Abstract

Antibiotic resistance is a significant global problem, which results in premature morbidity and mortality. Bacteria have evolved to repel, expel and modify antibiotics, which are administered to treat them and this is largely due to the inappropriate prescription of these treatments. As humans evolve and habits change, niches have been created which support the colonisation of human mucosa and skin by bacteria. Two bacterial pathogens of note, *Helicobacter pylori* and methicillin-resistant *Staphylococcus aureus* (MRSA) will be discussed in some depth as to how their resistance came about and what is being done to address these invasive pathogens. While a number of antibiotics are still used to treat these infections, it is likely that the evidence base will grow for the introduction of complementary medicines to treat antibiotic-resistant bacterial strains, which are likely to emerge. Evidence is presented, which suggests that Chinese herbs such as Fuzheng Tuodu Qingre Huoxue and Danshen may have an anti-bacterial role to play and at the correct pharmacokinetic dose, are effective in inhibiting bacterial infections, at least in the *in vitro* setting. Escalation to clinical trials remains aspirational but may be the future of bacterial treatment regimens.

Introduction

In healthy patients, the skin and mucous membranes are intact and able to resist infection with many pathogens. However, at some point during the life course, it is inevitable that the human host will become infected with a bacterial pathogen and in immunocompetent individuals, this will precipitate an inflammatory immune response. The pathogen will either be cleared by the patient or the infection may necessitate topical or systemic treatment with an appropriate agent such as an antibiotic. In some instances, the infection cannot be cleared and may result in sepsis with ensuing multi-organ failure and death.

The above scenario is a rather simplistic summary of bacterial infection and in this essay, I aim to fully explore the epidemiology and pathogenesis of bacterial infections and the subsequent immune response, where inflammation is the main driver of that response. I shall discuss the pharmacokinetic and pharmacodynamic properties of broad spectrum antibiotics and how inappropriate prescribing have contributed towards the emergence of multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase producing (ESBL) *Escherichia coli*. I shall then discuss the subject matter in the context of complementary medicine, specifically with reference to Chinese herbs and whether they are a robust alternative to the prevention and treatment of bacterial infectious disease.

The inflammatory immune response

When the human body encounters something which is foreign, it begins the process of an immune response. This assumes that the bacterium has penetrated the skin or mucosal tissues and has come into contact with the lymph, where it will likely proliferate. The innate immune system is the first responder and cells such as macrophages, neutrophils and dendritic cells will migrate towards the site of infection. Here, through toll-like receptors (TLRs) and other ligands, the process of phagocytosis can commence, where endocytosed bacteria can be digested and their antigens presented to T helper cells (Delves *et al.,* 2011). Clonal expansion of T and B cells arm the immune system to 'remember' the pathogen that caused the infection, while also stimulating the immune response to specifically target the infection. While, this is a simplistic summary of the basic immune response, we will deal with specific immunological issues when addressing the pathogens of interest.

MRSA

Perhaps the most notorious bacterial pathogen in the last two decades is MRSA and this has received significant media and political attention. It is generally considered to be a healthcare-associated infection (HAI) and has been responsible for causing many deaths, particularly in the elderly (Office for National Statistics, 2011). Although *Staphylococcus aureus* is a commensal and exists on the skin and on mucous membranes without causing pathology in most people, MRSA is an antibiotic-resistant organism which can cause infections with a broad range of symptoms from boils and abscesses to much more serious manifestations such as septicaemia, multi-

organ failure and death (Naber, 2009). The difference between MSSA and MRSA is that the former is amenable to treatment, whereas treatment options for MRSA are becoming severely limited.

In the UK, deaths due to MRSA infection have reduced in the last few years although they still account for considerable premature morbidity and mortality (Office for National Statistics, 2011). In the USA, it is the most commonly identified bacterial pathogen from in-patients and the second most prevalent infection from out-patients (Naber, 2009). Its importance in clinical infection is therefore undisputed.

