

PATIENTS AND METHODS (Supplementary material)

Additional definitions regarding infection

Site of infection acquisition

Infections diagnosed at admission or within 2 days after admission were classified as healthcare-associated (HCA) in patients with a prior contact with the healthcare environment (hospitalization or short term-admission for at least 2 days in the previous 90 days, residence in a nursing home or a long-term care facility or chronic hemodialysis). The remaining infections were considered community-acquired when they were present at admission or develop within the first 48 hours after hospitalization and nosocomial when the diagnosis was made thereafter.

Resolution

Infections were considered cured when all clinical signs of infection disappeared and on the presence of: a) urinary infections: normal urine sediment and negative urinary culture; b) spontaneous or secondary bacteremia: negative control cultures after antibiotic treatment; c) Pneumonia: normal chest X-ray and negative control cultures if positive at diagnosis; d) bronchitis: negative bronchial aspirate/sputum culture; e) Cellulitis: normal physical exam of the skin and negative control cultures if positive at diagnosis; f) Cholangitis: improvement of cholestasis, resolution of clinical symptoms and negative control cultures if positive at diagnosis; g) SBP and SBE: polymorphonuclear cell count in ascitic/pleural fluid < 250/mm³ and negative control cultures if positive at diagnosis. Resolution of the rest of infections was based on conventional clinical criteria.²⁰

Appropriate/inappropriate empirical antibiotic strategies

Rules used to consider an initial antibiotic therapy appropriate were the following: 1) For culture positive infections if an antibiotic with in vitro activity appropriate for the isolated pathogen or pathogens was administered at diagnosis of infection; 2) For culture-negative infections, when antibiotic strategies administered at the time of infection diagnosis solved the infection without need for further escalation. Otherwise, the initial therapy was considered inappropriate. We decided not to use the criteria of fulfillment of international guidelines since at the time of performing the Canonic study there were no broadly accepted norms for empiric management of bacterial infections in cirrhosis. Time of antibiotic therapy administration (hours after diagnosis of infection) was not recorded in the study.

SUPPLEMENTARY FIGURE LEGENDS

Figure 1A

Probability of developing proved bacterial infections during follow-up in patients with ACLF (red line) and AD (green line) without proved infections at diagnosis. Probability was significantly higher in patients with ACLF, especially in the first week after diagnosis.

Figure 1B

Incidence of proved bacterial infections within follow-up in patients with AD and with ACLF-1, ACLF-2 and ACLF-3 without proved bacterial infections at diagnosis. Incidence correlated with the grade of ACLF, being especially high in patients with ACLF-3.

Figure 2

Plasma concentrations (Individual values; Napierian logarithm) of different inflammatory cytokines (TNF-alpha, IL-6, IL-8, IL-10 and IL-1RA) at diagnosis of ACLF in patients with bacterial infection at diagnosis of the syndrome, patients who developed bacterial during follow up and those without bacterial infections during the whole study period. Concentrations were significantly higher in infected patients, especially in those who had an infection as trigger of the syndrome. However, a marked overlap was observed among groups.

Figure 3

Probability of 90-day transplant-free survival in patients with AD and ACLF with and without proved bacterial infections. Survival was significantly shorter

($p < 0.001$) in patients with ACLF and proved bacterial infections [either at diagnosis (ACLF-pBiD) or during follow-up (ACLF-pBiFu); continuous red and orange lines, respectively] than in patients with ACLF without proved bacterial infections (discontinuous red line; ACLF-NopBi) and in patients with AD with (continuous green line; AD-pBi) and without proved bacterial infections (discontinuous green line; AD-NopBi).