CASE REPORT

An adolescent with severe neurogenic pulmonary oedema after spontaneous cerebellar haemorrhage

B Stessel1, GAM van der Nat2, JH Zwaveling2

1 Department of Anesthesiology, Academic Hospital Maastricht, Maastricht, The Netherlands
2 Department of Intensive Care, Academic Hospital Maastricht, Maastricht, The Netherlands

Abstract - This report presents a patient who developed fulminant pulmonary oedema as a complication of spontaneous cerebellar haemorrhage. In spite of persisting hypoxaemia under ventilation with high levels of FiO2 and PEEP, it was decided to proceed with a surgical evacuation of the haematoma. Fortunately, after the patient was turned to the prone position, oxygenation improved rapidly. This observation suggests that prone ventilation can be a valuable tool in the treatment of neurogenic pulmonary oedema (NPE). This report also comprises an overview of pathophysiology, diagnostic measures, monitoring and treatment of NPE. Although the exact mechanism remains unclear, there is growing evidence that NPE is caused by a pressure overload mechanism, which is supported by this case.

Keywords - Neurogenic pulmonary edema, spontaneous cerebellar hemorrhage, adolescent, prone ventilation, severe central nervous system (CNS) injury, pathophysiology, diagnosis, monitoring, therapy, hydrostatic pulmonary edema, increased lung vascular permeability, pressure overload mechanism, catecholamine storm.

Introduction
Neurogenic pulmonary oedema (NPE) is a potentially life-threatening complication of severe central nervous system (CNS) injury. It has been frequently reported in cases of subarachnoid haemorrhage and traumatic brain injury, but can be observed after any form of cerebral or even cervical spinal cord injury [1]. We report a case of severe early pulmonary oedema following spontaneous intracerebellar haemorrhage in an adolescent.

Case Report
A previously healthy, 18-year-old man was at home when he suddenly became nauseous and complained of a severe headache. His parents noticed a progressive loss of consciousness. On arrival at the emergency room, he was comatose with a Glasgow Coma Scale of E1M4V1. Pupils were isocoric with normal reaction on light, the corneal reflexes were positive and there were no focal deficits. Further examination showed a blood pressure of 190/110 mmHg, a heart rate 120 of bpm, and oxygen saturation (Spo2) of 98% with 2L oxygen supplementation. He was coughing up profuse pinkish foamy sputum and bilateral crackles were noted. A severe central nervous system (CNS) injury complicated by NPE was suspected. Prompt endotracheal intubation was performed and mechanical ventilation was started. During transport to the radiology unit, the patient became haemodynamically unstable with hypotension and alternating tachycardia and bradycardia, which was treated with colloids, atropine and norepinephrine. Brain computed tomography (CT) scan (Figure 1) revealed a large cerebellar haematoma with blood in the ventricular system resulting in a hydrocephalus and signs of brainstem compression. During transport to the ICU he developed progressive hypoxaemia, despite mechanical ventilation with an inspired oxygen concentration (FiO2) of 100% and positive end-expiratory pressure (PEEP) of 15 cm H2O. Arterial blood gas (ABG) analysis showed pH 7.27, PaCO2 6.2 kPa, PaO2 8.9 kPa, HCO3 20.8 mmol/L and O2 saturation 92%. Chest X-ray (Figure 2) revealed diffuse bilateral pulmonary infiltrates. ECG showed a sinusbradycardia of 50 bpm with ST segment depression in II, III, AVF, V5 and V6 with inverted T-waves in I, aVL, V5 and V6 and frequent ventricular extrasystoles. Dobutamine was started to treat a possible cardiogenic component of the pulmonary oedema.

In consultation with the neurosurgeon, it was decided to surgically evacuate the haematoma.

On arrival in the operating room, oxygen saturation was 80%. Fortunately, after the patient was turned to the prone position, his oxygen saturation rose to 100%. The procedure consisted of acute release of the cerebellar haematoma and placement of an external ventricular drain which went uneventfully. After readmission to the ICU, the patient was respiratorily stable and PEEP and FiO2 were scaled down to 5 cm H2O and 25% respectively over the following days. However, vasomotor instability with hypotension and sinusbradycardia persisted for 2 days. This was treated with vasopressors and inotropics. Echocardiography demonstrated a globally reduced left ventricular function without regional wall motion abnormalities. Heart enzymes were slightly elevated with a CK-MB of 21.5 ng/L and TroponineT of 1.52 ng/L. After two days, the patient became also haemodynamically stable and inotropic support was stopped. His neurological condition also improved. An angiography was performed but revealed no evidence of arterio-venous malformation (AVM) or aneurysm as a cause of bleeding. After four days, an attempt to detubate was made but failed because of excessive sputum production and inadequate coughing. A tracheotomy was performed and the patient was discharged to the neurological medium care unit. After two months of hospitalization, he was discharged to the neurological medium care unit.
a rehabilitation centre. His gait was ataxic and he could already communicate by shaking his head for “yes” and nod for “no”.

