

Review

Bench-to-bedside review: Oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shockDieter Rixen¹ and John H Siegel²¹Department of Trauma/Orthopedic Surgery, University of Witten/Herdecke at the Hospital Merheim, Cologne, Germany²Department of Surgery & Department of Cell Biology and Molecular Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey (UMDNJ), Newark, New Jersey, USACorresponding author: Dieter Rixen, dieter.rixen@uni-wh.de

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Critical Care 2005, **9**:441-453 (DOI 10.1186/cc3526)**Abstract**

Evidence is increasing that oxygen debt and its metabolic correlates are important quantifiers of the severity of hemorrhagic and post-traumatic shock and may serve as useful guides in the treatment of these conditions. The aim of this review is to demonstrate the similarity between experimental oxygen debt in animals and human hemorrhage/post-traumatic conditions, and to examine metabolic oxygen debt correlates, namely base deficit and lactate, as indices of shock severity and adequacy of volume resuscitation. Relevant studies in the medical literature were identified using Medline and Cochrane Library searches. Findings in both experimental animals (dog/pig) and humans suggest that oxygen debt or its metabolic correlates may be more useful quantifiers of hemorrhagic shock than estimates of blood loss, volume replacement, blood pressure, or heart rate. This is evidenced by the oxygen debt/probability of death curves for the animals, and by the consistency of lethal dose (LD)_{25,50} points for base deficit across all three species. Quantifying human post-traumatic shock based on base deficit and adjusting for Glasgow Coma Scale score, prothrombin time, Injury Severity Score and age is demonstrated to be superior to anatomic injury severity alone or in combination with Trauma and Injury Severity Score. The data examined in this review indicate that estimates of oxygen debt and its metabolic correlates should be included in studies of experimental shock and in the management of patients suffering from hemorrhagic shock.

Introduction

In a noninjured, nonseptic, healthy state, oxygen consumption (VO_2) is a closely regulated process because oxygen serves as the critical carbon acceptor in the generation of energy from a wide variety of metabolic fuels. Post-traumatic hemorrhage leads to a hypovolemia in which blood flow and consequently oxygen delivery to vital organs are decreased. When oxygen delivery is decreased to a degree sufficient to

reduce VO_2 to below a critical level, a state of shock occurs, producing ischemic metabolic insufficiency [1-3]. This degree of restriction in VO_2 can also be produced by cardiogenic or vasodilatory shock, in which oxygen delivery is restricted by low flow. When this critical level of oxygen restriction is reached, an oxygen debt (O_2D) occurs. In the literature, the terms 'oxygen debt' and 'oxygen deficit' are used interchangeably and are defined as the integral difference between the prehemorrhage/pretrauma resting normal VO_2 and the VO_2 during the hypovolemic, hemorrhage period [4-9]. For purposes of simplification, the term O_2D ('oxygen debt') is used in this review. The presence and extent of an O_2D is further highlighted by an increase in the unmetabolized metabolic acids generated by the anaerobic processes. It is the close congruence of O_2D and related metabolic acidemia that permits precise quantification of the severity of the ischemic shock process in both animals and humans.

The aim of this review is to demonstrate the quantitative similarity between experimental O_2D shock and that induced in humans by post-traumatic or severe hemorrhagic, hypovolemic conditions. It also examines the use of metabolic correlates of O_2D as indices of the severity of the shock process in two mammalian species and in humans, and the value of these correlates as guides to the adequacy of volume-mediated resuscitation.

This review is based on a search of the Medline and Cochrane Library databases from 1964 to December 2004. The search terms 'oxygen debt or deficit', 'base excess or deficit', 'lactate', 'hemorrhagic shock' and 'multiple trauma' were used. These terms were mapped to Medline Subject

ARDS = acute respiratory distress syndrome; BD = base deficit; GCS = Glasgow Coma Scale; ICU = intensive care unit; ISS = Injury Severity Score; LD = lethal dose; MOF = multiple organ failure; O_2D = oxygen debt; PO_2 = partial oxygen tension; ROC = receiver operating characteristic; SBV = shed blood volume; TRISS = Trauma and Injury Severity Score; VO_2 = oxygen consumption.

Headings (MESH) terms, as well as being searched for as text items. The following combinations were studied: 'oxygen debt' or 'oxygen deficit' and 'hemorrhagic shock', 'lactate' and 'multiple trauma', as well as 'base excess' or 'base deficit' and 'multiple trauma'. No language restrictions were applied.

The clinical problem of quantification of hemorrhagic shock severity and the effectiveness of resuscitation

That post-traumatic shock is initiated by acute volume loss was first noted by Cannon [10] and later demonstrated by the experimental studies conducted by Blalock [11]. Subsequently, Wiggers [12] and Guyton [13] developed a variety of animal models based on controlled hemorrhage. Other models involving uncontrolled bleeding [14,15], fixed volume loss [16-20], or a defined level of hypotension [16,19-22] have been used. In previous studies, the severity of shock was defined by the degree and duration of the resulting hypovolemia. Thus, attempts were made to quantify the effectiveness of resuscitation by assessing the improvement in blood pressure or perfusion occurring in response to different volumes of electrolyte, colloid, or blood-containing fluids, which are administered to prevent death during the immediate postshock period.

In the clinical arena, this issue became acute during World War II, when fluid transfusion and use of blood and blood products as a means of effectively restoring blood volume became a realistic possibility. Consequently, volume infusion and blood or blood product transfusion were used extensively for the first time during the North African Campaign by US and UK forces [23], and was a primary modality for treatment of shock in the Korean War [24]. These clinical advances led to extensive efforts to elucidate human hypovolemic shock and to establish experimental models that emulate clinical shock. The most extensive series of clinical/physiologic studies were performed in postoperative [25,26] and post-trauma [27] shock patients, in whom the response to volume infusion was evaluated. These and other studies [28,29] of resuscitation after hypovolemic shock demonstrated the fall in VO_2 associated with the decrease in cardiac output, and demonstrated the arterial vasoconstriction that occurred in an attempt to compensate for the fall in blood pressure. They also demonstrated the postresuscitation hyperdynamic state, in which cardiac output rises to permit an increase in VO_2 , apparently compensating for and even exceeding the initial fall in VO_2 [1,2,26]. These data appeared to validate in humans the 'oxygen deficit' concept initially enunciated by Crowell and Smith [4] based on experimental findings. Nevertheless, in spite of these animal and clinical physiological studies, controversy remains with regard to the optimal nature and magnitude of postshock volume resuscitation. Options include massive isotonic fluid replacement [30,31], use of intravascular colloid containing fluids [32], and substitution with small volume hypertonic saline after hemorrhage [33].

