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Is periodontitis a risk factor for infections in cirrhotic patients?

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Introduction

Infections in patients with cirrhosis

Infections are one of the most frequent and life-threatening complications of liver cirrhosis (LC). It is generally accepted that cirrhotic patients present increased risk, frequency and severity of infections when compared with hospitalized patients without liver disease [1–3]. Moreover, infections in LC patients are associated with deterioration of liver function [4–6], greater hospital admissions and prolonged hospitalization [3,7–10] and increased risk of mortality [3,11,12]. The most prevalent infections in cirrhotic patients are spontaneous bacterial peritonitis (SBP), urinary tract infections, respiratory infections, bacteremia, cellulitis, and skin and soft tissue infections [2,3,8,13,14].

Etiopathogenesis of infection in patients with cirrhosis

Some mechanisms have been proposed to explain the increased prevalence of infections in LC patients. Small-intestinal bacterial overgrowth (SIBO) is highly prevalent in LC patients and appears to be related to the development of infections [15,16]. SIBO has been attributed to intestinal hypomotility [17,18], obstruction of bile flow and reduction of bile constituents [19,20] and reduced expression of Paneth cell defensins [21].

Another mechanism that explains higher susceptibility to infection in cirrhotic subjects is the impairment of the intestinal mucosal barrier function [10,22,23]. Disruption of intestinal epithelial tight-junctions and widening of intracellular spaces leads to increased intestinal permeability [24], which facilitates gut bacteria translocation *via* mesentheric lymph nodes (MLN) [25,26]. In healthy subjects, commensal intestinal bacteria are transported to MLN by dendritic cells and are killed *in situ* by mononuclear cells [27]. In contrast, translocated bacteria in immunosuppressed cirrhotic patients can survive inside the MLNs, from where they can spread systemically [25].

Cirrhotic patients present impairment of the innate and adaptive immune responses, both at the liver and systemic levels (for review, see Albillos et al., 2014 [28]). At the liver, LC patients present disruption of the hepatic reticuloendothelial system (RES) that is primarily characterized by reduction and impairment of phagocytic activity of Kupffer cells (resident macrophages of liver) [28–30]. At the systemic level, LC patients present reduced neutrophil function (i.e., chemotaxis, adhesion, degranulation, phagocytosis and intracellular killing) [31–35]; deficiencies in the complement system [31,36]; down-regulation of monocyte HLA-DR surface expression [37]; decreased number and bactericidal activity of monocytes [2,38]; decreased number and altered function of T and B-cells [39–43] and impaired function of natural killer cells [44]. Taken together, bacterial translocation associated with impairments of the host immune system may explain the increased susceptibility and vulnerability of patients with cirrhosis to infection.

Sources of infection in patients with cirrhosis

Endogenous seeding from the gastrointestinal tract is the main source of bloodstream infections [10] and SBP [45] in cirrhotic patients. Gram negative enteric bacteria, such as *Escherichia coli*, *Kebsiella* spp. and *Enterobacter* spp. are the most commonly isolated microorganisms [8,13,25,26]. However, the increased use of invasive procedures associated with antibiotic prophylaxis resulted in an increase of Gram-positive bacterial infections, primarily caused by *staphylococci*, but also *Enterococcus faecalis* and *Streptococcus pneumoniae* [11,46,47].

Interestingly, some papers have reported cases of SBP caused by streptococci from oral origin. Bert et al. (2005) [48] reviewed 246 episodes of SBP, and reported that streptococci were isolated in 84 (34.2%) episodes. Of these, 62 (73.8%) were viridans group streptococci, such *as Streptococcus oralis*, *Streptococcus mitis*, *Streptococcus salivarius* and *Streptococcus sanguis*, which are commensals of the oropharyngeal microflora, and are frequently found in periodontal pockets [49]. Moreover, Gautam et al. (2007) [50] described 10 episodes of *Streptococcus salivarius* bacteremia in 9 patients listed for liver transplantation (LT). Altogether, these studies suggest that the oral cavity may be a source of infection in patients with cirrhosis. It could be conjectured that bacteria found in periodontal pockets may translocate into the peritoneal cavity in immunosuppressed LC subjects.

Periodontal disease and its association with systemic conditions

Periodontitis is an infectious disease resulting in inflammation of the periodontal tissues (gingiva, cementum, periodontal liga-

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ment and alveolar bone), progressive periodontal attachment loss, alveolar bone loss, and characterized by periodontal pocket formation and/or gingival recession [51].

Periodontitis is currently conceptualized as a multifactorial disease, in which several risk factors play a role [52,53]. One of the most important risk factors is the dental biofilm. Dental biofilms can be arbitrarily divided in supragingival (above the gingival margin) and subgingival (below the gingival margin). Subgingival biofilm contain Gram-positive and Gram-negative bacteria, the latter being causally associated with the initiation and progression of periodontitis [54].

Periodontal pockets may yield up to 10^7 bacteria, which are in direct contact with the pocket epithelium. Those bacteria and their products are able to alter the epithelium structural integrity and function, resulting in disruption of tight junctions and altered expression of matrix metalloproteinases [55]. The surface area of the ulcerated pocket epithelium in periodontitis subjects is supposed to be about 72 cm^2, which corresponds to the size of the palm of adult hand [56]. Subgingival microorganisms can translocate from the periodontal pocket into the bloodstream through the ulcerated epithelium [56]. Indeed, there is strong evidence that even daily oral care [57], routine dental procedures [58] and chewing [59] result in bacteremia in healthy subjects.

