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Review

Antibiotics and the liver – A love-hate relationship

Debasish Das, Robert Lo, Adam Lawson, Andrew S. Austin, and Jan G. Freeman*

Digestive Diseases Centre, Derby Hospitals NHS Foundation Trust, Uttoxeter Road, Derby, DE22 3NE, UK

ABSTRACT

Antibiotic therapy is often an essential part of the management of hepatobiliary disease, and yet can cause significant hepatic morbidity and mortality. This review article examines the epidemiology and pathogenesis of antibiotic induced liver injury, and discusses the role of antibiotics in the treatment and prophylaxis of infectious diseases of the liver, both in patients with and without pre-existing liver disease.

KEYWORDS: antibiotics, drug-induced liver injury, drug metabolism, liver abscess, spontaneous bacterial peritonitis, variceal haemorrhage, hepatorenal syndrome

INTRODUCTION

Antibiotics have a significant role in the management of hepatobiliary disorders. Their place in the management plans of variceal bleeding, spontaneous bacterial peritonitis etc. is well established. However confusion often arises when patients present with acute or acute on chronic liver injury as they often have had antibiotics prescribed which themselves may cause the hepatotoxicity. Thus the liver has a love-hate relationship with antibiotics. The aim of this review is to put into perspective the relationship between the use of and the causation of hepatotxicity by antibiotics.

Antibiotic induced liver injury

Drug-Induced liver injury (DILI) accounts for 2% of jaundice in hospital inpatients, contributes up to 10% of all adverse drug reactions, and is the biggest contributor (46% related to paracetamol and 11% related to other DILI) to acute hepatic failure in western populations [1]. DILI is an uncommon adverse event with the majority of drugs (1 in 10 000 to 1 in 100 000 persons exposed), however most drugs have had reports linking them with drug induced liver injury and it is the commonest reason for post marketing drug withdrawal. Several studies point to antibiotics being responsible for between 12 to 15% of DILI [2-3], with co-amoxiclav being the most common offender. The other commonly prescribed antibiotics accounting for DILI are flucloxacillin [5, 6], minocycline, isoniazide [7], rifampicin [8], nitrofurantoin [9], trimethoprim-sulfamethoxazole [10], and several quinolones including ciprofloxacin, norfloxacin and trovafloxacin [11, 12].

The mechanisms of DILI are broadly classified into Type A and Type B, though as with all drugs, antibiotic-induced liver injury may have components of both.

Type A hepatotoxicity is dose dependent, predictable and generally due to a direct effect of the parent drug or reactive metabolite on the liver. Drug metabolism via the cytochrome P450 (CYP-450), glutathione mediated thiol and free-radical formation pathways like lipid peroxidation lead to the production of potentially hepatotoxic metabolites. Drug excretion pathways such as glucuronidation, N-acetyl transferase- mediated acetylation and glutathione-mediated glutathione conjugation also play an important role. Genetic polymorphism of these pathways plays a considerable role in the direct hepatotoxicity of drugs, including several antibiotics. Polymorphism of the CYP-450

*Corresponding author
j.freeman115@btinterenet.com

isoenzymes is increasingly implicated in direct drug induced toxicity due to variation in rate of oxidative metabolism of drugs. Genetic polymorphisms can impart a protective effect by slowing down oxidative metabolism, or alternatively increase susceptibility to hepatotoxicity through rapid metabolism into toxic metabolites. The metabolism of isoniazid,for example, is affected by polymorphism of the CYP-450 2E1 gene. CYP2E1 c1 / c1 homozygotes are more susceptible to isoniazid associated hepatotoxicity compared with c2 / c2 or c2 / c1 mutant genotypes [13, 14]. Genetic polymorphism in genes coding N-acetyltransferase (NAT2) is responsible for the phenotypic classification of individuals as either slow acetylators (homozygote for defective NAT2 alleles) or rapid acetylators (heterozygous or homozygous for wild-type NAT2). Slow acetylator status of NAT2 has been demonstrated to correlate with isoniazid hepatotoxicity [15, 16].

