

Secondary sclerosing cholangitis in critically ill patients

Colangitis esclerosante secundaria en pacientes críticamente enfermos

Carlos Alberto Peña-Pérez^{1*} and Juan Alberto Díaz-Ponce-Medrano²

¹Adult Intensive Therapy Unit; ²Medical Management Office. Hospital General Naval de Alta Especialidad, Secretaría de Marina/Armada de México, Mexico City, Mexico

Abstract

Primary sclerosing cholangitis (PSC) is a rare idiopathic condition with immunopathogenic mechanisms where there is chronic progressive destruction of the biliary tree. Secondary sclerosing cholangitis (SSC) is clinically comparable to PSC, but is caused by specific processes which directly damage the biliary tree; examples include recurrent pancreatitis, bile duct malignancy, congenital bile duct abnormalities. A new cause of SSC has been described during or following significant critical illness associated with severe respiratory insufficiency, vasopressor requirement, shock and sepsis. This condition rapidly progresses to cirrhosis, frequently requiring liver transplantation for definitive management.

KEY WORDS: Secondary sclerosing cholangitis. Critically ill patient. Endoscopic retrograde cholangiopancreatography.

Resumen

La colangitis esclerosante primaria (CEP) es una condición idiopática rara con mecanismos inmunopatogénicos en la que existe una destrucción crónica y progresiva del árbol biliar. La colangitis esclerosante secundaria (CES) es clínicamente comparable a la CEP, pero está causada por procesos específicos que dañan directamente el árbol biliar; ejemplo de esto son enfermedades como la pancreatitis recurrente, las neoplasias de la vía biliar y las anomalías congénitas de la vía biliar, entre otras. Una nueva causa de CES ha sido descrita durante o después de una enfermedad crítica, en muchas ocasiones relacionada con las intervenciones de soporte o con condiciones de ingreso propias de la unidad de terapia intensiva, como son la ventilación mecánica invasiva, los vasopresores, el estado de choque y la sepsis. Esta condición progresa rápidamente a cirrosis, y con frecuencia requiere un trasplante de hígado para su manejo definitivo.

PALABRAS CLAVE: Colangitis esclerosante secundaria. Paciente crítico. Colangiopancreatografía retrógrada endoscópica.

Introduction

Medical and technological progress in critical care medicine has allowed increasing the survival rates of patients with life-threatening injuries. However, this increase in seriously ill patients' survival rate has

been accompanied by the emergence of new diseases that are "acquired at or related to" intensive care. In recent years, there have been increasing reports of new diseases related to intensive care.

The development of secondary sclerosing cholangitis (SSC) in critically ill patients (SSC-CIP) was first observed in patients with severe burns and multiple

Correspondence:

*Carlos Alberto Peña-Pérez

Calzada de la Virgen, s/n

Col. Presidentes Ejidales 1ra Sección, Del. Coyoacán

C.P. 04470, Ciudad de México, México

E-mail: galeno_78@yahoo.com.mx

Date of reception: 18-08-2017

Date of acceptance: 14-02-2018

DOI: 10.24875/CIRUE.M18000008

Cir Cir. 2018;86:49-55

Contents available at PubMed

www.cirugiyacirujanos.com

trauma but, subsequently, it has also been described in other critical life-threatening acute events.

SSC-CIP is characterized by cholestasis and necrosis of the bile ducts, and can be diagnosed based on typical cholangiographic findings. This condition appears to be irreversible and to rapidly progress to biliary cirrhosis and liver failure. With no exception, medical history of all SSC-CIP cases reveals previous treatment at the intensive care unit (ICU)¹⁻⁴. There is no doubt that SSC-CIP triggering factors are found in the time interval between the initial life-threatening event and the onset of cholestasis. Whether this condition is caused by initial injury itself or by the treatment provided at the ICU, is still unclear. Therapeutic options for SSC-CIP are limited, the mortality rate during initial ICU stay is high and many patients who survive have to undergo liver transplantation.