The host immune response to MRSA is complicated by the fact that this pathogen has a number of virulence factors and properties, which subvert the immune response. MRSA can resist phagocytosis due to the presence of Protein A on its surface and by virtue of excreting chemotaxis inhibitory protein, which prevents opsonisation by neutrophils (Haas *et al.,* 2004). Expression of superantigens such as toxic shock syndrome toxin activate specific T cells, which consequently become anergised and non-responsive. Ultimately, the bacterium continues to thrive and multiply where the immune system struggles to contain the infection and this results in serious infection where the patient must seek medical attention and treatment.

It could be argued that MRSA is the first 'superbug' and has largely emerged due to inappropriate prescription of broad spectrum antibiotics across the globe. The bacterium is now resistant to methicillin, nafcillin and other

antibiotics, which previously were effective. The acquisition of the *mecA* gene have facilitated this resistance and while vancomycin and teicoplanin have been used to treat MRSA infections, resistance to these has been noted in the clinical setting (Maor *et al.,* 2009).

Ceftaroline is a new broad-spectrum cephalosporin, which has been suggested as a potentially effective antibiotic against MRSA. One of the properties, which makes this antibiotic so attractive is that it can be given intravenously and appears to be less toxic than vancomycin (600mg every 12 hours vs 1g every 12 hours) (Drusano, 2010). The pharmacokinetics and dynamics of this are comparable to other cephalosporins and it is both safe and clinically effective. Despite this however, the situation is becoming increasingly worrying since it would suggest that MRSA may become untreatable using most modern day antibiotics.

Complementary medicine and MRSA

Given the aforementioned situation, it is becoming more important to assess the effects of complementary medicine on bacteria such as MRSA. Propolis, a product from honey, has been used as a potent anti-inflammatory and has been found to have anti-bacterial action against MRSA, at least in animal models (Onlen *et al.,* 2007). Unfortunately, there have been no clinical trials testing this product and therefore its efficacy in the clinical setting is not known.

The Chinese complementary medicine, Fuzheng Tuodu Qingre Huoxue, has been used in a case series of 62 diabetic patients, who had deep carbuncles (Que *et al.,* 2008). Unfortunately, the article was in Chinese so the efficacy of this therapy is unknown as was the microbiology of the aetiological agent, which caused the carbuncles. Presumably *Staphylococcus* spp. were involved but it is not possible to comment on the efficacy of this product on MRSA. However, *in vitro* studies have trialled the effects of kurarinone, a Chinese herb which has Qing Re Jie Du function. This herb was used on a number of antibiotic-resistant bacteria including MRSA and vancomycin-resistant Enterococci (VRE) and it was found to inhibit the bacterial growth of both of these pathogens (Chen *et al.,* 2005). As the assays were trialled under the same conditions to determine microbial inhibitory capacity (MIC) of antibiotics, the study appeared robust. Therefore, there is some evidence to suggest that Chinese herbs may have some role in the treatment of bacterial infections with MRSA.

Helicobacter pylori

H. pylori is becoming more prevalent in the developing and developed world and infects the mucosa of the stomach lining. It causes a range of symptoms from gastritis to peptic ulcer and has even been associated with the development of gastric carcinoma in some patients (Chisholm & Owen, 2009). The condition is likely to be under-diagnosed since not all those with infection attend general practice and as such, its mode of infection could be considered to be chronic rather than acute. Risk factors for acquisition include male gender, age, tobacco smoking and lower socio-economic status (SES) and

transmission is considered to be via person-to-person spread (Ford & Avon, 2010).

The gut mucosa (from stomach to colon) is equipped with a number of physiological and biological factors, which help to resist pathogen colonisation. These include mucus, host bacterial flora, hostile environmental conditions e.g. acidic pH of the stomach and secretory immunoglobulin. Therefore, for pathogens such as *H. pylori* to colonise and infect the gastro-intestinal epithelium, the pathogen must itself be resistant to such hostile innate factors. Furthermore, it must also survive the acquired immune response.