Recently, however, a new resuscitation concept has emerged for application when the degree of autogenous vascular control is uncertain, namely permissive hypotension; this is achieved by administering small volumes of resuscitation fluid, permitting only minimal increase in perfusion until full vascular control of hemorrhage can be achieved by surgical intervention [34,35]. Although the statistical validity of the initial human studies [34] has been questioned [36], the concept appears to have some utility, provided that sufficient levels of tissue VO_2 can be achieved to prevent the acute consequences of cellular ischemia [37]. These issues focus on the need for accurate and easily measured correlates of O_2D that can quantify the severity of O_2D and that can be monitored on a continuing basis during resuscitation.

Experimental models of hemorrhagic hypovolemic shock

A large number of animal models have been developed to simulate the critical end-points of hemorrhagic shock. Deitch [38] divided these models into three general categories: uncontrolled bleeding, controlled bleeding volume, and controlled decrements in blood pressure.

A more physiologically relevant animal model is needed because of the clinical requirement to progress beyond the traditional end-points of volume loss and subsequent blood pressure levels [39]. Furthermore, such a model is needed to determine why a state of hyperdynamic cardiovascular compensation develops after hypovolemic shock [25,40]. Also, numerous clinical studies have shown that hypovolemic trauma patients can remain in a state of shock, with evidence of inadequate tissue perfusion and metabolic acidosis [29,41,42], even if the traditional end-points have been normalized [1,2,25,40]. This is reflected in the present definition promulgated by the American College of Surgeons: 'Shock is an abnormality of the circulatory system that results in inadequate organ perfusion and tissue oxygenation' [3]. This understanding of the relationship between shock and inadequate perfusion has led to the development of a possibly more clinically relevant fourth general category of experimental hemorrhagic shock models, based on the concept of repayment of shock-induced O_2D . Table 1 summarizes the historical development of hemorrhagic shock models with O_2D as an end-point. It is based on a systematic Medline/Cochrane Library literature search using the terms 'oxygen debt or deficit' and 'hemorrhagic shock'. From 52 suggested articles, only 13 that strictly dealt with defined O_2D in a hemorrhagic shock model are included.

Thus, development of models of hemorrhagic shock must follow current knowledge and must consider indices of inadequate organ perfusion and tissue oxygenation, which are more meaningful end-points in the clinical setting [4]. Up to the 1990s O_2D was used as a secondary end-point in pressure-controlled or volume-controlled models of hemorrhagic shock (Table 1); in contrast, Dunham and coworkers

Table 1**Historical development of hemorrhagic shock models with oxygen debt as an end-point**

Author (year) [ref.]	Model	Method	Result
Crowell and Smith (1964) [4]	Dog	Hypotension of 30 mmHg; various oxygen deficits were allowed to accumulate	O ₂ D as an indicator of survival
Rush <i>et al.</i> (1965) [5]	Dog	30 min hemorrhage with varying hemorrhage volumes; achieved O ₂ D varied	O ₂ D as an indicator of cardiovascular change; the end-point 'survival' was not evaluated
Goodyer (1967) [90]	Dog	Hypotension of 30–50 mmHg; various oxygen deficits were allowed to accumulate	Irreversibility of shock is determined by peripheral mechanisms; the end-point 'survival' was not evaluated
Jones <i>et al.</i> (1968) [7]	Dog	Hypotension of 30 mmHg; an oxygen deficit of 120 cm ³ /kg was allowed to accumulate	O ₂ D as an indicator of survival
Rothe (1968) [6]	Dog	Hypotension of 30 mmHg; various oxygen deficits were allowed to accumulate	No correlation between O ₂ D and survival
Neuhof <i>et al.</i> (1973) [8]	Rabbit	30 min hemorrhage (1 ml/kg per min); achieved O ₂ D varied	O ₂ D as an indicator of survival
Schoenberg <i>et al.</i> (1985) [21]	Dog	Hypotension of 30 mmHg; various oxygen deficits were allowed to accumulate	No correlation between O ₂ D and survival
Reinhart <i>et al.</i> (1989) [91]	Dog	Hypotension of 40 mmHg; various oxygen deficits were allowed to accumulate	Excess oxygen uptake in recovery with hydroxyethylstarch; the end-point 'survival' was not evaluated
Dunham <i>et al.</i> (1991) [9]	Dog	Predetermined O ₂ D after 60 min; independent of blood pressure or hemorrhage volume	O ₂ D as an indicator of survival and O ₂ D probability of death defined for dog
Sheffer <i>et al.</i> (1997) [92]	Computer	Computer simulation of myocardial oxygen deficit	For hemorrhage of 100 ml/min: time interval from injury to cardiac O ₂ D inversely related to infusion rate; the end-point 'survival' was not evaluated
Siegel <i>et al.</i> (1997) [43]	Dog	Predetermined O ₂ D after 60 min; independent of blood pressure or hemorrhage volume	Superiority of recombinant hemoglobin over colloid or whole blood in resuscitation
Rixen <i>et al.</i> (2001) [44]	Pig	Predetermined O ₂ D after 60 min; independent of blood pressure or hemorrhage volume	O ₂ D as an indicator of survival and O ₂ D probability of death defined for pig.
Siegel <i>et al.</i> (2003) [37]	Dog	Predetermined O ₂ D after 60 min; independent of blood pressure or hemorrhage volume	Determination of critical level of partial resuscitation as 30% of blood volume loss to return O ₂ D to survival levels without vital organ cellular injury

O₂D, oxygen debt.