Just as critical illness polyneuropathy, SSC-CIP is a complication of severe critical illness and its successful management. SSC-CIP is an important cause of unexplained acute liver failure in ICU patients, and it contributes to poor outcomes. In SSC-CIP, either critical illness itself or its management can turn previously healthy bile ducts into severely destroyed ducts after a few days. This harm to the bile ducts begins within the first 7 days after ICU admission. Several risk factors have been considered, with the most relevant being the state of shock, arterial hypotension, high doses of vasopressor drugs, sepsis, total parenteral nutrition and invasive mechanical ventilation strategies with positive end-expiratory pressure (PEEP) > 10 cmH₂O. However, the debate remains with regard to which of these risk factors is the main promoter of bile duct damage in SSC-CIP.

Following Hill's criteria, possible risk factors can be:

- Present prior to the onset of cholestasis (temporality).
- Common to all patients with this problem (consistency).
- Biologically plausible; e.g., capable of driving the pathogenesis of “toxic bile” or “ischemic cholangiopathy” (plausibility).

Temporality, consistency and plausibility tests are a *sine qua non* condition for the investigation of causal mechanisms⁵.

Bile ducts destruction in SSC-CIP appears to be the consequence of a single event, during which a large number of cholangiocytes are directly and irreversibly damaged. Direct damage to cholangiocytes can be induced by ischemia/hypoxia or by the detergent properties of the so-called “toxic bile”. Ischemia and toxic

bile are conceivable as two underlying pathophysiological mechanisms of SSC-CIP.

The ischemic cholangiopathy concept

In comparison with hepatocytes, which have a double supply of oxygenated blood, the biliary epithelium is irrigated only by hepatic arteries. Consequently, the biliary epithelium is more susceptible to ischemia than hepatocytes. Prior to the decade of 1960, ischemic cholangiopathy was virtually unknown, and our clinical information on ischemia-induced bile duct injuries was almost exclusively based on experience with liver transplantation⁶ (Fig. 1).

Shortly after liver transplantation, arterial blood supply interruption (e.g. by thrombosis of the hepatic artery) results in necrosis of the bile ducts. Further support to the concept of ischemic cholangiopathy came from observations made in the 1980s, which demonstrated that floxuridine administration in the hepatic artery results in necrosis of the bile ducts and sclerosing cholangitis^{7,8}. Ischemic necrosis of the biliary epithelium can occur when blood supply to the bile ducts is disrupted, at the level of either macrocirculation or microcirculation.

The toxic bile concept

In the absence of protective mechanisms, hydrophobic bile acids detergent properties will immediately destroy cholangiocytes lipid cell membrane. An important protective mechanism is hepatocellular secretion of phospholipids, which form protective mixed micelles together with bile acids. In addition, biliary secretion of bicarbonate results in the formation of a protective alkaline film on cholangiocytes apical membrane, with this mechanism contributing as part of the defense strategy⁹. A finely adjusted balance between bile acids and protective mechanisms is essential to preserve the integrity of bile ducts epithelium. Therefore, alterations in this balance will result in serious damage to the biliary epithelium and in the development of sclerosing cholangitis¹⁰⁻¹³. These alterations can be the result of functional disorders of the hepatobiliary transport system.

Macrocirculatory alterations as promoters of ischemic cholangiopathy

In the case of an incipient circulatory collapse with arterial hypotension, deterioration of hepatic perfusion

