

Dental Management of Patients with Upcoming Liver Transplantation

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Abstract

Organ transplantation is now a widely undertaken procedure and the increase in the number of patients who have significant liver disease or having undergone liver transplant therapy will seek either preoperative or postoperative care. The successful management of oral health in organ transplantation patients necessitates close cooperation of a dental physician with the various transplant teams. This article reviews main medical problems impacting dental treatment in liver transplantation candidates: dental focus of infection; oral source of infection (periodontal disease, mucosal lesions, bacterial and fungal infections, etc); oral manifestations in transplant patients; bleeding problems; antibiotic prophylaxis and general medical conditions.

Key words: liver, transplantation, dental management, oral health

Background

Liver transplantation has become a standard treatment for end-stage liver disease and the number of recipients has grown rapidly in the last few years. There are several liver conditions that cause chronic or continuing liver inflammation, and the most common causes of end-stage liver disease are chronic viral hepatitis B and C, alcohol-related liver disease, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, steatohepatitis, liver disorders inherited or present at birth, and drug-induced liver damage (1, 2, 3, 4, 5). In Bulgaria, Takorov et al. in a research report about 111 patients with hepatocellular carcinoma find 40,5% of all patients suffer HCV, 29,7% – HBV, 10,8% – Hepatitis D virus (6).

The compromised health and immune system of such patients place them at increased risk for systemic as well as oral infections. It has been estimated that 60 to 80% of liver transplant recipients develop an infection (2, 7). The cumulative effects of poor dental health, untreated dental disease, and increased susceptibility to infection suggest that dental infections could pose a significant risk for the physically debilitated transplant candidate, as well as immunosuppressed transplant recipients (7). I. Takorov reports about general diseases accompanying the compromised liver function. 62,2% with cardiovascular disease, diabetes – 23%, respiratory system disorders – 22%, excretory organs malfunction - 20%, obesity – 10%, hypothyroidism – 4%, neurologic disorders – 7%. Severe accompanying disorders may be contraindicated for radical surgical manipulations (6).

A survey of organ transplant centers in USA for 1 year (2003 and 2004), found that among the 294 respondents, 9% reported that they had encountered 1 or more incidents of sepsis from a dental source in a transplant recipient (2). In addition, 34 centers (11%) experienced 1 or more episodes of a dental infection prior to transplantation that necessitated cancellation or postponement of the surgery (2, 4).

Aim

This article reviews main medical problems impacting dental treatment in liver transplantation candidates.

Review Results and Discussion

Oral health status in patients with liver disease

Several studies indicate that patients with chronic hepatitis have poor oral health resulting not only in a large number of extracted teeth, caries lesions, but also involve a presence of gingival inflammation and periodontal disease (4, 8, 9, 10, 11). According to research made by Guggenheimer et al. 48-55% of the patients from all age groups suffer gingivitis or any periodontal disease. VI. Panov and A. Krasteva assess the oral status of patients with chronic liver disease in Bulgaria. The authors reveal that the patients have an increased number of decayed and missing teeth, poor oral hygiene and presence of gingival inflammation resulting in elevated value of Papilla Bleeding Index (PBI), Debris Index (DI) and Calculus Index (CI).

The same findings are mentioned by J. Guggenheimer and al. who establish that the presence of 2 or more carious teeth and/or 2 or more teeth that are mobile due to periodontal disease are indicators of severe dental disease as well as neglect of oral health (4).

A. Anand et al., and G. Novacek et al. report that oral hygiene, dental care, and periodontal parameters are worse and the number of teeth requiring treatment is higher in hepatitis patients with or without cirrhosis than in healthy subjects (9, 11).

P. Barbero et al. describe the dental status of 80 transplant recipients. Very poor dental hygiene is found in 85% of the patients while 45% were affected by advanced periodontal disease and 12% by chronic gingivitis. Dental caries is observed in 67% while in 20% of cases endodontic periapical lesions are found. Indicated dental care consists in 87% of cases in dental hygiene instructions, in 85% in scaling and root planing, in 63% in conservative restorations and in 40% in endodontic treatments (10).

Paulo Sérgio da Silva Santos et al. review pre-liver transplant recipients. Fifty invasive dental procedures are carried out on the 33 patients. Three of them are subjected to basic periodontal treatment and 47 are subjected to multiple or simple extractions. Three surgical procedures result in postoperative complications (12).

The conclusion of the presented studies is that the monitoring of oral health by dentists before transplantation and the achievement of specific protocols of prophylaxis are helpful in the prevention of complications after transplantation in these patients. The authors mention that the main concern before the transplantation is to eliminate oral foci of infection, such as those of periapical and periodontal origin (1, 4, 13).

