2 Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol* 1988; **64:** 789–95.
3 Horner RL, Innes JA, Morrell MJ, Shea SA, Guz A. The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans. *J Physiol* 1994; **476:** 141–51.
4 American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; **22:** 667–89.
5 Remmers JE, DeGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978; **44:** 931–38.

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Terlipressin for norepinephrine-resistant septic shock

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Norepinephrine-resistant hypotension when associated with septic shock has a high rate of mortality, which might possibly be reduced by infusion of low-dose vasopressin. However, rebound hypotension often arises after treatment is stopped, and the drug usually has to be administered for several days. We report use of terlipressin, a long-acting vasopressin analogue, in eight patients with septic shock who did not respond to corticosteroids and methylene blue. A significant rise in blood pressure that lasted for at least 5 h was seen in all patients after a single bolus, allowing reduction or cessation of norepinephrine administration in seven patients. We were able to discharge four patients from intensive care subsequently. Terlipressin seems to be an effective rescue therapy, which is able to restore blood pressure in patients with catecholamine-resistant septic shock, without obvious complication.

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People with septic shock generally have a high cardiac output and low systemic resistance circulation. A combination of vasodilatation and pronounced vascular hyporeactivity to conventional vasopressor treatment with norepinephrine often results in resistant hypotension. Results of a phase III study of septic shock suggest that inhibition of nitric oxide synthase, though successful in raising blood pressure and reducing norepinephrine requirements, can reduce survival (personal communications, Richard Knowles, GlaxoSmithKline). As a rescue therapy for non-responders to high-dose norepinephrine, we use dexamethasone 16 mg bolus or methylene blue 2 mg/kg over 15 min, or both. Corticosteroids restore adrenoceptor sensitivity and inhibit nitric oxide synthase, whereas methylene blue inhibits both guanylate cyclase and nitric oxide synthase. These approaches result in raised blood pressure, and they allow the administration of a reduced dose of catecholamine in about two thirds of patients; non-responders often die from intractable hypotension within a day.

Infusion of low-dose vasopressin might also be useful in norepinephrine-resistant shock. However, rebound hypotension often occurs when the drug is stopped, and vasopressin generally has to be given for several days.[1–3] Terlipressin (Glypressin, Ferring, Slough, UK), a long-acting synthetic analogue of vasopressin, has a half-life of 6 h and, like vasopressin, is used for treatment of variceal haemorrhage and diabetes insipidus. When used for these indications, terlipressin does not cause hypertension. Here, we describe its use in eight unselected patients with septic shock and high cardiac outputs, whose hypotension (mean arterial pressure 50 mm Hg, range 50–55) had not responded to fluid loading to maximal stroke volume, high-dose norepinephrine infusion, or dexamethasone and methylene blue rescue therapy. Patients were enrolled between January, 1999, and June, 2001. Patients were unselected but were enrolled when at least one of three doctors involoved in the study was present. Ethics committee approval and relatives' agreement were obtained beforehand.

In all patients, an intravenous bolus dose of terlipressin (1–2 mg) produced a progressive increase in mean arterial pressure over 10–20 min that was sustained for at least 5 h, allowing reduction or cessation of the high-dose norepinephrine infusion in seven patients (tables 1 and 2). We later discharged four patients from intensive care, three of whom survived to hospital discharge. The four survivors needed no subsequent increase in norepinephrine dose. Seven patients received concomitant renal replacement therapy; two patients with oliguria both increased their urine output to more than 50 mL/h after administration of terlipressin. The fall in cardiac output after terlipressin was commensurate with the rise of blood pressure and did not seem to compromise organ perfusion. We noted no major chronotropic effects or obvious deleterious consequences—eg, digital, splanchnic (abdominal distension, bloody stool), or myocardial (electrocardiographic) ischaemia, or worsening metabolic acidosis. We gave one patient, who relapsed, a repeat bolus of terlipressin (table 2).

Cause of septic shock	Age (years)	Apache II score	Terlipressin (mg)	Initial norepinephrine (μg/kg/min)	Further norepinephrine requirements	Outcome
Dog bite	56	25	2·0	0·41	None, needed glyceryl trinitrate to lower mean arterial pressure	Discharged to ward after 1 month
Unknown cause	68	25	1·0	0·34	Unchanged dose though good pressor response	Died 10 days later
Streptococcal pneumonia	50	25	1·0	0·85	Weaned off over 24 h	Discharged to ward after 2 months
Staphylococcal septicaemia	52	37	2·0	0·53	Effect lasted 5 h then steady increase in norepinephrine	Died within 24 h
Streptococcal septicaemia	40	30	1·0	0·30	Effect lasted for 5 h then steady increase in norepinephrine to 0·7 μg/kg/min over next 15 h*	Died within 24 h
Faecal peritonitis	68	31	1·0	0·73	Weaned off over 24 h	Discharged to ward 2 weeks later
Salmonella gastroenteritis	82	25	2·0	0·73	Weaned off over 2 days	Discharged to ward 17 days later
Meningococcal septicaemia	62	28	1·5	0·82	Continued on low dose norepinephrine for 4 days, then gradual deterioration	Died after 6 days

*Given a 2nd dose of terlipressin at 5 h; the effect was similar but only lasted 3 h.