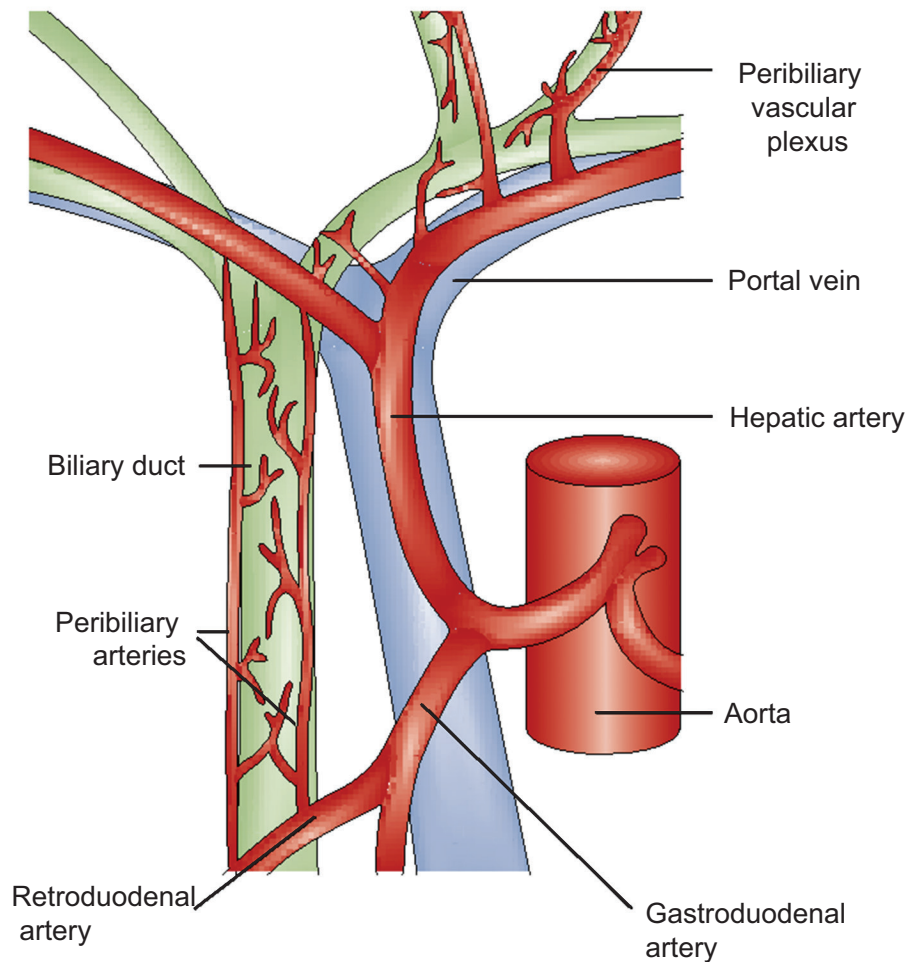


Figure 1. Hepatic ducts irrigation characteristics.

with later hepatic ducts blood supply alterations is to be expected, since hepatic perfusion can be maintained by self-regulation only for a limited period¹⁴. The state of shock with decreased blood pressure is a common phenomenon in patients admitted to ICUs, with a frequency of up to 58% according to recent reports¹⁵.

When parenteral solutions administration fails to adequately restore systemic blood pressure, and in the face of a critical clinical situation, initiating management with vasoactive agents is indicated. However, since the increase in systemic blood pressure does not always correlate with better hepatosplachnic perfusion, prolonged hepatic ischemia can end up being masked. Commonly used vasoactive agents, such as epinephrine, norepinephrine, dopamine and dobutamine, have the capacity to increase systemic blood pressure, but each one with different effects on hepatosplachnic blood flow. Dopamine not only increases mesenteric blood flow, but apparently also has a

positive effect on hepatic perfusion¹⁶. In contrast, epinephrine and norepinephrine have a dose-dependent negative effect on visceral organ perfusion. Owing to its vasoconstrictive properties, norepinephrine has the potential to decrease splanchnic blood flow. Epinephrine, in particular, is known for its deleterious effect on splanchnic perfusion in patients with sepsis^{17,18}.

Microcirculatory alterations as promoters of ischemic cholangiopathy

As already known from experimental models, bile duct ischemic damage increases as the size of occluded arteries decreases¹⁹⁻²¹. This indicates that the microcirculatory alterations that affect the permeable plexus have a particular clinical significance. The question on why SSC-CIP occurs more often in surgical patients remains to be answered. Two thirds of SSC-CIP published cases correspond

to patients with trauma, burned and undergoing major surgery. Polytrauma and major surgery are usually accompanied by extensive tissue damage. Clinical studies have demonstrated that this tissue damage can be an initiator of hypercoagulation state²²⁻²⁷. This could contribute to peribiliary plexus occlusion. Ischemic damage to the bile duct has often been found in a series of conditions known to be associated with a hypercoagulation state, such as antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria and systemic lupus erythematosus, among others²⁸⁻³².

Other important factors that affect microcirculation are increased blood viscosity and red blood cell aggregation. Trauma, burns and major surgery are conditions that can increase plasma viscosity. In addition, extensive muscle destruction, accidents with electrical energy and ischemia-reperfusion syndrome are often associated with a marked release of myoglobin, which can lead to an increase in plasma viscosity³³. Parenteral infusion of colloidal solutions, such as hydroxyethyl starch, can also increase blood viscosity. Unfavorable effects of these solutions on peribiliary plexus blood flow have been reported in clinical studies and supported by others of an experimental nature^{34,35}.

