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Review Article

Infectious Endocarditis in Patients with Cirrhosis: Epidemiology, Characteristics and Outcome

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Abstract

Bacterial infections are frequent in patients with cirrhosis with a 4-fold increase mortality. Spontaneous bacterial peritonitis, urinary tract infections and pneumonia are the most common infections observed but few data concerning infectious endocarditis (IE) are available. Some old studies suggested a higher prevalence of IE in patients with cirrhosis compared to general population. Regarding clinical features, patients were usually men, older than 55 years old with an alcoholic cirrhosis and a cardiopathy history. IE were mostly located on aortic and mitral valve. Gram positive bacteria were involved in 74-100% of cases with about 26-80% of Staphylococcus aureus, due to nosocomial infections. Enterococci and Gram negative bacteria were observed respectively in 6-19% and 3-5% of cases. Compared to general population, fewer patients underwent cardiac valve surgery, a fact grossly related toliver insufficiency. Selection criteria for surgery have to be refined since postoperative mortality could be less than 10% in selected cirrhotic patients with liver insufficiency. Mortality rates were high and associated with the severity of the liver disease. A prothrombin time ≤40% appeared as an independent risk factor of mortality.

ABBREVIATIONS

IE: Infectiousendocarditis; LPS: Lipopolysaccharide; OR: Odd Ratio; PT: Prothrombin Time

INTRODUCTION

Due to an immunocompromised state, patients with cirrhosis are prone to bacterial infections and consequently to develop sepsis, sepsis-induced organ failure and death [1]. Some risk factors are clearly identified such as chronic alcohol intake [2,3], degree of hepatic insufficiency [2,3] and intestinal bleeding [4]. Recently, new risk factors have been discussed such as diabetes mellitus [5], chronic use of proton pump inhibitors [6,7] and positive viral load in case of chronic hepatitis C infection [7]. The most common infections observed in case of cirrhosis are spontaneous bacterial peritonitis, urinary tract infections, pneumonia, septicemia and soft tissue infections. Bacterial infections are the first cause of acute or chronic liver failure and account for a 4 fold higher mortality ratecompared to general population, estimated to 30% at 1 month and 63% at 1 year [8].

Various mechanisms of increased susceptibility to infections in cirrhosis have been described. Bacterial translocation, due to altered intestinal permeability and intestinal bacterial overgrowth, leads to chronic exposure to pathogen-associated molecular patterns such as lipopolysaccharides (LPS) and activation of related pattern-recognition receptors like LPS toll-like receptor-4 which induce an inadequate release of pro-inflammatory cytokines called cytokine storm. This state is also facilitated by porto systemic shunts. Due to chronic inflammation, adaptative immunity cells are constantly stimulated which, by early senescence and turnover in memory T cells, leads to a decrease in total and naive T cells. An impairment of systemic reticuloendothelial system, a decrease in bactericidal capacity of phagocytic cells and a reduction in complement have also been described to explain altered innate immunity system. At the end, altered innate and adaptative immunity, cytokine storm and sepsis-induced nitric oxyd lead to inadequate tissue perfusion, organ failure and death [9-13].

Despite an improvement of the health system in the past decades, incidence of infectious endocarditis (IE) has not decreased [14-16]. This apparent paradox can be partly explained by epidemiological changes such as the emergence of new risk

factors and evolution of bacterial ecology. So far, few data about IE in patients with cirrhosis are available. Some studies have shown a higher prevalence of IE and a higher mortality in case of cirrhosis compared to general population. The aims of the review were to describe epidemiological data, clinical data and prognosis of IE in patients with cirrhosis.

Infectious endocarditis in general population

In general population, the incidence of IE were estimated between 3-10 new cases per 100,000 inhabitants per year with an in-hospital mortality rate around 20% and a mortality rate of 25-30% at 6 months [14-20]. Diagnosis relies on Dukes modified criteria (Table 1) [21]. Clinical presentation is diverse andnotspecific.IE must be considered in case of *Staphylococcus aureus* bacteremia and sepsis with unknown origin. The majority of patients were often more than 70 years old and incidence increased with age. Sex ratio was 2 males for 1 female and about 50% of patients had underlying preexistent heart disease. Fever and heart murmur were frequent and a location on the aortic and mitral valve was observed respectively in about 35% and 20% of patients but, in case of drug addiction, tricuspid injury was more common (more than 50% of cases) [14-20].