Type B hepatotoxicity is an idiosyncratic reaction and not related to dose or duration of therapy. It is typically immune-mediated and often associated with a generalised immune reaction encompassing fever, pruritus, arthropathy and eosinophilia. Antibodies are formed when the parent drug or an active metabolite acts as an antigen either directly or after binding with specific cellular proteins. Direct activation of normally quiescent autoreactive B lymphocytes is seen with some drugs during metabolism by the CYP-450 pathway. This can lead to release of anti-CYP-450 autoantibodies and result in an autoimmune hepatitis. There is considerable overlap of these pathways and often an initial direct hepatotoxicity predates the onset of immune-mediated hepatotoxicity. There is also emerging evidence that genetic polymorphism plays an important role in susceptibility to immune mediated hepatotoxicity. In the case of sulphonamides, genetic polymorphism of N-acetyl transferase results in a slow acetylator state, predisposing to immune-mediated hepatotoxicity and other adverse drug reactions [17]. Polymorphism in the HLA haplotype also plays a modulating role and an association between HLA DR6 and nitrofurantoin related hepatotoxicity [18], and HLA DRB*1501 and co-amoxiclav related hepatotoxicity [18] has been shown. Whatever the mechanism, the manifestation of antibiotic related hepatotoxicity is very variable and may range from a subclinical transaminitis to acute hepatic failure.

Classes of antibiotics and hepatotoxicity:

- Penicillins

Of the penicillins, co-amoxiclav is most commonly associated with hepatotoxicity, accounting for up to 14 % of cases of DILI in some series, with a frequency of up to 9.91 per 100 000 users [19]. Hepatotoxicity is more severe in the elderly and in those given the drug for more than ten days. The onset may vary between 7 to 90 days after starting therapy and in the majority manifests 1 to 4 weeks after stopping therapy. There are often systemic symptoms and eosinophilia. The histological appearance is of a cholangitis with an inflammatory infiltrate consisting of neutrophils, eosinophils and occasional granuloma formation. Perivenular bilirubinostasis with intracellular and intracanalicular bile plugs on biopsy has been reported [20]. A recent large prospective case series suggested that the type of hepatic injury varies according to the time from onset of therapy. Hepatocellular injury predominates in the first week, while cholestatic injury predominates at 2-3 weeks and mixed liver injury after the third week. There was a 7% probability of an unfavourable outcome (death, liver transplantation or persistent liver damage) in that series [4]. An association of HLA haplotype HLA DRB*1501 has been found with increased risk of hepatotoxicity with co-amoxiclav [20].

Amoxicillin itself is a less common cause of hepatotoxicity (3 cases per 100,000 users), and is usually well tolerated in those who have experienced DILI with co-amoxiclav. In rare instances it can cause cholestasis including vanishing bile duct syndrome [21].

Flucloxacillin is a frequently prescribed antibiotic and, therefore, results in several cases of DILI even though the frequency of adverse events per user is low. Females, the elderly and those on a prolonged course are more affected with symptoms appearing between 10 to 30 days after starting therapy. Clinical and, histological features and outcomes are similar to those seen with co-amoxiclav. Prolonged cholestasis with vanishing bile duct syndrome is occasionally seen and there

are reports of benefit from treatment with ursodeoxycholic acid [22].

- Cephalosporins

Cephalosporins are less frequently associated with hepatotoxicity than penicillins, but the clinicopathological pattern is similar [23]. Ceftriaxone use has been associated with biliary pseudolithiasis and though generally asymptomatic and reversible on cessation of therapy, there are reports of it leading to cholangitis and pancreatitis.

- Tetracyclines

Tetracycline and its derivatives are known to cause microvesicular hepatic steatosis in animal models, but steatosis in humans is usually mild. Clinically significant lesions are rare and are generally associated with high dose intravenous use, renal impairment and pregnancy. A Reye's like syndrome associated with renal failure, pancreatitis and often death has been reported with high dose intravenous tetracycline, as have a few cases of vanishing bile duct syndrome with both tetracycline and doxycycline [24, 25].

- Macrolides

Most macrolides are associated with hepatotoxicity, which can be immune mediated, cholestatic or mixed. The mechanism of immune activation is thought to be due to modification of cellular proteins by electrophilic intermediates of macrolide metabolism [26]. Most cases present within the first two weeks of therapy and is generally associated with a good prognosis following cessation of therapy. Rechallenge with the same macrolide leads to recurrence within 24 to 48 hours, but cross-reactivity is generally not seen. Erythromycin and telithromycin are more commonly associated with hepatotoxicity than clarithromycin and azithromycin.

