Research

The influence of N-acetyl-L-cysteine infusion on cytokine levels and gastric intramucosal pH during severe sepsis

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Abstract

Introduction The purpose of the present study was to evaluate the effects of continuously infused N-acetyl-L-cystein (NAC) on serum cytokine levels and gastric intramucosal pH in humans suffering from severe sepsis.

Methods Fifty-three patients were included in the study. In the NAC group (n = 27), after an initial intravenous bolus of NAC (150 mg/kg over 5 min), a continuous intravenous infusion of 12.5 mg/kg per hour was given for 6 hours. Patients in the control group (n = 26) were administered dextrose (5% solution) at the same dosage. We recorded the following: haemodynamic parameters, nasopharyngeal temperature, arterial blood gas changes, plasma cytokine levels, biochemical parameters, intramucosal pH, length of stay in the intensive care unit, duration of mechanical ventilation and mortality. All measurements were taken at baseline (15 min before the start of the study) and were repeated immediately after the bolus infusion, and at 24 and 48 hours after initiation of the continuous NAC infusion.

Results No differences were found between groups in levels of the major cytokines, duration of ventilation and intensive care unit stay, gastric intramucosal pH and arterial oxygen tension/inspired fractional oxygen ratio (P > 0.05).

Conclusion We found that NAC infusion at the doses given did not affect cytokine levels, outcomes, or gastric intramucosal pH in patients with severe sepsis. Because of the limited number of patients included in the study and the short period of observation, our findings need confirmation in larger clinical trials of NAC infused in a dose-titrated manner. However, our results do not support the use of NAC in patients with severe sepsis.

Keywords: cytokine levels, gastric intramucosal pH, haemodynamic parameters, intensive care unit, N-acetyl-L-cystein, severe sepsis

Introduction

Sepsis is defined as the systemic response to infection [1,2]. The deleterious effects of invasion of body tissues by bacteria result from the combined actions of enzymes and toxins, produced both by the micro-organisms themselves and by endogenous cells in response to the infection. Patients with severe infections have extremely low concentrations of protective antioxidants and high levels of the metabolic products of free radical damage, with the greatest increases seen in the most severely ill [3,4].

N-acetyl-L-cysteine (NAC), a derivative of the naturally occurring amino acid L-cysteine, is currently indicated for acute paracetamol overdose [5]. Pharmacological actions include

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IL = interleukin; NAC = N-acetyl-L-cystein; pHi = gastric intramucosal pH; TNF = tumour necrosis factor.
repletion of intracellular glutathione stores, scavenging of toxic oxygen free radicals (both directly and indirectly via increased glutathione concentrations) and suppression of tumour necrosis factor (TNF) production [6]. NAC may also exert a beneficial effect on the oxidation and downregulation of essential thiol groups in β-adrenergic receptors [7]. Furthermore, NAC has been shown to decrease lipoperoxidative damage in early clinical septic shock [8].

Gastric intramucosal pH (pHi) in experimental animals decreases as splanchnic perfusion decreases below the level at which local oxygen transport can no longer sustain aerobic energy production [9]. Therefore, it may be possible to use pH as an early and noninvasive index of systemic tissue oxygenation, given that selective reductions in splanchnic perfusion occur with decreases in systemic oxygen transport [9].

The purpose of the present study was to evaluate the effects of continuously infused NAC on serum cytokine levels and pH in humans suffering from severe sepsis.

Methods

Patient population and study design

The Regional Committee on Medical Research Ethics approved the study. Written informed consent was obtained from patients (wherever possible) or from the next of kin. Critically ill patients with bacteriologically documented infections were included in the study as soon as they met at least two of the following criteria for sepsis, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [2]: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or arterial carbon dioxide tension <32 mmHg; and leucocyte count >12 x 10^9 cells/l or <4 x 10^9 cells/l. In addition, at least one of following conditions was required: hypoxaemia (arterial oxygen tension/fractional inspired oxygen ratio <250); oliguria (urine output <0.5 ml/kg body weight for 2 hours); lactic acidosis (lactate concentration >2 mmol/l); thrombocytopenia (platelet count of <100 x 10^9/l); or a recent change in mental status without sedation. Patients who were under 18 years old, pregnant, or receiving corticosteroids, immunosuppressants, or chemotherapy, and those with a known irreversible underlying disease, such as end-stage neoplasms, were excluded.