Dendritic cells are found between the epithelial layers of the gut and constantly sample antigens, which may be present in order to assess whether an immune response is required. Their responses must be very specific so that they do not react to normal commensal bacteria. Once *H. pylori* infects the gut, dendritic cells are attracted to the site of infection but rather than stimulate T cells to drive an inflammatory Th1 response towards the pathogen and eradicate it, the interaction with *H. pylori* results in disease exacerbation and a Th2-type immune response, which favours prolonged residence within the gut (Bedoui *et al.,* 2010). The factors associated with this immune response have still to be resolved in the patient but *in vitro* and *ex vivo* studies appear to confirm these findings.

Treatment of *H. pylori* infection is defined by the Maastricht guidelines, which suggest a form of triple therapy and this entails: a proton pump inhibitor (PPI)

(to increase the pH of the stomach); clarithromycin and metronidazole or amoxicillin (Malfertheiner *et al.,* 2007). However, treatment of this condition with such broad-spectrum antibiotics has inevitably resulted in antibiotic resistance and as such, it is becoming harder to eradicate this pathogen in infected patients. Notwithstanding the resistance issues, the triple therapy has been found to have significant health effects on individuals and adherence to long-term therapy is a problem. This is partly due to the different metabolisms and pharmacodynamics exhibited by patients infected with this pathogen and how they respond to PPI treatment (Yang & Lin, 2010).

Given the aforementioned treatment issues, it is perhaps not surprising that complementary medicine with Chinese herbs has been proposed for people infected with *H. pylori*. A number of *in vitro* studies have shown that Chinese herbs such as *Radix scutellariae* and *Lonicera* have inhibitory effects on the pathogen, while a number of clinical trials have also been carried out to ascertain their effectiveness (Lin & Huang, 2009). To date, the collated evidence appears to suggest that these herbs are not as effective as triple therapy in eradicating the pathogen from the gut but they are much more tolerated with regards to adverse health effects. What is know is that aqueous extracts from *Magnolia* and *Cassia* have potent activities against the urease enzyme from *H. pylori* and as this enzyme is fundamental to continued survival in the stomach of this pathogen, their anti-bacterial actions are profound (Shi *et al.,* 2011).

A large problem with the above trials was that they were methodologically unreliable, where herb dosage differed and was not standardised. This makes it very difficult to assess their efficacy and a properly conducted randomised controlled trial should be considered for these potential therapies. A double-blind RCT was conducted in 2005 and using a combination of both Western and Chinese medicine, was shown to promote eradication and healing of gastric infection with *H. pylori* (Feng *et al.,* 2005). It is much more likely that a combination of treatment using Chinese herbs, PPIs and an antibiotic could be the future for treatment of this bacterial pathogen.

Role of Chinese herbs in bacterial sepsis

So far, the essay has assessed how established infections may be treated with Chinese herbs but if a bacterial infection progresses to sepsis, the situation becomes critical and prompt anti-bacterial therapy is required. Late pro-inflammatory cytokines such as HMGB1 are thought to be important in the inflammatory-driven pathology, which contributes to mortality. Therefore, it is of interest to note that Chinese herbs such as Danggui and Danshen have been shown to ameliorate the sepsis process and reduce mortality, at least in a murine model (Zhu *et al.,* 2008). These complementary medicines may well have a role in the clinical management of human sepsis and future trials should be conducted.

Conclusion

In this essay, a number of bacterial infections have been addressed with respect to their epidemiology, the immune response to these and how the

pathogens have adapted to these hostile responses. Furthermore, I have detailed how these bacterial infections have been previously treated with broad-spectrum antibiotics and still are to this day. Despite this, antibiotics resistance in both *H. pylori* and MRSA, amongst many other bacterial pathogens is increasing worldwide and it is only a matter of time before clinical solutions are even more sparse than they are today.

Alternative therapies such as complementary medicine are commonly used to treat conditions such as insomnia, viral infections (echinacea) and the menopause (evening primrose oil). However, bacterial infections are not routinely treated with complementary medicines such as Chinese herbs, yet the evidence suggests that these may be increasingly utilised in years to come. Properly conducted studies must be trialled for Chinese herbs and used in conjunction with Western medicine since there may be synergistic anti-bacterial effects, which are more effective than either the Western or Oriental form of medicine.