Managing the oral health of patients prior to liver transplantation

Managing of the oral health before organ transplantation includes several factors that must be considered (14, 15, 16, 17, 18, 19):

- Dental focus of infection
- Oral source of infection (periodontal disease, mucosal lesions, bacterial and fungal infections etc)
- Oral manifestations in transplant patients
- Bleeding problems
- Antibiotic prophylaxis
- General medical conditions

Dental focus (odontogenic focus, disturbance field) of infection

Oral focus (disturbance field) on one side may cause a disease, but on other side it can prevent or delay the treatment of another disease by blocking basic vital functions (20). The most common complication during organ transplantations is the transplanted organ rejection within the first 4 months of transplantation immunosuppressive drug therapy.

Therefore oral and dental foci of infection should be managed radically if they are present, especially in medically compromised patients (14, 15, 16).

Paulo Sérgio da Silva Santos et al. describe the tooth extraction criteria in patients for liver transplantation: presence of residual roots; extensive carious lesions with partial crown destruction and risk of pulpal involvement; teeth with periapical lesions; semi-erupted teeth; teeth with periodontal involvement; as well as the capacity and interest of the patient in caring for and maintaining oral hygiene (21).

Oral source of infection

Miller, in "The Human Mouth as a focus of Infection" proposed a role for oral microorganisms in the development of a variety of disease in sites remote from the oral cavity (18).

Oral microbial flora is rich and unique; 300 or more different microbial species live in dental plaque, oral mucosa, gingival pockets and tongue.

Infections from dental foci are opportunistic infections from normal flora, where few bacteria dominate (aerobic and anaerobic gram-positive streptococci, anaerobic gram-negative rods e.g. Prevotella and fusobacterium species) (19, 22). Spreading of the infection from dental foci depends on: bacterial

virulence; host factors; the localization of the infection (local, general, distant) and risk for distant infection is higher in patients with systemic factors e. g. blood malignancies, autoimmune diseases, and immunosuppressive treatment (22, 23).

Oral infections, especially periodontitis, have been found to be a risk factor for several systemic diseases such as diabetes mellitus, cardiovascular disease, respiratory disease and preterm pregnancy with low birth weight (20).

If the pre-transplant patients have periodontal disease the dental recommendation is to treat it accurately before liver transplantation. The periodontal treatment consists in scaling and root planing divided into several sections, starting from the supra-gingival area, gingival and subgingival level for cases of mild to moderate periodontitis, and prescription of 5% tranexamic acid mouthwash rinse three times a day for 7 days (21).

Candidiasis, which may arise from colonization in the oropharynx, can be a significant source of infection in liver transplant recipients. Guggenheimer identifies 17 liver transplant candidates with oral candidal lesions. All 17 patients have risk factors for candidiasis, including symptoms of xerostomia or diuretic therapy, and 15 of them have a denture or are smokers. Diabetes is another contributing factor to candidal overgrowth (4).

Although bacteria are the main cause of sialadenitis, viruses such as HCV have been implicated as causes of sialadenitis associated with xerostomia (24).

Dental treatment, including the elimination of oral and mucosal infection foci, is essential for transplant patients during both preparation and post-surgery periods; patients should be under constant dental care and undergo mycological tests, especially in the first months. Oral-source infections are a potential threat to transplant candidates because oral diseases tend to be more severe if left untreated in people who have received transplants (12).

Oral manifestations in transplant patients

Manifestations of a reduction in saliva are found in 56% of the liver transplant candidates (LTCs). The management of ascites and/or edema, frequent complications of cirrhosis, may require the use of diuretic agents that can reduce saliva production. Hyposalivation in turn, promotes the deposition and retention of dental plaque. Guggenheimer mentions that 70% of the liver transplant candidates are taking 1 or more diuretic agents, and this is significantly associated with the presence of dental plaque (4).

Liver transplant recipients have a high risk of developing squamous cell carcinoma of the upper digestive tract, which is also associated with prolonged use of immunosuppressant drugs, but it is primarily attributed to smoking (4, 12). Also a greater predisposition to epithelial dysplasia and carcinoma of the lip has been observed and Kaposi's sarcoma in areas of gingival hyperplasia induced by treatment with cyclosporine (25). These conditions require special care when monitoring these patients in the post-transplant period.

As a result of the long term immunosuppressive therapy the patients' immune response is reduced, which makes them more susceptible to developing infections: fungal, bacterial and viral infections. There is an

increased prevalence of oral candidiasis and fungal infection has the highest degree of mortality rate, compared to bacterial and viral ones (25).