The Acute Physiology and Chronic Health Evaluation II [10] and Sepsis-related (or Sequential) Organ Failure Assessment [11] scores were employed to determine the initial severity of illness. If required, patients underwent surgical procedures before the start of the study. No invasive surgery was performed during the 48-hour study period. All patients were ventilated in volume-controlled mode (Puritan Bennett 7200; Puritan Bennett Inc., Carlsbad, CA, USA) and received continuous analgesic sedation with midazolam and fentanyl. Ventilator settings, and levels of positive end-expiratory pressure and fractional inspired oxygen were kept constant during NAC or placebo infusion. Antibiotic treatment was adjusted according to the results of bacteriological culture (blood or other samples). In all patients fluid replacement was administered to keep the central venous pressure between 4 and 8 mmHg. No inotropic agent was administered during the study. Those patients who met the above criteria for severe sepsis were enrolled in the study within 4 hours of intensive care unit (ICU) admission.

Protocol

Randomization was done using a computer-steered permuted block design. The study was prospective, randomized, double blind and placebo controlled. In order to perform the study in a double-blind manner, drug solution and infusion was administered to all patients by a nurse without any knowledge about the study protocol. Follow up was done by an anaesthetist without any knowledge of the study protocol. Patients in the NAC group (n = 27) were given NAC (ASIST®; Istanbul, Turkey; 300 mg/3 ml, 10%) as an intravenous bolus of 150 mg/kg over 30 min, and then as a continuous intravenous infusion of 12.5 mg/kg per hour for 6 hours. In the control group (n = 26), patients were given 5% dextrose as bolus and infusion over 6 hours (same dosage).

A tonometer (TRIP NGS Catheter; Tonometrics Inc., Worcester, MA, USA) was inserted via the nasogastric route before infusion of the bolus. The tonometer was advanced until the balloon was located in the lumen of the stomach. The position of the balloon was confirmed radiographically. The silicone balloon of the tonometer was filled with 2.5 ml 0.9% saline. After sufficient time for equilibration of carbon dioxide tension between saline and the gastric lumen, anaerobic samples of the tonometer saline and of arterial blood were taken simultaneously and analyzed using standard pH and blood gas analyzers. pH was calculated by a modification of the Henderson–Hasselbalch equation:

\[
\text{pHi} = \frac{6.1 + \log_{10}(\text{arterial bicarbonate concentration})}{F \times \text{tonometer saline PCO}_2}
\]

Where F is a time dependent factor for partly equilibrated samples provided by the manufacturer of the device.

Measurements

All patients had arterial catheters placed (arterial line kit, monitoring kit transpac® IV; Abbott, Sligo, Ireland) and central venous catheters via subclavian (Certofix trio V 720 "7F x 8"; Braun, Melsungen, Germany). Arterial blood samples were simultaneously withdrawn for measurements of pH, oxygen and carbon dioxide tensions, and arterial oxygen saturation (Easy BloodGas; Medica, MA, USA). Central venous pressure, mean arterial pressure, heart rate and nasopharyngeal temperature were continuously monitored (Model 90308, SpaceLabs Inc., Redmond, WA, USA). All measurements
were obtained at baseline (15 min before the start of the study) and again after the bolus infusion, and at 24 and 48 hours after the start of the continuous infusion. Platelets, leukocytes, bilirubin, alanine aminotransferase, and creatinine were determined at the same times (Vitalab Flexor, Dieren, The Netherlands).

TNF-α, IL-1β, IL-2 receptor, IL-6 and IL-8 levels were also measured, at the time points indicated above. Venous blood was collected into a 10 ml sterile plain tube (without anticoagulant) before administration of any medications and stored at -20°C. Before assay, all samples were thawed to room temperature and mixed by gentle swirling or inversion. All sera were assayed on the same day to avoid interassay variation. TNF-α, IL-1, IL-2 receptor, IL-6 and IL-8 levels were measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay method (Immulite TNF-α, Immulite IL-1β, Immulite IL-2 receptor, IL-6 Immulite and IL-8 Immulite; EURO/DPC, Llanberis, UK). The antibodies used in this procedure have no known cross-reactivities with other cytokines. The lowest detectable limits of IL-1β, IL-2 receptor, IL-6, IL-8 and TNF-α were 1.5 pg/ml, 5 U/ml, 5 pg/ml, 2 pg/ml and 1.7 pg/ml, respectively.