Characteristics of patients evolved in recent decades. Indeed, until the 1970s, congenital valve diseases and chronic rheumatic

Table 1: Modified Dukes criteria for diagnosis of infectious endocarditis (adapted from2015 ESC Guidelines(21)).

Major Criteria	**Positive blood culture** Two separate blood cultures positive for causative organisms or ≥2Blood Cultures drawn >12 hours apart demonstrate causative organism or Blood cultures drawn with at least 3/3 or ≥3/4 positive for causative organism with ≥1 hour between first and last blood draw or Single Blood Culture positive for *Coxiellaburneti* or Phase 1 Immunoglobulin G antibody titer >1:800
	Endocardial involvement Paravalvular lesions by cardiac computed tomography or Positive Echocardiogram Vegetation or Intracardiac abscess or Pseudoaneurysm or Intracardiac fistula or Valvular perforation or New partial dehiscence of prosthetic valve or Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG positron emission tomography/ computed tomographyor radiolabeled leukocytes single photon emission computerized tomography/ computed tomography
Minor Criteria	**Fever**>38 °C
	Predisposing condition Heart valve disorder Drug abuse
	Immunologic findings Glomerulonephritis Osler's Nodes Roth's spots Rheumatoid factor
	Microbiologic findings Positive Blood Culture that does not meet major criteria Serologic evidence of active infection with endocarditis causative organism
	Vascular findings Major arterial emboli Septic pulmonary infarcts Mycotic aneurysm Intracranial hemorrhage Conjunctival hemorrhage Janeway'sLesion
Interpretation	**Definitive Endocarditis Diagnosis** Pathology specimens from surgery or autopsy or Two major criteria or One major criteria and three minor criteria or Five minor criteria **Possible Endocarditis Diagnosis** One major criteria and 1-2 minor criteria or Three minor criteria

heart disease were the main factors predisposing to IE. Currently, new risk factors are emerging: use of intravenous drugs, heart materials, prosthetic valves, elderly people with degenerative valve disease, cancer, haemodialysis and immunosuppression states (diabetes mellitus, HIV infection and cirrhosis). There are also an increase of nosocomial and health-care acquired IE (accounting for 25-30% of contemporary cohorts) and variation in bacterial ecology [15,18,19]. In recent series, gram-positive bacteria were the most common germs foundwith a majority of streptococci (32-58%) and *Staphylococcus aureus* (23-27%) and were frequently associated with invasive procedures and drug use. Enterococci were observed in 7-11% of cases and infections with Gram-negative bacilli in 3-10% of cases [15,18,19]. Potential sources of infections were usually oral, dental, intestinal, urogenital and cutaneous. Some associations were observed such as *Staphylococcus aureus* with invasive procedures and intravenous drug use, *Streptococcus gallolyticus* with digestive neoplasia and elderly population [14,15].

Treatment of IE depends on a multidisciplinary approach. Bactericidal antibiotics are a cornerstone of therapy and must be administrated according to consensus data based on empirical treatment secondarily adapted to germ and resistance profile (Table 2)[20,21]. Long term treatment and high doses must be used to ensure diffusion into the vegetations and kill dormant bacteria. Parenteral therapy is usually recommended. Surgery must be considered in case of refractory cardiac failure caused by valvular insufficiency, persistent sepsis under medical therapy and persistent life-threatening embolism. In acute infections, surgery was necessary for 25-30% of patients and for 20-40% in later phases with a survival rate at 10 years of 61% [14,15].

Septic embolisms (25-50%) and heart failure (34%) were the most common observed complications. Heart failure was the first cause of death, followed by neurological complications and uncontrolled infections. Mortality predictive factors were identified as age > 50 years old, location on prosthetic valve, heart failure, diabetes mellitus, kidney or neurological complications and virulence of the causative organism especially for *Staphylococcus aureus* [14,15,18,19]. Because of its severity, IE should be prevented whenever possible according to patient risk factors and type of invasive procedures.