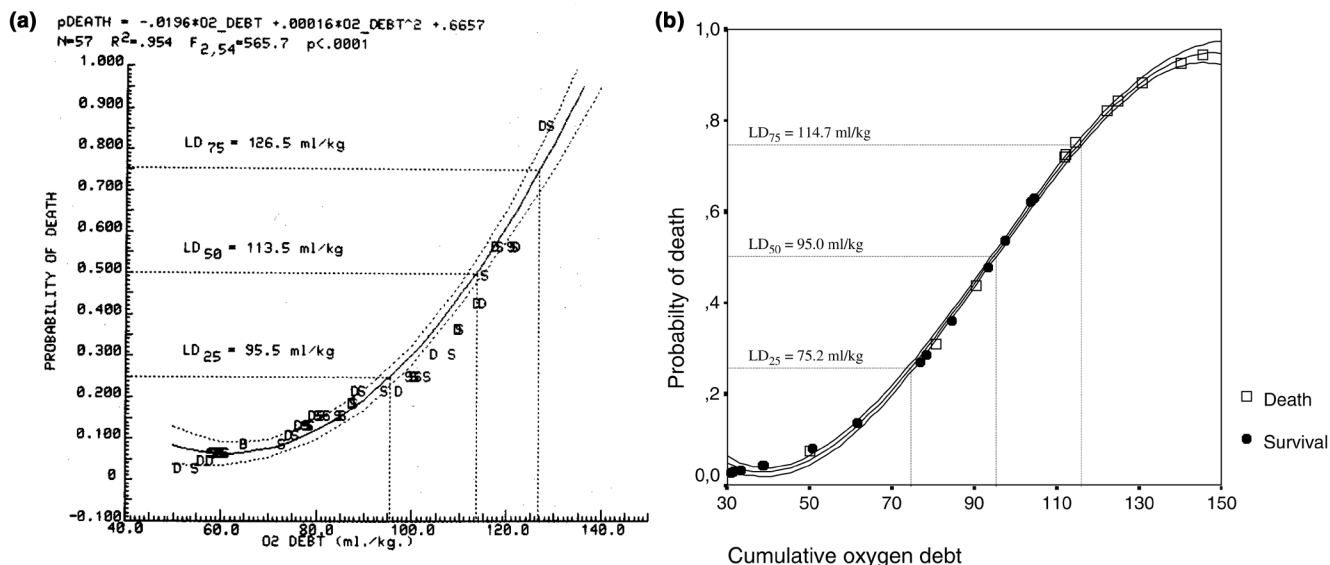
[9] described a canine model of hemorrhagic shock in which O₂D was used as the independent predictor of the probability of death and organ failure. This canine model, which was validated in subsequent studies [37,43], follows the hypothesis that the total magnitude of O₂D reached during hemorrhage is the critical determinant of survival, and that this variable and its metabolic consequences of lactic acidemia and base deficit better reflect the severity of the cellular insult than do traditional variables such as bleeding volume and blood pressure. This hypothesis was also verified in a pig model of O₂D hemorrhagic shock [44].

General principles in the identification and quantification of oxygen debt

In healthy young men, the resting VO₂ has been shown to average 140 ml/min per m². If this VO₂ is decreased by reduced blood flow with restriction in organ and tissue perfusion, a critical level of ischemia is induced, with a

disparity between the oxidative requirement mandated by the level of metabolism and the level of oxygen delivery – an O₂D occurs. Physiologically, if resuscitation is performed before a fatal metabolic debt is incurred then there is rapid repayment of the O₂D, with VO₂ overshoot as the unmetabolized acids are oxidatively metabolized during the reperfusion period. This is effected by an increase in oxygen delivery mediated by a rise in cardiac output – the 'hyperdynamic state' [1,26]. However, as the O₂D accumulates the likelihood of cellular injury increases, with reduction in cellular membrane integrity and consequent cell swelling as intracellular water increases. Later in the process intracellular organelles become damaged, cellular synthetic mechanisms cease, and finally lysosomes are activated, which results in cell necrosis and death [45]. Even at less severe O₂D levels, mechanisms that initiate later apoptosis are activated [46]. Depending on the extent and severity of the cellular injury, specific features of multiple organ failure (MOF) are initiated. Cells with the

Figure 1



Probability of death as a function of oxygen debt. **(a)** Regression-derived relation of Kaplan–Meier probability of death as a function of increasing oxygen debt (O_2D) in a canine O_2D hemorrhagic shock model. Noted on the figure are the O_2D values for lethal dose (LD_{25} (i.e. a dose sufficient to kill 25% of the population studied), LD_{50} , and LD_{75} probabilities. Points plotted along the regression line and its 95% confidence limits represent the actual Kaplan–Meier survival (S) values at 60 min of hemorrhage, or values at the time of death (D) for nonsurviving animals dying during the hemorrhage period or within 5 min of the 60 min hemorrhage sample. Note the good correlation of Kaplan–Meier points to the regression-estimated line. Reproduced with permission from Dunham and coworkers [9]. **(b)** Probability of death as a function of O_2D in a pig O_2D hemorrhagic shock model. Noted on the figure are the O_2D values for LD_{25} , LD_{50} , and LD_{75} probabilities. Points plotted along the regression line and its 95% confidence limits represent the values of cumulative O_2D (in ml/kg) at 60 min of hemorrhage for survivors (marked with circles) and nonsurvivors (marked with squares). Modified from Rixen and coworkers [44].

greatest oxidative requirements (e.g. brain, liver, kidney, myocardium and immunologic tissues) appear to be most vulnerable to O_2D -induced injury or cell death.

Although evidence of cellular and organ failure often appears at various time points after recovery from O_2D , it has long been known that the relationship between O_2D and acute death can be quantified. Crowell and Smith [4] were the first to describe the effect of O_2D in terms of a lethal dose (LD) effect. In their canine studies, O_2Ds of 100 ml/kg or less were not lethal; O_2Ds of 120 ml/kg led to an LD_{50} (i.e. a dose sufficient to kill 50% of the population studied); and O_2Ds of 140 ml/kg or more were invariably fatal. A more precise quantification of the probability of death with increasing O_2D in the same animal species was conducted by Dunham and coworkers [9], who established a complete probability of death function (Fig. 1a). Their studies noted an exponential relationship between probability of death and O_2D , such that although the LD_{25} was at an O_2D of 95.5 ml/kg, the LD_{50} lay at 113.5 ml/kg and the LD_{75} was at 126.5 ml/kg. This relationship has repeatedly been confirmed in dogs by more recent studies [37,43]. Studies in pigs [44] have found a nearly identical relationship, although the LD_{50} for the pig is at a slightly lower O_2D/kg (95 ml/kg; Fig. 1b), corresponding with values calculated by Hannon and coworkers [19] in the same species. This difference between the two animals

appears to reflect the greater percentage of adipose tissue in the pig as compared with the much leaner hound dog over the same range of body weight.

