Digestive and Liver Disease 49 (2017) 579–584

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Antibiotic stewardship and empirical antibiotic treatment: How can they get along?

Valentina Zuccaro[a], Paola Columpsi[a], Paolo Sacchi[a], Maria Grazia Lucà[b], Stefano Fagiuoli[b], Raffaele Bruno[a,c,*]

[a] Department of Infectious Diseases — Fondazione IRCCS Policlinico San Matteo,Pavia
[b] Gastroenterology Hepatology and Transplant Unit, Departement of Specialty and Transplant Medicine Azienda Socio Sanitaria Territoriale (ASST) Papa Giovanni XXIII, Bergamo, Italy
[c] Department of Diagnostic, Paediatric, Clinical and Surgical Science University of Pavia, Pavia, Italy

ARTICLE INFO

Article history:
Received 4 October 2016
Received in revised form 11 January 2017
Accepted 13 January 2017
Available online 22 January 2017

Keywords:
Antibiotic stewardship
Cirrhosis
Empirical antibiotic treatment

ABSTRACT

The aim of this review is to focus on the recent knowledge on antibiotic stewardship and empiric antibiotic treatment in cirrhotic patients. The application of antimicrobial stewardship (AMS) rules appears to be the most appropriate strategy to globally manage cirrhotic patients with infectious complications: indeed they represent a unique way to provide both early diagnosis and appropriate therapy in order to avoid not only antibiotic over-prescription but, more importantly, selection and spread of antimicrobial resistance. Moreover, cirrhotic patients must be considered "frail" and susceptible to healthcare associated infections: applying AMS policies would assure a cost reduction and thus contribute to the improvement of public health strategies.

1. Introduction

The aim of this review is to focus on the recent knowledge on antibiotic stewardship and empiric antibiotic treatment in cirrhotic patients.

Literature research was done through Medscape and Pubmed databases, using the key words "antibiotic stewardship; empiric antibiotic treatment; cirrhosis"; including reviews of the literature; abstracts from conferences and original papers published from 1990 to 2015.

1.1. Infections in cirrhosis: prevalence and epidemiology

Bacterial infections are among the most relevant complications of cirrhosis and are associated with poor outcomes. The mortality rates are still high and have not been modified significantly over the last decades. The global prevalence of bacterial infections in hospitalized patients ranges between 5% and 7%, however in cirrhotic patients it is 4 to 5-folds higher, up to 32–34%. The severity of liver disease and the onset of gastrointestinal hemorrhage represent two of the most relevant factors playing a key role in the development of bacterial infections in cirrhotic patients. Indeed, in cirrhotic patients who experience a gastrointestinal bleeding, the infection rate is remarkably higher (up to 45–60%) with 17%–45% of the cases presenting as SBP or bacteriemia [1].

The most prevalent sites of infection in cirrhotic patients are represented by spontaneous bacterial peritonitis (SPB) (25%–31%) and urinary infections (20%–25%), followed by pneumonia (15%–21%), cellulitis (11%) and bacteremia [2]. The presence of cirrhosis increases the risk of sepsis, severe sepsis and death.

On one hand, bacterial infections become progressively more frequent with the development of liver disease, but on the other hand they can definitely worsen liver function and are considered a leading factor in the progression from compensated to decompensated stages of cirrhosis. Moreover, infections increase the probability of death in patients with advanced or decompensated cirrhosis, bearing a mortality rate of 30% at 1 month and of 63% at 1 year after the episode of infection [3]. Bacterial infections, particularly SBP or pneumonia, represent the most common precipitating event for acute-on-chronic liver failure, according to the CANONIC study by the CLIF consortium [4].

In a large report Singal et al. showed an increased prevalence of infections among hospitalized patients with cirrhosis in the US associated with in-hospital mortality [5].

Gram-negative enteric bacteria, i.e. *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., are the major causative organisms

* Corresponding author at: Unità di Malattie Infettive Tropicali e Epatologia, Dipartimento di Scienze Clinico — Chirurgiche Diagnostiche e Pediatriche, Università degli Studi di Pavia, Dipartimento Malattie Infettive, Fondazione IRCCS Policlinico San Matteo, Via Taramelli, 5-27100 Pavia, Italy. Fax: +39 0382 501080.
E-mail address: raffaele.bruno@unipv.it (R. Bruno).

http://dx.doi.org/10.1016/j.dld.2017.01.157
1590-8658/

of development of SBP or UTI. Infections due to gram-positive bacteria, especially *Enterococcus* spp. and *Staphylococcus aureus* represent about 20% of infections, affecting mainly hospitalized patients undergoing invasive procedures or those receiving antimicrobial prophylaxis. Anaerobic infections are rare and occur in about 3% of cases [1].

The epidemiology of bacterial infections in cirrhosis is undergoing a notable change due to the striking emergence of multi-resistant bacteria, wich are currently isolated in approximately 30% of the infections. These infections are especially frequent in hospital or healthcare-related setting (20–35%) as compared to the community-acquired ones (4–16%) and are associated with a high incidence of septic shock and/or death. ESBL *enterobacteriaceae* are the most frequently multidrug resistant bacteria, followed by *P. aeuriginosa*, methicillin-resistant *S. aureus* MRSA and *E. faecium* [6].