References

Bedoui S, Kupz A, Wijburg OL *et al.* (2010) Different Bacterial Pathogens, Different Strategies, Yet the Aim Is the Same: Evasion of Intestinal Dendritic Cell Recognition. *J Immunol*, vol. 184, pp. 2237-2242.

Chen L, Cheng X, Shi W. (2005) Inhibition of Growth of *Streptococcus mutans*, Methicillin-Resistant *Staphylococcus aureus*, and Vancomycin-Resistant Enterococci by Kurarinone, a Bioactive Flavonoid Isolated from *Sophora flavescens. J Clin Microbiol*, vol. 43, pp. 3574-3575.

Chisholm SA, Owen RJ. (2009) Frequency and molecular characteristics of ciprofloxacin- and rifampicin-resistant *Helicobacter pylori* from gastric infections in the UK. *J Med Microbiol*, vol. 58, pp. 1322-1328.

Delves PJ *et al.* Roitt's Essential Immunology. 12th Edition. (2011) Wiley.

Drusano GL. (2010) Pharmacodynamics of ceftaroline fosamil for complicated skin and skin structure infection: rationale for improved anti-methicillin-resistant *Staphylococcus aureus* activity. *J Antimicrob Chemother*, vol. 65, pp. 33-39.

Feng L-Y, Yao X-X, Jiang S-L. (2005) Effects of killing *Helicobacter pylori* quadruple therapy on peptic ulcer: A randomized double-blind clinical trial. *World J Gastroenterol*, vol. 11, pp. 1083-1086.

Ford AC, Avon AT. (2010) Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter*, vol. 15, pp. 1-6.

Haas PJ, de Haas CJ, Kleibeuker W *et al.* (2004) N-terminal residues of the chemotaxis inhibitory protein of *Staphylococcus aureus* are essential for blocking formylated peptide receptor but not C5a receptor. *J Immunol*, vol. 173, pp. 5704-5711.

Lin J, Huang W-W. (2009) A systematic review of treating *Helicobacter pylori* infection with Traditional Chinese Medicine. *World J Gastroenterol*, vol. 15, pp. 4715-4719.

Maor Y, Hagin M, Belausov N *et al.* (2009) Clinical features of heteroresistant vancomycin-intermediate Staphylococcus aureus bacteremia versus those of methicillin-resistant S. aureus bacteremia. *J Infect Dis*, vol. 199, pp. 619-624.

Malfertheiner P, Megraud F, O'Morain C *et al.* (2007) Current concepts in the management of Helicobacter pylori infection: The Maastricht III Consensus Report. *Gut*, vol. 56, pp. 722-781.

Naber CK (2009) *Staphylococcus aureus* Bacteremia: Epidemiology, Pathophysiology, and Management Strategies. *Clin Infect Dis*, vol. 48, pp. 231-237.

Office for National Statistics (2011) http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-mrsa/2006-to-2010/statistical-bulletin.html [accessed 23/01/12].

Onlen Y, Duran N, Atik E *et al.* (2007) Antibacterial activity of propolis against MRSA and synergism with topical mupirocin. *J Altern Complement Med*, vol. 13, pp. 713-718.

Que HF, Tang HJ, Xing J *et al.* (2008) [Clinical study of Fuzheng Tuodu Qingre Huoxue therapy in treating 62 diabetic patients with deep rooted carbuncle]. *Zhong Xi Yi Jie He Xue Bao*, vol. 6, pp. 1065-1067.

Shi DH, Liu YW, Liu WW, Gu ZF. (2011) Inhibition of urease by extracts derived from 15 Chinese medicinal herbs. *Pharm Biol,* vol. 49, pp. 752-755.

Yang JC, Lin CJ. (2010) CYP2C19 genotypes in the pharmacokinetics/pharmacodynamics of proton pump inhibitor-based therapy of Helicobacter pylori infection. *Expert Opin Drug Metab Toxicol*, vol. 6, pp. 29-41.

Zhu S, Li W, Li J, Sama AE, Wang H. (2008) Caging a Beast in the Inflammation Arena: Use of Chinese Medicinal Herbs to Inhibit a Late Mediator of Lethal Sepsis, HMGB1. *Int J Clin Exp Med*, vol. 1, pp. 64-75.