To understand better the concept of hemorrhage-induced O_2D accumulation and its repayment by volume infusion, experimental animal responses were recently studied by Siegel and coworkers [37]. In that study 40 dogs were bled to achieve an O_2D of 104 ± 7.6 ml/kg at 60 min after initiation of hemorrhage (estimated probability of death: 35.7% [9]; actual death rate: 40%; shed blood volume [SBV]: $71.0 \pm 6.8\%$ of the animals' estimated total blood volume [37]). Following hemorrhage, the animals were either given no initial resuscitation for 2 hours and then fully resuscitated with a volume of 5% colloid equivalent to 120% of their SBV. Alternatively, they were randomly assigned to initial resuscitation (R1) with a predetermined percentage of their SBV (again by infusing 5% colloid) equivalent to 8.4%, 15%, 30%, or 120% of their SBV. Then, after a 2 hour delay period in which no further volume resuscitation was given, the animals were given the remaining portion of the calculated 120% of the SBV lost during hemorrhage (delayed resuscitation: R2). This made the final quantity of volume replacement in each animal equal to 120% of the SBV. It is important to note that in those animals given no initial resuscitation, the O_2D accumulation rate continued to rise

either at the same (or slightly lower) rate as during the hemorrhage to or above the 90% mortality level, even though no further blood loss occurred. However, in all instances of R1, the O_2D also continued to rise slightly until a critical quantity of R1 was given (at least 30% of the SBV), but the initial rate of recovery from the hemorrhage-induced O_2D level was increased proportionately to the increase in R1. This relationship between the magnitude of initial resuscitation and the rate of O_2D decrease was highly significant ($P < 0.001$) and predicted later evidence of cell death and organ failure in 7-day postshock survivors [37]. In contrast to the significant discrimination provided by O_2D level, the simultaneously measured mean blood pressure responses were not found to be significantly predictive of the adequacy of resuscitation [37].

These canine data and parallel data obtained in the O_2D pig model [44] demonstrate that quantity of blood volume loss or replacement, blood pressure, and even cardiac output response do not reflect well the severity of shock or the effectiveness of volume resuscitation. However, these endpoints are well defined in a quantitative manner by the magnitude of the O_2D and by its rate of resolution during the resuscitation period, independent of species.

Metabolic correlates of oxygen debt

A considerable body of evidence has accumulated that strongly suggests, both in the animal setting [9,37,43,44] and in humans [29,41,47-49], that metabolic acids in blood or plasma are indices that reflect the degree of tissue hypoxia associated with hypovolemic ischemia. In this review the strict definition of base deficit (BD) – namely, a negative base excess – is used [29,49,50], with a decrease in base excess with increasing metabolic decompensation implying progressively negative values (e.g. -6 mmol/l to -10 mmol/l). However, because BD implies a negative base excess, only positive values of BD (without the minus sign) are used in the present review.

As the concept of O_2D as the key process determining outcome evolved, one of the major goals of experimental studies was to examine the relationship between lactate or BD and hemorrhage-induced O_2D [9,37,43,44]. This significant relationship was repeatedly demonstrated in progressive hemorrhage, with increases in BD or lactate being paralleled by increases in O_2D [9,37,43,44]. Similar significant relationships were noted between decreases in these metabolic variables; the O_2D fell during volume resuscitation, regardless of whether the fluid was crystalloid, hypertonic saline, carbonate/gelatine, colloid, or whole blood [9,37,43,44,51]. The rate of decline in O_2D (and BD and lactate) was significantly more rapid when an oxygen-carrying solution of recombinant hemoglobin was employed for resuscitation [43]. The relationship between BD and O_2D tended to reflect better the effectiveness of increases in initial volume resuscitation, whereas lactate reflected the overall trend in

effectiveness of resuscitation but with less discrimination [37]. Very similar, albeit more variable, significant relationships ($P < 0.0001$) for the two metabolic correlates of O_2D were also noted in the pig model [44]. The greater variability found in the pig may reflect a closer similarity to the broad range of adipose tissue found in humans. Nevertheless, BD and lactate appear to correlate best with O_2D in experimental hemorrhagic shock. This relationship is significant across species [9,44].

Finally, the relationship between O_2D and BD can be used to address the problem of quantifying the effectiveness of small volume resuscitation during permissive hypotension. In other words, the paramedic, surgeon, or intensivist could resuscitate a hypovolemic patient to a level at which perfusion will yield a reduction in O_2D that will allow critical organ oxidative metabolism to be maintained, at a blood pressure that will not encourage further hemorrhage until all open vessels are controlled. Although it is generally not practical to measure O_2D in humans, a model for this approach using BD can be derived from animal data. In a canine O_2D shock model, Siegel and coworkers [37] demonstrated that animals that were effectively volume resuscitated moved progressively down the O_2D /BD regression line to lower values compatible with a reduced probability of death [37]. However, those animals that received inadequate volume resuscitation, particularly those that died during the 2 hour postshock period, moved to progressively higher points in the O_2D /BD relationship. A similar but less quantifiable relationship was found for the O_2D /lactate relationship.

In this respect attention must be paid to the recent development of hemorrhagic shock models with a target endpoint of metabolic acidosis [52-54]. Schultz [52] and Powell [53] and their groups studied bacterial translocation and restoration of central venous oxygen saturation after BD-guided hemorrhagic shock in rats. Also, DeAngeles and coworkers [54] studied resuscitation from BD/lactate guided hemorrhagic shock with diaspirin cross-linked hemoglobin, blood, and hetastarch in sheep. Thus, the use of BD and lactate as clinically useful surrogates for O_2D is strongly supported by experimentation in numerous animal species.

Metabolic correlates of oxygen debt in determining the severity of shock and the effectiveness of resuscitation in humans

Lactate

The search for identifiable and easily measured metabolic correlates of shock that could be used to quantify the severity of human circulatory failure began with the pioneering work of Huckabee [55], Weil and Afifi [56] and Harken [57]. These studies confirmed that the circulating level of lactate provided an indication of the anaerobic component induced by the shock process. Bakker and coworkers [58] reported evidence that the dependency on oxygen supply to body tissues was associated with increasing lactate levels.