The duration of mechanical ventilation was recorded. Survival was defined as being alive at hospital discharge.

**Statistics**

Repeated measures analysis of variance was used to evaluate the differences between and within groups. If significant differences were present then the groups were tested by independent samples t-tests to determine which difference was significant. Data are expressed as means ± standard deviation. \( P < 0.05 \) was considered statistically significant.

**Results**

**Patient characteristics**

The clinical and demographic characteristics of the NAC and control patients studied are summarized in Tables 1 and 2, respectively. Of the 53 patients, 27 received NAC (NAC group) and 26 received placebo (control group). Seventeen patients had septic shock on admission (seven in the NAC group, and 10 of the placebo-treated patients) and five died while in the ICU for reasons unrelated to infection (pulmonary embolism, cardiac death as determined by clinical and post-mortem studies). Baseline Acute Physiology and Chronic Health Evaluation II scores (13.14 ± 3.79 and 15 ± 3.58 for the NAC and control groups, respectively) and Sepsis-related Organ Failure Assessment scores (5.62 ± 2.52 and 6.53 ± 2.2 for the NAC and control groups, respectively) were similar (\( P > 0.05 \)). Infection was documented in all patients.

**Haemodynamic parameters and oxygen transport variables**

There were no significant differences between the groups with respect to pH, oxygen tension, carbon dioxide tension, arterial oxygen tension/fractional inspired oxygen ratio and arterial oxygen saturation (\( P > 0.05 \)). No significant change in mean arterial pressure or heart rate was found in either group (Table 3). Also, there were no significant differences between the groups in biochemical parameters (\( P > 0.05 \)).

**Outcome**

Outcomes are listed in Tables 1 and 2. The overall hospital mortality was 26% (seven patients) in the NAC group and 31% (eight patients) in the group control (\( P > 0.05 \)). All of the patients who died did so while they were being mechanically ventilated. In the NAC and placebo groups, the durations of mechanical ventilation were 8 ± 2 and 8 ± 3 days, respectively (\( P > 0.05 \)), and the numbers of ventilator-free days were 9 ± 3 and 8 ± 3, respectively (\( P > 0.05 \)). The length of ICU stay of NAC-treated survivors was not significantly different from that of placebo-treated survivors (10 ± 2 days versus 11 ± 4 days; \( P > 0.05 \)).

**Plasma cytokine levels**

TNF-α, IL-1β, IL-2 receptor, IL-6 and IL-8 levels remained unchanged during the study (Table 4).

**Gastric intramucosal pH**

There was no significant difference between the groups with respect to pHi (\( P > 0.05 \); Table 4).

**Side effects**

The NAC infusion was well tolerated by all patients who received it, and no side effects were noted during or after administration of NAC.

**Discussion**

Systemic inflammatory response leading to postoperative organ dysfunction and sepsis remains a formidable clinical challenge and carries a significant risk for death. Recent clinical studies suggest that patients with sepsis undergo relative oxidative stress [12]. Overwhelming production of oxygen free radicals is thought to play a central role in the inflammatory process [3]. Many investigators have suggested that use of exogenous agents such as NAC may be of benefit in preventing oxygen free radical damage in patients suffering from septic shock [13,14]. NAC acts as a powerful oxygen free radical scavenger, and it replenishes depleted glutathione stores, thus enhancing defence against endogenous antioxidants [15].

Sepsis and septic shock remain major causes of death in ICUs. Complications of sepsis result from an intense host response caused by a disturbance of the delicate equilibrium between various proinflammatory and anti-inflammatory medi-
ators [16]. Overwhelming production of proinflammatory cytokines such as TNF-α, IL-1β, IL-2 receptor, IL-6 and IL-8 may induce biochemical and cellular alterations either directly or by orchestrating secondary inflammatory pathways. NAC can also exert important anti-inflammatory effects on neutrophils and monocytes [17]. Zhang and coworkers [13] found that this decreased inflammatory response was reflected by complete inhibition of TNF release with pretreatment NAC. Peristeris and coworkers [6] demonstrated that pretreatment with NAC significantly inhibited TNF production both in serum and in spleen in a mouse model of endotoxemia. This attenuating effect of NAC on TNF production is most likely due to decreased release of oxygen free radicals. Furthermore, in patients with sepsis who were administered NAC, Paterson and coworkers [18] found decreased nuclear factor-κB activation, which was associated with decreased levels of IL-8 but not of IL-6 or soluble intercellular adhesion molecule-1. That pilot study suggested that NAC may blunt the inflammatory response to sepsis by interfering with nuclear factor-κB activation.