Several types of the human herpes virus could be found in transplant patients: cytomegalovirus is common in the first months after transplant; Epstein-Barr virus with hairy leukoplakia; herpes simplex virus, varicella-zoster virus and human herpesvirus-8. All of these viruses may display oral manifestations: Epstein-Barr virus is associated with hairy leukoplakia, herpes simplex virus is associated with aphthae, human herpesvirus-8 with Kaposi's sarcoma, varicella-zoster virus (25, 26).

Another side effect of the use of cyclosporine is gingival hyperplasia, which usually interferes with the patient's oral hygiene, leading to an increased susceptibility to infections, caries and periodontal disease (25).

Bleeding problems

Several factors can cause bleeding problems in organ transplant candidates, such as organ dysfunctions or their medications. Many may cause anticoagulation, and some may have a decreased platelet count. Patients with end-stage liver disease may have excessive bleeding because the liver is no longer producing sufficient amounts of clotting factors. Before treatment, assess the patient's bleeding potential with the appropriate laboratory tests and take precautions to limit bleeding (27) (Table 1).

Table 1. Blood tests and their regular values

Tests	Normal values
INR	0,9- 1,1
Platelet count	150 000-400 000/mm ³ <50 000mm ³ - bleeding
Bleeding time	1-3 min
Prothrombin time	11-15 sec
Thromboplastin time	25-35 sec
Thrombin time	15-20 sec

In cases with patients suffering from liver disease and awaiting liver transplantation (2, 4, 27) when dental treatment is indicated: the first step is consultation with the patient's gastroenterologist about whether antifibrinolytic drugs, vitamin K, fresh frozen plasma, or other interventions are appropriate. The physician may decide to temporarily decrease the patient's level of anticoagulation before extensive dental surgeries. Some patients are only suitable for surgery in a hospital setting. Practical pieces of advice to the dentist are: to use aggressive suctioning techniques when performing extractions or other invasive procedures to prevent the patient from swallowing blood and manage bleeding sites with careful packing and suturing techniques. In a very small number of patients with advanced liver disease, swallowed blood may increase risk for hepatic coma. Patients with liver failure from any cause are difficult to evaluate from the standpoint of risk for oral bleeding (4, 25)

Knowing the compromised general condition of the patients for liver transplantation, it is recommended: Before any surgical dental manipulation for some laboratory tests to be performed, characterizing general status of the patients and providing the possibility to assess the condition and to decide whether additional measures are required. Usually pre-operative assessment should include bleeding time (BT), hematocrit, total blood count (TBC), differential blood count (DBC), platelet count, partial thromboplastin time (PTT) and INR (International Normalized Ratio) used especially for assessing MELD (Model for End-Stage Liver Disease) value (27, 28).

There are various systemic methods that can be used to help compensate for the coagulopathies seen in these patients and decrease the risk of prolonged bleeding from invasive dental procedures. Vitamin K (at doses of 10 mg IM) corrects hypoprothrombinemia. Fresh frozen plasma will lower the PT, and platelet transfusion addresses both quantitative and qualitative platelet defects. In the case of more significant coagulopathies the patient should be observed postoperatively in hospital (21, 28).

In patients with mild to moderate hemostatic impairment, (i.e., INR not greater than 3.5, or a platelet count not less than 50×10^9 L) careful surgical technique, including an attempt at obtaining primary wound closure and use of local hemostatic measures will usually suffice. The use of absorbable hemostatic materials improves clot formation and stability (21).

If the platelet count is less than $50.000/\text{mm}^3$, the patient should be transfused with fresh plasma. After treatment, it is obligatory to use local hemostatic measures (25).

Antibiotic prophylaxis

Bacterial infections like dentoalveolar abscess, dental caries and periodontal abscesses, purulent periodontitis, severe gingivitis, and aggressive periodontal disease need proper culture and sensitivity tests and antibiotic prophylaxis (29). Usually selective antibiotic should be prescribed to the patient before and after dental treatment to prevent systemic infection (3).

D. Tong (30) similarly separates dental procedures into ones containing different degrees of risk of bacteremia occurrence (Table 2).

Table 2. Dental procedures requiring antibiotic prophylaxis for patients under risk

Dental procedures requiring antibiotic prophylaxis for patients under risk - High risk category	
<ul style="list-style-type: none"> ▪ Tooth extraction ▪ Periodontal procedure that includes surgery ▪ Ultrasound scaling ▪ Root probing and planing ▪ Implant placing and tooth reimplantation ▪ Endodontic instrumentation or surgery beyond root apex 	<ul style="list-style-type: none"> ▪ Subgingival application of antibiotic fibers and bands ▪ Initial placing of orthodontic rings but not brackets ▪ Intraligamentary local anesthesia ▪ Preventive cleaning of teeth or implants with expected bleeding

Table 3. Dental procedures that do not require antibiotic prophylactics for patients under risk