In recent years, the existence of risks secondary to red blood cell transfusion has been brought to light, which mainly are associated with storage-related effects. Stored red blood cells adhere to the endothelium or lose their deformability capacity, which results in microcirculation obstruction³⁶⁻³⁸. These observations suggest that, apart from severe hypotension, certain additional microcirculatory disorders may be involved in SSC-CIP pathogenesis. Possibly, severe arterial hypotension can only have implications on the bile duct when it occurs in combination with additional microcirculatory disorders.

Invasive mechanical ventilation as a driver of ischemic cholangiopathy

Experimental studies indicate that mechanical ventilation with high PEEP for prolonged alveolar protection purposes has negative effects on gastrointestinal tract microcirculation. Based on these studies, it is suspected that, in particular, an elevated PEEP contributes to biliary ischemia, and that patients with a low oxygenation index are at risk for developing SSC-CIP^{2,39}.

Systemic inflammatory response syndrome and sepsis as drivers of “toxic bile” for the development of secondary sclerosing cholangitis in critically ill patients

Proinflammatory cytokines, such as tumor necrosis factor alpha and interleukins 1 and 6, negatively regulate hepatobiliary transporters function or expression. Animal models indicate, for example, that the conjugated bilirubin canalicular pump is sensitive to cytokines, and that bile salts export pump mRNA is negatively regulated by the influence of inflammatory mediators⁴⁰⁻⁴². These data have been confirmed in human hepatocytes. However, data on the phospholipids export pump are not conclusive, but some studies in experimental inflammation models suggest a decrease in their hepatic expression⁴³.

As for the bile acid transporter, proinflammatory cytokines inhibit anionic exchanger AE2 activity⁴⁴. In the clinical setting, the inflammatory response syndrome and sepsis reflect an environment rich in proinflammatory cytokines release⁴⁵.

Clinical symptoms and diagnosis

At SSC-CIP initial stage, clinical symptoms are rare and nonspecific, and the only indicator of cholestasis are liver function tests abnormal results. In particular, alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT) serum concentrations are considerably high; however, no specific parameter indicates the presence of early SSC-CIP, and hence the diagnosis is usually late. As disease progresses, the presence of persistent cholestasis may be indicative of SSC-CIP. Most common clinical symptoms in this advanced stage are jaundice, pruritus and abdominal discomfort located in the upper right quadrant of the abdomen. Ascending biliary infection is present in almost all patients with SSC, and recurrent bacterial cholangitis episodes are typically observed⁴⁶⁻⁴⁸.

In the 16-patient series published by Leonhardt, et al.⁴⁹, cholestasis onset was observed 7 days (mean) after the start of the life-threatening clinical event. GGT was the first parameter to increase, with AP following a few days later. Hyperbilirubinemia could be observed after a mean of 15.5 ± 10 days (median, 13 days) and was, therefore, the last sign of the disease to be detected. This characteristic sequence of GGT, AP and bilirubin elevation was observed in 13 of the 16 patients. Cholestasis peaked after $31 \pm$

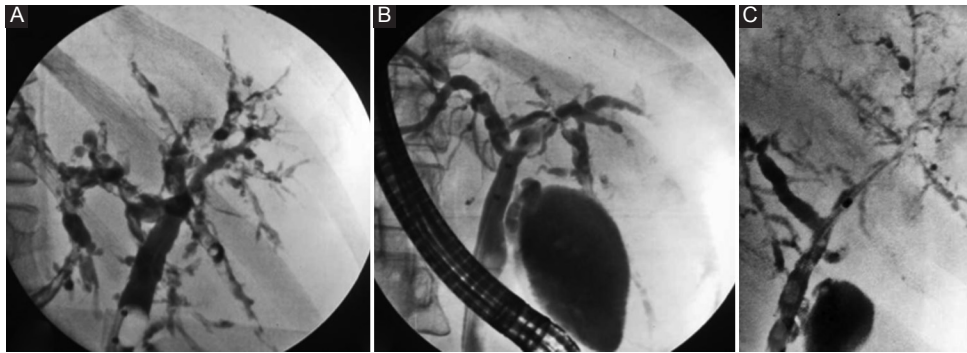


Figure 2. Cholangiographic patterns. **A:** early phase. Filling defects due to the presence of biliary cylinders. **B:** intermediate phase. Filling defects due to bile ducts destruction, which generates images resembling “beads”. **C:** late phase. Intrahepatic bile ducts obliteration with a filling defect that resembles a “pruned tree”.