Table 2 provides a summary of literature on lactate as an outcome predictor in adult multiple trauma patients based on a systematic Medline/Cochrane Library literature search, using the terms 'lactate' and 'multiple trauma'. Of 59 originally retrieved articles, 27 are specifically noted in the present review because they strictly deal with lactate as an outcome predictor in multiple trauma patients. In almost 3000 multiple trauma patients lactate was shown to predict outcome following postoperative complications, intracranial pressure, infection, sepsis, adult respiratory distress syndrome (ARDS), MOF, injury and hemorrhage severity, and survival.

Clinically, however, it is important to note that not all cases of hyperlactatemia are accompanied by acidosis, and neither are all cases of hyperlactatemia caused by O₂D. Other metabolic dysfunctions may also be associated with hyperlactatemia [59] and can confuse assessment of the O₂D effect, as can excessive alcohol intake and acute cocaine use. The most prominent group of patients with increased lactate levels in the absence of hypovolemia are patients with severe sepsis [28]. However, diabetic patients with ketoacidosis have increased lactate, and in patients with impaired hepatic function lactate uptake may be reduced and lactate levels may rise. Of specific importance in patients resuscitated from hemorrhagic shock is that administration of large quantities of exogenous lactate (e.g. via mass infusion of Ringer's lactate) has been shown to increase lactate to levels significantly greater than those expected to result from the shock process alone [60]. This clearly may distort interpretation of lactate levels as a clinical diagnostic tool. Furthermore, the reduction in oxygen delivery that induces O₂D also causes other metabolic acids to accumulate in the extracellular/intravascular components, and so plasma lactate levels may not always quantitatively reflect the O₂D process. Thus, the origin of a hyperlactatemia is clinically important and has direct implications for treatment choice.

Although the use of lactate-free resuscitation fluids may become routine in the future [60], the current widespread use of Ringer's lactate may be a further reason why it remains unclear whether the lactate level on hospital admission is prognostically significant in multiple trauma patients. Several studies have noted the predictive value of the initial lactate level [58,61,62], but others have shown other variables to be equivalent [63] or even better [29] in outcome prediction. In contrast, more than one study found no significant correlation between initial lactate level and post-trauma outcome [49,64-66]. Nevertheless, in a study of 375 trauma patients admitted directly from the scene of injury to a level I trauma center [62], simultaneously obtained arterial and peripheral venous lactate levels were shown to be highly correlated, and a lactate threshold level of >2 mmol/l appeared to predict the likelihood of the Injury Severity Score (ISS) being 13 or greater with a high degree of accuracy. Thus, lactate appears to represent a good triage tool.

Table 2

Literature on lactate as an outcome predictor in adult multiple trauma patients

Author (year) [ref.]	Trauma patients	Outcome prediction
Oestern <i>et al.</i> (1978/1979) [93,94]	50	Survival
Brandl <i>et al.</i> (1989) [95]	51	Survival
Siegel <i>et al.</i> (1990) [29]	185	Survival
Woltmann and Kress (1991) [96]	35	Survival
Nast-Kolb <i>et al.</i> (1992) [97]	100	Survival
Waydhas <i>et al.</i> (1992) [98]	100	MOF, sepsis
Roumen <i>et al.</i> (1993) [99]	56	MOF, ARDS
Abramson <i>et al.</i> (1993) [61]	76	Survival
Sauaia <i>et al.</i> (1994) [100]	394	MOF
Dunham <i>et al.</i> (1994) [101]	17	MOF, ARDS
Scalea <i>et al.</i> (1994) [102]	30	Intracranial pressure
Manikis <i>et al.</i> (1995) [103]	129	MOF, survival
Ivatury <i>et al.</i> (1995) [104]	27	Survival
Regel <i>et al.</i> (1996) [105]	342	MOF
Mikulaschek <i>et al.</i> (1996) [64]	52	Survival
Charpentier <i>et al.</i> (1997) [106]	20	Survival
Nast-Kolb <i>et al.</i> (1997) [107]	66	MOF
Cairns <i>et al.</i> (1997) [85]	24	MOF
Sauaia <i>et al.</i> (1998) [108]	411	MOF
Blow <i>et al.</i> (1999) [109]	116	MOF, survival
Claridge <i>et al.</i> (2000) [110]	364	Infection, survival
Crowl <i>et al.</i> (2000) [111]	77	'Postoperative complications'
Rixen <i>et al.</i> (2000) [77]	80	ARDS
Ertel <i>et al.</i> (2001) [112]	20	Severity of hemorrhage, survival
Cerovic <i>et al.</i> (2003) [113]	98	Injury severity, survival
Egger <i>et al.</i> (2004) [114]	26	Injury severity

ARDS, acute respiratory distress syndrome; MOF, multiple organ failure.

Base deficit

In the search for a more precise quantifier of severity of post-trauma hemorrhagic shock, Siegel [29], Rutherford [47], Davis [50], and Rixen [49] and their groups studied the value of BD as a single predictor of the severity of post-trauma hemorrhagic shock. The findings of those studies, which represent more than 8000 trauma patients with varying severities of injury, are shown in Fig. 2. All of the studies indicate that BD can be used to stratify trauma patients with respect to their likelihood of dying, and suggest that BD can also be used to provide an index of the effectiveness of resuscitation in humans as well as in experimental animals.

With respect to studies in patients with greater injury severity, Table 3 provides a summary of literature on BD as an outcome predictor in adult multiple trauma patients based on a systematic Medline/Cochrane Library literature search using the terms 'base excess' or 'base deficit' and 'multiple

trauma'. From 34 originally retrieved articles, 15 are noted because they strictly deal with base excess/BD as an outcome predictor in adult multiple trauma patients. Among the 6567 multiple trauma patients represented in Table 3, BD was found to predict outcomes in terms of hemodynamics, transfusion requirements, metabolism, coagulation, volume deficit, neutrophil chemiluminescence and CD11b expression, complement activation, acute lung injury, ARDS, hepatic dysfunction, MOF, and survival.

Although multiple trauma patients were not included exclusively, attention must be given to the studies conducted by Mackersie [67] and Davis [68] and their groups in more than 6000 trauma patients; those investigators showed that BD may also be considered an indicator of significant abdominal injury. Furthermore, the admission BD was also found to be an important prognostic indicator with respect to injury severity and death in pediatric [69-71] and elderly [72] trauma populations.

