www.nature.com/clinicalpractice/gasthep

Liver transplantation for sclerosing cholangitis in a polytraumatized patient

Andreas A Schnitzbauer*, Tung-Yu Tsui, Gabriele Kirchner, Marcus N Scherer, Thomas Bein, Hans J Schlitt and Aiman Obed

SUMMARY

Background Following a motorcycle accident, a 30-year-old male with multiple traumas—including liver rupture, traumatic fractures, cerebral hemorrhage, hepatic hematoma and respiratory failure—was referred to a university medical center. After initial stabilization, the patient developed pneumonia, acute kidney failure requiring intermittent hemodialysis, superinfection of the hepatic hematoma and systemic bacterial infection with multiple drug-resistant bacteria. The patient developed acute liver failure 8 weeks after the initial trauma.

Investigations Laboratory investigations, Doppler ultrasound, CT, ultrasound, angiography, endoscopic retrograde cholangiography, liver biopsy, bacteriology and X-ray.

Diagnosis Sclerosing cholangitis in a critically ill patient.

Management Orthotopic liver transplantation.

KEYWORDS liver transplantation, polytraumatized patient, post-transplant lymphatic disease, SC-CIP, sclerosing cholangitis in a critically ill patient

AA Schnitzbauer and T-Y Tsui are Surgical Residents, MN Scherer is a Transplant Surgical Consultant and responsible for the liver transplant program, HJ Schlitt is Director of the Surgical Clinic and A Obed is Head of Transplant Surgery in the Department of Surgery at the Regensburg University Hospital. G Kirchner is a Hepatology Consultant in the Department of Internal Medicine and T Bein is a Consultant for Surgical Intensive Care Medicine in the Department of Surgery and in the Department of Anesthesiology at the Regensburg University Hospital, Regensburg, Germany.

Correspondence
*Regensburg University Hospital, Department of Surgery, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany
andreas.schnitzbauer@klinik.uni-regensburg.de

Received 5 September 2008 **Accepted** 18 November 2008 **Published online** 23 December 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep1333

THE CASE

A 30-year-old man with severe trauma and an initial Glasgow Coma Scale score of 3 was referred to a university medical center. The patient had been previously admitted to a different hospital for primary clinical trauma management and diagnostic evaluation after a motorcycle accident. At this hospital, physical examination revealed a fracture of the right clavicle and a rupture of the right axillary plexus. Radiological scans revealed multiple fractures of the right arm and leg. Abdominal ultrasound showed little free intra-abdominal perisplenic fluid. The patient was transferred to the university medical center 3 h later, after primary wound closure and hemodynamic stabilization with crystalloid and colloidal infusion therapy and vasopressors (exact amounts and dosages not available). The patient had no medical history that could have influenced the subsequent clinical course.

In the university medical center, ultrasound investigation revealed free fluid in the abdominal area, and a subsequent CT scan showed multiple fractures of the right side of the body (clavicle, scapula, humerus, femur, patella and tibia) with rupture of the subclavian artery, fracture of the spine (dens fracture, Anderson type III), hematocephalus, a right-sided subarachnoidal hemorrhage and a subdural hematoma alongside the tentorium of the cerebellum. Additionally, the CT scan also revealed a severe contusion of both lungs with an open thoracic bilateral trauma. Finally, CT scans of the abdomen showed a grade IV–V liver rupture (American Association for the Surgery of Trauma hepatic injury scale[1]) in segment VI and VII with an 8.5×5.5 cm hematoma (Figure 1), and a splenic rupture.

Immediate laparotomy with splenectomy and packing of the liver was performed—packing flaps were removed from the liver 4 days later. The patient's multiple fractures were then stabilized and the subclavian artery reconstructed with a venous interposition graft.

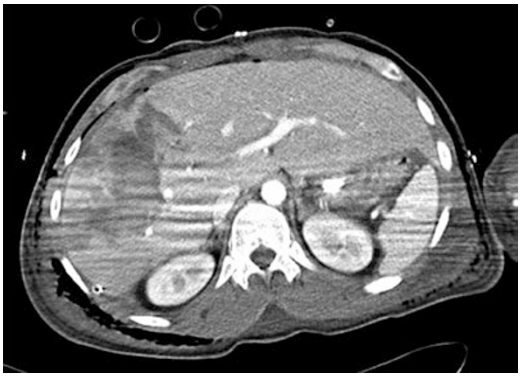

Figure 1 CT scan showing a liver hematoma in the right lobe of the liver.