In accordance with a large perspective study in cirrhotic patients with infections, the efficacy of empirical antibiotic treatment is lower in nosocomial infections (40%), compared to community-acquired and healthcare-associated ones (83% and 73%, respectively), especially in SBP, UTI, and pneumonia (26%, 29% and 44%, respectively) [7]. As a result of an increased use of broad-spectrum antibiotics (ATB), it is speculated that infections with multi-resistant gram-negative organisms and *Enterococcus* spp. will be largely more common and far more challenging in the near future. Indeed, the current guidelines of empiric antibiotic therapy in cirrhosis do not take into account this feature.

1.2. Risk factors for infections in cirrhotic patients

Patients with cirrhosis bear an increased susceptibility and vulnerability to infection; despite new advances in the knowledge of the pathophysiological mechanisms involved, the intrinsic mechanism of this frailty has not been fully clarified yet.

The current hypothesis is that cirrhosis causes a state of immune dysfunction which is mainly related to both decreased general bactericidal activity and low serum levels of complement factors (which are under-produced by a dysfunctional liver) [8]. In physiological conditions, the liver is the first line of defense against gut-derived pathogens through the activation of Kupffer cells, but in cirrhotic patients the antigen-rich portal blood is not adequately processed by these macrophages, whose functionality is progressively compromised with the development of liver failure. In this setting bacterial infections induce a deranged cytokine response with an excessive activation of pro-inflammatory cytokines (CK) that transform a natural response against infection into a damaging inflammation-driven process. Moreover, the hyper-dynamic circulatory status typical of cirrhosis predisposes to harmful complications following the release of nitric oxide and cytokine storm in sepsis which lead to intractable hypotension, insufficient tissue perfusion, multiple organ failure and death [1].

The presence of portal hypertension and porto-systemic shunts, are additional important factors in these patients' vulnerability to infection. Indeed, homeostasis between intestinal microbiota and gut-associated lymphatic tissue is unbalanced in liver cirrhosis with portal hypertension. The prevalence of pathogens among the normal components of the intestinal flora is higher than in healthy individuals, and bacterial translocation from the intestinal lumen to systemic circulation through mesenteric lymph nodes and portal vein is frequent. Microbial translocation products are thus involved in the development of systemic pro-inflammatory syndrome and hyperdynamic circulation through the release of bacterial DNA or bacterial products at extra-intestinal sites [9].

Moreover, patients with decompensated cirrhosis have a high rate of hospitalization with longer hospital stays and this is a recognized risk factor for healthcare-associated infections (HAI). The same criteria used to define HAI also fit well for patients with cirrhosis, who are also at increased risk of acquiring MDR pathogens.

Another crucial point is how to identify patients at risk of poor outcome during an infectious episode, but so far we lack of data specific for cirrhotic patients. Generally, we could use the same methods and clinical scores available for critically ill patients, but subjects with advanced CPT and MELD scores are at high risk of liver decompensation.

All these factors clearly explain the higher rate of spontaneous bacterial peritonitis (SPB), spontaneous bacteremia and serious infectious complications among patients affected by chronic liver disease.

1.3. Challenges of antimicrobial use in cirrhotic patients

Metabolic liver pathways are primarily involved in the clearance of most drugs, including antibiotics. The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of antibiotics are profoundly altered in cirrhotic patients as a result of both chronic functional impairment and portal hypertension-related shunting: those changes depend on the nature and degree of hepatic impairment and on the characteristics of the dosed drug. However, there is a lack of information about the specific kinetics of most drugs in cirrhotic patients [10].

The pathophysiologic process that leads to abnormal drug availability, is related to progressive hepatocytes function impairment, blood flow alteration (porto-systemic shunting), reduction in the concentration of drug-binding proteins and abnormal drug metabolism with both pharmacokinetic and pharmacodynamic alterations [10]. Moreover, ascites and/or the presence of a transjugular intrahepatic portosystemic shunt (TIPS) can certainly modify drug availability and distribution. The degree of impairment of drug metabolism is proportional to the stage of liver dysfunction. Patients with well-compensated cirrhosis and near-to-normal synthetic function show a lower impairment of drug metabolism as compared to patients with decompensated cirrhosis with significant synthetic dysfunction and severe portal hypertension.

Specific testing aimed at determining the adequate drug dose in cirrhotic patients are not available as yet. In the guidelines proposed by both FDA and EMEA the recommendations are usually based upon the Child–Pugh score (CPS) [11].

In patients with advanced chronic liver disease the frequent PK changes should prompt specific drug dose adjustments to provide a safe use and avoid adverse reactions. Lower doses or reduced frequency of administration is often recommended to avoid hepatotoxicity and other untoward events, such as renal failure or encephalopathy [11].

Drug metabolism is largely based on cytochrome P450 enzymes and CYP3A is the most relevant isoform. Due to reduced liver cells mass, altered vascular liver perfusion and intestinal metabolism, CYP3A activity is profoundly altered in cirrhotic patients. Indeed, in the midazolam clearance model, a positive correlation between liver function scores (CPS and MELD) and CYP3A activity has been shown [12].

In patients with advanced liver disease, the role of hypoalbuminemia and hypertensive gastropathy must be also considered, in particular for high-distribution volume drugs. This can lead to a significant variability in drug circulating levels and impacts drug toxicity: indeed, hypoalbuminemia leads to an increased distribution volume, mainly for hydrophilic drugs. Furthermore, the presence of ascites and edema can affect the distribution volume and consequently modify bioavailability and half-life elimination. For this reason, the maintenance dose of lipophilic antimicrobials should be reduced, mainly according to Child–Pugh score. Also the efficacy of antibiotic therapy should be improved by increasing its dose, shortening the administration interval, or prolonging