Non-antibiotic therapies for infectious diseases

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Abstract

The emergence of multiple antibiotic resistant organisms in the general community is a potentially serious threat to public health. The emergence of antibiotic resistance has not yet prompted a radical revision of antibiotic utilisation. Instead it has prompted the development of additional antibiotics. Unfortunately, this does not relieve the underlying selection pressure that drives the development of resistance. A paradigm shift in the treatment of infectious disease is necessary to prevent antibiotics becoming obsolete and, where appropriate, alternatives to antibiotics ought to be considered. There are already several non-antibiotic approaches to the treatment and prevention of infection including probiotics, phages and phytomedicines. There is some evidence that probiotics such as *Lactobacillus* spp. or *Saccharomyces boulardii* are useful in the prevention and treatment of diarrhoea, including *Clostridium difficile*-associated diarrhoea that can be difficult to treat and recurs frequently. Bacteriophages have received renewed attention for the control of both staphylococcal and gastrointestinal infections. Phytomedicines that have been utilised in the treatment of infections include artesunate for malaria, tea tree oil for skin infections, honey for wound infections, mastic gum for *Helicobacter pylori* gastric ulcers and cranberry juice for urinary tract infections. Many infections may prove amenable to safe and effective treatment with non-antibiotics. *Commun Dis Intell* 2003;27 Suppl:S144–S147.

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Introduction

Increased use of alternative medicines has come about largely as a result of the general community's interest in alternative therapies rather than by demand from healthcare professionals for alternative agents. Both groups have their own prejudices; lay people often assume natural products are completely safe and effective while many health professionals dismiss therapeutic agents or methods that do not fit the conventional paradigm. Both groups often maintain their biases in the face of contradictory evidence, or view the absence of evidence as evidence in its own right. A survey published in 1996 indicated that nearly 50 per cent of the Australian population had used at least one non-medically prescribed alternative medicine.[1] With specific regard to antimicrobials, there are several non-antibiotic approaches to the treatment and prevention of infection including probiotics, bacteriophages and phytomedicines.

Probiotics

Probiotics have been suggested as an alternative therapy for the treatment of infectious gastroenteritis, or the treatment and prevention of antibiotic-associated diarrhoea due to *Clostridium difficile*. Probiotics are preparations of ostensibly non-pathogenic organisms known to have a beneficial effect on the digestive and other systems by conferring resistance to infection or eliminating infectious agents. Both bacteria and yeasts have been used as probiotics. The mechanisms of action of probiotics have been summarised by Filho-Lima *et al*.[2] Four possibilities exist: 1. antagonism through production of inhibitory substances; 2. competition with the pathogen for adhesion sites or nutrients; 3. immunomodulation of the host; and 4. inhibition of toxins.

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Lactobacillus GG has been the most widely studied of probiotic agents. In addition to having been used, with varying degrees of success, for treating or preventing urinary tract infections, vulvo-vaginal candidiasis and bacterial vaginosis,[3] *Lactobacillus* GG, in the form of a milk preparation, was recently reported as having some modest but consistent benefits in terms of preventing and reducing the severity of respiratory infections at day care centres.[4] While the relevance of this latter observation to the prevention of antibiotic resistance may not be immediately apparent, any intervention which results in reduced use of antibiotics in a particular setting will eventually lead to a decline in antibiotic resistance. Another well-studied probiotic is *Saccharomyces boulardii*, a yeast that is effective in preventing relapses of *Clostridium difficile*-associated diarrhoea and treating various types of infectious diarrhoea.[5] Several other possible probiotics have been looked at, such as non-toxigenic strains of *C. difficile* and a strain of *Enterococcus faecium*. However, enthusiasm for enterococci as probiotics has waned since the emergence of vancomycin resistant enterococci.

Bacteriophages as antimicrobial agents

An old idea ignored since the beginning of the antibiotic era by all but a few former Soviet bloc countries is bacteriophage therapy where phages are used to lyse bacterial pathogens. There has been renewed interest in bacteriophage therapy with the emergence of antibiotic resistance as a major problem in modern medicine.[6] Several reports from Poland in the 1980s described the treatment of various infections, the majority of which were staphylococcal and included bacteraemia. *In vitro* testing indicated that bacteriophages were active against specific pathogens. Efficacy *in vivo* was assessed on a clinical basis alone and positive results were obtained in over 90 per cent of cases, however, there were no untreated controls.[7] Similar studies were carried out in the former Soviet Union from the early 1970s. In those studies where staphylococci (presumably *Staphylococcus aureus*) were involved, bacteria were eliminated after phage therapy in the majority of cases.[6] Phages were applied either topically, sub-cutaneously, or via irrigation or drains.

Studies in the United Kingdom have predominantly concentrated on the treatment of diarrhoeal disease, mainly caused by *Escherichia coli*, using animal models.[8] Soothill[9] treated experimental *S. aureus* infections in mice with bacteriophage. Bacteriophage and *S. aureus* (the same strains as had been used in some of the Polish studies) were injected intraperitoneally simultaneously. In this situation bacteriophage was not protective although infections involving *Acinetobacter baumanii* and *Pseudomonas aeruginosa* could be prevented by their respective bacteriophages.