- Sulphonamides

Sulphonamide therapy is associated with hepatotoxicity primarily in slow acetylators and may cause damage due to reactive hydroxylamines. The mechanism seems to be immune mediated and is associated with systemic symptoms. Liver biopsy may show hepatic granulomas and the picture is generally of mixed cholestatic and hepatitis type [27, 28].

- Quinolones

Ciprofloxacin and norfloxacin are commonly used in cirrhotic patients to reduce infections following gastrointestinal haemorrhage and in prophylaxis of spontaneous bacterial peritonitis. There are, however, reports of hepatotoxicity related to ciprofloxacin and other quinolones, including a large number of cases with trovafloxacin. The clinicopathological presentation is variable and includes asymptomatic transaminitis through to jaundice with vanishing bile duct syndrome [11, 12].

- Nitrofurantoín

Middle aged and elderly females are most susceptible to hepatotoxicity with nitrofurantoin, which may represent a prescribing bias for this drug. Hepatotoxicity generally occurs within five weeks of therapy, with the mechanism thought to involve immune system activation by a reactive metabolite. This is associated with systemic symptoms, eosinophilia and mixed hepatitic and cholestatic picture. Occasionally chronic hepatitis may develop including cirrhosis [9]. There are some reports of HLA DR2, HLA DRw6 and HLA B8 haplotypes predisposing to hepatotoxicity with nitrofurantoin [18].

- Isoniazid

Isoniazid causes hepatotoxicity in about 1% of patients treated and in 20% there is subclinical transaminitis, often representing hepatic adaptation [29]. The hepatitis is generally cytolytic in mechanism, without immunologic manifestation. The peak period of hepatotoxicity is during the second month of therapy and 80% of cases occur within six months of initiating treatment. The genetic polymorphism of acetylator status plays an important role in determining susceptibility to hepatotoxicity. Nausea and abdominal pain are evident early, while jaundice presents late. Coagulopathy, hypoalbuminaemia and hypoglycaemia signify a poor prognosis. Early cessation of therapy usually results in complete regression of hepatotoxicity, though this may take several weeks. Increasing age, alcohol abuse, concomitant use of other hepatotoxic drugs including rifampicin, active Hepatitis B infection, previous liver transplantation and malnutrition increase the risk

of hepatotoxicity. Coinfection of Hepatitis C and HIV increases the risk of hepatotoxicity with tuberculosis treatment by about 14 fold [30].

- Rifampicin

Rifampicin can cause a transient unconjugated hyperbilirubinaemia by competing with bilirubin uptake into hepatocytes. Conjugated hyper-bilirubinaemia may also arise due to rifampicin inhibiting the major bile salt exporter pump. Asymptomatic hyperbilirubinaemia may also result from dose-dependent competition with bilirubin for clearance at the sinusoidal membrane, or from impeded secretion at the canalicular level. Rifampicin on its own seldom causes hepatotoxicity but as an inducer of enzymes in the hepatocyte, it modulates toxicity of other drugs such as isoniazid and pyrazinamide. The risk of hepatotoxicity with isoniazid increases 5 to 8 fold when used in combination with Rifampicin and toxicity occurs earlier in treatment. Current guidelines recommend an evaluation of risk factors associated with higher toxicity and measurement of LFTs before embarking on treatment of Tuberculosis, with subsequent close monitoring on therapy [30].

Use of antibiotics in liver disease

Antibiotic use in liver disease can be for the complications of cirrhosis such as bleeding oesophageal varices and spontaneous bacterial peritonitis or primary infections of the liver such as liver abscess or cholangitis.

