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Review

Bacterial interference for the prevention and treatment of infections

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Abstract

Bacterial interference refers to the antagonism between bacterial species during the process of surface colonisation and acquisition of nutrients. The clinical evidence on the potential applications of microorganisms for the prevention and/or treatment of infections in the upper respiratory, urogenital and gastrointestinal tracts was reviewed through the PubMed and Scopus databases. Data regarding factors that may affect the human microflora, thus contributing to tissue colonisation from potential pathogens, were also retrieved. The clinical evidence for application of the interfering ability of non-virulent bacteria to prevent or treat infections has been rather limited, although promising for certain purposes. A number of relevant preliminary trials suggest that in the upper respiratory tract the rate of recurrence of otitis media or streptococcal pharyngotonsillitis appears to decrease using selected bacteria with inhibitory ability against common pathogens of upper respiratory tract in combination with appropriate antibiotic treatment. Regarding the urogenital tract, specific non-pathogenic strains of *Escherichia coli* and probiotic organisms were successfully applied to decrease the recurrence of local infections. The interfering ability of specific probiotic organisms (strains of *Lactobacilli* and *Bifidobacteria*) within the gastrointestinal tract against common pathogens was also demonstrated. In conclusion, randomised controlled trials are warranted to investigate the effectiveness and safety of potential applications of the principle of bacterial interference in the prevention and treatment of infections of various sites. Such trials should initially employ selected strains of probiotics for which there are preliminary data regarding their effectiveness and lack of common or serious toxicity.

Keywords: Bacterial interference; Upper respiratory tract infection; Urogenital tract infection; Gastrointestinal infection

1. Introduction

Symbiosis, commensalism and competition are the three possible forms of relationship between species encountered in nature [1]. 'Symbiosis' refers to the co-existence of two different species where there is benefit at least for one of the partners without any harm for the other [2]. The word 'commensal' is of Latin origin meaning 'together at the table' and implies the neutral coexistence of two species without benefit or harm for the partners. The term 'competition' describes the antagonism between different species for space and energy through the acquisition of nutrients. Thus, development of an infection in the human body is the clinical or laboratory expression of this competition between microorganisms and the human body.

Through centuries of evolution, both man and various microbes have also learnt to cope with each other for a mutual benefit in survival terms. However, this kind of 'symbiosis' is so well tolerated from both sides that it sometimes escapes our attention. It is well known that not all human surfaces and mucosa are sterile; our skin, oral cavity, upper respiratory tract (URT), large intestine and urogenital tract (UGT) possess a natural microflora of various microbes with different properties, however vital for our survival. Maybe the best example is the gastrointestinal tract (GIT) where the normally colonising flora nourish the colon and participate in the production of vitamins and other substances, which serve a defending role against other pathogens [1,3]. As is evident by the example of antibiotic-related or *Clostridium difficile*-associated diarrhoea, elimination of resident microflora may provide the space and nutrients that certain pathogens need in order to adhere to, proliferate in and finally cause infection within human tissues.

The term bacterial interference refers to the antagonism between bacterial species during the process of surface

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colonisation. In other words, bacteria have developed special mechanisms in order to interfere with the capability of other antagonistic bacteria to colonise and potentially infect the host organism [4,5]. This interfering ability of the indigenous microflora may be one important line of defence along with the other defence mechanisms of the host organism. The purpose of this article is to evaluate the existing clinical evidence on the use of the bacterial interference phenomenon in the prevention and/or treatment of infections of the URT, UGT and GIT, to review factors that may alter normal microflora and consequently affect the interference ability, and finally to combine these lines of evidence to facilitate a conclusion regarding relevant future applications.

2. Literature search

A review of the available evidence was performed through searches of PubMed and Scopus databases using the following keywords: 'bacterial interference' AND/OR 'upper respiratory tract infection' AND/OR 'urogenital tract infections' AND/OR 'gastrointestinal infections'. No year of publication restrictions was set in the literature search. Using these keywords; relevant clinical trials and review papers were retrieved and evaluated.