Spapen and colleagues [19] found that NAC had no significant effect on plasma TNF, IL-6 or IL-10 levels, but acutely decreased IL-8 and soluble TNF receptor/p55 levels. They

| Patient | Age (years) | Sex | Type of infection | Pathogen | Outcome  |
|---------|-------------|-----|-------------------|----------|----------|
| 1       | 86          | F   | Pneumonia         | *Pseudomonas aeruginosa* | Survived |
| 2       | 54          | F   | Pneumonia         | *Klebsiella pneumoniae*<sup>1</sup> | Died (MOF) |
| 3       | 52          | F   | Pneumonia         | *Escherichia coli* | Survived |
| 4       | 52          | F   | Pneumonia         | *Staphylococcus aureus* | Survived |
| 5       | 67          | M   | Pneumonia         | *P. aeruginosa* | Survived |
| 6       | 37          | M   | Pneumonia         | *K. pneumoniae* | Died (MOF) |
| 7       | 39          | M   | Peritonitis       | *Enterococcus faecalis* | Survived |
| 8       | 70          | M   | Peritonitis       | *S. aureus*<sup>1</sup> | Survived |
| 9       | 90          | M   | Pneumonia         | *P. aeruginosa* | Survived |
| 10      | 45          | F   | Pneumonia         | *S. aureus* | Survived |
| 11      | 82          | M   | Pneumonia         | *E. faecalis*<sup>1</sup> | Died (PE) |
| 12      | 70          | M   | Pneumonia         | *P. aeruginosa* | Survived |
| 13      | 82          | M   | Pneumonia         | *E. faecalis* | Survived |
| 14      | 65          | F   | Peritonitis       | *E. coli*<sup>3</sup> | Survived |
| 15      | 80          | M   | Pneumonia         | *Streptococcus pneumoniae* | Died (PE) |
| 16      | 72          | M   | Pneumonia         | *P. aeruginosa*<sup>1</sup> | Survived |
| 17      | 70          | F   | Pneumonia         | *E. faecalis* | Survived |
| 18      | 70          | F   | Peritonitis       | *S. aureus* | Survived |
| 19      | 70          | M   | Pneumonia         | *K. pneumoniae* | Died (CD) |
| 20      | 62          | F   | Pneumonia         | *S. aureus* | Survived |
| 21      | 55          | M   | Pneumonia         | *S. aureus*<sup>1</sup> | Survived |
| 22      | 70          | F   | Peritonitis       | *E. coli*<sup>1</sup> | Survived |
| 23      | 90          | M   | Pneumonia         | *E. faecalis* | Died (MOF) |
| 24      | 65          | F   | Pneumonia         | *E. coli*<sup>1</sup> | Survived |
| 25      | 60          | M   | Pneumonia         | *S. pneumoniae* | Died (MOF) |
| 26      | 65          | F   | Pneumonia         | *E. faecalis*<sup>1</sup> | Survived |
| 27      | 60          | F   | Peritonitis       | *E. faecalis, E. coli*<sup>1</sup> | Survived |

<sup>1</sup>Isolated from blood. CD, cardiac death; MOF, multiple organ failure; PE, pulmonary embolism.
demonstrated that the attenuated production of IL-8 – a potential mediator of septic lung injury – might have contributed to the lung protective effects of NAC.

In contrast to the findings of those studies, in the present study we found that NAC infusion did not affect cytokine levels in patients with severe sepsis. Cytokine levels in plasma do not necessarily reflect local synthesis of cytokines by cells. Many cells have surface receptors for these cytokines, with high binding properties, and target cells and soluble receptors can trap cytokines. Thus cytokines released locally may remain undetected in plasma. In the present study we found that plasma cytokine levels remained unchanged over a period of 48 hours. Spapen and coworkers [19] found that a short-term (4 hour) infusion of NAC in patients with early diagnosed septic shock improved systemic oxygenation and static lung compliance without influencing systemic and pulmonary haemodynamics, and NAC-treated survivors had a less complicated weaning period and a shorter length of stay in the ICU than did the placebo-treated group. Spies and coworkers [14] documented improvements in cardiac function, tissue oxygenation and survival in patients in whom NAC (150 mg/kg intravenous bolus, followed by 18.75 mg over 90 min) increased oxygen consumption. NAC improved lung compliance, chest radiographic oedema score, and arterial oxygenation in patients with acute respiratory distress syndrome (ARDS)

