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Short-course antimicrobial treatment for acute cholangitis with Gram-negative bacillary bacteremia☆

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SUMMARY

Objectives: The optimal antimicrobial treatment duration for patients with acute cholangitis with bacteremia remains unknown. The updated Tokyo Guidelines 2013 recommend a minimum duration of 2 weeks only when bacteremia with Gram-positive cocci is present. Since May 2013, a shorter antimicrobial treatment duration of under 2 weeks has been implemented at the authors' institution for acute cholangitis with Gram-negative bacillary bacteremia. The aim of the present study was to validate this modified practice.

Methods: A single-center retrospective cohort study was conducted. The antimicrobial treatment duration, 30-day mortality rate, and recurrence rate within 3 months were compared between patients treated before May 2013 and after May 2013.

Results: Ninety-one patients with cholangitis with bacteremia were analyzed. The median antimicrobial treatment duration was 14.5 days in patients treated before May 2013 and 10.0 days after May 2013 ($p < 0.001$). While the 30-day mortality rate did not differ significantly, the recurrence rate was higher in those treated before May 2013 (5.7% vs. 0.0%, $p = 0.17$ and 13.3% vs. 0.0%, $p = 0.03$, respectively). The median treatment duration after May 2013 was 8 days for grade I patients, 10 days for grade II patients, and 11.5 days for grade III patients.

Conclusions: The results of this study suggest that acute cholangitis with Gram-negative bacillary bacteremia can be treated safely with a shorter antimicrobial treatment duration of <14 days.

Introduction

Acute cholangitis is a morbid condition with an acute infection in the bile duct.[1] Complete biliary duct obstruction can increase biliary pressure and frequently results in bacteremia.[1] The principal treatment for patients with acute cholangitis includes early relief from the biliary obstruction and drainage of the infected bile, along with the intravenous administration of antibiotics.

The optimal treatment duration in patients with acute cholangitis with bacteremia remains to be established. Intra-abdominal infection guidelines published by the Surgical Infection Society and the Infectious Diseases Society of America (SIS/IDSA) recommend antimicrobial treatment for only 4–7 days, unless it is difficult to achieve adequate source control.[2] The updated Tokyo Guidelines 2013 (TG13) also recommend 4–7 days of antimicrobial treatment once the source of infection is controlled and a minimum duration of 2 weeks only when bacteremia with Gram-positive cocci is present.[3] However, this recommendation does not refer to the treatment duration in patients in whom acute cholangitis is complicated by Gram-negative bacillary bacteremia, and Gram-negative bacilli are the most commonly detected pathogens causing acute cholangitis. In addition, because no well-designed trials have been conducted to determine the optimal treatment duration, these guidelines are based on expert opinion. Moreover, it is increasingly important to define the minimum treatment duration for common infectious diseases to reduce antibiotic consumption and minimize the emergence of drug-resistant organisms.[4]

Before the publication of TG13, it was recommended that all patients with acute cholangitis with bacteremia at the authors'

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institution were treated for at least 2 weeks; however, since May 2013, the treatment duration has been reduced to <2 weeks in patients without Gram-positive coccal bacteremia. It is hypothesized that the treatment duration could be reduced to <2 weeks in patients with Gram-negative bacillary bacteremia if the source of infection is controlled. The aim of the present study was to validate this modified practice.

Methods

Study design

A retrospective cohort study was conducted at Kameda Medical Center, a tertiary-care teaching hospital with 925 beds, from July 2012 to March 2014. The TG13 guidelines were published online in January 2013. Before May 2013, 2 weeks of antimicrobial treatment was recommended for patients with acute cholangitis with Gram-negative bacillary bacteremia. After May 2013, it was recommended that the treatment duration be shortened to <2 weeks with the agreement of the gastroenterologist and infectious disease (ID) physician in charge of patient care, who considered each patient's condition and clinical course. The characteristics and prognosis of the patients treated before and after May 2013 were compared. The study protocol was approved by the Institutional Review Board at Kameda Medical Center.

