Journal of Infection (2017) 74, 172—178

BIAM British Infection Association

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Characteristics, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: A prospective cohort study

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Accepted 30 October 2016
Available online 5 November 2016

KEYWORDS
Bacteremic cholangitis;
Bacteraemia;
Bloodstream infection;
Cholangitis;
Cancer;
Solid tumour;
Solid neoplasm;
Biliopancreatic diseases

Summary *Objectives:* To asses the clinical features, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours (ST).
Methods: All consecutive episodes of bacteraemia in hospitalized patients were prospectively analysed (2006—2015).
Results: Of 1852 episodes of bacteraemia, 750 involved patients with ST. Among them, 173 episodes (23%) were due to cholangitis. The most frequent neoplasms were hepato-biliary-pancreatic tumours (68.2%) and gastrointestinal cancer (18.5%); 57.2% of patients had a biliary stent in place. The most frequent causative agents were *Escherichia coli* (39.3%) followed by *Klebsiella pneumoniae* (15.1%) and *Enterococcus faecium* (7.8%). Forty-one episodes (18.7%) were caused by multidrug-resistant (MDR) microorganisms. Patients with a second episode of cholangitis were more likely to have an MDR isolate and to had received inadequate empirical

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http://dx.doi.org/10.1016/j.jinf.2016.10.008

antibiotic therapy. 7-day and 30-day case-fatality rates were 7.6% and 26%, respectively. The only risk factors independently associated with 30-day case-fatality rate were corticosteroids and malignancy-related complications.
Conclusions: Bacteraemic cholangitis is frequent in patients with ST, and is mainly caused by Enterobacteriaceae and *E. faecium*. The emergence of MDR is of special concern, particularly in patients with a second episode of bacteraemia. Case-fatality rates are high, especially among patients receiving corticosteroids and presenting malignancy-related complications.

Introduction

Bacteraemia is a frequent complication in patients with cancer and is associated with high morbidity and mortality. The source and aetiology of bacteraemia in patients with solid tumours may vary depending on the underlying malignancy.[1]

Cholangitis is a common source of bacteraemia in cancer patients, occurring mainly in those with hepato-biliary-pancreatic tumours.[2] Compared with other bacteraemia sites cholangitis may present some distinctive clinical characteristics, and outcomes of patients with the condition may be closely related to the resolution or drainage of the focus of infection. Cancer patients with cholangitis often present an irreversible obstruction due to tumoral infiltration, and in most cases drainage of infected bile or stent placement or replacement is required.[3,4] Management of patients with cancer and biliary stent obstruction is particularly challenging.

In spite of the clinical relevance of cholangitis in patients with cancer, information regarding this common infection in this specific population is lacking. In recent decades the epidemiology of bacteraemia in cancer patients has changed, with an increase in Gram-negatives as the leading cause, and the rise in antibacterial resistance reported at some institutions, especially among Gram-negatives, is a matter for concern.[5–9] The emergence of antibacterial resistance is particularly worrying in immunocompromised patients with cancer, since administration of adequate empirical antibiotic therapy in patients with bacteraemia has been shown to have a beneficial impact on their outcome.[10] So far, the impact of the emergence of multidrug-resistant (MDR) organisms in cancer patients with cholangitis has not been elucidated.

We sought to analyse the clinical features, aetiology, antimicrobial resistance and outcomes of patients with solid tumours and bacteraemic cholangitis in an era of widespread antimicrobial resistance.

Methods

Setting, patients, and study design

We conducted a prospective observational study at a 200-bed university referral cancer centre for adults in Barcelona, Spain. We analysed all consecutive episodes of bacteraemic cholangitis occurring in patients with solid tumours from January 2006 to September 2015. Information on baseline characteristics, clinical features, aetiology, empirical antibiotic therapy, and outcome were prospectively collected in a database, as part of the standard infectious disease management at our hospital. We also compared the characteristics of patients who died with those who survived in order to determine the factors influencing mortality. The study was approved by The Clinical Research Ethics Committee and Institutional Review Board of Hospital Universitari de Bellvitge.

Definitions

Bacteraemic cholangitis was defined as positive blood cultures in association with two or more of the following criteria: (i) fever and/or abdominal pain in the right upper quadrant; (ii) endoscopic or radiological (by sonography or computed tomography) evidence of biliary tract obstruction owing to stones, stricture or tumour; (iii) laboratory evidence of hyperbilirubinemia and elevated alkaline phosphatase level, and (iv) positive bile culture.[3,11,12]

Chronic advanced cancer was considered in patients with confirmed metastatic disease (stage IV) and some stage III tumours (lung, pancreas, gastric, oesophagus, and urothelium) which were not suitable for treatment or were in progressive outbreak during treatment. Breast and prostate cancer with bone metastasis, colorectal cancer with resectable hepatic and lung metastasis and metastatic germinal tumours were excluded.

Bacteraemia was considered to be nosocomial-acquired, healthcare-related or community-acquired as previously described.[13] Polymicrobial bacteraemia was defined when 2 or more organisms were isolated from blood culture specimens collected from a patient during a period of $<$72 h. Neutropenia was defined as an absolute neutrophil count $<500/mm^3$. Corticosteroid therapy was recorded if a patient was receiving corticosteroids at the time of bacteraemia or at any point in the previous month. Shock was defined as a systolic blood pressure $<$90 mmHg which was unresponsive to fluid treatment or required vasoactive drug therapy.

Initial empirical antibiotic therapy was considered inadequate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.

Gram-negative bacilli were MDR in the following situations: a) extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae; b) AmpC-cephalosporinase hyper-producing Enterobacteriaceae; c) carbapenem-resistant Enterobacteriaceae d) microorganisms with intrinsic resistance mechanisms, such as *Stenotrophomonas maltophilia*; and e) MDR strains, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[14]