As with other alternative therapies, there have been concerns about the safety of bacteriophage therapy. One concern has been the development of antiphage antibody during therapy. This was assessed in Poland in 57 patients following oral administration of bacteriophage and found no measurable antibody in 44 patients during treatment. In two cases high titre antibody developed.[10] Another major problem has been the presence of various toxins in crude phage lysates, however, this can now be addressed during preparative process.[11] The bioavailability of phage administered systematically has also been a concern, with early studies indicating that phage was quickly cleared by the reticuloendothelial system. Mutant phages with the ability to evade the reticuloendothelial system have now been produced.[11] It is possible that bacteria will ultimately become resistant to phage lysis in the same way that antibiotic resistance has emerged. However, phage used as a single dose, may be less likely to result in resistance than using antibiotics for a long period. Other problems include the observation that some methicillin-resistant *S. aureus* (MRSA) seem to be inherently less susceptible to bacteriophages than antibiotic-susceptible *S. aureus*. Finally, there is concern of the possibility of lysogenic conversion, whereby bacteriophage could acquire various toxin genes and introduce these into susceptible bacteria. The likelihood of this occurring, or of virulence genes being introduced by transduction, is unknown.

Phytomedicines

Phytomedicines are plant-derived remedies and many, such as tea tree oil (TTO), honey and cranberry juice, are targeted towards infectious diseases. TTO is the essential oil derived from certain species of Australian native plants in the genus *Melaleuca*, mainly *Melaleuca alternifolia*.[12] Originally developed in the pre-antibiotic era, its antimicrobial properties were first reported in the 1920s when it was shown to be more active than one of the widely used disinfectants of the day, phenol.[12] The antimicrobial activity and tolerability of TTO made it a popular skin antiseptic for the next 20 years. The dawn of the antibiotic era precipitated the demise of interest in TTO which could not compete with the potency and selective toxicity of the new agents. Consequently, TTO was discarded as an antimicrobial agent before its properties could be elucidated fully. Sixty years later, the widespread occurrence of multiple antibiotic-resistant organisms in hospital and community settings suggests new antimicrobial agents, preferably with novel mechanisms of action, are required and it seems prudent to re-examine previously superseded products such as TTO. *In vitro*, TTO has broad spectrum antibacterial activity[13] including activity against MRSA.[14] Antifungal and antiviral properties have also been demonstrated *in vitro* and preliminary *in vivo* work suggests that it may be useful in the treatment of acne[15] and oral candidiasis,[16] and in the decolonisation of MRSA carriage.[17] An understanding of its mechanisms of action against bacteria is being reached[18,19] and it appears that multiple mechanisms are involved, perhaps diminishing the rate at which resistance is likely to develop.

In contrast to TTO, honey has a much longer recorded history of medicinal use. Scattered reports in the medical literature describe the antibacterial properties of honey and honey products, and their potential as antimicrobial agents, particularly in wound care.[20] More recently, *in vitro* antibacterial activity has been described and a wide range of organisms is inhibited by honey including *E. coli*, *Proteus mirabilis*, *Ps. aeruginosa*, *Enterococcus faecalis* [21] and *Helicobacter pylori*.[22] The activity of honey has been attributed to the high osmolarity, the low pH and the presence of hydrogen peroxide. However, these factors alone or in combination do not account for all of the antibacterial activity and the identity of the main antimicrobial component of some honeys and its mechanism of action remains unclear.

Cranberries were used by North American Indians for food and medicine and they still enjoy popularity today. Commercially available cranberry juice may be useful in the treatment and prevention of urinary tract infections. Its putative medicinal properties have been partly investigated with occasional papers appearing in the medical literature. In a recent study, the effect of regular cranberry juice consumption on the recurrence of urinary tract infections was examined.[23] The time to first recurrence of a symptomatic urinary tract infection was compared in three groups of women randomised to receive daily 50 mL of European cranberry juice, 100 mL of a *Lactobacillus* GG drink or no intervention. Of the 50 patients randomised to cranberry juice, the cumulative rate of first recurrence of urinary tract infections during the 12-month follow-up was significantly reduced compared to the 50 patients receiving no intervention. In contrast, consumption of the *Lactobacillus* GG drink offered no benefit. Earlier work by Avorn *et al*.[24] suggested that daily ingestion of 300 mL of cranberry juice reduced the frequency of bacteriuria with pyuria in older women. A number of mechanisms have been postulated although a direct antibacterial effect and acidification of the urine have been excluded as the primary mechanisms of action. Exposure of uropathogenic *E. coli* to cranberry juice or extracts diminishes expression of P-fimbriae and inhibits their adherence to uroepithelial cells.[25] Similar work has shown that a high molecular weight constituent of cranberry juice can inhibit *H. pylori* adhesion to gastric mucosa.[26] While cranberry juice may not prove to be an effective treatment for current urinary tract or *H. pylori* infections, it may prevent *de novo* infections or prevent reinfection.

Conclusions

Alternative therapies are viewed favourably by many patients because they are often not being helped by conventional therapy and they believe there are fewer detrimental side effects. In addition, many report significant improvement while taking complementary and alternative medicines. Unfortunately, the medical profession has been slow to embrace these therapies and good scientific data are scarce at present.[3] However, as we approach the 'post-antibiotic era' the situation is changing. Further research is needed to validate the claims made for alternative therapies.

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