Patients

Inclusion criteria were a diagnosis of acute cholangitis and a positive blood culture. TG13 diagnostic criteria were used to confirm the diagnosis of acute cholangitis,[5] and the diagnoses of patients who were diagnosed using the Tokyo guidelines of 2007[6] criteria were reinterpreted in the light of TG13. In this hospital, two sets of blood cultures were routinely taken from all patients before they received antibiotics, and ID physicians examined all patients with positive blood cultures.

Clinical information such as the patient's age, sex, whether the infection was community- or hospital-acquired, history of acute cholangitis, vital signs, laboratory data, pathogens detected in blood culture, and antimicrobials administered to all patients diagnosed with bacteremic acute cholangitis were obtained from the electronic medical records. Bacteremic cholangitis was defined as community-acquired if it was diagnosed based on a blood culture obtained within 48 h of hospital admission, and as hospital-acquired if it was diagnosed based on a blood culture obtained more than 48 h after admission. The empirical antimicrobial regimen was defined as the agents chosen by the gastroenterologist at first contact. Appropriate empirical antimicrobial treatment was defined as the empirical administration of antimicrobials to which the pathogens subsequently isolated from blood culture were susceptible in vitro.

Exclusion criteria were (1) malignant biliary obstruction, (2) bacteremia caused by Gram-positive cocci, (3) complication of cholecystitis or hepatic abscesses, (4) non-receipt of drainage procedures, and (5) the occurrence of another illness during the treatment of patients with acute cholangitis. The TG13 severity grade (Table 1)[5] and Pitt bacteremia score were calculated to assess severity, and the Charlson comorbidity index was calculated to assess underlying conditions.

At first contact, the gastroenterologist determined whether to perform emergency drainage considering the severity of the condition, underlying conditions, receipt of antiplatelet or anticoagulation therapy, and history of gastric surgery of each patient. After positive blood cultures were obtained, the ID physician recommended continuing or changing the empirical antimicrobial regimen according to the results of susceptibility testing.

Outcomes

The primary outcomes were the 30-day mortality rate and the recurrence rate within 3 months of onset. The secondary outcomes were the treatment duration and length of hospital stay. The treatment duration according to the TG13 severity grading subgroup was also analyzed. Recurrence was defined as the relapse of acute cholangitis, occurrence of bacteremia caused by the same organism, or occurrence of a hepatic abscess.

Statistical analysis

The Student *t*-test for continuous variables, Mann–Whitney *U*-test for ordinary variables, and Chi-square test or Fisher's exact test for categorical variables were used to compare the characteristics of patients treated before and after May 2013. A *p*-value of <0.05 was considered to represent statistical significance. All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

Table 1
TG13 severity assessment criteria for acute cholangitis[a].

Grade III (severe) acute cholangitis	
Grade III acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the following organs/systems:	
1. Cardiovascular dysfunction	Hypotension requiring dopamine ≥5 μg/kg per min, or any dose of norepinephrine
2. Neurological dysfunction	Disturbance of consciousness
3. Respiratory dysfunction	PaO_2/FiO_2 ratio <300
4. Renal dysfunction	Oliguria, serum creatinine >2.0 mg/dl
5. Hepatic dysfunction	PT-INR >1.5
6. Hematological dysfunction	Platelet count $<100 \times 10^9$/l
Grade II (moderate) acute cholangitis	
Grade II acute cholangitis is associated with any two of the following conditions:	
1. Abnormal WBC count ($>12 \times 10^9$/l, or $<4 \times 10^9$/l	
2. High fever (≥39 °C)	
3. Age (≥75 years old)	
4. Hyperbilirubinemia (total bilirubin ≥5 mg/dl)	
5. Hypoalbuminemia (< STD × 0.7)	
Grade I (mild) acute cholangitis	
Grade I acute cholangitis does not meet the criteria of grade III (severe) or grade II (moderate) acute cholangitis at initial diagnosis	

TG13, Tokyo guidelines 2013; PT-INR,PT-INR, International Normalized Ratio of Prothrombin Time ; WBC, white blood cell count; STD, lower limit of normal value.
[a] Adapted from Kiriyama et al.[5]