In healthy subjects, this bacteremia is a transient phenomenon and is quickly cleared via the hepatic reticuloendothelial system. However, immunocompromised cirrhotic subjects are unable to effectively clear bacteria. In a clinical study, Ashare et al. (2009) [60] demonstrated that 94% of cirrhotic subjects developed bacteremia after brushing their teeth. In addition, while the level of bacteria in the bloodstream returned to baseline levels after 5 min in healthy subjects, the bacterial load in cirrhotic subjects remained elevated even after 15 min.

Oral bacteria that enter the bloodstream can survive, translocate and adhere to non-oral organs and tissues, such as heart valves, carotid atheromatous plaque, brain, spleen, bone, pancreas and liver, among others [61,62]. The presence of oral bacteria at these sites and their impact on the host inflammatory responses may predispose to a wide range of systemic diseases. In fact, accumulating evidence suggests an association between periodontitis and non-oral diseases, such as cardiovascular disease [63], metabolic control in patients with diabetic [53], chronic kidney disease [64], and preterm/low-weight birth [65]. Periodontitis has also been associated with respiratory infections. Respiratory pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and enteric Gram-negative bacteria can be found in the dental biofilm. These bacteria may shed into the saliva and then may be aspirated into the respiratory tract, causing infection of the lungs [62]. This association is more likely to occur in hospitalized patients, including patients in mechanical ventilation [62,66].

Dental infections as sources of infections in patients with cirrhosis

So far, few studies have investigated the association between oral diseases and systemic infection in subjects with cirrhosis. Experiments in animal models have shown presence of *Porphyromonas gingivalis* (*P. gingivalis*), an important periodontal pathogen, in the liver of mice. Furusho et al. (2013) [67] detected *P. gingivalis* in Kupffer cells and hepatocytes of mice, after infecting pulp chambers with the pathogen. Along with the same lines, Ishikawa et al. (2013) [68] demonstrated that *P. gingivalis* inoculated into the oral cavity of mice translocated to the liver, where it was internalized by the hepatocytes. It could be speculated that these bacteria invaded vascular endothelial cells in the periodontal tissues, entered the blood circulation and reached the liver of the animals.

Besides the evidence from animal studies, some case reports have identified oral microorganisms in the liver of patients diagnosed with liver abscess. Ohyama et al. (2009) [69] reported an autopsy case of a 59-year-old woman with pyogenic liver abscess and severe periodontal disease. The liver puncture identified several periodontal pathogens in the abscess, such as *Prevotella melaninogenica*, *Treponema denticola*, *Prevotella intermedia* and *P. gingivalis*. Further, Wagner et al. (2006) [70] isolated *Streptococcus intermedius* from oral smears, liver and blood sample of a 39-year-old aggressive periodontitis patient, referred for treatment of brain and liver abscesses. Collectively, these findings suggest that subgingival bacteria can enter the bloodstream through the periodontal epithelium and translocate to the liver, where they manage to survive, causing a reaction that resulted in the abscesses.

Up to now, only one observational study has suggested a possible association between oral diseases and infections in LC patients [14]. The authors retrospectively investigated 116 liver cirrhotic subjects listed for liver transplant. Among the 38 patients with accurate laboratory follow-up data, 10 developed spontaneous bacterial peritonitis. In these cases, both *Staphylococcus aureus* and *Streptococcus viridans* (*S. viridans*) were isolated from the ascitic fluid. Interestingly, SBP caused by *S. viridans* occurred only in patients that had multiple tooth extractions.

Effect of periodontal treatment on systemic inflammation and infection

Treatment of periodontal disease is based on removal of soft and hard microbial deposits from the root surfaces, a procedure known as scaling and root planning (SRP). The local effect of SRP is the disruption of supragingival and subgingival biofilm and a dramatic reduction in the total counts of subgingival bacteria [71]. Moreover, the counts and proportions of putative periodontal pathogens, such as *P. gingivalis*, are reduced, while the proportions of health-associated species, such as oral streptococci, increase after treatment [72]. Periodontal treatment has also an effect on local and systemic inflammation. There is moderate evidence that SRP reduces C-reactive protein level, oxidative stress and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 [73–75].

It is tempting to speculate that periodontal treatment reduces the risk of systemic infection. Although periodontal procedures result in bacteremia in the short-term [58], it has been demonstrated that the total counts of bacteria in the bloodstream decrease 30 min after SRP [76]. Periodontal treatment leads to a decrease in the total number of bacteria residing in the periodontal pockets, which may reduce the incidence and magnitude of translocation of microorganisms from the periodontal pocket into the bloodstream. Furthermore, periodontal treatment and antiseptic decontamination of the oral cavity reduces the risk of microbial aspiration, pneumonia and other adverse respiratory events [66,77]. Thus, it is possible that periodontal treatment also reduces the risk of systemic infection on cirrhotic patients.

Hypothesis

We hypothesize that cirrhotic patients with periodontitis have increased risk of developing systemic infections. This hypothesis is supported by animal studies and case reports that isolated subgingival microorganisms in the liver. In addition, one observational study has described cases of SBP caused by oral streptococci in cirrhotic patients [14]. It can be speculated that bacteria from periodontal pockets translocate to distant sites, such as the peritoneal cavity, liver and kidney, where they manage to survive and cause infections in the immunocompromised cirrhotic