The patient required an intensive transfusion regimen because of the initial shock and the enormous blood loss, and was administered 20 U of packed red blood cells and 43 U of fresh frozen plasma. He was also administered colloid and crystalloid substitution therapy (1,500 ml of hydroxyethyl starch 10% and 3,000 ml of sodium chloride 0.9%) and high dosages of a vasopressor (noradrenaline 1.5 mg/h). On the day of the initial trauma, pumpless extracorporal lung assistance was implemented to support the traumatized lung. By day 3 after the initial trauma, plasma pH had normalized (pH 7.0 before lung assistance and 7.4 after), and there were substantial improvements in the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (the Horowitz index; paO_2:FiO_2) and in the arterial partial pressure of carbon dioxide ($paCO_2$). Specifically, on day 1 paO_2:FiO_2 was 55 mmHg and $paCO_2$ 50 mmHg; on day 3 paO_2:FiO_2 was 180 mmHg and $paCO_2$ was 27 mmHg (paO_2:FiO_2 typically >500 mmHg in healthy people and <100 mmHg in people with severe lung injury; normal range for $paCO_2$ 35–45 mmHg). These improvements meant that the lung protective ventilation could be decreased to 7 ml/kg body weight, with a target tidal volume of 450 ml, and the dosage of the vasopressor could be lowered (noradrenaline to between 0.5 mg/h and 1.0 mg/h). The patient was then intermittently positioned prone and dorsally for 3 days, after which both ventilation and vasopressor administration were discontinued.[2]

On day 7, the patient developed acute respiratory distress syndrome, pneumonia caused by extended-spectrum β-lactamase-producing Gram-negative bacteria and *Enterococcus faecium*—both detected following a bacteriologic analysis of sputum—and an infection of the soft tissue of the right arm, as made evident by bacterial analysis of putrid secretions (positive for *E. faecium*) and clinical signs (fever, reddening and pain). The patient had also developed acute kidney failure with anuria on day 1. Permanent continuous venovenous hemodiafiltration was started on day 1 and performed for 14 days, until renal function recovered (spontaneous return to urine output over 1 l/day, decrease of serum urea nitrogen to below 71.4 mmol/l). The severe progressive pneumonia and the infected right arm caused recurring septic boosts and permanent severe inflammatory response syndrome, so the right arm had to be exarticulated on day 16 after the initial motorcycle accident.

On day 28, the hepatic hematoma became superinfected with *E. faecium*, *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, as ascertained by puncture and bacteriologic detection. Consequently, 4 weeks after initial packing, the liver was drained (Figure 2). Results from repeated Doppler ultrasound and angiography excluded a stenotic or thrombotic process of the hepatic artery. Serum levels of cholestatic parameters continuously increased over 2 weeks (Figure 3). Serum alkaline phophatase level reached 312 U/l (reference range 40–129 U/l) and serum bilirubin reached 167.6 μmol/l (reference range 3.4–22.2 μmol/l). On day 39, an endoscopic retrograde cholangiography was performed that revealed signs of sclerosing cholangitis in a critically ill patient (SC-CIP), with the typical stenosis of the intrahepatic biliary ducts and the presence of biliary sludge and early sludge cast formations (Figure 4). Neither magnetic resonance cholangiography nor endoscopic ultrasound would have delivered further information that could have influenced medical decisions, and magnetic resonance cholangiography especially gives no opportunity for direct immediate intervention; therefore, neither test was performed.

Following papillotomy of the duodenal papilla of Vater (day 40) with concomitant removal of biliary sludge, extensive calculated antibiotic therapy (linezolid 2 × 600 mg/day orally and ciprofloxacin 2 × 400 mg/day intravenously) and ursodeoxycholic acid therapy (3 × 500 mg/day orally), liver and infectious parameters stabilized (serum alkaline phophatase 300 U/l and serum bilirubin 150 μmol/l), but did not decrease as hoped.

