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Original research

Antibiotic resistance pattern and clinical outcomes in acute cholecystitis: 567 consecutive worldwide patients in a prospective cohort study

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HIGHLIGHTS

- Infections by ESBL+ and KPC + bacteria are increasing in acute cholecystitis also in community-acquired infections.
- Adequate empirical antimicrobial therapy is fundamental in reducing the formation of bacterial resistance.
- Patients risks for resistances and possible bacteria should be kept in mind in deciding the antibiotic therapy.

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ABSTRACT

Introduction: Postoperative complications for cholecystitis and cholelithiasis are important causes of intra-abdominal infections (IAIs). There have been no previous reports on intra-abdominal bacteriology in complicated IAIs due to acute cholecystitis (AC).

Material and methods: The data came from two prospective multicenter observational cohort studies (CIAO: the "Complicated Intra-Abdominal infection Observational" study and CIAOW: the "Complicated Intra-Abdominal infection Observational World" study) which involved 116 medical institutions worldwide with consecutive patients who underwent surgery, interventional drainage or conservative treatment for AC.

Results: Of 567 patients, there were 291 males (51.3%). The mean and median age were 62.5 and 64 years respectively. 546 (96.3%) had community-acquired and 21 (3.7%) patients had health-care-associated infections. 267 bacteria were isolated, 21 (7.8%) were resistant bacteria. No resistant Fungi or Anaerobes were isolated. 4 out of the 21 resistant bacteria were health-care-associated. Multivariate analysis demonstrated health-care associated infection ($p = 0.03$), inadequacy of empiric antimicrobial therapy ($p = 0.003$) and recent antimicrobial therapy ($p < 0.0001$) to be factors associated with resistant bacteria. The factors associated with mortality were presence of generalized peritonitis ($p < 0.0001$) and inadequate source control ($p = 0.018$). The factors associated with ICU admission were severe sepsis ($p < 0.0001$), generalized peritonitis ($p = 0.001$), concomitant malignancy ($p = 0.037$), inadequate source control ($p = 0.025$), delay in initial intervention ($p < 0.0001$) and age over 70 years ($p = 0.025$).

Conclusion: The number of infection caused by Extended Spectrum Beta-Lactamase bacteria (ESBL+) and Klebsiella pneumoniae Carbapenemase-producer bacteria (KPC+) were common in acute cholecystitis and in community-acquired infections. An adequate empirical antimicrobial therapy was fundamental to reduce bacterial resistance and to improve outcomes.

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1. Introduction

Intra-abdominal infections (IAIs) comprise of a broad variety of pathological conditions which range from uncomplicated appendicitis to fecal peritonitis [1]. In complicated IAI, the infection proceeds beyond a singularly affected organ and causes either localized or diffuse peritonitis. Effective treatment of patients with complicated IAIs involves both source control and antimicrobial therapy [2–4]. Understanding the microbiological profile is therefore important to optimize therapy.

Although postoperative complications for cholecystitis and cholelithiasis are important causes of IAIs arising from the biliary tract, little data have been published on the bacteriology of bile in patients undergoing cholecystectomy for AC [5–12]. Bacteria have been identified in the bile of 41%–63% of patients with Acute Cholecystitis (AC) [13]. There have been previous studies on bacteriology of intra-abdominal fluids in complicated IAIs due to AC. An insufficient or otherwise inadequate antimicrobial treatment regimen is an important variable strongly associated with unfavorable outcomes in such critically ill patients [14,15]. Effective empiric antimicrobial therapy targeting the frequently encountered bacteria causing the disease should be started as soon as possible in patients with sepsis, or severe sepsis with or without septic shock [16–18].

The aim of this study was to determine the microbiological profile of complicated IAIs secondary to AC, the risk of antibiotic resistance and the role of empiric antimicrobial treatment in relation to mortality and ICU admission. Special attention was paid to determine the increasing positive cultures for Extended Spectrum Beta-Lactamase bacteria (ESBL+) and Klebsiella pneumoniae Carbapenemase-producer (KPC) worldwide.