Table 1: **Details of patients and response to terlipressin**

	Pre-terlipressin (n=8)	2 h post-terlipressin (n=8)	6 h post-terlipressin (n=8)	12 h post-terlipressin (n=8)	24 h post-terlipressin (n=6)	Overall p
Mean arterial pressure (mm Hg)	52 (3)	72 (7)*	65 (5)*	62 (7)†	69 (5)	0·005
Norepinephrine (μg/kg per min)	0·59 (0·22)	0·29 (0·18)†	0·25 (0·16)†	0·28 (0·25)†	0·19 (0·26)	0·002
survivors (n=4)	0·68 (0·19)	0·26 (0·26)	0·17 (0·14)	0·14 (0·10)	0·08 (0·03)	..
non-survivors (n=4)	0·50 (0·24)	0·31 (0·09)	0·34 (0·14)	0·42 (0·29)	0·71, 0·17 (n=2)	..
Cardiac output (L/min)	8·1 (1·6)	6·4 (2·0)†	6·6 (1·9)‡	7·0 (1·0)	7·1 (1·5)	0·014
Heart rate (beats per minute)	109 (12)	103 (15)	99 (18)‡	99 (15)‡	94 (10)	0·049

Data are mean (SE). One-way repeated measures ANOVA with post-hoc Bonferroni *t* tests done up to 12 h post-terlipressin (not to 24 h because of two informative missing datapoints): *p<0·001, †p<0·01, ‡p<0·05 *vs* baseline values.

Table 2: **Haemodynamic variables and norepinephrine dose**

Low-dose vasopressin (0·01–0·04 IU per min) is an effective pressor agent in about 85% of patients with norepinephrine-resistant hypotension.[1–3] However, discontinuation of vasopressin results in rapid hypotension, requiring immediate resumption of vasopressin, or increase in norepinephrine. Tsuneyoshi and colleagues[3] reported an average duration of vasopressin infusion of 93 h (range 18–284) in 14 patients with septicaemia who had a significant pressor response. We cannot explain why a single bolus of terlipressin was an effective treatment in our patients, despite their much higher baseline norepinephrine requirements (mean 0·59 [SD 0·08] *vs* 0·25 [0·01] μg/kg per min in the Tsuneyoshi study). Interaction with the previously administered steroids or methylene blue, or both, might be relevant but requires confirmation.

Vasopressin, an endogenous hormone produced in the hypothalamus, is released from the posterior pituitary gland in response to increased plasma osmolarity, hypovolaemia, and hypotension. Concentrations of vasopressin in plasma consistently rise in cardiogenic and hypovolaemic shock states but, for unknown reasons, are inappropriately low in sepsis. Landry and co-workers[1] reported mean plasma concentrations of 1·45 (0·15) pg/mL in healthy individuals and 22·7 (2·2) pg/mL in 12 patients with cardiogenic shock, but only 3·1 (1·0) pg/mL in 19 patients with septicaemia with similar blood pressures. An infusion of vasopressin (0·01 units per min) was sufficient to raise plasma concentrations to 30 pg/mL, with corresponding rises in systolic blood pressure (83–115 mm Hg) and a reduction in norepinephrine requirements.

V_1-receptor stimulation in vascular smooth muscle produces more potent vasoconstriction than either angiotensin II or norepinephrine. The lack of pressor response in non-septic patients might be related to an intact baroreflex response, resulting in heart rate reductions. The absence of a large negative chronotropic effect to terlipressin in our study concurs with previous findings.[1–3] Mechanisms underlying increased pressor sensitivity to vasopressin and its analogues in septic shock remain unknown. Using human gastroepiploic arteries, Hamu and colleagues[4] showed that vasopressin, acting on V_1 receptors, potentiated responses to norepinephrine in normal and endotoxin-treated tissues. Similarly, vasopressin potentiated the vasoconstrictor effects of norepinephrine, electrical field stimulation, and potassium chloride depolarisation, effects mediated via an increase in intracellular calcium through voltage-dependent calcium channels.[5]

Overall survival rates of 40–50% are quoted for septic shock, though anticipated mortality would be much higher in the subset who fail to respond to high-dose norepinephrine plus dexamethasone and methylene blue rescue therapy. Terlipressin offers a potentially important and inexpensive therapeutic alternative in hypotensive septic patients not responding to high-dose catecholamine therapy, which seems safe and is easy to administer. The response to a single dose suggests restoration of vascular reactivity, and thus enhanced sensitivity to endogenous and exogenous catecholamines. Our findings also provide a new perspective on the pathophysiology underlying sepsis-induced vascular hyporeactivity.

Contributors
A O'Brien and M Singer had the original idea for the study and did the clinical work. A O'Brien, L H Clapp, and M Singer jointly interpreted the data and wrote the report.

Conflict of interest statement
None declared.

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1 Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilatation of septic shock. *Circulation* 1997; **95:** 1122–25.
2 Malay MB, Ashton RCJ, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; **47:** 699–705.
3 Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA. Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. *Crit Care Med* 2001; **29:** 487–93.
4 Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N. The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastroepiploic arteries in vitro. *Anesth Analg* 1999; **81:** 542–48.
5 Noguera I, Medina P, Segarra G, et al. Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. *Br J Pharmacol* 1997; **122:** 431–38.

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Vitamin A deficiency and genital viral burden in women infected with HIV-1

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The relation between vitamin A (retinol) deficiency and perinatal transmission of HIV-1, if it exists, might be mediated through an increased viral load in the mother's genital tract. To ascertain whether or not such an association is present, we measured the serum concentration of retinol with high performance liquid chromatography, and correlated the results with concurrent quantified HIV-1 RNA concentrations in cervicovaginal lavage fluid in 301 women infected with the virus. We noted no association between retinol status and genital HIV-1 load. Our findings lend support to those of studies that reported no association between retinol deficiency and perinatal HIV-1 transmission.

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An association between vitamin A (retinol) deficiency and perinatal transmission of HIV-1 has been reported in African