Sepsis-associated Cholestasis in Adult Patients: A Prospective Study

He-Bin Fan, PhD, Dong-Liang Yang, PhD, An-Shen Chen, MD, Zhi Li, MD, Li-Tong Xu, MD, Xiao-Ju Ma, MD, Hao Zhou, MD, Zhan-Fei Tian, MD, Juan-Juan Wu, MD and Fu-Ming Yan, MD

Abstract: *Background:* Sepsis-associated cholestasis is a common problem in neonatal patients. However, there are limited data related to sepsis-associated cholestasis in adults. In this study, the authors assessed the clinical characteristics, risk factors and outcome of adult patients with sepsis-associated cholestasis. *Methods:* An observational prospective single-center study was conducted. A total of 608 patients with sepsis (66 patients with cholestasis and 542 without evidence of cholestasis) from January 1, 2005, to December 31, 2011, were included from the infectious disease unit. Demographic, clinical and laboratory information were recorded on admission for all patients. Additional data were also collected on the day of the 1st episode of bacteremia for patients who developed cholestasis. Accordingly, the organ dysfunction scores (Acute Physiology and Chronic Health Evaluation [APACHE] II and Sequential Organ Failure Assessment [SOFA]) were assessed on the same day. *Results:* The mean age of the 608 patients was 49.3 ± 11.4 years (range, 22–83 years); 312 (51.3%) patients were men, 296 (48.7%) were women. The mean APACHE II and SOFA score were 15.2 ± 6 and 5.6 ± 2.3, respectively. Sepsis-associated cholestasis was strongly associated with older age, biomarkers of organ dysfunction and clinical composite scores (APACHE II and SOFA). Mortality was higher in patients with sepsis-associated cholestasis (10.6%) compared with subjects with sepsis without cholestasis (1.5%) ($P < 0.05$). *Conclusions:* The authors found that sepsis-associated cholestasis affects the outcome of patients with sepsis in the infectious disease unit. Additional clinical studies are necessary to elucidate the pathology and pathophysiology of sepsis-associated cholestasis.

Key Indexing Terms: Sepsis; Cholestasis; SOFA; APACHE II. **[Am J Med Sci 2013;346(6):462–466.]**

Cholestasis is commonly associated with a wide variety of bacterial sepsis.[1] The relationship between septicemia and cholestasis, particularly in neonates, was reported as early as 1837.[2] In general, inflammatory cholestasis may result either directly from bacterial components or as a consequence of the host's immune response to infection. These 2 factors play important roles in the development of cholestasis. In addition, hepatic infection can cause liver injury along with jaundice. Critically ill patients with progressive jaundice and/or cholestasis make this pathology more complex for clinical manifestations, diagnosis and treatment.

Sepsis-associated cholestasis caused by gram-negative bacteria is mediated primarily through endotoxin (lipopolysaccharide [LPS]); however, gram-positive bacteria and other microorganisms can also induce cholestasis. Circulating endotoxin is rapidly cleared by the liver, where Kupffer cells (activated by LPS) release a group of proinflammatory cytokines. These locally secreted cytokines, in turn, activate the membrane receptors of hepatocytes and intrahepatic bile duct cells, resulting in signaling pathways modifications, thereby changing the expression and function of a number of transporters, such as NTCP, IBAT and Mrp2.[3–5] In liver cells, during this pathology, the function of detoxification systems and hepatic uptake and excretory systems is reduced, resulting in bile formation damage and increased formation of bile acids and liver toxicity.[6–9]

LPS-induced proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1β and interleukin-6, are important mediators in hepatic acute-phase response.[10,11] These and other secreted cytokines are primarily produced by LPS-stimulated Kupffer cells and activate sinusoidal endothelial cells. Induction of cytokines in mononuclear cells by endotoxin and other bacterial components, in addition to the ability of these cells to recognize these products and secreted proteins, determines the degree of changes in transporter function and the extent and duration of cholestasis.

Sepsis-associated cholestasis is reported commonly in pediatric intensive care units but much less frequently in adults. Sepsis is often ignored as a potential cause of clinical cholestasis. The purpose of this study was to determine the morbidity and significance of the risk factors of sepsis-associated cholestasis in adult patients, its relationship with hospitalization prognosis and the optimal treatment of these clinical problems.

Patients

Patients consecutively admitted with the diagnosis of sepsis to the infectious disease unit in the 161 People's Liberation Army Hospital between January 1, 2005, and December 31, 2011, were enrolled in this study. Sepsis-associated cholestasis is a type of hepatocellular cholestasis that occurs as a result of sepsis and jaundice subside after positive anti-infection treatment.[3] In most cases, the manifestations of sepsis are the main clinical features before the development of cholestasis.[6] The diagnosis of sepsis-associated cholestasis is a challenging problem and is often confounded with the exclusion of other causes for cholestasis and delayed clinical manifestations. Exclusion criteria were as follows: age less than 18 years; other causes of cholestasis, such as viral hepatitis, primary biliary cirrhosis, autoimmune hepatitis, drug use (that may cause cholestasis as described in the literature), parenteral nutrition and biliary obstruction (obtained through endoscopic retrograde cholangiopancreatography, magnetic resonance imaging, B-ultrasound examination or computed tomography); and refusal of the patient to participate in the study.

METHODS

Clinical sepsis was defined according to the criteria of the American College of Chest Physicians/Society of Critical

From the Department of Infectious Disease (H-BF, A-SC, ZL, L-TX, X-JM, HZ, Z-FT, J-JW, F-MY), The People's Liberation Army 161 Hospital, Wuhan, Hubei Province, China; and Department of Infectious Diseases, (D-LY), Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China.

