Combatting Antimicrobial Resistance in Liver disease, we need better diagnostics

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Liver disease represents 2-3% of all deaths globally[1]. In the UK, mortality rates have increased by 400% since 1970 and one million hospital admissions a year are alcohol-related, causing costs to the NHS of £3.5 billion[2]. Patients developing liver failure are termed acute decompensation (AD) or acute-on-chronic liver failure[3]. They are highly prone to bacterial infection secondary to immune dysfunction[4], with nosocomial (hospital-acquired) infection rates of 35% compared to 5% in other hospital inpatients without cirrhosis[5]. In the absence of immune restorative therapies we "coat" our patients in antibiotics in order to prevent infections. A Cochrane review concluded appropriate empiric antibiotic treatment may reduce mortality in certain circumstances, e.g. following acute upper gastrointestinal bleeding in patients with very severe liver disease[6]. However, these data, from largely single centre studies, have been applied to all liver patients, even those without significant disease, leading to widespread over-prescription[7]. Cirrhosis patients represent a particularly high risk for AMR as they are frequently prescribed antibiotics, undergo many invasive procedures and have recurrent hospital admissions encouraging both increased AMR rates and spread of resistant pathogens. This has led to a substantial reduction in empirical antibiotic treatment efficacy with MDR bacteria resistant to 60% of recommended drugs prevalent in certain countries[7]. There is the very real threat that we will face a future in which antibiotics no longer work. Governmental-industry initiatives are developing new antibiotics and novel strategies to address AMR (e.g. COMBACTE). Whether these will cope with rising rates of AMR is moot. As antibiotic resistance is a direct consequence of their use, *the* crucial strategy must be sound antimicrobial stewardship.

Microbiology culture represents the current gold standard for diagnosis of bacterial infection but results take 24-48hrs which is considered too long to wait by clinicians. In the meantime almost every cirrhosis patient suspected of infection will be commenced on broad spectrum empirical treatment. Furthermore these cultures are positive in only 40-50% of those treated but most clinicians agree that cirrhosis infection rates are much higher (more like 65%) and therefore antibiotics are continued in many for 7-10 days even culture negative patients. It is considered that this over-prescription has increased antimicrobial resistance (AMR) rates, in turn leading to an increase in empirical antibiotic treatment failure, with 11-45% of spontaneous bacterial peritonitis (SBP) patients now culturing bacteria resistant to first line empirical choices[7]. The importance of correctly selecting the first line antibiotic is underlined by data in cirrhosis and septic shock showing that each hour of delay in appropriate antimicrobial therapy was associated with an almost doubling of hospital mortality[8]. Hepatologists faced with the dilemma of whether to escalate empirical/prophylactic treatment to "antibiotics of last resort" (e.g. Meropenem) or to restrict antibiotic use with potential unfavourable consequences often choose the former, perpetuating the vicious cycle leading to further resistance and increased empirical treatment failure. Evidently we need to improve our choice of first line treatment and restrict unnecessary antibiotic use, however in order to do so we need more precise diagnostics.

Industry rapid diagnostic platforms e.g. from Biocartis and Abbott have been developed. These techniques examine pathogen DNA using real-time PCR to detect bacteria from 5 ml of body fluid. The Abbot system, IRIDICA demonstrated an increase in pathogen identification over standard blood

cultures (37% vs 11%)[9]. Although these data suggest that we may fail to identify bacteria in a significant number of patients, the clinical significance of these pathogens remains undetermined. This may be even more difficult to interpret in cirrhosis patients because of increased gut bacterial translocation into the systemic circulation. Furthermore this system takes 6 hours. The Biocartis platforms offers potential for (near) point-of-care systems within 3-5 years, results within 60-90 minutes, albeit with more restricted pathogen panels. A strategy focusing on host response biomarkers to complement pathogen detection may yield important data. Serial procalcitonin measurements are being used increasingly in sepsis, although values alter with hepatic dysfunction and specific gene expression infection bio-signatures have also been developed in sepsis. There may be scope to apply to these approaches in cirrhosis.

We also need to develop non-antibiotic strategies targeting gut-bacterial translocation in order to prevent infection. Oral probiotics, live microorganisms, have been shown to reduce intestinal permeability and reduce bacterial translocation. However these findings have not translated into meaningful clinical effects and caution is warranted given the increased mortality in a randomised controlled trial of probiotics given for acute pancreatitis[10]. A further possibility is Fecal microbiota transplant which involves infusion of healthy donor stool into a patient's intestine with the goal of rebalancing normal intestinal microbiota. This can reverse intestinal colonisation with multi-drug resistant organisms e.g. extended-spectrum beta-lactamase producing *E.coli.*[11], however data in cirrhosis is limited. Non selective Beta-Blockers used to treat portal hypertension have been associated with a reduction in bacterial translocation. However clinical data regarding infection prevention is conflicting with two retrospective studies demonstrating a lack of effect and one Meta–analysis in favour of SBP prevention[7]. Statins have been proposed to improve host immune defence and a recent retrospective cohort study in patients with compensated cirrhosis concluded that there was a decrease in severe bacterial infections in statin users with a hazard ratio of 0.42[12]. Finally experiment evidence exists for a beneficial immune effect following 20% Human Albumin Solution infusions[4] and large scale RCTs are in progress. We await formal prospective clinical trials of these agents.

In the longer term hepatologists, infectious disease specialists, microbiologists, epidemiologists and industry must work together to improve treatment of bacterial infection in cirrhosis, to preserve the lifespan of our antibiotics and to prevent a future in which patients die for lack of effective therapy.

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