14 days. GGT values reached a peak of about 20-50 times the upper limit of normal, while AP elevation was less pronounced (5-21 times the upper limit of normal). Alanine aminotransferase and aspartate aminotransferase values were moderately elevated. Initial cholestasis was accompanied by a transient elevation of serum creatinine in half the patients⁴⁹.

After obtaining abnormal results in the liver function tests, ultrasonography (USG) is used to identify patients with suspected bile duct disease or liver structural abnormalities. USG has the capacity to detect gallstones, bile duct dilation or presence of a liver abscess in patients in whom chronic biliary obstruction is the main cause of sclerosing cholangitis. However, in patients with SSC without bile duct obstruction or dilation, USG does not facilitate the diagnosis.

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard diagnostic method in all patients with suspected SSC. ERCP typical findings in SSC are bile duct lesions with multifocal stenosis and intermediate segments of normal or dilated ducts that give intrahepatic bile ducts an appearance of “beads”. Small peripheral bile ducts may show poor filling or complete obliteration, giving the intrahepatic bile duct a “pruned tree” appearance.

ERCP has three cholangiographic patterns, depending on the stage of disease (Fig. 2):

- Early phase: formation of biliary cylinders. The early stage of disease is characterized by the presence of multiple ribbon-like intraductal biliary tract filling defects.
- Intermediate phase: progressive destruction of intrahepatic bile ducts. The subsequent course of the disease is characterized by intrahepatic bile ducts rapid and progressive destruction, beyond the second bifurcation. Intrahepatic bile ducts destruction by epithelial necrosis is

observed in ERCP as irregularly contoured ducts and multiple filling defects at the edges of the wall.

- Late phase: intrahepatic bile ducts obliteration (the “pruned tree” image). As a result of progressive destruction, intrahepatic bile duct branches are eventually “erased”, leaving only a rudimentary central biliary system. In ERCP, contrast enhancement of the bile ducts is only observed below the second bifurcation. In this, last stage, the cholangiographic image it is similar to that of a “pruned tree”. At least one side of the biliary system is obliterated but most times, both sides are affected⁴⁹.

Magnetic resonance cholangiopancreatography is less invasive than ERCP, but it is not as useful for the detection of mild early lesions⁵⁰.

Secondary sclerosing cholangitis complications in critically ill patients

SSC-CIP entails a high risk of hepatobiliary complications, with acute acalculous cholecystitis, gallbladder perforation, liver abscess and septic cholangitis standing out⁴⁹.

In this regard, Voigtländer et al.⁵¹, in a prospective study carried out in 2010, evaluated 169 patients (72 diagnosed with SSC-CIP and 97 diagnosed with primary sclerosing cholangitis [PSC]). In their study, by means of ERCP, they obtained bile samples of each patient in order to perform cultures. Of the processed bile samples, 81.1% of cases had positive cultures. Among all samples, 94.4% (68/72) were positive in patients with SSC-CIP, in comparison with 71.1% (69/97) in those with PSC. Monomicrobial growth was more common in patients with SSC-CIP. Gram-positive strains were more commonly isolated than

gram-negative strains in both cohorts. The most abundantly isolated microorganism among the gram-positive ones was *Enterococcus* spp. (36%), and among gram-negatives, it was *Escherichia coli* (13%), *Klebsiella* spp. (9%) and *Pseudomonas* spp. (6%) *Candida albicans* was isolated in 11% of cases. According to these results, an initial antimicrobial therapy with vancomycin and piperacillin-tazobactam $\pm$ fluconazole may be efficacious in most patients with SSC-CIP⁵¹.

Progression and need for liver transplantation

Two aspects contribute to the short latency between the onset of cholestasis and the need for transplantation in SSC-CIP reported cases. In the first place, hepatic fibrosis clinical and histological evolution is of an unusually rapid progression, in a few months. This rapid and extensive fibrotic response can be explained by the significant initial destruction of intrahepatic bile ducts cholangiocytes. Second, owing to the risk of septic cholangitis and irreversible destruction of bile ducts due to recurrent cholangitis, it is necessary to consider transplantation as an urgent priority for these patients⁵²⁻⁵⁴. Survival after liver transplantation is variable; an 85% survival rate has been reported at 1 year, and 83% at 3 years⁴⁹.