**Discussion**

**Pathophysiology**

Exactly 100 years ago, the first case report of NPE in a human being was described by Shahanan [2]. However, the exact pathophysiological mechanism still remains unclear. Some data suggest a pressure overload mechanism with formation of hydrostatic oedema: increased intracranial pressure (elicited by the central nervous system injury) will alter the function of the neurons in the so-called NPE trigger zones [3]. These centres are located in the hypothalamic, brainstem and cervical spinal cord nuclei and are responsible for a massive sympathetic discharge, resulting in systemic and pulmonary vasoconstriction with redistribution of blood to the pulmonary circulation and an increase in pulmonary capillary hydrostatic pressure. This will lead to formation of hydrostatic pulmonary oedema. Subsequently, ‘the catecholamine storm’ can result in reversible cardiac injury, myocardial depression and worsening of the hydrostatic pulmonary oedema [4].

Another theory states that NPE is caused by increased lung vascular permeability. Indeed, several case reports have pointed out that the oedema of patients, who have developed NPE, may have a protein concentration similar to that of plasma [5]. This can be explained by the activation of a systemic inflammatory response with extravasation of intravascular fluid [1]. Both a central and a peripheral origin of cytokines and chemotactic factors produced following a severe CNS injury, have been suggested. Indeed, a severe CNS injury causes a local inflammatory reaction. Cytokines produced by this reaction can gain access to the systemic circulation after disruption of the blood-brain barrier and cause the stimulation of target cells in the peripheral organs. Severe biological insults may also directly result in a peripheral inflammatory response in the lung and other organs. The catecholamine storm elicited by a severe CNS injury may be responsible for the stimulation of cytokine expression and an inflammatory process in the lungs [1]. However, the formation of protein-rich oedema can also be explained by increases in hydrostatic forces and subsequent barotrauma to the basement membrane of the alveolar capillaries and alveolar epithelium. Our case-report also provides support for a hydrostatic mechanism since the formation of NPE was within one hour after the injury whilst the cascade of an inflammatory response would take a longer time to cause such extravasation of intravascular fluid [3].

In the literature, NPE after spontaneous cerebellar haemorrhage has already been described [6,7]. This is not surprising considering the anatomical proximity of the NPE trigger zones. Moreover, animal studies have pointed out that the cerebellum also takes part in cardiovascular and respiratory control, particularly through the IX-b vermian sublobe. Goncalves et al even state that isolated IX-b sublobule dysfunction without compression of the underlying brainstem, can elicit NPE [7]. This hypothesis may explain why our patient was already coughing up pinkish foamy sputum before the brainstem reflexes were affected.

**Diagnosis and monitoring**

The clinical features of NPE are non-specific. A decreased Glasgow Coma Scale or other signs of CNS injury (headache, nausea and vomiting) combined with signs of acute pulmonary oedema (dyspnoea, tachypnoea, pink frothy sputum, cyanosis, basal bilateral pulmonary crackles) must raise suspicion of the presence of NPE. Other causes of acute respiratory failure include aspiration pneumonia and acute heart failure, which can resemble the clinical signs of NPE [8]. Moreover, ECG abnormalities and increased levels of CK-MB and TnT are observed in more than 50% of patients with NPE, including in our case [9]. Bilateral diffuse pulmonary infiltrates seen on chest X-ray, are also not specific for NPE. A brain CT scan is an important diagnostic tool.
to clarify the cause of NPE. Extended haemodynamic monitoring may facilitate treatment of patients with NPE, without improving mortality. The transient increase in the pulmonary artery occlusion pressure (PAOP), elicited by the catecholamine storm, is usually not found in clinical practice because of its short duration and the delay in measurement [3]. A decreased cardiac output, due to reversible cardiac injury, is seen in one third of the patients [9].