Infectious endocarditis in patients with cirrhosis

Epidemiological data: In series of IE, the proportion of patients with cirrhosis varied from 5 to 17% [14,17,22]. So far, few studies are available regarding prevalence of IE in case of cirrhosis and three of them are not recent and conducted in autopsy series. The first one, published in 1942 reported an IE rate of 6.7% in patients with cirrhosis versus 3.4% in the control group [23]. This trend was also confirmed by Snyder et al. in 4,215 autopsied veterans (1.8% in patients with cirrhosis versus 0.9% in controls, p<0.06) [24]. However, no significance difference have been observed between the two groups in 2,350 autopsies according to Hernandez et al. [25]. So far, data based on autopsies are discordant and do not allow us to draw any conclusion.

Recently, after adjusting for age, sex and comorbidities in 81,633 patients of the National Insurance Database in Taiwan, during a follow up of three years, Hung et al. showed a higher risk of IE in case of cirrhosis (0.3%) compared to general population (0,17%, odd ratio [OR]=2.04; p<0.001) [26].

Clinical features: Regarding clinical data, several series of IE in patients with cirrhosis are available and the largest one described by our group included 101 patients [27]. As observed in general population, the average age varied between 35 and 72 years old with a sex ratio of 2 males for 1 female and a preferential location on the aortic and mitral valves. Regarding the series of patients with cirrhosis, characteristics of patients differed according to the geographic origin of the study (viral cirrhosis in Asia vs. alcohol cirrhosis in industrialized countries), the medical history (valvular prosthesis present in 12.9-25% of patients) and habits of the patients (drug addiction associated with younger patients, viral cirrhosis and tricuspid location). No difference existed according to fever and positive blood culture between general population and patients with cirrhosis [27-32].

Table 2: Empirical antibiotics treatment strategy in case of suspicion of infectious endocarditis(adapted from 2015 ESC Guidelines (21)).

Community-acquired native valvesendocarditis or Late prosthetic valves (≥12 months post surgery) endocarditis	Ampicillin + (Flu)cloxacillin or oxacillin + gentamicin For penicillin-allergic patients: vancomycin +gentamicin
Nosocomial endocarditis or Healthcare associated endocarditis or Early prosthetic valves (<12 months post surgery) endocarditis	Vancomycin + gentamicin + Rifampin

Table 3: Causal microorganisms of infectious endocarditis in patients with cirrhosis and general population.

	Patients with cirrhosis	General population
Gram-positive bacteria	74-100%	78-87%
Streptococci	10-39%	32-58%
Enterococci	6-19%	7-11%
Staphylococci		
Coagulase-negative staphylococci	4-6%	6-10%
Staphylococcus aureus	26-80%	23-27%
Gram-negative bacteria	3-5%	3-10%
Fungi	0-3%	1-2%

Infectious characteristics: As in the general population, bacteriological ecology changes were also observed with time in patients with cirrhosis. In the last studies, Gram-positive bacteria (85-100%), especially *Staphylococcus aureus* (26-80%) predominated. Enterococci were observed only in 6-19% of cases and Gram negative bacilli were rare (3-5%) (Table 3) [28-30,32]. However, data on multidrug resistance bacteria were poorly available. Nosocomial infections were frequent and estimated to 45% in the study of Fernández Guerrero et al.[28]. Some IE were described after transjugular intrahepatic portosystemic shunt procedure, upper endoscopy and hepatic biopsies but there is no recommendation about prevention related to invasive procedures [28,33,34]. Potential source of infections were mostly oral and dental, intestinal, urogenital and cutaneous.

Medical treatment and cardiac surgery: As described in Table (2), antibiotics recommendations are available [21]. Nevertheless, in patient with cirrhosis, less aminoglycosides and rifamycin were used, probably due to their potential renal and liver toxicity [27]. As these antibiotics are a key point in treatment strategy, this issue might impact the outcome. Further studies are needed to evaluate the real impact and complications of aminoglycosides and rifamycin in patients with cirrhosis.