Conclusions

SSC-CIP can be caused by a broad spectrum of events that lead to severe injury of the intrahepatic and extrahepatic bile duct. It is a progressive disease that, in most cases, involves the destruction of the biliary tree and results in a significant reduction of life expectancy. Although the pathogenesis of SSC is typically associated with a known cause, such as chronic obstruction, ischemic bile duct injuries or damage secondary to infections or toxins, the variant related to the patient in critical condition, which is not associated with underlying pathological processes or bile duct obstructions, is a new disease that is increasingly being recognized. Patients with SSC-CIP have an even faster rate of progression of disease than those with SSC "classic" forms. During the initial stages of the disease, clinical features are nonspecific and do not reliably allow differentiating it from endotoxin-induced jaundice, which is quite common in critically ill patients. Early diagnosis is, therefore, particularly difficult. ERCP is the only reliable method to diagnose SSC-CIP, but this invasive procedure is generally

avoided in critically ill patients. Thus, SSC-CIP is likely to be underdiagnosed in many cases, and the true prevalence of this disease may be substantially underestimated. A greater understanding of SSC-CIP pathogenesis opens the way to prevention and new treatment strategies for this catastrophic condition.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments have been conducted on humans or animals for this research.

Confidentiality of the data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient appear in this article.

Funding

For the development of this work, there was no funding for the authors.

Conflict of interests

The authors declare not having any conflicts of interests relevant to the development and publication of the present work.

References

- Schmitt M, Kölbel CB, Müller MK, Verbeke CS, Singer MV. Sclerosing cholangitis after burn injury. *Z Gastroenterol*. 1997;35:929-34.
- Gelbmann CM, Rümmele P, Wimmer M, Hofstädter F, Gohlmann B, Endlicher E, et al. Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. *Am J Gastroenterol*. 2007;102:1221-9.
- Engler S, Elsing C, Flechtenmacher C, Theilmann L, Stremmel W, Stiehl A. Progressive sclerosing cholangitis after septic shock: a new variant of vanishing bile duct disorders. *Gut*. 2003;52:688-93.
- Jaeger C, Mayer G, Henrich R, Gossner L, Rabenstein T, May A, et al. Secondary sclerosing cholangitis after long-term treatment in an intensive care unit: a clinical presentation, endoscopic findings, treatment, and follow-up. *Endoscopy*. 2006;38:730-4.
- Hill AB. The environment and disease. Association or causation? *Proc R Soc Med*. 1965;58:265-300.
- Sherlock S. Chronic cholangitides: aetiology, diagnosis, and treatment. *BMJ*. 1968;3:515-21.
- Hohn D, Melnick J, Stagg R, Altman D, Friedman M, Ignoffo R, et al. Biliary sclerosis in patients receiving hepatic arterial infusion of floxuridine. *J Clin Oncol*. 1985;3:98-102.
- Ludwig J, Kim CH, Wiesner RH, Krom RA. Floxuridine-induced sclerosing cholangitis: an ischemic cholangiopathy? *Hepatology*. 1989;9:215-8.
- Beuers U, Hohenester S, de Buy Wenniger LJ, Kremer AE, Jansen PL, Elferink RP. The biliary HCO₃(3)(-) umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *Hepatology*. 2010;52:1489-96.
- Smit JJ, Schinkel AH, Oude Elferink RP, Groen AK, Wagenaar E, van Deemter L, et al. Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. *Cell*. 1993;75:451-62.
- Mauad TH, van Nieuwkerk CM, Dingemans KP, Smit JJ, Schinkel AH, Notenboom RG, et al. Mice with homozygous disruption of the mdr2 P-glycoprotein gene. A novel animal model for studies of nonsuppurative inflammation cholangitis and hepato-carcinogenesis. *Am J Pathol*. 1994;145:1237-45.

