

Mini Review

Staphylococcus aureus Bacteraemia: A Hidden Factor in the Pathogenesis of Human Disease

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Abstract

Chronic low grade inflammation is a pathogenic factor in a range of common conditions including atherosclerosis, Alzheimer's disease, diabetes mellitus, depression and obesity. *Staphylococcus aureus* is a prime candidate as a causative factor of chronic inflammation because carriage is common, the organism is potentially invasive and many strains produce superantigens which induce a non-specific non-targeted inflammatory response. The majority of adults has measurable serum IgG antibodies to these common superantigens (pyrogenic toxins) and since they are only produced in significant amounts at body heat or above this indicates that invasion is common and recurrent throughout life. Staphylococcal toxins are found in the urine of some adults with chronic disease but always in association with specific anti-toxin IgG. The most likely explanation is that immune complexes form in the circulation and are actively secreted (not passively filtered) into the urine. The diagnostic approach in patients with chronic low grade inflammation should be to measure urinary IgG and quantify faecal staphylococcal carriage. Establishing a causal relationship will then depend on reducing staphylococcal carriage and noting a reduction in inflammatory markers and an improvement in clinical symptoms. There is theoretical and experimental evidence to indicate that the consumption of natural yoghurt will reduce staphylococcal carriage in the oropharynx and oesophagus, which are potential sites for amplifying nasopharyngeal carriage. Thus long term yoghurt consumption is a possible preventive factor in human disease.

INTRODUCTION

There is increasing evidence that chronic low grade inflammation is a factor in the development of a wide range of degenerative human conditions, including atherosclerosis and its complications [1] as well as Alzheimer's disease [2], diabetes mellitus [3], depression [4,5] and obesity [6]. A prime candidate for a role in this process is low grade recurrent transient bacteraemia [7] by pathogenic staphylococci and streptococci resident in the upper airways and oropharynx.

Staphylococcus aureus is a single species with many different strains which produce a number of potent toxins [8]. Most strains secrete alpha-haemolysin which is a perforin that lyses cells by inserting ion channels into cell membranes. Some strains also secrete superantigens such as toxic shock syndrome toxin (TSST), and staphylococcal enterotoxins. Superantigens cause non-specific proliferation of T lymphocytes and this in turn leads to a non-targeted generalized inflammatory response [9]. These toxins are secreted when the organism invades the body and is at or above body heat [10]. Episodes of bacteraemia are quickly cleared by neutrophils in the post capillary venules of the lung and by filtration in the spleen. Thus whilst bacteraemia is common, and might well occur on a daily basis, life threatening staphylococcal sepsis is rare.

Superantigens cause inflammation. At first sight this seems somewhat paradoxical because inflammation is the body's

attempt to destroy bacteria and yet the super antigen genes must confer an advantage on the bacteria in terms of growth and spread. The answer, of course, is that the superantigens cause a non-specific and non-targeted inflammatory response and this dilutes any direct attack. In fact the normal inflammatory response is designed to cause maximal damage to bacteria with minimal damage to the host. Superantigens turn this around; they produce maximal damage to the host with minimal damage to the bacteria. Bacteria which invade the body and cause transient bacteraemia are going to almost certain death and this also appears somewhat odd in evolutionary terms. But staphylococci grow on and in the surface epithelium and only a minority of the organisms will enter the blood stream. The majority grows close to the surface and they spread from it to colonise and infect other hosts.

We all have circulating IgG antibodies that specifically recognize the staphylococcal toxins alpha-haemolysin, TSST and the more common staphylococcal enterotoxins [11,12]. These toxins are only produced at or above body heat when the organisms invade and this indicates that invasion is common and must occur on a regular basis in everybody. The toxins, TSST, staphylococcal enterotoxin B (SEB) and staphylococcal enterotoxin C (SEC) have been detected in the urine of infants using a highly sensitive ELISA [13]. But they were not detected in samples of urine from adults using the same ELISA [14,15]. The explanation is that free toxin is present in the blood stream

in infancy because levels of anti-toxin IgG are low, particularly around 2 to 3 months of age. The free toxin is then filtered by the glomeruli and appears in the urine. By contrast all adults have higher levels of circulating anti-toxin IgG and these will form complexes in the blood stream. The complexes are too large to be passively filtered into the urine.