- Liver abscess

The dual blood supply of the liver and the sinusoidal architecture makes the liver prone to infection. The portal vein drains blood from the intestine, which may harbour a myriad of bacteria and parasites. During inflammatory processes involving the gut or when there is impairment of its mucosal integrity there may be increased transmucosal bacterial translocation, resulting in portal bacteraemia. Diverticulitis, appendicitis, enteroinvasive bacterial infections (E. *coli*, *Salmonella*), amoebiasis, active inflammatory bowel disease and chronic and acute ischaemic colitis are examples of situations in which portal bacteraemia may lead to liver abscesses. Retrograde infection from the biliary tree is the other leading cause of liver abscess. The development of antibiotics, better diagnostic and therapeutic radiological interventions and improved surgical management has dramatically improved the prognosis for patients with liver abscesses. Systemic antibiotic therapy remains the mainstay of therapy, with the need for prolonged courses of targeted antibiotics. The most commonly used antibiotic regimens combine a 3rd generation cephalosporin with either metronidazole or clindamycin to add anaerobic cover. Other antibiotics in common use are ciprofloxacin, amikacin, imipenem and carbapenem. The commonest organisms isolated are streptococcal species and gram-negative enteropathogens with anaerobic organisms isolated in almost 25% cases. Not uncommonly polymicrobial infections are noted. There is emerging evidence, however, of a rise in both drug resistant and atypical infections, especially in cases relating to IV drug abuse, immunosupression and following invasive procedures such as chemoembolisation of hepatic tumours [31]. Liver abscess with ESBL producing Klebsiella pneumoniae needing imipenem [32] and MRSA infection needing linezolid/ tygecycline/ clindamycin have been reported [33].

Abscesses >3 cm in diameter, multi-loculated abscesses, and treatment with antibiotics for less than four weeks, are associated with a high risk of treatment failure with antibiotics alone. Several studies have shown the need for combining antibiotics with radiologically guided aspiration, drainage or surgery (de-roofing or partial hepatectomy). In a recent report of 107 cases, abscesses < 3 cm were cured by antibiotic treatment alone in 100% cases. Uniloculated abscesses > 3 cm resolved in 83% cases with a combination of antibiotics and percutaneous drainage but for multiloculated abscesses this fell to 33%. Those large multiloculated abscesses treated with surgical therapy did not recur [34].

A recent population based study covering a 10 year period from 1994 to 2005 identified 17,787 hospital discharges with pyogenic liver abscess (PLA). This equated to an incidence of 3.6 per 100,000 population, with a year on year increase of 4.1%. In-hospital mortality was 5.6% with older age, type of health insurance and comorbidities such as cirrhosis,chronic renal failure and cancer

found to be associated with an increased mortality. Percutaneous aspiration was associated with a reduction in mortality, whereas surgical drainage and endoscopic retrograde cholangiopancreatography had no significant effect on mortality. The most commonly recorded bacterial infections were Streptococcus species (29.5%) and Escherichia coli (18.1%). Patients with bacteremia or septicemia had an increased risk of death [35].

- Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a severe complication of cirrhosis and carries a poor prognosis. Several factors have been associated with an increased risk of SBP, of which the most important are a low serum sodium level, low ascitic fluid total protein, and worsening hepatic failure as evidenced by an increased Model for End-Stage Liver Disease (MELD) score. In the past, SBP was associated with up to 90% mortality but with antibiotic treatment the mortality has been significantly reduced to about 20% [36].

The prevalence of SBP varies depending on the clinical setting. Cirrhotic patients undergoing large-volume paracentesis as an outpatient will have a prevalence between 0-0.5%, while between 10 to 30% of symptomatic cirrhotic patients admitted to hospital have SBP, with a mortality rate of 10% to 32.6% [36, 37]. The diagnosis of SBP is based on the presence of > 250 polymorph per mm^3 ascitic fluid, with or without positive bacterial culture. The technique of measuring ascitic fluid polymorph count is, however, highly operator dependent, time consuming and prone to giving false negative results due to *in vitro* degradation of the specimen if processing is delayed. Yield from ascitic fluid culture is low and often delays diagnosis. Gram staining of ascitic fluid is rarely helpful in making the diagnosis of SBP. Analysis of 796 ascitic fluid samples by Chinnock *et al.*, demonstrated Gram stained organisms in only 31 samples (3.9%; 95% confidence interval [CI] 2.6% to 5.4%). Gram stain had a sensitivity of 10%, specificity of 97.5%, positive predictive value of 48%, and negative predictive value of 81.3% in the detection of spontaneous bacterial peritonitis [38].

There is, therefore, a need to find alternative methods for diagnosing SBP, that can preferably be done at the bedside (near-patient testing) and give a rapid accurate result. Ascitic fluid lactoferrin is increased in SBP. A threshold of 242 ng/mL has a sensitivity and specificity of 95.5% and 97%, respectively, with an area under the receiver operating characteristic curve was 0.98 [39]. Rapid identification of bacterial DNA in ascitic fluid by microarray analysis can identify infection much earlier than conventional culture techniques, although the overall yield is similar [40]. In addition the detection of bacterial DNA in ascites, even without true SBP, is an independent poor prognostic factor in cirrhotic patients [41]. Several studies have evaluated the role of bedside reagent strips utilising leucocyte esterase reactivity with variable results. Though independently most of the studies seem to suggest a positive outcome, a recent critical review of nineteen studies found a low overall sensitivity and high rate of false negative results when each of the reagent strip types were compared to the results of cytobacteriological methods [42].