Treatment
The primary goal in the management of NPE is to treat the underlying CNS injury as soon as possible [1]. The neurological outcome would probably have been more favourable in this case if neurosurgery had been started immediately after imaging. Further therapeutic options are primarily supportive but are extremely important since the hypoxia that results from NPE may worsen the neurological injury. These options include mechanical ventilation with high levels of FiO2 and PEEP. However, high levels of PEEP can theoretically increase ICP by increasing intrathoracic pressure and subsequently impeding venous cerebral drainage. Furthermore, PEEP may decrease cardiac output, with a consequent decrease in cerebral perfusion pressure (CPP). Nevertheless, PEEP values lower than 15 cmH2O have been shown not to influence cerebral perfusion pressure [1]. This case report also demonstrates the beneficial effect of the use of prone ventilation on arterial oxygenation in patients with NPE. A tremendous increase in oxygen saturation was noted after the patient was turned to the prone position. This can be explained by alveolar recruitment in dorsal lung regions combined with minor derecruitment in ventral regions when PEEP is applied [10]. Reduced lung compression by the heart in the prone position has also been proposed as a mechanism for improved ventilation-perfusion matching [11]. In addition, lung perfusion in the prone position is more homogeneous. Shunt conditions are therefore reduced [12]. Mechanical ventilation in the prone position is a worldwide accepted alternative in the treatment of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). On the other hand, the application of prone ventilation in the setting of NPE has been described only once [13]. In this case report, Fletcher et al postulate that prone ventilation should only be undertaken in conjunction with measurement of ICP because of the risk of increases in ICP during prone position. In our case, prone ventilation was also not applied until the operation for neurosurgery had been started immediately after imaging. A decreased cardiac output, due to reversible cardiac injury, is seen in one third of the patients [9].

Conclusion
This case illustrates that a dramatically evolving case of NPE can have a moderate and even favourable outcome if the diagnosis is made in time and if treatment of the CNS injury is not delayed. Thus, it is important to consider the development of this clinical entity in patients with respiratory failure and conceivable CNS injury. Application of prone ventilation can be valuable if hypoxaemia is refractory to conventional mechanical ventilation in the setting of NPE. Although the exact mechanism still remains unclear, there is growing evidence that NPE is caused by a pressure overload mechanism, which is supported by this case.

The work was performed at the Academic Hospital Maastricht. The Netherlands
Support was provided solely from institutional and/or departmental sources.

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Conjugated hyperbilirubinaemia in a trauma patient

BM Kors1, AME Spoelstra – de Man2, ARJ Girbes3

1 Department of Intensive Care, Kennemer Gasthuis, Haarlem, The Netherlands
2 Department of Intensive Care, Ter Gooi Ziekenhuizen, Blaricum, The Netherlands
3 Department of Intensive Care, University Hospital VU Medical Center, Amsterdam, The Netherlands

Abstract - This case report describes a 49-year-old male trauma patient, admitted to intensive care after laparotomy with intra-abdominal bleeding and haemorrhagic shock. He needed massive blood transfusion and he developed multiple organ failure (MOF). After six days, severe jaundice developed due to conjugated hyperbilirubinaemia which peaked on day nine at a total serum bilirubin concentration of 650 µmol/l of which 90% was conjugated. From day 20 his serum bilirubin suddenly dropped to subnormal levels. Liver synthesis function remained intact. No signs of extra-hepatic bile duct injury or obstruction were found. Alongside massive blood transfusion-related haemolysis and resorption of haematomas, the occurrence of shock, sepsis and MOF plays an important role in the development of conjugated hyperbilirubinaemia and hepatic dysfunction in critically-ill trauma patients. This is related to a reduced hepatic excretory capacity for conjugated bilirubin, which can be aggravated by pre-existent liver disease and use of hepatotoxic drugs.

Keywords - conjugated hyperbilirubinaemia, jaundice, shock, trauma, intensive care

Introduction
Hyperbilirubinaemia has an incidence in surgical intensive care units as high as 45%, mostly related to postoperative intra-abdominal sepsis or severe trauma [1,2]. Multiple factors can contribute to the development of jaundice in intensive care patients; these can be divided into pre-hepatic-, intra-hepatic-, and post-hepatic causes. Patients who have also been in shock, appear to be especially at risk of developing jaundice [3,4].

