

2016 Liver Transplantation: Global view

Selective intestinal decontamination for the prevention of early bacterial infections after liver transplantation

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Abstract

Bacterial infection in the first month after liver transplantation is a frequent complication that poses a serious risk for liver transplant recipients as contributes substantially to increased length of hospitalization and hospital costs being a leading cause of death in this period. Most of these infections are caused by gram-negative bacilli, although gram-positive infections, especially *Enterococcus* sp. constitute an emerging infectious problem. This high rate of early postoperative infections after liver transplant has generated interest in exploring various prophylactic approaches to surmount this problem. One of these approaches is selective intestinal decontamination (SID). SID is a prophylactic strategy that consists of the administration of antimicrobials with limited anaerobic activity in order to reduce the burden of aerobic gram-negative bacteria and/or yeast in the intestinal tract and so prevent infections caused by these organisms. The majority of studies carried out to date have found SID to be effective in the reduction of gram-negative infection, but the effect on overall infection is limited due to a higher number of infection episodes by pathogenic enterococci and coagulase-negative staphylococci. However, difficulties in general extrapolation of the favorable results obtained in specific studies together with the potential risk of selection of multiresistant microorganisms has conditioned controversy about the routinely application of these strategies in liver transplant recipients.

Key words: Selective intestinal decontamination; Liver transplant; Infection; Gram-negative bacterial infection; Gram-positive bacterial infection; Multiresistant

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Core tip: Liver transplantation has become the treatment of choice for many liver diseases. It is currently a routine procedure but is still associated with significant morbidity being infectious complications the leading cause of death. Selective intestinal decontamination (SID) is a prophylactic strategy that consists of the administration of non-absorbable or systemic antibiotics with scarce anaerobic activity in order to prevent or minimize the impact of endogenous infections by potentially pathogenic microorganisms. In this review, we focus on the knowledge regarding the current role of SID in liver transplant recipients. Multiple studies have evaluated the role of SID in the critically ill patient, and several observational studies, randomized clinical trials and a meta-analysis have focused in liver transplantation. Our aim is to consolidate the current literature to better outline the impact of SID in the prevention of infections in this setting.

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INTRODUCTION

Since 1963, when Starzl *et al.*^[1] performed the first successful liver transplantation, the outcomes and long-term survival rates after liver transplantation have significantly improved over the last 5 decades. Major advances in transplantation biology, organ procurement and preservation, techniques of surgical implantation, immunosuppressive therapy and the prevention and management of infection have made liver transplantation the treatment of choice in many liver diseases^[2-5]. Although long-term survival rates have been currently improved^[6], this procedure it is still associated with significant morbidity, being infection one of the most feared complications.

Liver transplant patients are highly vulnerable to bacterial infection, particularly due to gram-negative organisms. It is believed that most of these infections are endogenous and arise from aerobic gram-negative bacteria and yeasts that have previously colonized the oropharynx, stomach, and bowel^[7]. This has led to the development of selective intestinal decontamination.

SID aim to eradicate potential pathogenic microorganisms (PPM) from the digestive tract, especially aerobic gram-negative bacilli (AGNB), but also *Staphylococcus aureus*, *Enterococcus* and yeasts, in order to prevent infections in patients at high risk of infection.

In general, the target of SID is to prevent or eradicate the state of gastrointestinal carrier by PPM keeping other microbial commensal flora as intact as possible since this it is assumed to have an important role

in the resistance to colonization by PPM. The final endpoint of this strategy should be reduction of mortality and morbidity associated with infection in these high-risk patients.

ABNORMAL COLONIZATION OF THE GASTROINTESTINAL FLORA AND OROPHARYNGEAL

After the introduction of antibacterial agents it has been postulated that the usual gastrointestinal and oropharyngeal commensal flora (mainly anaerobic flora) has an important role in regulating the proliferation of flora that includes aerobic PPM. Anaerobic antibiotics secreted inside the colon lumen can exert a suppressive effect on endogenous commensal flora, with consequent overgrowth of *S. aureus*, AGNB and, as recently stated, microorganisms with lower pathogenicity as enterococci, including *E. faecium* and vancomycin-resistant *Enterococcus*^[8,9].