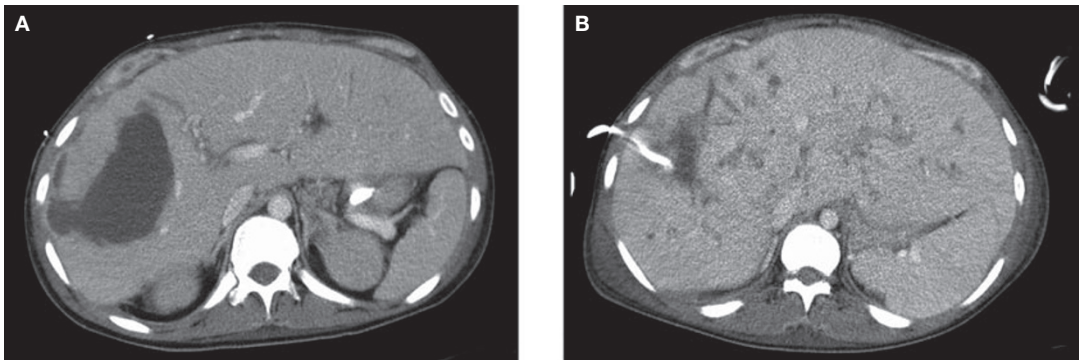

Figure 2 CT scan showing superinfection of a hepatic hematoma and subsequent treatment outcome. (**A**) Superinfected hematoma in the right liver lobe. (**B**) The right liver lobe after draining of the hematoma.

Between day 60 and day 72, serum glutamate pyruvate transaminase levels increased from 132 U/l to over 1,400 U/l (reference range 7–56 U/l) and serum bilirubin levels increased from approximately 154 μmol/l to 239.4 μmol/l (Figure 3). On day 72, the patient developed grade 3 hepatic encephalopathy and experienced a cardiac arrest, for which he received advanced cardiac life support. On day 73, the patient developed acute liver failure and was, therefore, listed as a high-urgency case for liver transplantation throughout the countries participating in the Eurotransplant network, headquartered in Leiden, The Netherlands.

Liver transplantation

After 48 h on the liver transplantation waiting list, a suitable organ became available and the patient underwent liver transplantation. Surgery was performed with complete clamping and resection of the retrohepatic caval vein, without portocaval bypass. Histology revealed significant canaliculary and intracytoplasmic cholestasis with landscape-like necrotic areas in the adjoining hepatocytes as well as a massive proliferation of biliary ducts with intracytoplasmic cholestasis (Figure 5). The patient received an immunosuppressive protocol consisting of 20 mg of basiliximab (an anti-CD25 monoclonal antibody) on day 0 and day 4 after transplantation, ciclosporin 1 mg/kg body weight twice a day as permanent maintenance therapy, a single dosage of 500 mg of prednisolone during reperfusion intraoperatively and 1 mg/kg body weight daily thereafter. Prednisolone dosage was tapered in 5 mg steps to 5 mg/day until 3 months after transplantation, when prednisolone administration was discontinued. The aim with ciclosporin administration was to reach a trough serum level of 120–140 ng/ml. After transplantation, serum transaminase levels decreased rapidly to 120 U/l and the patient improved moderately, with completely normal hemodynamic parameters, renal function and consciousness. Two days after transplantation, however, the patient developed a bleeding duodenal ulcer, which required surgery. The patient was discharged 8 weeks after transplantation, at which point he had a serum bilirubin concentration of 17.1 μmol/l, serum alkaline phophatase level of 121 U/l and serum glutamate pyruvate transaminase level of 27 U/l. Liver counts were stable after discharge. The patient did not experience any acute rejection episodes and did not show any signs of cholestasis or cholangitis, which led to the conclusion that the patient's biliary system was patent and working well. No further diagnostic evaluation of the biliary system was, therefore, carried out.

Six months after discharge, low-risk transplant-associated B-cell non-Hodgkin lymphoma was diagnosed (Ann Arbor stage IIA; international prognostic index 0), and the patient tested positive for the Epstein–Barr virus. CT scan revealed enlarged interaortocaval lymph nodes from which a biopsy sample was taken, which showed the typical features of a B-cell non-Hodgkin lymphoma. Complete remission was achieved after 6 cycles of the R-CHOP 21 regimen consisting of intravenous rituximab (375 mg/m^2 per day for 6 days), intravenous cyclophosphamide (750 mg/m^2 per day for 6 days), intravenous vincristine (1.4 mg/m^2 per day for 6 days), intravenous doxorubicin (50 mg/m^2 per day for 6 days), and oral prednisolone (100 mg per day for 6 days) repeated every 21 days. Twenty