2. Materials and methods

The study derives from two multicenter observational studies (CIAO: the “Complicated Intra-Abdominal infection Observational” study and CIAOW: the “Complicated Intra-Abdominal infection Observational World” study) which involved 116 medical institutions worldwide during a two six-month study periods (January–June 2012, October 2012–March 2013) [4,19]. These two studies prospectively included consecutive patients older than 18 years with IAIs who underwent surgery, interventional drainage or conservative treatment for complicated IAIs. From these studies patients who were affected by IAIs due to AC were extracted. Medical institutions from each of the continents participated in the study. The study met the standards outlined in the Declaration of Helsinki and Good Epidemiological Practices. The study was monitored by the coordinator center which continuously checked the data and their quality by repeatedly asking the centers to fill in incomplete or to correct wrong data. In each center, a coordinator collected and compiled data in an online case report form system. These data included the following: (i) patient and disease characteristics, i.e. demographic data, type of infection (community- or healthcare-acquired), severity criteria, previous antibiotic therapy administered in 7 days preceding the treatment; (ii) origin of infection and surgical procedures performed; effectiveness of empirical antibiotic therapy which was defined as clinical and laboratory improvement after starting therapy, and (iii) microbiological data, (i.e., identification of bacteria and microbial pathogens within the peritoneal fluid, presence of yeasts (if applicable), and antibiotic susceptibilities of bacterial isolates). Source control was defined as all those measures undertaken to eliminate the source of infection, to reduce the bacterial inoculum and to correct or control anatomic derangements to restore normal physiologic function [19–21].

Efficacy of the antibiotic therapy was defined as improvement of clinical, laboratory and/or radiological conditions following the introduction of antibiotic therapy. The study was performed according to the STROBE statement.

Descriptive statistical analysis was conducted for categorical and continuous data. Results were expressed as mean ± standard deviation (SD) or median and range. Univariate analysis and multivariate analysis were conducted to investigate factors related to mortality, Intensive care unit (ICU) admission and presence of resistant bacteria. The univariate analyses were performed with the Chi Square Test. The multivariate analyses were performed with the binary logistic regression method with significant variables on univariate analysis. A statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS for Windows, version 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3. Results

Of the 4020 patients included in the CIAO and CIAOW studies, there were 567 patients with AC (Table 1), 291 were male (51.3%) and 276 female (48.7%). The mean and median age were 62.5 and 64 (SD ± 17.4) (range 19–97) years respectively. There were 414 patients who were over 70 years old (73%). The clinical conditions on admission included sepsis, severe sepsis and septic shock in 254 (44.8%), 33 (5.8%) and 16 (2.8%) patients, respectively. 511 patients (90.1%) were admitted with localized peritonitis and 56 (9.9%) with generalized peritonitis. Of the treated patients 546 (96.3%) had community-acquired and 21 (3.7%) health-care-associated infections. 30 patients (5.3%) had concomitant malignancy, 32 (5.6%) were under immunosuppressive or corticosteroid therapy and 146 (25.7%) had concomitant serious cardiovascular disease.

The method of source control was reported in 562 patients (99.1%). Source control was performed by open cholecystectomy in 273 (48.1%) patients, laparoscopic cholecystectomy in 221 (39%), drainage in 23 (4.1%) and conservative treatment in 45 (7.9%) patients. The adequacy of source control was reported in 561 patients (98.9%). Source control was adequate in 537 (95.7%) and inadequate in 24 patients (4.3%). Delay in initial intervention (>24 h) was reported in 549 (96.8%) patients. 226 (41.2%) patients experienced delay in surgical intervention < 72 h.

In 306 (54%) patients intra-abdominal microbiological studies were performed. The bacteria isolated are described in Table 2. A total of 267 bacteria were isolated. 21 resistant bacteria were isolated (7.8%) with one case of 2 associated resistant bacteria in the same patient (Klebsiella pneumoniae (ESBL+) resistant to third generation cephalosporins and Klebsiella pneumoniae resistant to carbapenems (KPC)) (Table 3). 18 Gram-negative bacteria (9.7%) and 3 Gram-positive bacteria (4.6%) were resistant. There were no resistant Fungi or Anaerobes isolated. 4 out of the 21 isolated resistant bacteria were health-care-associated (Acynetobacter baumanii resistant to carbapenems, Escherichia coli (ESBL+) resistant to third generation cephalosporins, Klebsiella pneumoniae (ESBL+) resistant to third generation cephalosporins, Klebsiella pneumoniae resistant to carbapenems) the remaining bacteria were community-acquired. The duration of antimicrobial therapy was reported in 514 patients (90.7%). The mean and median duration of antimicrobial therapy were 7.8 and 7 (SD ± 17.4) (range 1–60) days, respectively. In 309 patients (60.1%) the antimicrobial therapy lasted for ≤7 days, in 166 (32.3%) 8–14 days and in 92 (7.6%) more than 14 days. In 296 (52.2%) patients the adequacy of empirical antimicrobial therapy was reported; in 270 patients (91.2%) it was adequate, in 26 (8.8%) it was not. A recent antimicrobial therapy (within 7 days before the admission) was reported in 555 (97.3%) patients. 97 patients (17.1%) were admitted to

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