Healthy mammals are able to eliminate very high concentrations of gram-negative bacilli (including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* y *Enterobacter cloacae*) contaminating the water they drink^[10]. The concept of colonization resistance has been defined through experimental animal models as the amount of inoculated bacteria in the colon necessary for converting in carriers of abnormal flora at least 50% of studied animals^[10].

The use of antibacterials disturbing protective commensal flora favors overgrowth of abnormal flora in the gastrointestinal tract^[11]. Although there are differences in the ability of different antibiotics to select potentially PPM, none of the currently available antibiotics are completely safe in this regard^[12]. Antibacterials with higher bactericidal activity against anaerobic flora are more prone to eradicate bacterial flora (*i.e.*, treatment with amoxicillin is associated with higher disruption of colonic flora than cephalosporins). This effect is more relevant with broad spectrum beta-lactams as amoxicillin-clavulanate, piperacillin-tazobactam and ceftriaxone. In contrast, aminoglycosides have minimal effect on the gastrointestinal commensal flora. Despite its low anaerobic activity, norfloxacin, ciprofloxacin and levofloxacin favor the overgrowth of yeast by eliminating aerobic flora and, therefore, decreasing oxygen consumption generating an unfavorable microclimate for the growth of anaerobic flora^[13].

Some underlying diseases have an evident influence on the ease for developing disorders in bacterial flora. Higher rates of oropharyngeal colonization and/or gastrointestinal by AGNB have been reported in patients with diabetes, alcoholism, chronic obstructive pulmonary disease or liver disease^[7].

In patients admitted to intensive care units (ICUs) a high proportion of abnormal colonization by AGNB ranging 30%-50% is observed, depending on the severity of patients^[14-16]. It is assumed that most of

the patients admitted to the ICU develop abnormal colonization during the first week of admission^[17]. Other factors that have been implicated with abnormal resistance to colonization in these patients are: (1) Anatomical integrity of the mucosa; (2) Conservation of pH in saliva and stomach; (3) Conservation of motility through the masticatory act, swallowing and peristalsis; (4) Presence of immunoglobulin A in the mucous membranes; and (5) Conservation of usual commensal flora in the mucous, mainly anaerobic flora.

SELECTIVE INTESTINAL DECONTAMINATION

The first description of the use of antibiotics to eliminate abnormal oropharyngeal and gastrointestinal flora dates back to the early 80's and initially consisted in the enteral administration of non-absorbable antibiotics (polymyxin and tobramycin) which eliminated colonization by AGNB without significantly affecting the normal commensal anaerobic flora, coining the concept of selective intestinal decontamination (SID)^[18]. It was subsequently shown that the addition of amphotericin B or nystatin allowed furthermore better control of the overgrowth of yeast without affecting the ecology of the patient^[12]. Other studies have shown that SID in oropharyngeal and intestine was able to control migration and translocation of the PPM at the lower respiratory tract and even in blood^[19,20]. This effect has been demonstrated particularly beneficial in critically ill patients as they present dysfunction of all the mechanisms of defense against abnormal colonization of the mucous membranes. Topical antibiotics against gram positive have also been used, mainly against oxacillin-resistant *S. aureus* in paste or gel formulations^[21].

Two forms of decontamination are currently globally distinguished: (1) Selective oropharyngeal decontamination (SOD) with non-absorbable topical antibiotics as a paste, gel or soluble tablets in the oropharynx^[22,23]. With the application of topical antibiotics in the oropharynx adequate eradication is achieved in about three days. Mouthwashes or oropharyngeal spray applications appear unsuitable due to insufficient contact time of the antibiotic with colonized mucosa; and (2) Gastrointestinal selective decontamination (SID) either with topical antibiotics in suspension formulations^[24,25] or administration of systemic antibiotics. Compared with oropharyngeal application, the time required for topical antibiotics in the intestine to achieve the eradication effect is more variable since it depends on patient peristalsis, being generally longer (about 7 d)^[26]. The most widely used systemic antibiotics for SID are short courses of 3-4 d of broad-spectrum antibiotics (mainly third generation cephalosporins) or prolonged administration antibiotics with little anaerobic activity such as quinolones^[27,28].