www.nature.com/clinicalpractice/gasthep

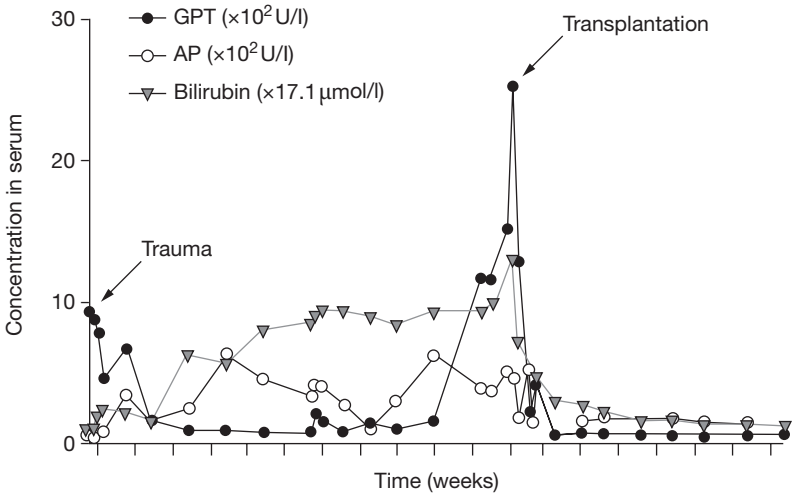

Figure 3 Variation over time (from 0 weeks to ~18 weeks) in serum concentration of cholestatic parameters glutamate pyruvate transaminase (GPT), alkaline phophatase (AP) and bilirubin in a patient with sclerosing cholangitis in a critically ill patient.

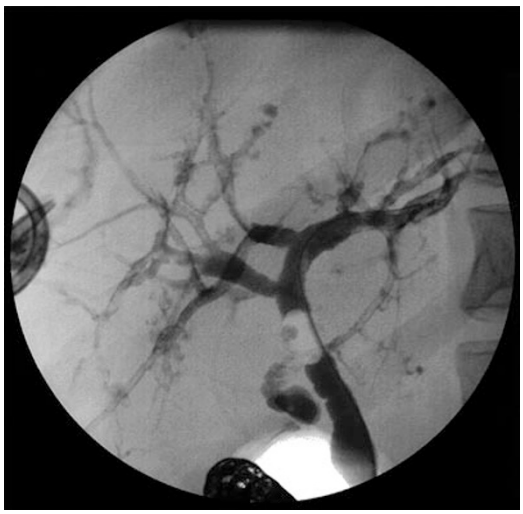

Figure 4 Endoscopic retrograde cholangiography revealing stenosis of the intrahepatic biliary ducts.

months after liver transplantation, a chest X-ray showed a broadened mediastinum. A thoracoscopy was performed because recurrent lymphoma was suspected. Microbiology and histology tests revealed mediastinal tuberculosis with *Mycobacterium tuberculosis*. Quadruple antibiotic therapy was initiated, which included administration of oral isoniazid and pyridoxine (400 mg/day and 80 mg per day) for 6 months, oral rifampicin (600 mg per day) for 6 weeks, oral pyrazinamide (1.5 mg per day) for 6 weeks and oral ethambutol (1.2 mg per day) for 6 weeks. This regimen was associated with good clinical response. After several further trauma operations, and 3 years after the initial motorcycle accident, a complex abdominal wall reconstruction was performed. At a follow-up visit 50 months after liver transplantation, the patient was in good health.

DISCUSSION OF DIAGNOSIS

Sclerosing cholangitis after severe trauma has been reported rarely. SC-CIP is characterized by slowly increasing cholestatic parameters, such as alkaline phosphatase and gamma-glutamyl transferase, and, as revealed by endoscopic retrograde cholangiography, by stenotic or irregular intrahepatic bile ducts, with or without biliary casts, that contain *E. faecium* and *Enterococcus faecalis* strains that are usually resistant to ciprofloxacin and gentamycin.[3,4] Although the pathophysiology of SC-CIP remains unclear, various authors postulate that SC-CIP is caused by sepsis-related and shock-related bile duct injury with secondary infection similar to bile duct necrosis after liver transplantation as a consequence of impaired arterial supply to biliary structures.[5–7] The septic process causes endothelial injury, with intestinal barrier failure, release of bacterial endotoxins, and bacterial translocation with excretion of proinflammatory cytokines and subsequent mucosal wall destruction.[8,9] Sepsis and shock are both responsible for ischemic hypoperfusion, which leads to endothelial damage of the highly perfusion-sensitive bile duct.[10] The resulting segmental cholangitis causes fibrosis and impaired biliary flow and leads to segmental stenosis of the intrahepatic biliary ducts and the formation of sludge casts, both of which lead to SC-CIP.[3] With regard to the present case, although secondary conditions such as hepatic artery thrombosis, portal vein thrombosis or multiple hepatic abscesses were missing, all the above-described principal features of SC-CIP were present; therefore, the diagnosis of SC-CIP was made.