Case history
A 49-year-old man fell out of a second floor window. He had no relevant medical history, apart from severe alcohol abuse for many years. He was about to be admitted at a detoxification clinic. On presentation in the emergency room, he was haemodynamically and respiratorily stable and his eye, motor and verbal (EMV) score was the maximum. Radiological examination revealed left-sided pelvic fractures of the ramus inferior and superior, and right-sided fractures of the sacrum, and mandibular fractures. Chest X-rays showed no abnormalities. On admission to the emergency room no signs of intra-abdominal or retroperitoneal bleeding were detected on ultrasound. His haemoglobin concentration was 8.3 µmol/l at that time.

However, during CT scanning shortly after presentation, his clinical condition deteriorated with the development of haemorrhagic shock, resulting in a cardiac arrest (haemoglobin 3.8 µmol/l, lactate 19.9 µmol/l). After four minutes of cardiac resuscitation his circulation was restored and a blood transfusion was started. On suspicion of intra-abdominal bleeding a laparotomy was performed in a critical condition of shock. Apart from a large retroperitoneal haematoma, extending bilaterally from the subhepatic region to the lower abdomen, no intra-abdominal bleeding locus, organ lacerations or any other signs of trauma were found (Figure 1). During subsequent angiography, the fourth lumbar artery and branches of the right arteria gluteus superior (art. sacralis lateralis) were coiled successfully and the patient was transported to the intensive care unit for further treatment.

A total of 31 packed red blood cells, 14 fresh frozen plasma and 6 platelet suspensions were used to optimize haemoglobin and coagulation. He developed severe MOF, requiring ventilatory (maximum PEEP 15 cm H2O, FiO2 60%), inotropic and vasopressor support (maximum dose norepinephrine 0.16 mg/kg/ min) and renal replacement therapy. During the first three days in the intensive care unit his serum showed slightly elevated liver enzymes and mild cholestasis. His total bilirubin levels did not rise during this three-day period (33 and 36 µmol/l respectively) but the percentage of conjugated bilirubin rose from 28 to 87%. On the fifth day, he developed jaundice with a bilirubin of 136 µmol/l of which 90% was conjugated, which increased to a maximum of 650 µmol/l (90% conjugated) on day 9 and 686 µmol/l (90% conjugated) on day 16. Alkaline phosphatase and gamma-glutamine-transferase serum levels were elevated to 758 and 352 U/l respectively (day 23), whereas liver transaminases were only mildly increased. From day 20, when his clinical condition in terms of respiratory and vasoactive support had already improved, total bilirubin levels rapidly decreased to subnormal levels. During these three weeks his haemoglobin concentration remained stable. On the sixth day haptoglobin was low (0.08 g/l, reference 0.3 – 2.0 g/l). Figure 2 shows the typical course of his total serum bilirubin, alkaline
phosphatase and alanine aminotransferase levels. From day 11 until day 18 it was impossible to measure his alkaline phosphatase and gamma-glutamyltransferase serum levels because of his severe hyperbilirubinaemia.

Despite distinct conjugated hyperbilirubinaemia, liver failure did not occur (Day 17: max INR/PT 1.14, factor V activity 160% and albumin 18 g/l). Serum ammonium levels, prothrombin time and CPK all remained within normal ranges. Ultrasound and CT scanning of the upper abdomen only showed hepatic steatosis with no signs of hypersplenism, vena porta thrombosis or portal hypertension. There were no signs of extra-hepatic bile duct injury or obstruction. Physical examination showed no stigmata of liver cirrhosis. Viral hepatitis serology was negative. In the absence of liver failure and the spontaneous resolution of the hyperbilirubinaemia, liver biopsy was not performed. There was no time relationship between total serum bilirubin and the start of temporary parenteral nutrition (gastric retention, mandibular fracture and fixation). He did not develop any signs of infection, although a culture of the tip of a central venous jugular line, which was removed because it was redundant, did show *Enterococcus faecalis* (+) and coagulase negative staphylococci (+) without fever or elevated CRP level. Our patient was treated with selective decontamination of the digestive tract, and therefore received intravenous cefotaxim for three days. No other antibiotics were needed during the rest of his stay.

As a differential diagnosis, a hepatotoxic side-effect of midazolam was initially considered, since the rapid decrease of bilirubin levels started only one day after withdrawal of midazolam. Other medications he received during the first two weeks were pantoprazole, oxazepam and fentanyl. He did not receive acetaminophen. The clinical, laboratory and radiological results from our patient were in line with the typical conjugated hyperbilirubinaemia which can be seen in critically ill trauma patients.