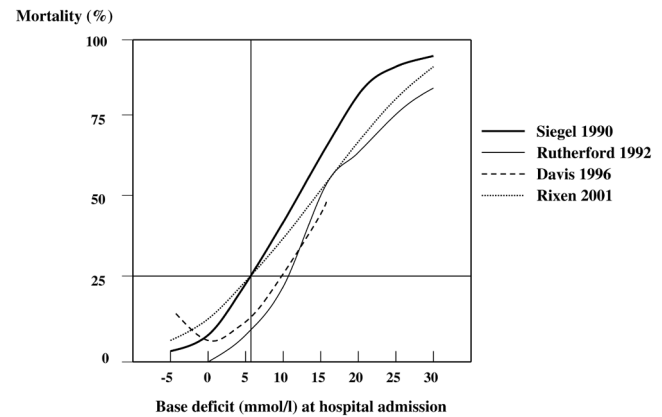
However, Siegel and coworkers [29] demonstrated that BD alone did not provide the best prediction of post-trauma mortality, and that it could be quantitatively coupled with an estimate of head injury, such as that provided by the Glasgow Coma Scale (GCS). The interaction between GCS score, BD, and mortality is illustrated in Fig. 3a, which was developed from findings in 185 patients whose major injury was blunt hepatic trauma. Also shown is the relationship of predicted to observed deaths based on the regression model (Fig. 3b). This relationship was verified in an independent group of 323 multiple trauma patients with pelvic fracture [29]. Indeed, the substantial differences in the proportion of trauma patients with severe head injury in the studies shown in Fig. 2 may account for the variation in the LD₂₅ and LD₅₀ points seen in these different clinical studies.

The validity of the use of BD in conjunction with other predictive variables was extended to a larger series of 2069 multiple trauma patients included in the German Trauma Society registry [73]. That study validated the probability of death relationship between BD and GCS, but it also showed that additional improvement in the sensitivity/specificity receiver operating characteristic (ROC) curve (ROC = 0.904, with greatest sensitivity and specificity of 82.3% and 83.0%, respectively) could be obtained by the addition of prothrombin time, age, and ISS to the equation. In this multifactorial analysis, the admission BD was one of the five best predictors for outcome (BD, GCS, age, prothrombin time, and ISS). Each of these five variables contributed significantly to the derived multifactorial regression model:

$$p\text{Death} = \frac{1}{1 + e^{-(\text{intercept} + \beta_1[\text{BD}] + \beta_2[\text{GCS}] + \beta_3[\text{prothrombin time}] + \beta_4[\text{age}] + \beta_5[\text{ISS}])}}$$

Where pDeath = probability of death, BD = hospital admission BD, intercept = -0.1551, $\beta_1 = 0.0840$, $\beta_2 = -0.2067$, $\beta_3 = -0.0359$, $\beta_4 = 0.0438$, and $\beta_5 = 0.0252$.

Figure 2



Mortality as a function of base deficit. Mortality curves presented as a function of the admission base deficit in more than 8000 multiple trauma patients derived from four independent studies. Modified from Zander [89].

Table 3

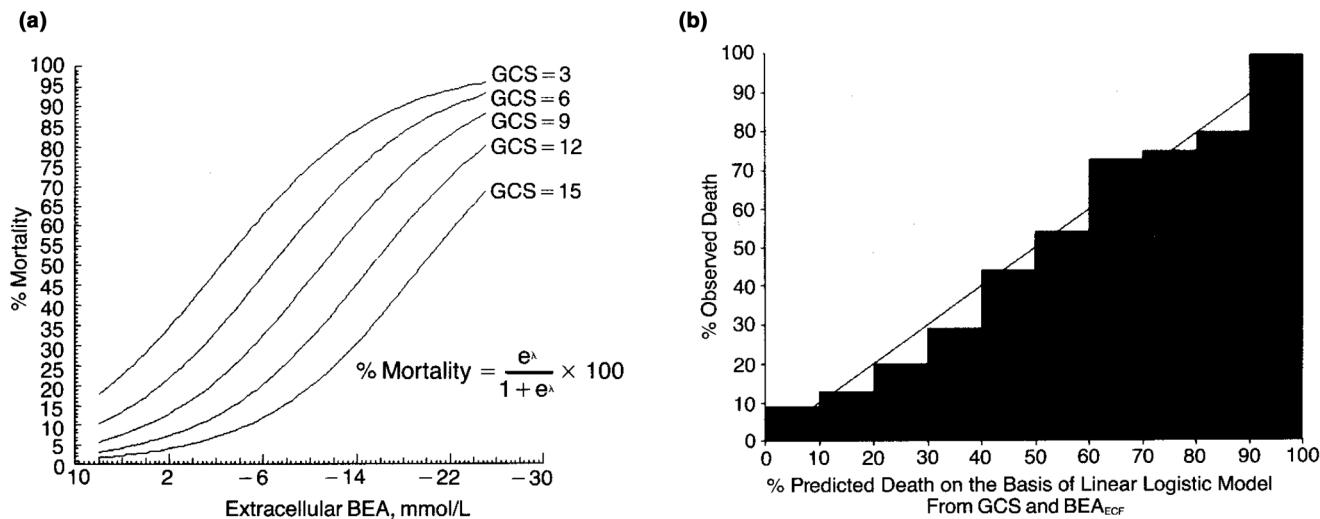
Literature on base excess/base deficit as an outcome predictor in adult multiple trauma patients

Author (year) [ref.]	Trauma patients	Outcome prediction
Oestern <i>et al.</i> (1978/1979) [93,94]	50	Survival
Davis <i>et al.</i> (1988) [41]	209	Blood pressure, severity of volume deficit
Siegel <i>et al.</i> (1990) [29]	508	Survival
Sauaia <i>et al.</i> (1994) [100]	394	MOF
Regel <i>et al.</i> (1996) [105]	342	MOF
Botha <i>et al.</i> (1997) [48]	17	Neutrophil CD11b expression
Davis <i>et al.</i> (1998) [115]	674	Survival
Krishna <i>et al.</i> (1998) [116]	40	Survival
Fosse <i>et al.</i> (1998) [117]	108	Complement activation
Brown <i>et al.</i> (1999) [118]	12	PMN chemiluminescence
Eberhard <i>et al.</i> (2000) [119]	102	Acute lung injury
Rixen <i>et al.</i> (2000) [77]	80	ARDS
Rixen <i>et al.</i> (2001) [49]	2069	Hemodynamic, transfusion requirements, metabolism, coagulation, survival
Harbrecht <i>et al.</i> (2001) [120]	1962	Hepatic dysfunction

ARDS, acute respiratory distress syndrome; MOF, multiple organ failure.