12. Popov Y, Patsenker E, Pickert P, Trauner M, Schuppan D. Mdr2 (Abcb4)-/- mice spontaneously develop severe biliary fibrosis via massive dysregulation of pro- and antifibrogenic genes. *J Hepatol*. 2005; 43:1045-54.
13. Strazzabosco M, Spirlì C, Okolicsanyi L. Pathophysiology of the intrahepatic biliary epithelium. *J Gastroenterol Hepatol*. 2000;15:244-53.
14. Lauth WW. Regulatory processes interacting to maintain hepatic blood flow constancy: vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. *Hepatol Res*. 2007;37:891-903.
15. Bahloul M, Samet M, Chaari A, Ben Aljia N, Ben Mbarek MN, Chelly H, et al. Use of catecholamines for shock a continuous debate! *Tunis Med*. 2012;90:291-9.
16. Hillebrand LB, Krejci V, Sigurdsson GH. Effects of dopamine, dobutamine, and doxepamine on microcirculatory blood flow in the gastrointestinal tract during sepsis and anesthesia. *Anesthesiology*. 2004;100:1188-97.
17. Meier-Hellmann A, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med*. 1997;25:399-404.
18. Martikainen TJ, Tenhunen JJ, Giovannini I, Usaro A, Roukonen E. Epinephrine induces tissue perfusion deficit in porcine endotoxin shock: evaluation by regional CO(2) content gradients and lactate-to-pyruvate ratios. *Am J Physiol Gastrointest Liver Physiol*. 2005;288:G586-92.
19. Deltre P, Valla DC. Ischemic cholangiopathy. *J Hepatol*. 2006;44:806-17.
20. Sonomura T. Optimal size of embolic material in transcatheter arterial embolization of the liver. *Nihon Igaku Hoshasen Gakkai Zasshi*. 1994; 54:489-99.
21. Doppman JL, Dunnick NR, Gilton M, Fauci AS, Popovsky MA. Bile duct cysts secondary to liver infarcts: report of a case and experimental production by small vessel hepatic artery occlusion. *Radiology*. 1979;130:1-5.
22. Differding JA, Underwood SJ, Van PY, Khaki RA, Spoerke NJ, Schreiber MA. Trauma induces a hypercoagulable state that is resistant to hypothermia as measured by thrombelastogram. *Am J Surg*. 2011;201:587-91.
23. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*. 2008;64:1211-7.
24. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury*. 2012;43:26-32.
25. Hunt BJ, Parrat RN, Segal HC, Sheikh S, Kallis P, Yacoub M. Activation of coagulation and fibrinolysis during cardiothoracic operations. *Ann Thorac Surg*. 1998;65:712-8.
26. Stahl RL, Duncan A, Hooks MA, Henderson JM, Millikan WJ, Warren WD. A hypercoagulable state follows orthotopic liver transplantation. *Hepatology*. 1990;12:553-8.
27. Lison S, Weiss G, Spannagl M, Heindl B. Postoperative changes in procoagulant factors after major surgery. *Blood Coagul Fibrinolysis*. 2011;22:190-6.
28. Kirby DF, Blei AT, Rosen ST, Vogelzang RL, Neiman HL. Primary sclerosing cholangitis in the presence of a lupus anticoagulant. *Am J Med*. 1986;81:1077-80.
29. Viola S, Meyer M, Fabre M, Tounian P, Goddon R, Dechelotte P, et al. Ischemic necrosis of bile ducts complicating Schönlein-Henoch purpura. *Gastroenterology*. 1999;117:11-4.
30. Le Thi HD, Valla D, Franco D, Wechsler B, De Gramont A, Auperin A, et al. Cholangitis associated with paroxysmal nocturnal hemoglobinuria: another instance of ischemic cholangiopathy? *Gastroenterology*. 1995; 109:1338-43.
31. Lamy P, Valla D, Bourgeois P, Rueff B, Benhamou JP. Primary sclerosing cholangitis and systemic lupus erythematosus. *Gastroenterol Clin Biol*. 1988;12:962-4.
32. Audan A, Bruley Des Varannes S, Georgelin T, Sagan C, Cloarec D, Serraz H, et al. Primary sclerosing cholangitis and systemic lupus erythematosus. *Gastroenterol Clin Biol*. 1995;19:123-6.
33. Chernysheva GA, Plotnikov MB, Smol'yakova VI, Avdoshin AD, Saratikov AS, Sutormina TG. Relationship between rheological and hemodynamic changes in rats with crush syndrome. *Bull Exp Biol Med*. 2000;130:1048-50.
