ventricular function. With the background history of fishing, along with hepatic and renal impairment, leptospirosis was suspected and appropriate samples sent to the reference laboratory. Samples were also sent for atypical screening.

Treatment was initially commenced with amoxicillin, later changed to benzylpenicillin. Platelets were transfused. Pressure control ventilation (PEEP 10 cmH_2O, peak airway pressure 27 cmH_2O, $F_{I_{O_2}}$ 0.9) was instituted, maintaining a Pa_{O_2} of 8.1 kPa. High-dose noradrenaline (0.8 $\mu gm\ kg^{-1}\ min^{-1}$) was required to maintain an MAP of 70 mm Hg. He had clinically adequate filling pressure and was started on a diuretic infusion to good effect. There was significant pulmonary bleeding for the first 4 days and his platelets were low; hence, activated protein C was not considered. He required sedation, and ventilatory support with lung protection strategy for 7 days before sedation and noradrenaline were able to be weaned off. A percutaneous tracheostomy was performed on day 7. Chest X-rays were compatible with ARDS and started to improve after 1 week. He was weaned slowly after more than 19 days and discharged to a medical ward on day 26.

The initial result for leptospirosis was negative. We sent a second specimen after 6 days, which resulted positive for leptospirosis, MAT positive at 1:640, ELISA IgM positive at 1:1280, and the infecting organism was reported as *Leptospiro icterohaemorrhagiae*. The appropriate health authorities were informed.

Leptospirosis is transmitted to humans usually by contact with soil or water contaminated with the urine of rats, cattle, rodents, and other wild animals. The disease usually presents as flu-like illness with mild hepatic and renal impairment. Severe forms of leptospirosis are characterized by severe hepato–renal dysfunction, mental status changes, haemorrhagic diathesis, and rarely with multiorgan dysfunction. Pulmonary involvement is not uncommon (20–70%),[3] but symptoms are usually mild without sequelae. ARDS requiring artificial ventilation is very rare and has a high mortality rate of up to 51%.[4] This is often associated with pulmonary haemorrhage because of endothelial damage.[5 6] In our patient, the progression to haemorrhagic ARDS was very rapid. Early recognition and institution of appropriate antibiotics is known to reduce the mortality.[7]

To conclude, clinicians need to be aware of the possibility of leptospirosis even if the illness presents with unusual clinical features. Elicitation of good history from the patient and a high level of suspicion are paramount in identifying this rare but potentially fatal disease. This condition should be considered in the differential diagnosis of all acutely ill patients with relevant history, and clinical manifestation and appropriate antibiotics should be started early.

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Effects of midazolam and dexmedetomidine on inflammatory responses and gastric intramucosal pH to sepsis, in critically ill patients

Editor—Despite advances in supportive care, the mortality rate in patients with severe sepsis continues to exceed 30%. Sedation is an important part of the therapy of critically ill patients in ICU. Although midazolam and dexmedetomidine are used for sedation in the ICU, there are limited data on its effects on inflammatory responses and gastric intramucosal pH. We studied the effect of midazolam and dexmedetomidine on the inflammatory responses [tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6] and gastric intramucosal pH in critically ill patients receiving sedation. The Regional Committee on Medical Research Ethics approved the study, and written informed consent was obtained from the patients wherever possible, or from the next of kin. Critically ill patients with bacteriologically documented infections were included in the study if they met at least two of the criteria of sepsis, defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.[1] Exclusion criteria were known allergy to midazolam or dexmedetomidine, possible or confirmed pregnancy, haemodynamic instability, heart, liver and renal failure, and patients with known or suspected brain death. The acute physiology and chronic health evaluation (APACHE II) was employed to determine the initial severity of illness.

Patients were allocated randomly, using sealed envelopes, to receive either dexmedetomidine or midazolam infusion together with an alfentanil infusion for analgesia if required. Patients received a loading dose of 0.2 mg kg^{-1} midazolam (Dormicum, Roche Laboratories, France) i.v. over 10 min followed by a maintenance 0.1–0.5 mg kg^{-1} h^{-1} infusion (n=20, Group M). Patients received a loading dose of dexmedetomidine (Precedex® 200 μg in 2 ml, Abbott, North Chigaco, USA) 1 μg kg^{-1} h^{-1} over 10 min followed by a maintenance 0.2–2.5 μg kg^{-1} h^{-1} (n=20, Group D) into a vein over 24 h infusion. Alfentanil was infused at 0.25–1.0 μg kg^{-1} min^{-1} if analgesia was required. The level of sedation was measured and recorded hourly using the Ramsay sedation score, and patients were maintained at a Ramsay sedation score <2 by adjustment to the sedative regimen. No other sedative or analgesic agents were given.

A tonometer (TRIP NGS Catheter, Tonometrics, Worchester, MA, USA) was inserted via the nasogastric route before the bolus dose. The silicone balloon of the tonometer was filled with 2.5 ml 0.9% saline. After sufficient time for equilibration of P_{CO_2} between the saline and the gastric lumen, anaerobic samples of the tonometer saline and of arterial blood were taken simultaneously and analysed with standard pH and blood-gas analysers. pH_i was calculated by a modification of the Henderson–Hasselbalch equation.