Submitted November 17, 2012; accepted in revised form March 28, 2013.

This study was supported by Chinese People's Liberation Army Logistics Department.

The authors have no financial or other conflicts of interest to disclose.

Correspondence: He-Bin Fan, PhD, Department of Infectious Disease, The People's Liberation Army 161 Hospital, Wuhan 430010, Hubei Province, China (E-mail: fan_hebin@126.com).

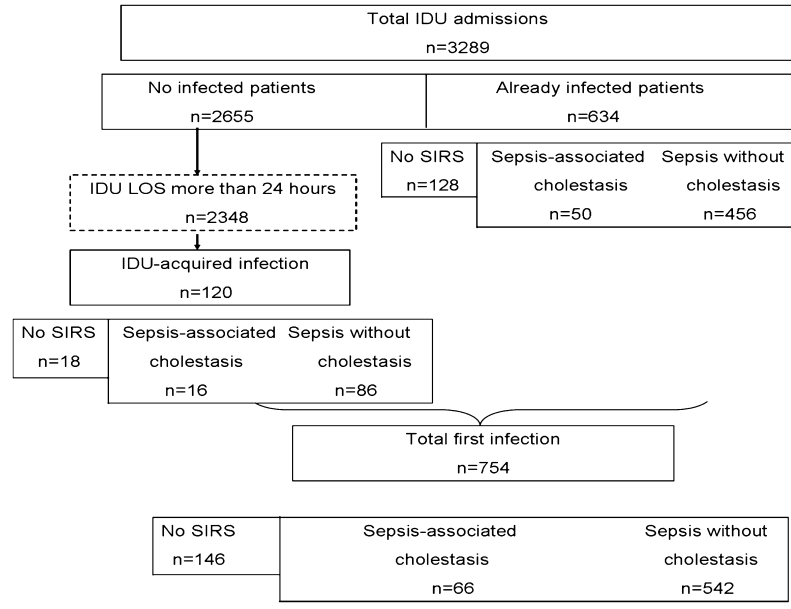

FIGURE 1. Flow diagram of the study subjects. IDU, infectious disease unit; LOS, length of stay.

Care Medicine Consensus.[12,13] Patients were assessed at the time of admission and throughout hospitalization. Clinical diagnosis of infection was assessed by a physician at admission (day 0), on day 2 and on the day of discharge or death of the patient. Clinical specimens (eg, urine, blood, pleural effusion and tracheal aspirates) were taken for diagnosis. Pneumonia was assessed according to radiographic evidence of pulmonary infiltration associated with purulent sputum. Cellulitis was defined as a skin infection associated with fever and leukocytosis. Other infections (eg, cholangitis and intestinal infection) were diagnosed according to clinical signs and symptoms, radiological evaluation and bacteriological findings. Furthermore, undetermined infections were diagnosed in patients without any identified source of infection but with fever (>37.5°C), leukocytosis (white blood cells count > 11,000/mm^3) and negative cultures.[14] A detailed history was obtained, and a complete physical examination was performed. Patients were followed up daily, in addition to daily blood cell count and urine analysis.

Laboratory measurements included complete blood count, liver function, erythrocyte sedimentation rate, C reactive protein, blood urea nitrogen, creatinine and myocardial enzyme spectrum. When the infection was suspected, blood, urine, ascites, sputum or swabs were taken for culture. Blood culture bottles (both aerobic and anaerobic bacteria) with 10 mL ascites or pleural fluid were also performed.[15] Functional liver parameters such as total bilirubin, γ-glutamyl transferase, alanine aminotransferase (formerly SGPT) and albumin were determined by using standard laboratory protocols. The study protocol was approved and monitored by the ethics committee of the 161 Hospital. Written informed consent was obtained from each participant enrolled in the study.

The clinical description data were reported as mean ± standard deviation, whereas categorical variables were expressed together with frequency and percentages. The intergroup differences of quantitative variables were verified using a Student *t* test, whereas the differences of categorical values were analyzed using a χ^2 test. All analyses were conducted using SPSS version 15.0 (SPSS, Chicago, IL). A $P < 0.05$ was considered statistically significant.

RESULTS

Case Study

Between January 1, 2005, and December 31, 2011, a total of 3289 patients were admitted to the infectious disease unit, of which, 634 (19.3%) were infected at admission (Figure 1). Of the patients without infection at the time of admission (n = 2655), 2348 stayed 24 hours or more, and 120 (5.1%) of these patients developed an infection during hospitalization. In addition, 754 patients had a 1st episode of infection, of which, 146 (19%) patients (because of insufficient information to classification) were excluded from this study. The study population consisted of 608 patients (312 men and 296 women), and 10.9% of the patients were diagnosed with sepsis-associated cholestasis and 89.1% with sepsis without cholestasis.

TABLE 1. Clinical data for the study groups according to categories between 2 groups (n [%])

	Sepsis-associated cholestasis	Sepsis without cholestasis	*P*
n	66	542	
Gender (male/female)	35/31	277/265	0.796
Age (yr)	65 ± 10.5	47 ± 9.9	0.000
WBC (1000/μL)	13.5 ± 5.2	14.3 ± 7.4	0.606
Temperature (°C)	38.6 ± 0.6	38.5 ± 0.7	0.300
SOFA score	8.6 ± 1.9	5.2 ± 2.0	0.000
APACHE II score	24.6 ± 5.4	14.0 ± 5.1	0.000
CRP (mg/dL)	25.0 ± 8.0	24.9 ± 7.4	0.934

APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SOFA, Sequential Organ Failure Assessment; WBC, white blood cells.