34. Heidenhain C, Pratschke J, Puhl G, Neumann U, Pascher A, Veltzke-Schlieker W, et al. Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation. *Transpl Int*. 2010;23:14-22.
35. Moench C, Moench K, Lohse AW, Thies J, Otto G. Prevention of ischemic-type biliary lesions by arterial back-table pressure perfusion. *Liver Transpl*. 2003;9:285-9.
36. de Moraes BS, Sanches MD, Ribeiro DD, Lima AS, de Abreu Ferrari TC, Duarte MM, et al. Association between the use of blood components and the five-year mortality after liver transplant. *Rev Bras Anestesiol*. 2011;61:286-92.
37. Ramos E, Dalmau A, Sabaté A, Lama C, Lladó I, Figueras J, et al. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. *Liver Transpl*. 2003;9:1320-7.
38. Van Bommel J, de Korte D, Lind A, Seigemund M, Trouwborst A, Verhoeven AJ, et al. The effect of the transfusion of stored RBCs on intestinal microvascular oxygenation in the rat. *Transfusion*. 2001; 41:515-23.
39. Fujita Y. Effects of PEEP on splanchnic hemodynamics and blood volume. *Acta Anaesthesiol Scand*. 1993;37:427-31.
40. Kubitz R, Wettstein M, Warskulat U, Häussinger D. Regulation of the multidrug resistance protein 2 in the rat liver by lipopolysaccharide and dexamethasone. *Gastroenterology*. 1999;116:401-10.
41. Trauner M, Arrese M, Soroka CJ, Ananthanarayanan M, Koeppl TA, Schlosser SF, et al. The rat canalicular conjugate export pump (Mrp2) is down-regulated in intrahepatic and obstructive cholestasis. *Gastroenterology*. 1997;113:255-64.
42. Vos TA, Hooiveld GJ, Koning H, Childs S, Meijer DK, Moshage H, et al. Up-regulation of the multidrug resistance genes, Mrp1 and Mdr1b, and down-regulation of the organic anion transporter, Mrp2, and the bile salt transporter, Spgp, in endotoxemic rat liver. *Hepatology*. 1998;28:1637-44.
43. Hartmann G, Kim H, Piquette-Miller M. Regulation of the hepatic multidrug resistance gene expression by endotoxin and inflammatory cytokines in mice. *Int Immunopharmacol*. 2001;1:189-99.
44. Spirlì C, Nathanson MH, Fiorotto R, Duner E, Denson LA, Sanz JM, et al. Proinflammatory cytokines inhibit secretion in rat bile duct epithelium. *Gastroenterology*. 2001;121:156-69.
45. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA*. 1995;273:117-23.
46. Deltre P, Valla DC. Ischemic cholangiopathy. *J Hepatol*. 2006; 44:806-17.
47. Sakrak O, Akpinar M, Bedirli A, Akyurek N, Aritas Y. Short and long-term effects of bacterial translocation due to obstructive jaundice on liver damage. *Hepatogastroenterology*. 2003;50:1542-6.
48. Sherlock S. Pathogenesis of sclerosing cholangitis: the role of nonimmune factors. *Semin Liver Dis*. 1991;11:5-10.
49. Leonhardt S, Veltz-Schlieker W, Adler A, Schott E, Eurich D, Faber W, et al. Secondary sclerosing cholangitis in critically ill patients: clinical presentation, cholangiography features, natural history, and outcome. *Medicine*. 2015;94:e2188.
50. Weber C, Kuhlencordt R, Grotelueschen R, Wedegaertner U, Ang TL, Adam G, et al. Magnetic resonance cholangiopancreatography in the diagnosis of primary sclerosing cholangitis. *Endoscopy*. 2008;40:739-45.
51. Voigtländer T, Leuchs E, Vonberg RP, Solbach P, Manns MP, Suerbaum S, et al. Microbiological analysis of bile and its impact in critically ill patients with secondary sclerosing cholangitis. *J Infect*. 2015;70:483-90.
52. Lazaridis KN, Strazzabosco M, Larusso NF. The cholangiopathies: disorders of biliary epithelia. *Gastroenterology*. 2004;127:1565-77.
53. Weisner RH, Porayko MK, Dickson ER, et al. Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology*. 1992;16:1290-9.
54. Farger O, Malassagne B, Sebahg B, Bismuth H. Primary sclerosing cholangitis: liver transplantation or biliary surgery. *Surgery*. 1995;117:146-55.