**Discussion**

In our patient, we expected unconjugated hyperbilirubinaemia because of the haematomas, mass blood transfusion and haemolysis, but remarkably conjugated hyperbilirubinaemia occurred. Therefore, his hyperbilirubinaemia must have been the result of insufficient excretion of bilirubin rather than of insufficient hepatocellular uptake or conjugation of bilirubin. The severe haemorrhagic shock contributed to hepatocellular excretory dysfunction, resulting in distinct conjugated hyperbilirubinaemia. Previous subclinical liver injury due to chronic alcohol abuse, might have contributed to this picture. In the early literature, the development of conjugated hyperbilirubinaemia in critically ill patients after trauma is addressed as post-traumatic jaundice [5], postoperative jaundice [6] or benign postoperative intra-hepatic cholestasis [7].

Shock is an important causative factor in the development of conjugated hyperbilirubinaemia in trauma patients. Shock can disrupt the liver metabolism by impaired heptosplanchic haemodynamics. The most vulnerable process is the energy-dependent excretion of conjugated bilirubin from hepatocytes into the biliary tract against the bilirubin concentration gradient between the hepatocytes and the bile canaliculus [8]. The normal liver can excrete bilirubin loads of several times the normal daily production rate of 250 – 300 mg bilirubin/day without developing jaundice. Patients with severe abdominal or pelvic trauma are especially at risk for developing conjugated hyperbilirubinaemia because of haemorrhage into traumatized soft tissues, at bone fracture sites and into body cavities. Breakdown of extravasated blood (5 gram bilirubin/litre) and accelerated haemolysis of transfused blood (500 mg bilirubin/litre), will deliver substantial loads of bilirubin. This can cause extreme jaundice by overloading the reduced hepatic excretory capacity. Severe shock states, sepsis, multiple organ failure, mechanical ventilation with PEEP

![Figure 1. CT scan showing large haematoma (1), injured m. psoas major (2) and pelvic fractures (3).](image)
and major surgery are important additional factors leading to liver dysfunction and progressive jaundice in critically ill patients [3,9]. Concurrent renal impairment due to tubular necrosis as a result of shock may enhance the degree of jaundice because the renal excretion of conjugated bilirubin is decreased. The presence of pre-existing chronic liver disease (viral hepatitis, cirrhosis Child-Pugh C, Gilbert’s syndrome) has been recognized as an important contributing factor for the development of cholestatic jaundice in trauma patients. Our patient had a history of severe alcohol abuse. Animal studies show that chronic ethanol consumption exacerbates microvascular failure after shock and resuscitation, and therefore increases the risk of post-traumatic complications and mortality [10].

Cholestatic jaundice accompanying conjugated hyperbilirubinaemia in critically ill trauma patients can be characterized by a typical biochemical pattern of cholestatic injury. Four to five days after the trauma incident, aminotransferase levels will increase modestly. Conjugated bilirubin levels reach their maximum levels on days 6 to 12, and generally recede by the third week post-trauma. Alkaline phosphatase levels will increase substantially after maximum bilirubin levels have been reached. Liver function tests, such as prothrombin time and albumin are only mildly disturbed. Because of the affinity of bilirubin to albumin, and the long half-life time of albumin of 14 days, clinical jaundice may persist beyond normalization of the patient’s physiology and laboratory tests. Therefore this pattern must be distinguished from a pattern of hepatocellular necrosis characterized by elevated serum transaminase levels, mild to moderate increase of conjugated (direct) bilirubin and impaired hepatic synthesis function. Our patient developed multiple organ failure after initial severe haemorrhagic shock. As another differential diagnosis of his conjugated hyperbilirubinaemia, we considered the hepatotoxic effect of midazolam, traumatic bile duct injury or bile duct obstruction and progressive sclerosing cholangitis. Conditions causing conjugated hyperbilirubinaemia are listed in Table 1.

A direct relationship between the use of midazolam and hyperbilirubinaemia has never been reported [11]. From retrospective data Ter Horst et al. found that levomepromazin as adjuvant sedation to midazolam, caused up to 10% more cholestasis than midazolam alone in mechanically-ventilated patients [12]. In this study midazolam was reported to be responsible for 12% of drug-induced cholestasis but hyperbilirubinaemia did not occur in either the index group or the reference group, and data about important confounding factors were not available. Pathophysiologically, midazolam is unlikely to have a hepatotoxic effect since it is mainly metabolized by the predominating hepatic cytochrome P450, CYP3A4. This cytochrome plays an important role in the detoxification of bile acid cholestasis but is upregulated in cholestasis [13].