DIFFERENTIAL DIAGNOSIS

Sclerosing cholangitis in a young polytraumatized patient can be induced by a large variety of disorders or medical constellations. A correct diagnosis is, therefore, important, and conditions with similar symptoms, such as primary sclerosing cholangitis and secondary sclerosing cholangitis, must be excluded.

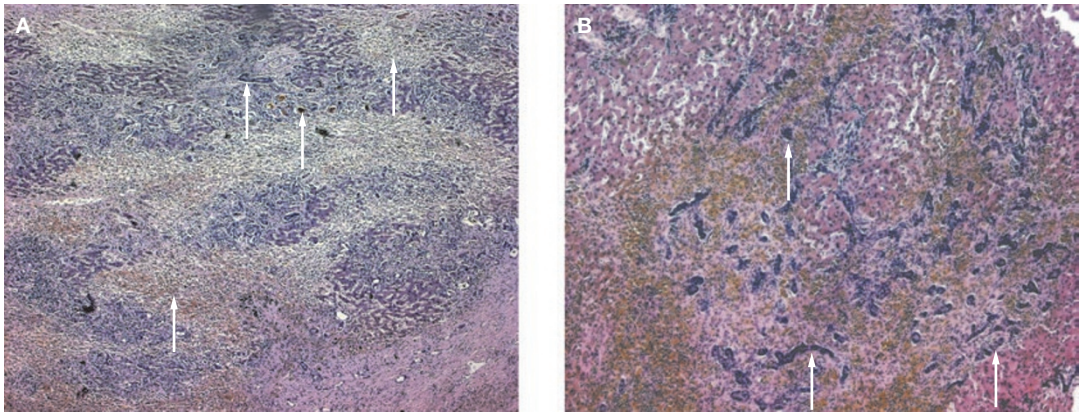

Figure 5 Liver histology in a patient with sclerosing cholangitis in a critically ill patient. (**A**) Histology sample showing canaliculary and intracytoplasmatic cholestasis with landscape-like necrotic areas of the adjoining hepatocytes. (**B**) Histology sample showing massive proliferation of biliary ducts and intracytoplasmatic cholestasis.

Table 1 Typical symptoms and causes of sclerosing cholangitis in a critically ill patient and secondary sclerosing cholangitis.

	SC-CIP	SC
Symptom		
Biliary casts	Yes	No
Bacterial superinfection	Yes	No
Inflammation (histology)	Mild	Severe
Cause		
Aggressive ICU treatment	Yes	No
Hepatic artery thrombosis and/or stenosis	No	Typical cause
Portal vein stenosis and/or thrombosis	No	Typical cause
Mechanical obstruction of biliary duct	No	Typical cause
History of liver disease	No	Typical cause

Abbreviations: ICU, intensive care unit; SC, secondary sclerosing cholangitis; SC-CIP, sclerosing cholangitis in a critically ill patient.

Primary sclerosing cholangitis

Primary sclerosing cholangitis is characterized by fibrotic strictures involving the intrahepatic and extrahepatic biliary tree, in the absence of any precipitating cause. The disease is often associated with chronic IBD.

Secondary sclerosing cholangitis

Secondary sclerosing cholangitis occurs after a pathologic process or an injury, such as abdominal trauma with liver injury, mechanical obstruction of bile ducts by tumors or concrements, cholestasis following surgical or endoscopic interventions, ischemic processes, infections, congenital hepatic or biliary abnormalities, and hepatic artery or portal vein thrombosis or stenosis.[5,11] Patients with secondary sclerosing cholangitis do not, however, have a history of the long stays in intensive care units associated with aggressive treatment. In addition, casts that lead to superinfection of the biliary tract and the development of sclerosing cholangitis have never been described as a typical first manifestation of secondary sclerosing cholangitis.[3] Histologically, SC-CIP produces morphologic changes in the liver, consisting of degeneration of the bile duct epithelium with only mild inflammatory changes but with massive cholestasis.[12] Differences in symptoms and causes of secondary sclerosing cholangitis and SC-CIP can be found in Table 1.

