Drugs and the Liver: High Risk Patients and Transplantation

Edited by

D. Galmarini
Institute of Surgical Researches and Transplantation, Ospedale Maggiore Policlinico di Milano, University of Milan, Milan, Italy

L.R. Fassati
Institute of Surgical Researches and Transplantation, Ospedale Maggiore Policlinico di Milano, University of Milan, Milan, Italy

R. Paoletti
Institute of Pharmacological Sciences, University of Milan, Milan, Italy

and

S. Sherlock
Royal Free Hospital School of Medicine, University of London, London, U.K.

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BACTEREMIA AFTER LIVER TRANSPLANTATION; FEW ISSUES IN SELECTION OF ANTIBIOTICS FOR TREATMENT AND PROPHYLAXIS

S. Kusne, M. Alessiani, M. Martin, J. Fung, T.E. Starzl

Infections after liver transplantation are still associated with significant morbidity and mortality. Bacterial infections account for up to 50% of such events according to various series. The majority of these infections are nosocomial and many of them are associated with technical surgical problems. Bacteremia represents "invasive" infection and knowing the common agents involved helps in selection of antibiotics for treatment and prophylaxis. Successful use of antibiotics requires familiarity with their characteristics, potential side effects and interactions with other medications.

COMMON BACTEREMIAS

In a previous study from our institution, we had a frequency of bacteremia of 26%, occurring after liver transplantation in 101 consecutive patients (1). All 33 bacterial isolates in that study are shown in table 1. Fifty one percent of episodes of bacteremia with a single isolate were due to gram negative enteric organisms, and only 27% to gram positive isolates. This is in contrast to what has been published by other centers that routinely use selective bowel decontamination in liver transplantation. In one study 81% of bacteremias were caused by gram positive organisms and only 6% by gram negatives (2). Anaerobes account for a very small portion of bacterial infections after liver transplantation in any center. This information is important for selection of empiric antibiotics in the septic patient. Empiric antibiotic coverage depends on the suspected source for bacteremia. For example, if cholangitis is suspected coverage should

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include gram negative enteric organisms and enterococci; if intravascular lines or wound infection is suspected staphylococcus coverage should be considered.

The most common source of bacteremia after liver transplantation is the abdomen and this is often related to surgical/or mechanical problems (surgical wounds, hepatic artery thrombosis and other vascular complications, biliary obstruction and leaks etc). Most bacteremias occur during the first two months after transplantation (primary or retransplantation), and in our original study 61% of thirty three bacteremias followed this rule.

SELECTION OF ANTIBIOTICS FOR PROPHYLAXIS

Perioperative antibiotic coverage for liver transplantation should include gram negative organisms and enterococci. In our institution we use cefotaxime or ceftizox in combination with ampicillin for the duration of 72 hours. Trimethoprim/sulfamethoxazole given for prevention of pneumocystis carinii pneumonia may also have an effect on prevention of bacterial infections. The routine use of selective bowel decontamination is practiced by some centers. The literature does not show clearly that there is an advantage to its use since: a. although infections caused by gram negative bacteria are low those caused by gram positive bacteria are higher, b. there is no difference in overall mortality and Intensive Care Unit stay, c. the emergence of resistant organisms is a possibility (3).

OTHER FACTORS IMPORTANT IN SELECTION OF ANTIBIOTICS

Cholangitis

It accounts for 6-10% of bacterial infections after transplantation and is associated with bacteremia in about 40%. Diagnosis is usually difficult due to the fact that biliary draining tubes (like T-tube) are often colonized with bacteria, inflammatory white cells are not easily recognized in bile and the latter is not always available for culture. Therefore empiric antibiotics should be started whenever there is clinical suspicion of bacterial cholangitis. The clinician should be familiar with the fact that some antibiotics do not penetrate well in bile (4). For example Imipenem/ Cilastatin has a very broad antibacterial coverage but penetrates bile very poorly, if at all. Cholangitis is usually associated with biliary obstruction which imply no penetration of antibiotics to bile, until obstruction is relieved. Some authors feel that serum concentration

of antibiotics is as important as biliary penetration. Although the most common antibiotics used in cholangitis are ampicillin or cephalosporins in combination with aminoglycoside, the ureido-penicillins (like mezlocillin, azlocillin and piperacillin) with or without aminoglycosides may have very important role because of their good biliary penetration.

Hepatotoxicity

Antibacterial agents prescribed after liver transplantation may be toxic to the new allograft. Medications prescribed for treatment and prevention of tuberculosis (like isoniazid, pyrazinamide and rifampin) may cause hepatitis. Hypersensitivity reactions with liver enzymes elevation can be seen with erythromycin and sulfonamides. SGOT elevation at times self limited can be seen with use of commonly prescribed antibiotics (like carbenicillin, cloxacillin, moxalactam etc.).

Bleeding

Some beta-lactam antibiotics may affect coagulation and cause bleeding. One mechanism which causes hypoprothrombinemia is probably through interference with vitamin k metabolism (5). This is described with cephalosporins that have Methyl-thio-tetrazole side chain (like cefamandole, moxalactam and cefoperazone). A second mechanism results in platelets dysfunction and is described with antibiotics like ticarcillin, piperacillin and mezlocillin. This is important to remember since these patients may have coagulation abnormalities secondary to liver disease.

Nephrotoxicity

The aminoglycosides are the main antibiotics to cause nephrotoxicity after liver transplantation. They usually damage the proximal tubules causing non-oliguric renal failure. This is more pronounced when an aminoglycoside is prescribed together with vancomycin. Some authors feel that there is increased risk of renal dysfunction due to interaction of liver disease and the aminoglycosides (6). Obviously when the clinician can choose non nephrotoxic antibiotic it is preferable, but in some infections (like enterococcus sepsis) there is no "other choice".

Interaction with other drugs

Before prescribing any antibiotics or anti-

microbials in patients after transplantation one has finally to consider possible interactions with other medications. The interactions of Cyclosporin (Cya) with antimicrobials were summarized by others (7). Through inhibition or induction of hepatic P-450 enzyme system some agents can increase and others can lower Cya levels. Erythromycin and ketoconazole can increase Cya level causing nephrotoxicity while rifampin can significantly lower Cya level leading to rejection of the allograft.

TABLE 1: All 33 bacteremia isolates that occurred in 101 consecutive liver transplant patients.

BACTERIA INVOLVED (No; %)	NUMBER EPISODES
Gram Negative Bacteremia (17; 51)	
Pseudomonas aeruginosa	7
Escherichia coli	4
Klebsiella pneumoniae	3
Citrobacter freundii	2
Enterobacter cloacae	1
Gram Neg./Pos. Bacteremia (4; 12)	
Gram Positive Bacteremia (9; 27)	
Enterococcus	4
Staphylococcus epidermidis	2
Staphylococcus aureus	1
Streptococcus bovis	1
Listeria monocytogenes	1
Anaerobic Bacteremia (3; 9)	
Bacteroides fragilis	2
Clostridia species	1

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