### Table 2

**Demographic and clinical characteristics of control patients**

| Patient | Age (years) | Sex | Type of infection | Pathogen | Outcome       |
|---------|-------------|-----|-------------------|----------|---------------|
| 1       | 66          | M   | Pneumonia         | *Enterococcus faecalis* | Died (MOF) |
| 2       | 63          | M   | Pneumonia         | *Pseudomonas aeruginosa* | Survived    |
| 3       | 67          | M   | Peritonitis       | *Staphylococcus aureus* | Survived    |
| 4       | 80          | M   | Pneumonia         | *P. aeruginosa*         | Survived    |
| 5       | 81          | M   | Pneumonia         | *Escherichia coli*      | Died (MOF)  |
| 6       | 57          | M   | Pneumonia         | *E. coli*               | Survived    |
| 7       | 67          | M   | Peritonitis       | *E. faecalis*           | Survived    |
| 8       | 75          | M   | Pneumonia         | *Klebsiella pneumoniae* | Died (PE)   |
| 9       | 67          | M   | Pneumonia         | *Staphylococcus aureus* | Survived    |
| 10      | 50          | M   | Peritonitis       | *E. faecalis*           | Survived    |
| 11      | 50          | F   | Pneumonia         | *S. aureus*             | Survived    |
| 12      | 78          | M   | Pneumonia         | *K. pneumoniae*         | Survived    |
| 13      | 65          | M   | Pneumonia         | *E. faecalis*           | Survived    |
| 14      | 50          | M   | Peritonitis       | *S. aureus*             | Died (MOF)  |
| 15      | 63          | M   | Pneumonia         | *S. pneumoniae*         | Died (CD)   |
| 16      | 45          | F   | Pneumonia         | *S. pneumoniae*         | Survived    |
| 17      | 67          | M   | Peritonitis       | *E. coli*               | Survived    |
| 18      | 91          | K   | Pneumonia         | *S. aureus*             | Survived    |
| 19      | 30          | M   | Peritonitis       | *E. faecalis*           | Survived    |
| 20      | 59          | M   | Pneumonia         | *S. pneumoniae*         | Died (MOF)  |
| 21      | 69          | M   | Pneumonia         | *S. pneumoniae*         | Survived    |
| 22      | 71          | M   | Peritonitis       | *S. aureus*             | Survived    |
| 23      | 58          | M   | Pneumonia         | *E. coli*               | Died (MOF)  |
| 24      | 46          | F   | Peritonitis       | *E. faecalis*           | Survived    |
| 25      | 66          | M   | Pneumonia         | *E. faecalis, E. coli*  | Survived    |
| 26      | 71          | M   | Pneumonia         | *K. pneumoniae*         | Died (MOF)  |

1 Isolated from blood. CD, cardiac death; MOF, multiple organ failure; PE, pulmonary embolism. [AU: for patient number 9, please define 'Sf' in the pathogen column.]
Recently, prolonged infusion of NAC (70 mg/kg for 10 days) was found to improve cardiac function and to attenuate lung injury in patients with ARDS [21].

Despite these encouraging findings, the role of NAC in critically ill remains controversial. Recent randomized, placebo-controlled studies found no significant differences between NAC and placebo in gas exchange, development of ARDS, and mortality in patients with ARDS and early septic shock [22,23]. Furthermore, several papers reported conflicting and undesirable effects of NAC administration. For example, Peake and coworkers [24] treated patients with a different NAC infusion scheme (150 mg/kg intravenous bolus, followed by 50 mg/kg over 4 hours, and then 100 mg/kg per 24 hours for 44 hours) and found significant depression of cardiovascular performance after 24 hours, together with increased mortality. In the present study we found that NAC infusion had no effect on the cardiovascular and pulmonary systems in patients with severe sepsis. However, the study was designed to assess the effects of NAC treatment given before septic shock but after the development of the systemic inflammatory response syndrome. For this reason no serious cardiovascular and pulmonary system problems were encountered in the patients studied.