In series of IE patients with cirrhosis, we observed a lower rate of cardiac surgery mostly due to hepatocellular dysfunction. In fact, cardiac surgery is known to be risky in case of cirrhosis and mortality is often linked to severe liver failure secondary to extracorporeal circulation and to anesthetic drugs that decrease hepatic blood flow. Coagulopathy and thrombocytopenia associated with cirrhosis and heparin use during surgery also promote perioperative bleeding events [35,36]. In series, about 26-30% of patients with cirrhosis underwent surgical replacement compared to 42-51% in the control group [35,36]. Interestingly, in the study of Fernández Guerrero et al., valve replacement was considered in 16 patients with cirrhosis but only performed in 9 patients(Child-Pugh A: 4 out of 4,Child-Pugh B: 4out of 7, Child-Pugh C: 1 out of 5) [28]. Postoperative death occurred in 8% of patients with liver cirrhosis versus 3% in the control group in the series of Pérez de Isla et al.[32], close to our results with 9.7% of patients with cirrhosis who died just after surgery compared to 8.7% in the control group [27]. In our series, among the 10Child-Pugh C patients, who underwent surgery, 9 were still alive at time of discharge [27]. We suggest that history of cirrhosis and time of decompensation should be taken into account to evaluate liver insufficiency, A recent decompensation due to the septic state is probably less harmful than an ancient long-term decompensation and should not be considered as an absolute contraindication to surgery. Nevertheless, due to a low number of surgery events in the cirrhotic group, surgical prognosis factors have not been pointed out. Selection criteria for surgery have to be refined since postoperative mortality could be less than 10% in selected cirrhotic patients with liver insufficiency.

Factors associated with mortality: In all series, mortality rates were high in patients with cirrhosis and increased according to liver dysfunction [11,27,29,32]. Few studies compared patients with cirrhosis to control population and identifying prognostic factors is difficult due to the coexistence of IE and cirrhosis. Long term mortality data is difficult to analyze as mortality can be impacted not only by IE but also by the cirrhosis, its complications and the underlying cause of chronic liver disease (viral infections, chronic alcohol intake, metabolic features). That's why we decided to discuss only data of in-hospital mortality. In the study of Pérez de Isla et al., no significant difference was observed regarding in-hospital mortality (20% for patient with cirrhosis versus 17% for controls, p=NS). After age-adjusting analysis, cirrhosis was identified as an independent risk factor of mortality (OR=2.59; p=0.012). Nevertheless, no information about the severity of cirrhosis was available [32]. In the series of Fernández Guerrero et al., considering 31 patients with cirrhosis (Child-Pugh A: 12 patients, Child-Pugh B: 8 patients, Child-Pugh C: 11 patients), occurrence of renal failure (61.2% versus 16.1%, OR=8.23, p=0.001)and in-hospital mortality rate due to IE were significantly higher for patients with cirrhosis (51.6% versus 17.7%, OR=4.95, p=0.001) but no prognosis factors analysis was performed [28]. In the series of Hsu et al, the 7 in-hospital deceased patients (Child-Pugh A: 2 patients, Child-Pugh B: 1 patients, Child-Pugh C: 4 patients) with cirrhosis out of 26 presented more nosocomial disease (71% versus 11%, p=0.006), more *Staphylococcus aureus* infection (71% versus 21%, p=0.028), high uremia (57% versus 5%, p=0.01), and less aortic location (14% versus 79%, p=0.005) compared to living patients [29]. The largest series available presented by our group also supported a significant higher in-hospital mortality rate related to IE in case of cirrhosis compared to control population (41.8% versus 23%, p=0.006). Prothrombin time (PT) ≤40% (p=0.001) and heart failure (p=0.03), were found to be independent risk factors of mortality in patients with cirrhosis [27]. Liver dysfunction reflected by a PT ≤40% and not cirrhosis alone should be considered as mortality risk factor.

CONCLUSION

Cirrhosis is a risk factor for IE occurrence. Clinical and infectious features are close to general population with an increase of Gram-positive bacteria mostly due to nosocomial infections. In case of cirrhosis, IE is associated with poor outcome with high in-hospital mortality. Cardiac surgery, rarely performed at that time, should be considered for some eligible patients in order to improve survival.

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