Traditionally intravenous 3rd generation Cephalosporins have been the standard therapy for SBP. Cefotaxime has been the most commonly used antibiotic due to its high penetration into ascitic fluid and its coverage of almost 95% of the flora isolated from ascitic fluid culture [43]. Previous studies had shown that a short 5 day course is as effective as longer courses [44] and that lower 2gm 6 hourly dosing was as effective as 2gm 12 hourly regimen [45]. More recent studies have reported a shift in the pattern of causative organisms and an increased resistance to cephalosporins [46]. A number of other antibiotics have been assessed as treatment options for SBP, including Co-amoxiclav [47], aminoglycosides [48], ciprofloxacin [49, 50] and ofloxacin [51]. A recent Cochrane review failed to find any evidence to suggest the superiority of any particular antibiotic regimen in the treatment of SBP, either in terms of therapeutic efficacy, duration and dosing of treatment or safety issues. This was mainly due to the heterogeneity of the studies available [52].

In an analysis of 41 culture-positive cases, the most commonly cultured pathogens were Escherichia coli and Enterococcus faecium. Antibiotic resistance was common with 33.3%,

38.6% and 45.2% of bacteria resistant to Cefotaxime, Co-amoxyclav and ciprofloxacin respectively. 64.4% of the isolates were resistant to one of the recommended first-line antibiotic regimens, and 24.4% of the isolates were resistant to all three [53]. Enterococcus is an emerging pathogen in SBP and is associated with a high degree of resistance to traditional antibiotics and increased in-hospital mortality as compared to non-enterococcal SBP [54]. It is, therefore, recommended that if there is no improvement in the clinical signs and symptoms of SBP after 48 hours of therapy then a repeat diagnostic tap should be undertaken. If there has not been a 25% reduction in the polymorph count from pre-treatment levels, then antibiotics should be changed accordingly.

Prevention of the first episode of SBP with long term antibiotic therapy is a much debated topic. [55] There is evidence to suggest that primary prophylaxis is effective in reducing the risk of SBP in a subgroup of cirrhotics with low protein ascites (<1.5 g/dL) and at least one of the following: serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, serum sodium ≤130 mEq/L or Child-Pugh ≥9 points with bilirubin ≥3 mg/dL demonstrated prevention of SBP as well as hepatorenal syndrome and a survival advantage in the norfloxacin group compared to placebo [56]. Fluroquinolones such as norfloxacin have been the mainstay of primary prophylaxis, but there is emerging evidence that this strategy results in breakthrough infections with a wide antibacterial resistance pattern and atypical pathogens [57]. In an effort to reduce the emergence of significant fluroquinolone resistance, continuous norfloxacin prophylaxis has been compared with prophylaxis only during hospital admission. Unsurprisingly perhaps, the continuous strategy was associated with an increased spectrum of antibiotic resistance, but with less breakthrough infections [58]. A recent retrospective analysis from a single centre suggested that trimethoprim-sulfamethoxazole may be as effective as norfloxacin but with less risks of development of bacterial antibiotic resistance and potential cost savings [59]. It may also reduce the risk of hospital acquired infections, particularly Clostridium difficile.

- Treatment of pruritus in primary biliary cirrhosis (PBC)

Rifampicin in a daily dose of 600 mg improves pruritus, and markers of cholestasis in PBC [60, 61]. It is also, however, a potential cause of hepatic morbidity, primarily through its hepatic microsomal enzyme inducing properties. Depletion of vitamin K-dependent coagulation factors (VII, IX, and X) during treatment has been reported, though the coagulation abnormalities were easily corrected by the administration of vitamin K. Proposed mechanisms include the decreased production of menaquinones by intestinal bacteria, a warfarin-like effect via inhibition of the vitamin K epoxide reductase and the increased oxidative degradation of vitamin K as a result of hepatic microsomal enzyme stimulation [62]. Rifampicin therapy can also be associated with hepatitis, though there are very few reports of this complicating treatment of PBC associated pruritus. [8, 63]. Patients with PBC who receive rifampicin are prone, however, to develop a rare but potentially serious immune haemolytic anaemia, requiring discontinuation, steroid therapy and even haemodialysis. The proposed mechanism is the development of anti-I (an erythrocyte antigen) specific IgM antibody [64].

