43. Bushinsky DA, Chabala JM, Gavrilov KL, Levi-Setti R. Effects of in vivo metabolic acidosis on midcortical bone ion composition. Am J Physiol 1999;277:F813-F819.
44. Bailey JL. Metabolic acidosis and protein catabolism: mechanisms and clinical implications. Min Electrol Metabol 1998;24:13-19.
45. Marx JO, Gordon SE, os NH, et al. Effect of alkalosis on plasma epinephrine responses to high intensity cycle exercise in humans. Eur J Appl Physiol 2002;87:72-77.
46. Graf H, Leach W, Arieff A. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 1985;227:754-756.
47. Rhee KH, Toro LO, McDonald GG, Nunnally RL, Levin DL. Carbicarb, sodium bicarbonate, and sodium chloride in hypoxic lactic acidosis. Chest 1993;104:913-918.
48. Cooper DJ, Walley KR. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. Ann Intern Med 1990;112:492-498.
49. Mathieu D, Neviere D, Billard V, Fleyfel M, Wattel F. Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. Crit Care Med 1991;19:1352-1356.
50. Leverve XM, Mustafa I. Lactate: A key metabolite in the intercellular metabolic interplay. Crit Care 2002;6:284-285.
51. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill-too little of a good thing? Lancet 1999;354:1283-1286.
52. Laffey JG, Engelberts D, Kavanagh BP. Injurious effects of hypocapnic alkalosis in the isolated lung. Am J Respir Crit Care Med 2000;162:399-405.
53. Blasetti A, Verrotti A, Chiarelli F, Morgese G. Immunologic changes in diabetic ketoacidosis. Minerva Pediatr 1992;44:181-184.
54. Tulzo YL, Shenkar R, Kaneko D. Hemorrhage increases cytokines expression in lung mononuclear cell in mice, involvement of catecholamines in nuclear factor-B regulation and cytokine expression. J Clin Invest 1997;99:1516-1524.