Dental Procedures where antibiotic prophylaxis is not needed	
<ul style="list-style-type: none"> ▪ Dental restorations with or without retraction cord ▪ Local anesthesia (excluding intraligamentary) ▪ Intracanal endodontic procedures after placing and build-ups ▪ Rubber dam pacing ▪ Post-operative suture removal 	<ul style="list-style-type: none"> ▪ Placement of orthodontic and prosthetic constructions ▪ Taking of dental impressions ▪ Teeth fluoridation ▪ Radiographs ▪ Adjustment of orthodontic constructions ▪ Replacement of milk teeth

Odontogenic bacteremia occurs in 100% of the cases of routine tooth extraction and in 55% of the cases following wisdom tooth extraction. In cases of periodontium and endodontic treatment – in 17 to 100% of patients. Oral bacteria cultivated from the blood circulation of patients subject to that type of surgery may include general parodontopathogens such as *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis* and *Bacterioides forsythus*. The gram-positive streptococcus *viridans* is of the greatest significance (22, 31).

The choice of antibiotic is better to be consulted with the patient's physician.

It is proven that there is a chance of hematogenous spread of oral infections to the brain, heart, lungs, kidneys and knee joints. Odontogenic bacteriemia is usually short-lived. Few bacteria can be cultivated from blood ten minutes after invasive dental treatment. Patients having chronic dental infections, however, may suffer from frequent or persistent bacteremia that could become active and trigger acute and chronic inflammations in other organs (18, 19).

Some literary sources (16, 28) contain descriptions of febrile conditions of unclear etiology following transplantation surgery. The lack of precise diagnosis also results in inappropriate treatment related to the prescription of unnecessary antibiotic consumption. A possible cause to be found in the oral cavity, for example asymptomatic periodontal changes, impacted and semi-impacted wisdom teeth, is very often neglected. J. Guggenheimer (5) has expressed an opinion that it is necessary to look back to the link between oral and systemic diseases and conditions.

General Medical problems

Patients preparing to undergo organ transplantation usually take multiple medications. These include anticoagulants, beta blockers, calcium channel blockers, diuretics, and others. The dentist must be aware of the side effects of these medications, which range from xerostomia and gingival hyperplasia to orthostatic hypotension and hyperglycemia, and their interactions with drugs you might prescribe (4, 5).

On the other hand many medications commonly used in dental practice, including NSAIDs and some antimicrobials, are metabolized by these organs and are not removed from circulation as quickly in patients with markedly reduced kidney or liver function. Prior to dental treatment, it is recommended to decide with the patient's physician on appropriate drug selection, dosage, and administration intervals (2, 3, 5).

Patients with end-stage organ failure usually have other major medical conditions (diabetes and/or significant pulmonary or heart disease, etc). The dentist must carefully review the patient's medical history to determine what additional treatment considerations the patient may need (20).

Dental deliberation for liver transplant candidates

Before liver transplant the dentist must be careful with the use of certain drugs (25, 29, 32)

1. Local anesthetics (lidocaine, prilocaine, mepivacaine and bupivacaine) can be used safely when the total dose of 7 mg/kg is not exceeded and when combined with epinephrine.
2. Analgesics: paracetamol should not be used on a regular basis (no more than two weeks) and must not exceed 2-2.5 g per 24h (with 4g per 24h max dose). Ibuprofen and aspirin should be avoided because they have a significant hepatic metabolism. It is preferable to use morphine as a narcotic analgesic rather than meperidine and codeine, because morphine has extra-hepatic metabolism.
3. Sedatives (diazepam, lorazepam and midazolam): these drugs can be used safely if we reduce the dose and if we increase dosing intervals between medications
4. Antibiotics (clindamycin, metronidazole and vancomycin): instead of these antibiotics we should use beta-lactam antibiotics (25).

Table 4. Dental drugs metabolized primary by the liver (32)

Local anesthetics (appear safe for use during liver disease when used in appropriate amounts)
Lidocaine Mepivacaine Prilocaine Bupivacaine
Anelgesics
Aspirin* Codein** Ibuprofen* Acetaminophen
Sedatives
Diazepam** Barbiturates **
Antibiotics
Ampicillin Tetracycline Vancomycin***

Legend:

* **reduced** dose or avoid if severe liver disease (active hepatitis and cirrhosis) or hemostatic abnormalities present

** **highly-reduced** dose or avoid if severe liver disease (active hepatitis and cirrhosis) or encephalopathy is present, or taken with alcohol

*** **avoid** if severe liver disease (active hepatitis and cirrhosis) presents

Conclusion

With the increased number of transplantations worldwide, the field of progress expands rapidly, demanding new treatment approaches and evaluation of old ones. A dentist needs vast knowledge in the field of general medicine to be able to minimize adverse outcomes secondary to the provision of oral health.

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