Oxygen radical scavengers, administered before or at the onset of sepsis, were shown to improve survival in animal models of sepsis [25]. NAC was shown to enhance oxygen consumption via increased oxygen extraction in patients 18 hours after the onset of fulminant liver failure [26]. Spies and coworkers [14] demonstrated that NAC provided a transient improvement in tissue oxygenation in about half of a group of patients with septic shock, and they identified increased whole body oxygen consumption and pH(i), and decreased veno-arterial carbon dioxide tension. Those investigators also found a higher survival rate in NAC responders, and half of the patients receiving NAC did not respond; they suggested that, in some patients, sepsis irreversibly damages the microvasculature.

Table 3

| Variable                              | Baseline | Immediately after NAC infusion | 24 hours after NAC infusion | 48 hours after NAC infusion |
|---------------------------------------|----------|--------------------------------|-----------------------------|-----------------------------|
| Heart rate (beats/min)                | NAC      | Control                        | 110.88 ± 25.9               | 113.00 ± 25.4               | 112.74 ± 22.4               | 108.70 ± 22.2               |
|                                       | Control  | 104.84 ± 18.2                  | 105.19 ± 23.5               | 105.23 ± 23.5               | 103.15 ± 22.7               |
| Mean arterial pressure (mmHg)         | NAC      | Control                        | 90.85 ± 16.67               | 88.92 ± 13.01               | 86.07 ± 13.21               | 85.96 ± 13.41               |
|                                       | Control  | 91.26 ± 18.25                  | 83.80 ± 14.77               | 85.42 ± 13.42               | 83.80 ± 11.31               |
| Arterial pH                           | NAC      | Control                        | 7.34 ± 0.10                 | 7.41 ± 0.07                 | 7.38 ± 0.10                 | 7.39 ± 0.06                 |
|                                       | Control  | 7.35 ± 0.09                    | 7.38 ± 0.07                 | 7.39 ± 0.08                 | 7.36 ± 0.08                 |
| Arterial carbon dioxide tension (mmHg)| NAC      | Control                        | 35.88 ± 12.7                | 34.62 ± 18.8                | 35.00 ± 14.2                | 38.54 ± 15.1                |
|                                       | Control  | 31.69 ± 20.1                   | 38.56 ± 20.2                | 36.46 ± 71.13               | 34.33 ± 21.6                |
| Arterial oxygen tension/fractional inspired oxygen ratio (mmHg) | NAC | Control | 172 ± 88 | 176 ± 76 | 178 ± 81 | 179 ± 126 |
|                                       | Control  | 174 ± 76                       | 177 ± 65                    | 181 ± 70                    | 179 ± 68                    |
| Arterial oxygen saturation (%)        | NAC      | Control                        | 96.1 ± 3.4                  | 95.1 ± 3.7                  | 95.2 ± 3.8                  | 95.6 ± 4.2                  |
|                                       | Control  | 95.9 ± 3.5                     | 95.0 ± 4.1                  | 94.8 ± 3.2                  | 95.1 ± 3.6                  |
| Temperature (°C)                      | NAC      | Control                        | 36.8 ± 0.75                 | 37 ± 0.78                   | 36.8 ± 0.75                 | 36.9 ± 0.48                 |
|                                       | Control  | 36.6 ± 0.57                    | 36.8 ± 0.45                 | 36.6 ± 0.57                 | 36.8 ± 0.53                 |

Data are expressed as mean ± standard deviation. We identified no statistically significant differences between groups. NAC, N-acetyl-L-cysteine.
which would account for the lack of effect of NAC in some patients. In the present study, we found that NAC infusion did not affect pHi in severe sepsis in humans.

In the present study we identified no positive effects of NAC. We were unable to detect differences in systemic oxygenation, ventilatory requirements, or mortality rate in NAC-treated patients, as reported by Szakmany and coworkers [22] and by Domenighetti and colleagues [23]. We also found that NAC infusion did not affect biochemical parameters in patients with severe sepsis, as reported by Szakmany and coworkers [22]. Vomiting and diarrhoea are the side effects most commonly experienced with NAC. Other reported side effects include increased blood pressure, chest pain, hypotension, rectal bleeding, respiratory distress, headache, lethargy, fever and skin allergy [27]. We did not encounter these side effects in the present study.