Further examination of the adult urine samples [14,15], however, has shown that the situation is more complicated. Staphylococcal toxins have been detected in the urine of patients presenting with myocardial infarction [15] and in patients receiving intensive care [14] using polyacrylamide gel electrophoresis (PAGE) and immunoblotting. Even though the same specimens were negative for free toxin using a more sensitive ELISA technique. The possibility that something in the urine was interfering with the ELISA has been excluded. The toxin positive urines, however, did contain IgG, and a proportion of the IgG was shown to be specific anti-toxin IgG. The most likely explanation is that immune complexes form in the circulation, in antibody excess, and are then actively secreted into the urine. There is no free toxin in the urine so that the ELISA is negative. But the immune complexes partially dissociate in the polyacrylamide gel and some toxin migrates and can be detected. Because the complexes are in antibody excess it is possible to demonstrate anti-toxin recognition sites using a reverse ELISA [14,15].

The appropriate diagnostic approach, therefore, in cases of chronic disease in which bacteraemia could have a role is to measure urinary IgG. If passive leakage due to renal disease can be ruled out then the next stage is to try and identify the toxins within the complex. This is not so easy but it should prove possible to dissociate the complexes and then measure the toxin by ELISA or by mass spectrometry. Once the causative agent is identified the next stage would be to try and reduce carriage of the organism and see if this reduces markers of inflammation and brings the disease into remission.

Staphylococcus aureus is the commonest significant pathogen which causes recurrent transient bacteraemia and therefore methods of reducing carriage should be explored. Perhaps the most promising approach is the consumption of natural live yoghurt. There is evidence that oral probiotics decrease carriage of both pathogenic staphylococci and streptococci in the nasopharynx [16]. This observation is at first sight counter intuitive but it is worth careful consideration. Lactobacilli, bifidobacteria and non pathogenic lactose fermenting streptococci are the natural constituents of yoghurt. These bacteria, together with other non pathogens are normally present in milk, including human milk [17]. They are not contaminants, but are transferred into the milk so that the infant (or calf) has the optimum flora from the outset. In natural yoghurt the carbohydrates are fermented to lactic acid and this produces an acid pH. Lactobacilli colonise the vagina in human females and produce an acid pH by fermenting glycogen in the epithelial cells to lactic acid. This inhibits the growth of other bacteria including *S. aureus*. The vagina is lined by non keratinizing stratified squamous epithelium and in the reproductive years in particular the surface cells have abundant glycogen. The epithelium of the oral cavity, oropharynx and oesophagus is also non-keratinizing stratified squamous epithelium. Thus it is easy to appreciate that oral consumption of yoghurt could decrease *S. aureus* in the oropharynx and perhaps

the oesophagus. Bacteria in the nasopharynx are carried by muco-ciliary action into the oropharynx and oesophagus and there is opportunity for growth in the epithelial lining thereby amplifying their presence. Anything that inhibits the growth will reduce the amount breathed out and passed on to others and thus carriage in the nasopharynx of that individual and of family members should fall.

Metchnikov, the Nobel laureate, who first described the process of phagocytosis, popularized the consumption of yoghurt as a health food. He was impressed by the observation that Bulgarian peasants, who consumed a lot of yoghurt, seemed to live long healthy lives, free of disease into old age. His concept was that toxins absorbed from the gut were a potential cause of disease and natural bacteria in yoghurt would reduce toxin absorption. There is a great deal of current interest in probiotics, using bacteria found normally in milk and yoghurt. But the main focus has been on their potential effect on the gut flora and the results in many respects have been disappointing. The gut flora is large, complex and stable. Short term oral consumption of probiotic bacteria has little effect on the gut flora regardless of dose. But oral consumption of yoghurt is likely to have a much larger effect on the carriage of pathogenic staphylococci and streptococci in the oropharynx, and perhaps that should be the new focus of research. It fits well with recent evidence on the link between chronic inflammation and degenerative disease and would explain the longevity and health of the Bulgarian peasants (notwithstanding the fact that modern epidemiologists are probably sceptical).

The research programme that we should pursue is therefore clear. Measure urinary IgG, serum inflammatory markers and faecal carriage of *S. aureus* in a wide range of chronic diseases. If there is evidence of increased staphylococcal carriage and staphylococcal bacteraemia then encourage the patient and family members to consume yoghurt (natural, live, no added sugar, full fat) on a daily basis thereafter. Success will be decreased urinary IgG, decreased inflammatory markers, decreased faecal carriage and remission of symptoms.

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