3. Bacterial interference and clinical evidence for upper respiratory tract infections

The potential role of bacterial interference in infections of the URT has been largely attributed to the presence of normal flora in the nasopharynx, mainly α-haemolytic streptococci, non-haemolytic streptococci, *Peptostreptococcus* and *Prevotella* [6]. The importance of this phenomenon in the development or recurrence of very common infections, such as tonsillitis/pharyngitis and otitis media, has been investigated in experimental animal and in vitro models as well as in a small number of heterogeneous clinical studies.

Four clinical studies were identified after a search of the PubMed database. Roos and colleagues have presented evidence from two randomised controlled trials regarding the adjunct use of α-haemolytic streptococcal spray following appropriate antibiotic treatment in 342 patients with streptococcal pharyngotonsillitis [7] and in 130 children prone to otitis media [8]. Both trials supported the fact that selected bacteria with inhibitory ability against common pathogens of URT, if sprayed after antibiotic treatment, can reduce the rate of otitis media or streptococcal pharyngotonsillitis recurrence.

Nasal colonisation by potential pathogens, especially *Staphylococcus aureus*, has been implicated as a source not only of URT infections but also for a 2–9-fold increase of the risk for development of surgical site or intravenous catheter infections [9]. So far, common strategies to prevent nasal colonisation have been nasal ointments, sprays and per os antibiotics, with variable efficacy and frequent emergence of resistance to antibiotics by certain microbial species, especially *S. aureus*. Uehara et al. [10] investigated the phenomenon of bacterial interference to prevent colonisation of nasal cavities by pathogens using *Corynebacterium* spp., a common bacterium of the normal nasal flora. They artificially implanted a strain of *Corynebacterium* spp. (Co304) into the nares of 17 volunteers who were carriers of *S. aureus*. The Co304 strain succeeded in eradicating the pathogen in 71% of the volunteers by a non-bacteriocin-like mechanism. A further study showed the capacity of viridans streptococci to hinder colonisation of the oral cavities of newborns by meticillin-resistant *S. aureus* (MRSA) [11].

In addition, two experimental animal [12,13] and three microbiological in vitro [14–16] studies examined the ability of certain strains of normal human flora of the URT, mainly streptococcal species, to prevent colonisation and infection from pathogens. Fujimori et al. [15] and Brook and Gober [16] presented microbiological evidence that in patients with recurrent otitis media with effusion and children with recurrent sinusitis, respectively, the normal flora had less interfering ability in comparison with that of patients with no recurrence(s).

4. Bacterial interference and clinical evidence for urogenital infections

Urinary tract and vulvovaginal infections are among the most commonly encountered infections in hospitalised patients as well as previously healthy women [17,18]. High rates of recurrence are observed especially for urinary tract infections (UTIs); 25–35% of the initial episodes will be followed by recurrence of the infection [18,19]. Several different approaches have been tested in order to identify new agents to protect and rebuild the glycosaminoglycan layer of the bladder after the infection in order to prevent re-infection [20,21]. Agents such as heparin [22], per os pentosan polysulfate [23] and hyaluronic acid [24] have been used in this direction, although with various levels of effectiveness.

Bacterial interference is a new approach currently tested for recurrent UTIs in patients who suffered spinal cord injury and neuropathic bladder. The strain 83972 of *Escherichia coli* appears to be non-virulent for man [25]. Moreover, it is established that long-term asymptomatic bladder colonisation with *E. coli* 83972 is possible in patients with injuries of the spine [26,27]. Two prospective, non-randomised clinical studies [27,28] of 21 and 44 patients, respectively, with neuropathic bladder after spinal cord trauma presented evidence that artificial colonisation of the bladder with the above strain could reduce the rates of recurrent UTIs. This statement was also supported by a small, randomised, placebo-controlled, double-blind pilot study [29] in 27 patients with spinal trauma. Patients colonised with *E. coli* 83972 were half as likely to have recurrent episodes of UTIs within 1 year of follow-up.