SELECTIVE INTESTINAL DECONTAMINATION IN THE LIVER TRANSPLANTATION

In liver transplantation, one of the main complications is bacterial infection, especially by gram-negative organisms. Their frequency varies between 20% and 80%. They contribute substantially to increase hospital stay, as well as hospital costs and are the leading cause of death in this population^[29-31]. Most of these infections occur in the first month after transplantation^[32] and especially during their stay in the ICU^[33]. As mentioned before, it is believed that most of these infections come from the gastrointestinal tract colonization by bacteria and fungi^[7].

Multiple studies have evaluated the role of selective intestinal decontamination in the critically ill patient, including more than 40 prospective randomized trials, with clinical benefits summarized in several meta-analyses^[24,34-40]. This intervention in intensive care units has repeatedly shown reductions in hospital-acquired infection rates (mostly in ventilator-associated pneumonia), and even reductions in overall mortality in some of these studies^[24,36-42]. However, SID remains controversial because of uncertainty regarding its net benefit and concerns about the potential promotion of the emergence of antimicrobial resistance. In a recent meta-analysis no evidence for increased colonization or infection with antimicrobial-resistant bacteria in patients receiving selective digestive decontamination or selective oropharyngeal decontamination could be concluded^[43]. Although there are robust data supporting the effectiveness of different forms of SD controversy persists about the benefit of SID and is extensive to the liver transplant population.

SID in liver transplant patients was introduced by Wiesner *et al.*^[44] in 1988 as a prophylactic strategy against infection. In this study, the incidence of infection following transplantation was markedly reduced by 50%. These investigators postulated that liver transplant recipients constitute a subset of patients that could specially benefit from SID prophylaxis. The fact is that, LTRs make up a relatively homogeneous group of critical care patients with a larger a priori chance of developing infections in comparison with mixed patients in intensive care; therefore, they theoretically should be optimal candidates for SID^[7,44].

Several observational studies^[44-49], randomized clinical trials (RCTs)^[50,51] and a meta-analysis^[52] of SID in liver transplantation have suggested a decrease in post-liver transplantation infection rates with SID, however, other studies have reported no benefit^[28,53-55] (Tables 1 and 2).

Gorensek *et al.*^[47] in a cohort study showed that selective bowel decontamination with a combination of norfloxacin and nystatin was well tolerated and highly

Table 1 Characteristics of randomized trials evaluating selective intestinal decontamination in liver transplant

Ref.	Type of study	SID regimen	Treatment perioperative (48 h)	Patients (n)		Patients with infection, n (%)		Period of observation posttransplantation (d)
				SID	Control	SID	Control	
Bion <i>et al</i> ^[50] , 1994	Randomized trial not placebo controlled	Tobramycin, amphotericin and polymyxin B for 5-15 d posttransplantation	Cefotaxime and ampicillin	21	31	3 (14.3)	12 (38.7)	15 d or until hospital discharge
Arnow <i>et al</i> ^[51] , 1996	Randomized trial not placebo controlled	Gentamicin, polymyxin and nystatin orally for 21 d posttransplantation	Cefotaxime and ampicillin	36	33	14 (38.9)	14 (42.4)	28
Hellinger <i>et al</i> ^[53] , 2002	Randomized placebo-controlled trial	Gentamicin, polymyxin E and nystatin 4 x/d for 21 d posttransplantation	Ceftazoxime	37	43	12 (32.4)	12 (28.9)	60
Zwaveling <i>et al</i> ^[28] , 2002	Randomized placebo-controlled trial	Norfloxacin, colistin,tobramycin and amphotericin B	Cefotaxime and tobramycin	29	29	22 (75.9)	25 (86.2)	30

SID: Selective intestinal decontamination.