However, when the three physiologic variables and age were added sequentially into the regression model, the ISS contributed only an additional 0.4% to the correctness of

Figure 3



Interaction between base excess, Glasgow Coma Scale (GCS) and mortality. (a) Linear logistic model for predicting mortality from GCS and admission extracellular base excess (BEA) for 185 patients with blunt traumatic hepatic injury ($\lambda = -0.21[\text{GCS}] - 0.147[\text{BEA}_{\text{ECF}}] + 0.285$; $P < 0.0001$ for model). (b) Predicted versus observed mortality in linear logistic model from GCS and BEA for patients with blunt traumatic hepatic injury. ECF, extracellular fluid. Reproduced with permission from Siegel and coworkers [29].

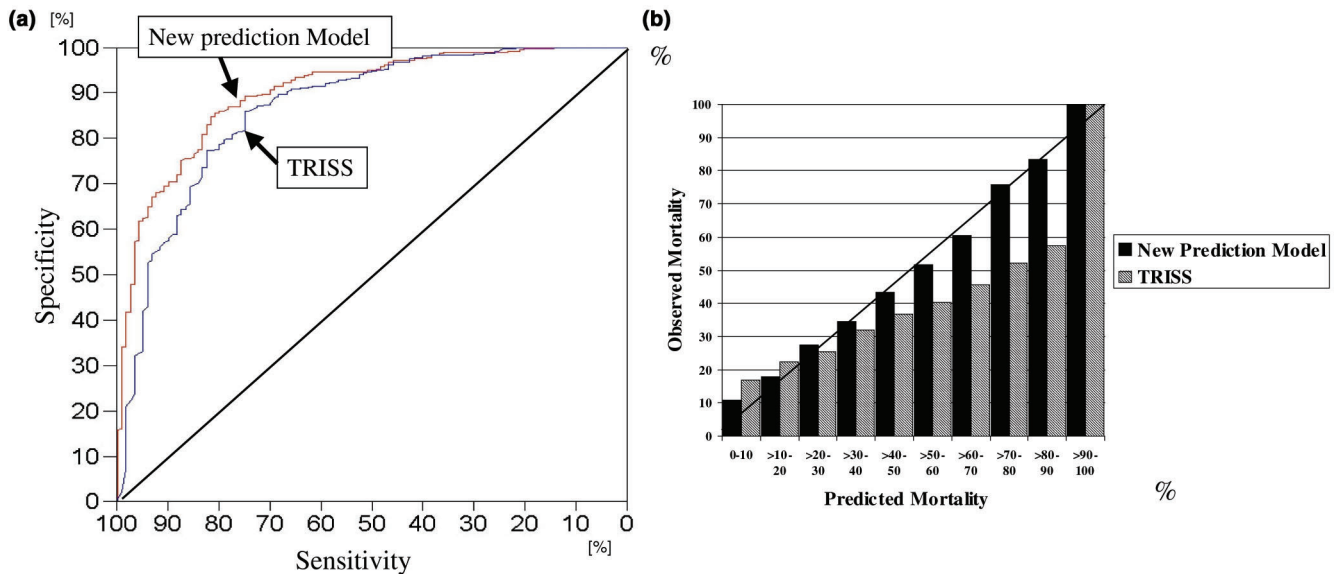
prediction. These data suggest that, because the full extent of the patient's injuries and their severities may not be readily evident on hospital admission, a reasonable immediate estimate of severity can be made on the basis of the patient's physiologic/metabolic response adjusted for age.

This prediction model was validated prospectively in an independent set of 1745 additional multiple trauma patients included in the German Trauma Society registry [73]. In both the development set (2069 patients) and in the independent validation set (1745 additional multiple trauma patients), the probability of death predicted by the model was compared with the observed mortality rate. The validation set yielded an area under the ROC curve for the model of 0.901, with greatest sensitivity and specificity of 82.2% and 83.3%, respectively (Fig. 4a). Using the goodness-of-fit test, there was no significant difference between the observed and predicted distributions of mortality. The model predicted the numbers of observed and expected events equally well across all strata in the development and validation sets (Fig. 4b), and therefore the model appeared to be well calibrated in both development and validation sets of multiple trauma patients.

The validation of this outcome prediction model for multiple trauma patients was completed by its comparison with the predictive ability of an international gold standard, namely the Trauma and Injury Severity Score (TRISS) score [74]. In the validation set of patients discussed above, TRISS discrimination yielded an area under the ROC curve of 0.866 (Fig. 4a). Although this difference in overall predictive ability may

appear to be small, when the predicted versus observed death rates are examined in detail it is apparent that there is under-prediction by the TRISS score from the 30% to the 90% mortality range, which is the region of greatest clinical interest (Fig. 4b). Using the goodness-of-fit test [75] there was a significant difference between the observed and predicted mortality distributions in the TRISS score. Thus, the TRISS score did not predict well the number of observed events across all strata as compared with the prediction model based on BD, GCS, prothrombin time, age, and ISS. This weakness of TRISS and other scoring systems based on the Revised Trauma Score and ISS alone, without inclusion of specific patient metabolic data, has been extensively examined in comparison with other systems and is consistent with these observations [76].

The use of BD allows critical thresholds to be established by which the clinician can be alerted to the beginning of a deleterious trend in O_2D or to progression of putative shock to a condition of life-threatening potential. In this regard, both the studies conducted by Davis [41] and Siegel [29] and their groups, as well as the more recent multicenter trial data [49], have shown that a critical threshold exists at or slightly above a BD of 6.0 mmol/l (Fig. 2). When the probability of death is analyzed as a function of BD [29], this is the point at which the exponential rise in probability of death begins, and it is also the point in the experimentally derived BD/ O_2D relationship [9] at which the O_2D begins to rise exponentially. In contrast to the animal studies, in post-trauma humans, where there is frequently an associated brain injury, the observed mortality induced by a rise in BD to 6.0 mmol/l is

Figure 4

Discrimination and calibration of the multivariate outcome prediction model. **(a)** Discrimination. Receiver operating characteristic curve of the multivariate outcome prediction model based on base deficit, Glasgow Coma Scale score, prothrombin time, age and Injury Severity Score, compared with that derived from the Trauma and Injury Severity Score (TRISS) in the validation set of 1745 multiple trauma patients. The diagonal line corresponds to a test that is sensitive or specific just by chance. The area under the curve for the multivariate outcome prediction model is 0.901 and that for the TRISS score is 0.866. **(b)** Calibration. Predicted versus observed mortality for the multivariate outcome prediction model and the TRISS score in the validation set of 1745 multiple trauma patients.

also a function of the level of impairment in GCS, rising from a probability of death of 15% with a GCS score of 15 to 30% with a GCS score of 9 and 45% at a GCS score of 6 (Fig. 3). Thus, the overall probability of death both in the initial study conducted by Siegel and coworkers [29] and in the more recent report by Rixen and coworkers [49] exceeded 25% (LD_{25}) when the admission BD was increased to 6.0 mmol/l or greater, independent of GCS score.