Competing interests
The authors declared no competing interests.

TREATMENT AND MANAGEMENT

The patient's early clinical course after trauma revealed signs of rapidly progressing SC-CIP. Considering the patient's young age, we decided to perform liver transplantation because this treatment was the only causal therapy that could cure his acute liver failure and the only approach that offered a possibility of survival. When acute liver failure caused by rapidly progressive SC-CIP occurred, the patient was stable with regard to pulmonary, renal, cardiac and circulatory conditions, his infections were under control, and he did not require intensive medical care. All these factors contributed favorably to our decision to proceed with transplantation. Retrospectively, our decision is supported by the fact that the patient overcame several adverse and critical episodes in the weeks after the initial trauma, with an enormous variety of injuries and complications recorded. Furthermore, more than 5 years after the procedure, the patient's health status is stable.

The decision of whether or not to proceed with liver transplantation in a patient with SC-CIP has to be made on a case by case base. In a setting where the acute liver failure brought on by SC-CIP is associated with multiorgan failure, liver transplantation would probably not be a viable therapeutic option. With regard to primary and secondary sclerosing cholangitis, the only causal therapy available for patients with either of these two conditions is also liver transplantation. Given that in these disorders there is often a longer time gap between cause, first symptoms and a worsening of the liver function than in SC-CIP, the task of preparing the patient for the transplantation procedure is less complex in primary and secondary sclerosing cholangitis than in SC-CIP.

CONCLUSIONS

This unusual case shows that liver transplantation might be the only therapeutic option for SC-CIP and patients should be considered on an individual basis, even those with severe concomitant injuries. Centers with an intensive care unit but no liver transplant program should consider contacting a transplant center if they have a patient with slowly increasing serum cholestatic and transaminase values. As intensive care medicine improves, post-traumatic sclerosing cholangitis will probably become more common and should possibly be considered as a novel indication for liver transplantation in the near future.

References

1 Pachter HL *et al.* (1996) Status of nonoperative management of blunt hepatic injuries in 1995: a multicenter experience with 404 patients. *J Trauma* **40:** 31–38
2 Bein T *et al.* (2006) A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* **34:** 1372–1377
3 Gelbmann CM *et al.* (2007) Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. *Am J Gastroenterol* **102:** 1221–1229
4 Jaeger C *et al.* (2006) Secondary sclerosing cholangitis after long-term treatment in an intensive care unit: clinical presentation, endoscopic findings, treatment, and follow-up. *Endoscopy* **38:** 730–734
5 Benninger J *et al.* (2005) Sclerosing cholangitis following severe trauma: description of a remarkable disease entity with emphasis on possible pathophysiologic mechanisms. *World J Gastroenterol* **11:** 4199–4205
6 Starzl TE *et al*. (1977) Biliary complications after liver transplantation: with special reference to the biliary cast syndrome and techniques of secondary duct repair. *Surgery* **81:** 212–221
7 Engler S *et al.* (2003) Progressive sclerosing cholangitis after septic shock: a new variant of vanishing bile duct disorders. *Gut* **52:** 688–693
8 Geier A *et al*. (2006) Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. *Nat Clin Pract Gastroenterol Hepatol* **3:** 574–585
9 Pastores SM *et al*. (1996) Posttraumatic multiple-organ dysfunction syndrome: role of mediators in systemic inflammation and subsequent organ failure. *Acad Emerg Med* **3:** 611–622
10 Moore FA and Moore EE (1995) Evolving concepts in the pathogenesis of postinjury multiple organ failure. *Surg Clin North Am* **75:** 257–277
11 Abdalian R and Heathcote EJ (2006) Sclerosing cholangitis: a focus on secondary causes. *Hepatology* **44:** 1063–1074
12 Esposito I *et al*. (2008) Secondary sclerosing cholangitis after intensive care unit treatment: clues to the histopathological differential diagnosis. *Virchows Arch* **453:** 339–345