We found that NAC infusion (150 mg/kg intravenous bolus, followed by intravenous infusion at 12.5 mg/kg per hour for 6 hours) did not affect cytokine levels, patient outcomes, or pHi in severe sepsis in humans. From the literature it appears that

### Table 4

| Variable                                           | Baseline | Immediately after NAC infusion | 24 hours after NAC infusion | 48 hours after NAC infusion |
|----------------------------------------------------|----------|--------------------------------|----------------------------|----------------------------|
| **APACHE II score**                                |          |                                |                            |                            |
| NAC                                                | 13.14 ± 3.79 | -                             | 13.33 ± 3.83               | 12.74 ± 3.87               |
| Control                                            | 15 ± 3.58 | -                             | 15.34 ± 3.30               | 15.69 ± 3.4                |
| **SOFA score**                                     |          |                                |                            |                            |
| NAC                                                | 5.62 ± 2.52 | 5.55 ± 2.04                   | 5.48 ± 2.57                | 5.48 ± 2.7                |
| Control                                            | 6.53 ± 2.2 | 6.92 ± 2.59                   | 7.15 ± 2.9                | 7.15 ± 2.86               |
| Tumour necrosis factor-α (pg/ml)                   |          |                                |                            |                            |
| NAC                                                | 25.58 ± 15.8 | 26.02 ± 16.1                 | 22.68 ± 13.9               | 28.17 ± 26.8              |
| Control                                            | 22.57 ± 28.2 | 24.90 ± 13.56               | 25.05 ± 21.8               | 28.25 ± 24.3              |
| **IL-1β (pg/ml)**                                  |          |                                |                            |                            |
| NAC                                                | 6.68 ± 1.85 | 6.38 ± 1.07                   | 5.91 ± 1.26                | 5.57 ± 1.62               |
| Control                                            | 5.35 ± 1.32 | 5.09 ± 0.30                   | 5.34 ± 1.01                | 5.11 ± 0.58               |
| **IL-2 receptor (U/ml)**                           |          |                                |                            |                            |
| NAC                                                | 1847 ± 1366 | 1918 ± 1450                 | 1829 ± 1427                | 1816 ± 1806               |
| Control                                            | 2288 ± 1503 | 2372 ± 1531                 | 2382 ± 1599                | 2168 ± 843                |
| **IL-6 (pg/ml)**                                   |          |                                |                            |                            |
| NAC                                                | 100.26 ± 88  | 100.22 ± 19.8              | 110.51 ± 37                | 100.38 ± 38               |
| Control                                            | 115.85 ± 85  | 115.64 ± 19.8              | 113.86 ± 27                | 119.48 ± 38               |
| **IL-8 (pg/ml)**                                   |          |                                |                            |                            |
| NAC                                                | 161.50 ± 55  | 161.6 ± 10.3                | 162.1 ± 12.4               | 168.8 ± 113               |
| Control                                            | 172.95 ± 27  | 163.3 ± 28.4                | 169.6 ± 28.6               | 171.0 ± 31                |
| **Gastric intramucosal pH**                        |          |                                |                            |                            |
| NAC                                                | 8.41 ± 0.21  | 8.43 ± 0.22                | 8.43 ± 0.17                | -                         |
| Control                                            | 8.26 ± 0.18  | 8.31 ± 0.16                | 7.45 ± 0.47                | -                         |
| **Gastric intramucosal carbon dioxide tension (mmHg)** |          |                                |                            |                            |
| NAC                                                | 67.2 ± 20.1  | 70.2 ± 15.6                | 69.0 ± 21.9                | -                         |
| Control                                            | 68.7 ± 22.8  | 69.7 ± 23                  | 68.9 ± 25.7                | -                         |

Data are expressed as means ± standard deviation. APACHE, Acute Physiology and Chronic Health Evaluation; IL, interleukin; NAC, N-acetyl-L-cysteine; SOFA, Sepsis-related Organ Failure Assessment.
lower doses of NAC are associated with favourable haemodynamic but no immunomodulatory effects [14] whereas higher doses do influence cytokine production but may cause cardiovascular dysfunction [13,19,24]. Because of the limited number of patients included and the short period of observation, our findings require confirmation in larger clinical trials of NAC infused in a dose-titrated manner. However, our findings do not support the use of NAC in patients with severe sepsis.

**Key messages**

NAC administration had no statistically significant effects on serum cytokine levels and pH. We identified no adverse effects associated with infusion of NAC.

On the basis of our findings, there appears to be no role for NAC in patients with severe sepsis.

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