Table 2 Characteristics of observational studies evaluating selective intestinal decontamination in liver transplant

Ref.	Type of study	SID regimen	Other antibiotics	Patients (n)		Patients with infection, n (%)		Period of observation posttransplantation (d)
				SID	Control	SID	Control	
Gorenssek <i>et al</i> ^[47] , 1993	Prospective nonrandomized study with historical control	Norfloxacin and nistatin. Oropharyngeal paste (polymyxin, gentamicin, nystatin)	Metronidazole and Third-generation cephalosporins for 5 d	17	34	1 (5.9) ¹	18 (52.9) ¹	30
San-Juan <i>et al</i> ^[54] , 2011	Prospective cohort study	Fluoroquinolones (norfloxacin or ciprofloxacin) 7 d	First- or second- or third generation cephalosporins, or antipseudomonal beta-lactams or glycopeptides	415	595	110 (26.5)	156 (26.21)	30
Sun <i>et al</i> ^[48] , 2012	Retrospective uncontrolled study	Rifaximin	Cefotaxime and ampicillin for 24 h	30	80	7 (23.3)	23 (28.7)	90
Katchman <i>et al</i> ^[55] , 2014	Retrospective cohort study	Colitin, gentamicin and nystatin	Cefazolin and metronidazole for 4 d	111	37	47 (42.7)	18 (46.8)	30

¹Only fungal and gram-negative infections reported. SID: Selective intestinal decontamination.

effective. A trend toward better short-term survival in patients receiving SID was also found, but long-term mortality was not different among the treatment and control groups.

Subsequently, Bion *et al*^[50] in a RCT including 52 patients, demonstrated a lower incidence of infections in patients receiving SID compared with the placebo group. The SID regimen was started at the time a donor organ was identified and was extended for 15 d or until hospital discharge.

In 1996, Arnow *et al*^[51] reported lack of benefit of SID in a clinical trial including 69 patients, although in the subgroup of patients receiving SID for 3 or more days before transplantation it was reported a lower incidence of infection due to aerobic gram-negative bacilli (0% vs 21%, *P* < 0.05) which included intra-abdominal, surgical site, respiratory tract and bloodstream infections.

In a placebo-controlled, double-blind RCT of 80 patients that were followed for the first 60 d after transplant and in which more than 85% of patients received the SID regimen for more than 3 d preoperatively, Hellinger *et al*^[53] reported that there were no statistically significant differences between both groups with regard to infection or mortality.

Zwaveling *et al.*^[28] in a placebo-controlled RCT including 58 patients (with a bacterial or fungal infection rate in the first month posttransplantation of 85% in both groups), no significant protective effects against the development of bacterial infections were found between SID and placebo group. However, the type of microorganism causing infection differed: infections due to Gram-negative bacilli and yeasts were significantly reduced in the group treated with SID. Conversely, infections due to Gram-positive cocci were more prominent among patients undergoing SID, although the difference did not reach statistical significance.

In a systematic review and meta-analysis by Safdar *et al.*^[52] 14 studies analyzing SID in liver transplantation were included (six were uncontrolled studies, four were controlled studies using historical controls and four were RCTs). Only the four RCTs were included in the meta-analysis. Overall, the controlled observational studies showed a reduction in infection with SID (range of RR in treatment groups, 0.09-0.62). Additionally, meta-analysis showed that SID significantly reduced the incidence of infections caused by gram-negative bacteria in the clinical forms of pneumonia and septicemia. However, no reduction was shown in the overall incidence of infection due to an increased incidence of enterococcal infections in patients receiving SID. They did not separately analyze the impact of invasive fungal infections, perhaps due to the low event rate. Neither was evaluated the difference in mortality with the use of SID since the sample size was insufficient.