It was important to exclude traumatic bile duct injury or bile duct obstruction in our patient because this would require immediate endoscopic, radiological or surgical intervention. Repeated radiological investigations did not show any evidence for this. Extra-hepatic bile duct injury or obstruction are rare but call for a high grade of suspicion, because their diagnosis is difficult and often delayed with major consequences for the patient [9].

The laboratory and radiological results of our patient were not compatible with progressive sclerosing cholangitis. Progressive sclerosing cholangitis can also complicate severe trauma [14]. Benninger et al. describe this progressive disease which is caused by ischaemia of the intrahepatic ducts due to arterial hypotension [15]. Patients with progressive sclerosing cholangitis show slowly increasing signs of cholestasis and primary sclerosing cholangitis – such as destruction of the intrahepatic bile ducts. Haemolysis and mass blood transfusion play no role in this clinical picture. It is important to distinguish this disease from distinct conjugated hyperbilirubinaemia in critically ill patients after trauma or septic shock, since these patients are at high risk for the development of liver cirrhosis with major clinical problems within two years.

### Table 1. Conditions causing conjugated hyperbilirubinaemia

<table>
<thead>
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<th>I. Increased bilirubin load</th>
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<tr>
<td>Haemolysis (Intra-, extra-vascular)</td>
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<td>Transfusions</td>
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<td>Resorption of haematomas, blood in extra-vascular spaces</td>
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<td>Impaired hepatocellular function</td>
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<td>Hepatitis-like picture</td>
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<td>Anaesthetic agents (e.g. halothane)</td>
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<td>Drugs</td>
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<td>Shock</td>
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<td>Viral hepatitis</td>
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<td>5. Alcoholic liver disease</td>
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<td>6. Cirrhosis</td>
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<tr>
<td>Cholestatic-like picture</td>
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<tr>
<td>Hypotension, hypoxaemia</td>
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<tr>
<td>Drugs</td>
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<td>Sepsis / septic shock</td>
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<td>4. Primary biliary cirrhosis</td>
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<td>5. Primary sclerosing cholangitis</td>
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<td>6. Prolonged total parenteral nutrition</td>
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<tr>
<td>Defective excretion</td>
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<tr>
<td>Intrahepatic obstruction</td>
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<td>Dubin-Johnson syndrome</td>
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<tr>
<td>Rotor syndrome</td>
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<td>Drugs</td>
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<td>Benign recurrent intrahepatic cholestasis</td>
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<td>Recurrent jaundice of pregnancy</td>
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<td>Extrahepatic obstruction</td>
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<td>Bile duct injury / obstruction</td>
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<td>Choledocholithiasis</td>
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The effect of cholestatic hepatocellular dysfunction on the long-term prognosis of patients after severe trauma is unknown. In the short term, progressive increase of bilirubin levels seems to be associated with mortality. Labori et al. studied 44 trauma patients with jaundice [1]. Patients with hepatic injury or pre-existing liver disease were excluded. In the non-survivors (n = 13) serum bilirubin levels increased progressively, reaching maximum levels at the time of death (median 231 µmol/l). In survivors (n = 31) bilirubin levels peaked around day eleven (median 189 µmol/l). Non-survivors were older, had a higher injury severity score (ISS) and received more units of blood. All these patients died in a setting of sepsis and multiple organ failure. Douzinas et al. investigated the morphological changes in liver biopsies taken from jaundiced patients with organ failure. The morphological hepatic changes are in line with cholestasis and the conservation of hepatic function with absence of coagulopathy despite severe hyperbilirubinaemia [16].

In conclusion, as demonstrated in our case report, patients with a severe (especially abdominal or pelvic) trauma may develop the typical pattern of conjugated hyperbilirubinaemia due to massive bilirubin overload, severe shock and cholestatic intra-hepatic dysfunction. In these critically ill patients multiple factors can contribute to the development of conjugated hyperbilirubinaemia such as sepsis, multiple organ failure and hepatotoxic drugs. A progressive increase in bilirubin levels is associated with mortality. It is important to identify conjugated hyperbilirubinaemia with only a mild increase in aminotransferase levels and conservation of normal liver function in critically ill patients and to recognize those patients with bile duct injury or extra-hepatic obstruction.

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