- Treatment of endotipsitis

A Transjugular Intrahepatic Portosystemic Stent Shunt (TIPSS) has become a useful armament in the management of refractory ascites and uncontrolled variceal haemorrhage. As a foreign object, however, it also has the potential to become a source of sepsis. The diagnosis of endotipsitis is based on the occurrence of fever with positive blood cultures, and either a thrombus or vegetation on the stent, or alternatively a persistent bacteremia without another detectable source of infection. Oral and enteric Gram-negative bacteria, gram-positive cocci, and fungi are the common pathogens. The clinical features include fever, tender hepatomegaly, hypoxemia, septic pulmonary emboli, septic shock, neutrophilia, and necrotising fasciitis. [65]. A prolonged course of appropriate antibiotics based on culture results generally eradicates the infection. In the presence of endotipisitis and a fistulous communication with

an infected biliary tree, insertion of a PTFE covered stent through the original TIPSS shunt may be effective [66]. There is conflicting evidence with regard to the benefit of peri-interventional antibiotic prophylaxis with cephalosporins in reducing post–TIPSS bacteraemia [67, 68].

- Antibiotics in the setting of gastrointestinal haemorrhage in cirrhotics

The association between infection and variceal haemorrhage is well established. Several studies demonstrate that cirrhotic patients hospitalised with variceal haemorrhage, are more likely to have concomitant infection, than those admitted for other reasons [69-71]. The presence of infection is one of the few independent predictors of failure to control bleeding and the risk of early rebleeding [72-74]. Bacteria derived endotoxins increase intrahepatic resistance and hence portal pressure through stellate cell contraction, and increase production of NO from endothelial cells, leading to platelet dysfunction. Reduced levels of activated protein C and the release of heparinoids from endothelial cells also contribute to bleeding through worsening of coagulopathy. Several studies have shown that antibiotics, mainly fluroquinolones, co-amoxiclav and third generation cephalosporins, reduce early rebleeding and early mortality (before six weeks), but have very little effect on long term survival [75-78].

Hypotension in the setting of acute variceal haemorrhage also increases the risk of developing SBP. Hypoperfusion of the bowel in this setting increases bacterial translocation, which in turn promotes endothelial dysfunction and perpetuates the sepsis pathway. The British Society of Gastroenterology (BSG) guidelines suggest the use of prophylactic antibiotics in all cases of variceal haemorrhage [79].

- Prevention of hepatorenal syndrome

Hepatorenal syndrome (HRS) is a severe complication of cirrhosis with a poor prognosis. The presence of SBP increases the risk of developing HRS, especially when associated with a low platelet count and low ascitic fluid protein levels. The combination of human albumin solution (1.5mg/kg body weight on day 1 and 1mg/kg body weight on day 3) and cefotaxime reduced the incidence of HRS by 66% in one study and also led to a significant reduction in in-hospital and 3-month mortality rates as compared to antibiotics alone [80]. There were, however, several methodological flaws to the study and further research is required to validate the findings. The beneficial effect of albumin may not be solely due to the volume expansion, particularly given that a similar benefit was not seen with hydroxyethyl starch solution [81]. Albumin has peculiar rheological properties together with an effect on toxin binding and endothelial stabilisation.

CONCLUSION

The liver both benefits and suffers from the prescribing of antibiotics. They account for a large proportion of drug induced liver injuries (DILI), and yet are essential in the treatment of hepatobiliary infection and in the prevention of infective complications in chronic liver disease and following liver transplantion. While the majority of antibiotic induced liver injuries are self-limiting transient events, there are some patients in whom it is a cause of significant morbidity and mortality. Patients with advanced liver disease are often functionally immuno-compromised and prone to potentially life threatening infection. Infection complicating gastrointestinal haemorrhage probably leads to more deaths in patients with cirrhosis than the actual failure to control bleeding itself. The emergence of bacterial antibiotic resistance, changes in the spectrum of pathogens and the problem of nosocomial infection poses major challenges for the future.

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