A further multicenter observational study conducted by San-Juan *et al.*^[54] failed to demonstrate differences in the incidence of early infections between LTR receiving fluoroquinolones for SID (FQ-SID) and those who did not, although SID was related with a relative increase of infections due to multi-resistant gram-negative bacilli suggesting a deleterious effect of SID in terms of selection of antimicrobial resistance.

Rifaximin has also recently been evaluated as SID with non reabsorbable antibiotics in LTR by Sun *et al.*^[49] in an observational study in which the rate of infections in the first 90 d post-transplant was compared between liver transplant recipients who did and did not receive rifaximin for hepatic encephalopathy while being on the waiting list. They found a protective effect of rifaximin against post-transplant infections in the more severely ill liver transplant recipients with no increase in multidrug-resistant bacterial infections.

Finally, a recent observational study failed to demonstrate a reduction in the incidence of early infection by the use of SID in living-donor liver transplant recipients although the application of SID was not related with an ecological impact in terms of the emergence of bacterial resistance^[55].

Several study analyzed *C. difficile* toxin-related diarrhea and it was not recognized any more frequently in patients treated with SID^[49,52,53,55]. Even in

studies where selective bowel decontamination was rifaximin, the risk of *C. difficile* colitis was lower but not statistically different in the treatment group^[49].

The important methodological heterogeneity of all these studies could partially explain the differences in the obtained results. Other crucial aspects that limit interpretation of the results reside on the high variability in the SID regimens used in the different studies either in the type of antimicrobials, the timing of administration (before or after transplantation) and the duration of the treatment.

Nevertheless, available data so far suggest that while the use of SID can be related to a relative decrease of specific infections such as infections due to enterobacteria, it does not seem to globally reduce infection and mortality rates^[28,53], although some experts continue to recommend combined SID strategies (systemic antibiotherapy and topical enteral antibiotherapy) given the high incidence of early bacterial infection in this population and the increased severity of infections caused by *Enterobacteriaceae*, which seem to be prevented to some extent with SID^[7,44].

On the other hand, these strategies seem to be safe as have not been found to promote selection of multiresistant microorganisms in the majority of RCTs evaluating this end point, although all these studies have been conducted in epidemiological contexts of low basal rates of multidrug resistance^[16,21,25,41]. Conversely, in other observational studies performed in areas with high rates of colonization or infection by gram-negative multiresistant^[56,57] or MRSA^[58] selection of these microorganisms have been particularly in relationship with the introduction of SID strategies.

Although the potential risk of selection of resistant microorganisms has conditioned reluctance of the scientific societies to recommend the SID as a preventive strategy, the fact is that whereas systemic administration of antibiotics as part of the SID presumably may favor the selection of microorganisms this deleterious effect is less plausible with the use of topical antibiotics, in which very high antibiotic concentrations are achieved therefore making the emergence of resistance more improbable. In fact, in the few studies of topical SID (oropharyngeal and/or intestinal) in which this problem has been specifically analyzed through directed colonization studies an ecological risk entailed by SID strategy could not be demonstrated^[41].

CONCLUSION

Current available data so far suggest that SID reduces the incidence of gram-negative and yeast infection at the expense of an increased incidence of infections due to some gram-positive microorganisms, generally with less pathogenicity and therefore causing less severe infections. However, none of the studies carried out to date has been able to detect a significant survival benefit probably due to limitations in their sample size.

Anyway, although pooled results trend to be favorable, methodological flaws present in the majority of the studies added to the potential risk of selection of multiresistant microorganisms have conditioned ongoing controversy about the routine use of these strategies. Because of these limitations in the studies conducted to date, randomized controlled studies evaluating SID strategies are needed, preferably analyzing non-absorbable antimicrobials or nonantibiotic products, such as the use of probiotics or prebiotics, which carry a theoretical lower ecological deleterious effect by the low risk for the selection of resistant strains.

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