Furthermore, change in BD over time is an important variable in the prediction of outcome following hypovolemic post-traumatic shock. Rixen and coworkers [49] noted that the change in BD between hospital and intensive care unit (ICU) admission was a further significant predictor of outcome. Those investigators analyzed the development of BD over the period from hospital to ICU admission with respect to mortality rate. The trauma patients were subdivided into two groups at the time of hospital and subsequent ICU admission with respect to the LD_{25} threshold value of 6 mmol/l, which was previously noted to be the critical level [29,41,49]; patients with a BD below 6 mmol/l were considered to have 'good prognosis', and patients with a BD of 6 mmol/l or greater were considered to have 'bad prognosis'. Patients with a BD below 6 mmol/l on hospital admission and who subsequently had a BD below 6 mmol/l on ICU admission had the lowest mortality rate (13%). Patients with a BD above 6 mmol/l on hospital admission and who subsequently had a

BD of 6 mmol/l or greater on ICU admission had the highest mortality rate (45%; $P < 0.0001$). Finally, the level of admission BD was shown to predict the probability of development of post-traumatic ARDS, with the incidence rising exponentially above a BD of 6.6 mmol/l [77].

Conclusion

The data reported above strongly indicate a need to add quantitative estimates of the effectiveness of perfusion and VO_2 to hemorrhagic shock studies. Currently, indirect measurement techniques that reflect cellular oxygen utilization and perfusion either systemically (lactate and BD) or locally (gastric intramucosal pH and microdialysis [78]) predominate. It would be ideal to measure O_2D at the cellular level as an end-point of experimental and clinical hemorrhagic shock. The muscle beds, subcutaneous tissue, and even skin have been advocated as sites at which perfusion may be more directly measured at the tissue level. Hartmann and coworkers [79] found good correlations between subcutaneous and transcutaneous partial oxygen tension (PO_2), and with gastric tonometry in pigs. Subcutaneous PO_2 tissue probes have been used in the experimental setting [80] as well as in severely injured patients [81,82]. McKinley and coworkers [83] studied skeletal muscle PO_2 , partial carbon dioxide tension, and pH using fiberoptic technology in hemorrhaged dogs, and Knudson and coworkers [84] examined the posthemorrhage and resuscitation oxygen

tension response in muscle and liver in pigs. Another technique that holds promise for the future is that of near infrared spectroscopy [85]. All of these techniques, along with others currently being developed, may move the end-points of hemorrhagic shock models to the organ, cellular, and subcellular levels. However, at present these newer technologies require the use of relatively complex and expensive or invasive methodologies, whereas relatively inexpensive handheld devices now exist for rapid field, emergency room, or ICU determinations of lactate and BD [86].

However, it is clear from experimental [87] and clinical studies [81,88] that some vascular beds may be more vasoconstricted than others; the skin, subcutaneous and muscle tissue, and intestinal perfusion are sacrificed to preserve cardiac, central nervous system, renal, and hepatic perfusion. Consequently, probes placed in the physiologically expendable tissues may not reflect the true total body situation, and especially vital organ O_2D s. This contention is supported by the findings reported by Siegel and coworkers [37], which showed that adequate resuscitation with a volume of 30% of SBV could preserve essential organ histology and physiologic function from an LD_{35-40} of O_2D without increasing the cardiac index above control preshock levels. Only when the remaining volume of delayed full resuscitation was given did the cardiac index and oxygen consumption rise to hyperdynamic levels, suggesting that a large percentage of this hyperdynamic state is devoted to repayment of the O_2D in less essential organs, which collectively represent the greater portion of body cell mass.

Nevertheless, both animal and clinical data strongly suggest that the overall O_2D and/or its metabolic correlates (BD and lactate) better reflect the severity of shock than do currently available measures of local tissue or organ perfusion. This is shown by the probability of death curves for individual species, and by the relative consistency of LD_{25} and LD_{50} points for BD across species and especially in humans, when adjusted for GCS and other significant variables.

We require a more precise technique for assessing total body O_2D , or at least that of critical organs, that can easily and repeatedly be applied in the clinical setting. Until such a technique becomes available the use of BD, either alone or in combination with GCS score and other significant variables of high predictive accuracy (e.g. prothrombin time and age), represents the best present system for clinical assessment of shock severity and success of resuscitation. These variables may be used to obtain information rapidly on a patient's level of compensation in response to post-trauma or hemorrhagic shock either by immediate reference to a predetermined graph (Fig. 3) or by entry of data into a handheld computer for computation of an estimate of probability of death using the regression equation shown above. This would facilitate clinical decision making at the bedside, in the emergency room, or in the ICU.

In conclusion, the data examined in this review strongly indicate that there is a need to add quantitative estimates of O_2D and resulting metabolic acidosis to clinical studies, and that these variables should be considered in the management of patients sustaining severe hemorrhagic shock. The data also suggest that evaluation of metabolic correlates of the total body O_2D (BD and, to a lesser extent, lactate) may be more useful in quantifying the responses of trauma or nontrauma patients to hemorrhage than are estimates of blood loss, quantitative measurements of volume replacement, or blood pressure and heart rate. Finally, we believe that further research based on the parameters of oxygen utilization and O_2D will achieve even better, clinically suitable variables by which to assess the magnitude and severity of human stress physiology and to quantify the effectiveness of resuscitation therapies in the multiple trauma patient or the patient with life-threatening hemorrhage from a gastrointestinal lesion.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

Both authors (DR and JHS) made substantial contributions to the conception and design of this review, and to the acquisition, analysis, and interpretation of data. Furthermore, both authors were involved in drafting the article and revising it critically for important content, and gave final approval of the version to be published.

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