Mean arterial pressure and heart rate were monitored continuously. All measurements were obtained at baseline (before start of the study) and were repeated at 24 h. Lactate, platelets, leucocytes, bilirubin, alanine aminotransferase, creatinine, and pH_i were determined at the same times, as were TNF-α, IL-1β, and IL-6 levels. 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-1β, and IL-6 levels were measured with a solid-phase, two-site chemiluminescent enzyme immunometric assay method (Immulite TNF-α Immulite IL-1β, and IL-6 Immulite; EURO/DPC, Llanberis, UK). The lowest detectable limits of IL-1β, IL-6, and TNF-α were 1.5, 5, and 1.7 pg ml^{-1}, respectively. Group means were compared, using the Student's t-test if the variables had a normal distrubition and the Mann–Whitney U-test if they did not have a normal distrubition.

Five patients had septic shock on admission [3 (15%) in Group M and 2 (10%) in Group D] and died in the ICU. Baseline APACHE II [18.10 (5.7) and 20 (4.72), Groups M and D, respectively] was similar (P>0.05). The alfentanil requirements were similar in the two groups. The median (range) dexmedetomidine infusion rate was 0.90 (0.48–1.1) μg kg^{-1} h^{-1} and midazolam infusion rate was 0.29 (0.18–0.4) mg kg^{-1} h^{-1}. Sedation was similar in the two groups (P=0.71). No side-effects were noted during or after administration of midazolam and dexmedetomidine infusion. There were no statistically significant differences between the groups during the study with respect to haemodynamic and biochemical measurements, or gastric intramucosal pH. There were significant decreases in TNF-α [19.5 (5.8) *vs* 14.6 (4) pg ml^{-1}], IL-1β [6.29(2) *vs* 5 (0.30) pg ml^{-1}], IL-6 [455.6 (338.4) *vs* (212.4) (198.3) pg ml^{-1}], at 24 h in Group D ($P < 0.05$) (Table 1).

Gastric intramucosal pH in experimental animals decreases as splanchnic perfusion decreases below the level where local oxygen transport can no longer sustain aerobic energy production. Intramucosal acidosis has been associated with a poor prognosis and the appearance of multi-organ failure in critically ill patients, even in the absence of systemic acidosis or hypotension. In our study, we did not find a change in gastric intramucosal pH_i.

Midazolam is known to inhibit certain aspects of the immune function.[2] It was suggested that benzodiazepines bind to specific receptors on macrophages and inhibit their capacity to produce IL-1, IL-6, and TNF-α.[3] Several studies have found that midazolam inhibits human neutrophil function and the activation of mast cells induced by TNF-α *in vitro* and suppresses the expression of IL-6 mRNA in blood monoclear cells.[4] In contrast, several investigators reported that midazolam did not alter lipopolysaccharide (LPS)-stimulated cytokine response *in vitro*.[5,6] In our study, midazolam infusion did not affect cytokine production in septic patients.

Only a few reports have dealt with the effects of dexmedetomidine during endotoxemia and endotoxic shock. Several investigators have published reports on the effects of dexmedetomidine and α2-adrenergic receptors agonists on cytokines,[7] and α2-agonists modulated LPS-induced TNF-α production on macrophages.[8] Taniguchi and colleagues[9] demonstrated that dexmedetomidine has an inhibitory effect on cytokine responses to endotoxemia. These findings suggest that one of the mechanisms of anti-inflammatory effects of dexmedetomidine may be

Table 1 TNF-α, IL-1β, and IL-6 and gastric intramucosal pH levels. Values are expressed as mean (SD). *There were significant decreases in TNF-α, IL-1β, and IL-6, at 24 h in Group D (P<0.05)

	Baseline	24 h
TNF-α (pg ml^{-1})		
Group M	21.4 (3.6)	19.5 (5.8)
Group D	23.5 (4.2)	14.6 (4)*
IL-1β(pg ml^{-1})		
Group M	6.09 (2.7)	6.29 (2)
Group D	6.3 (1.8)	5 (0.30)*
IL-6 (pg ml^{-1})		
Group M	470 (295)	455.6 (338.4)
Group D	430 (150)	212.4 (198.3)*
Gatric intramucosal pH		
Group M	6.21 (0.3)	6.4 (0.5)
Group D	6.26 (0.4)	6.37 (0.3)

modulation of cytokine production by macrophages and monocytes. We found that the dexmedetomidine infusion decreased cytokine production in sepsis.

Critically ill patients in sepsis and septic shock suffer a high degree of stress because of pain and anxiety and organ specific responses to sepsis. An important objective in the management of these patients is to achieve an adequate level of sedation and analgesia. Our findings suggest that dexmedetomidine may prevent inflammatory effects in sepsis patients during sedation.

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