ARE SUSCEPTIBILITY TO INFECTIVE ENDOCARDITIS AND EFFECTIVENESS OF ANTIBIOTIC PROPHYLAXIS LINKED TO FLUCTUATIONS OF THE IMMUNE SYSTEM? A NOVEL HYPOTHESIS

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ABSTRACT

Introduction*: An amendment incorporated into the 2007 AHA and 2009 ESC guidelines on infective endocarditis led to a substantial restriction in indications for the administration of antibiotic prophylaxis. This may have resulted in a subsequent steady increase in the number of cases of infective endocarditis worldwide.*

Methods*: It has been hypothesised that susceptibility to infective endocarditis, together with effectiveness of antibiotic prophylaxis, may be linked to fluctuations of the immune system. Throughout a person's lifetime, individual susceptibility to infective endocarditis may vary in an identical situation of risk. As a consequence, a personalised targeted approach should be adopted when prescribing antibiotic prophylaxis to prevent onset of endocarditis, taking into account a series of factors including age, comorbidities, cortisol levels, and ethnicity. Children affected by bicuspid aortic valve and injection drug users are amongst the newly-emerging higher risk populations.*

Conclusion*: This up-to-dated narrative review summarizes all the available scientific evidence concerning the variable influence of the immune system on susceptibility to infective endocarditis.*

Keywords:*infective endocarditis, antibiotic prophylaxis, immune system, bacteria.*

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Introduction

Infective endocarditis (IE) is a relatively rare and potentially life-threatening infection affecting the heart valve leaflets or endocardium, i.e. the innermost lining of the heart chambers. As a general rule, IE is produced following entry of bacteria into the bloodstream (bacteraemia) and infection of the heart[(1)].

The administration of antibiotic prophylaxis to prevent onset of IE prior to invasive surgery in patients with predisposing heart conditions was recommended in line with the findings of observational studies and animal models. In 1955 therefore, the American Heart Association (AHA) released a set of initial guidelines advocating the use of antibiotic prophylaxis in patients with rheumatic heart disease or congenital heart disease[(2)]. The suggestions put forward were approved and subsequently also introduced in the European Society of Cardiology (ESC) consensus paper in 1995[(3)].

However, from 2002 onwards, the indications for antibiotic prophylaxis were progressively restricted as follows according to their risk-benefit analysis[(4)]:

- in the field of evidence-based medicine, literature supporting antibiotic prophylaxis in IE is derived from animal models or non-randomized controlled trials in the context of teeth extraction[(5)];
- the efficacy of IE prophylaxis was questioned due to a purported failure rate of up to 50%[(1)];
- the widespread use of antibiotics may result in antibiotic resistance[(6)];
- the implication of dental procedures in onset

of IE was debated following the findings of a few studies which failed to identify invasive dental procedures as a major risk factor for the disease. Moreover, persistent episodes of low-grade bacteraemia may be manifested frequently during routine activities such as brushing of teeth, flossing or chewing, as well as in patients with poor dental hygiene. Therefore, the risk of IE is likely related to cumulative low-grade bacteraemia generated in the context of daily routines rather than to sporadic high-grade bacteraemia manifested in the context of dental interventions[1,7];

• a slight risk of anaphylaxis may be associated with the administration of antibiotics; this risk however is extremely low in the presence of oral amoxicillin[8].

In the light of the above observations, guidelines published by the UK National Institute for Health and Care Excellence (NICE) in 2008 advised against the use of 'any antibiotic prophylaxis' in the context of dental and other procedures irrespective of the patient's degree of risk. Subsequently, in 2016, the term "any" was replaced with "routinely"[9,10].

The AHA and ESC Guidelines were once again substantially revised in 2007 and 2009 to further regulate the prescription of preventive antibiotic prophylaxis for IE. Today, as established also by the 2015 ESC Guidelines, IE antibiotic prophylaxis is only prescribed in patients at extremely high risk (i.e. patients with very high incidence of IE and/or risk of adverse outcome from IE) following dental procedures[11-13].

High-risk patients

The previously cited AHA and ESC guidelines consistently list "high risk" patients as those featuring:

• Prosthetic cardiac valve or use of prosthetic material for valve repair (the phrase "including a transcatheter valve" is specified in the ESC guidelines);

• Previous IE

• Unrepaired cyanotic CHD, including palliative shunts and conduits ("any type of cyanotic CHD" in the ESC guidelines);

• Congenital heart defect successfully repaired using prosthetic materials or devices by means of surgery or catheter intervention within 6 months of the initial procedure;

• Repaired CHD having residual defects at/or adjacent to the site of a prosthetic patch ("or valvular regurgitation" in the ESC guidelines);

• Heart transplant recipients who develop valvulopathy[11-13].

In the NICE guidelines, specification of the term "routinely" implies the appropriateness of prescribing antibiotic prophylaxis in individual cases[10].

Potential consequences of restricted indications for antibiotic prophylaxis

Although cautious optimism was initially manifested with regard to the potential impact of significantly restricting indications for antibiotic prophylaxis, growing concern was registered in view of a possible significant increase in cases of IE in recent years.

An observational study conducted in the UK to assess the impact produced by the 2008 NICE recommendations advocating a complete withdrawal of antibiotic prophylaxis in the prevention of IE, demonstrated an increase in the incidence of IE in both high- and lower-risk patients following introduction of the guidelines[14].

In 2012, a UK survey described how the overwhelming majority of cardiologists and cardiothoracic surgeons perceived an effective need for antibiotic prophylaxis in patients with a prosthetic valve or previous IE[15].

Again, a recent report highlighted a clear upward trend in the incidence of IE in the UK, ascribing this finding to a more extensive use of advanced cardiac imaging and increase in the implantation of cardiovascular devices[16].

An increase in IE-related hospitalizations has been observed amongst both high- and moderate-risk patients in the wake of the 2007 modification to the AHA guidelines on IE as well[17].

This post-2007 increased incidence of IE incidence was detected for all types of bacteria, although proving particularly significant for streptococci[14]. However, it was not clarified whether the increased incidence was associated with oral streptococci in intermediate- or high-risk patients.

A significantly increased trend in IE incidence was observed amongst high-risk subjects, whilst a borderline significant increase was detected in subjects at moderate risk; no change was reported for subjects with a low/unknown risk[18]).

On a European level, the changes to recommendations provided in the guidelines also led to an increased incidence of IE in Germany, although no demonstrable causal effect was reported[19]. Likewise, in the Netherlands, the introduction of the 2009 ESC guidelines resulted in a similar upward

trend. Europe-wide moreover, a steady increase in streptococci-related IE cases was reported[20].

However, in view of the extensive disparity in the sources analysed, the true outcome produced following the changes the AHA and ESC IE guidelines is hard to pinpoint[21].

Hypothesis

A recent attempt to identify factors determining the transition from uncomplicated bacteraemia to IE led to the recognition of three key elements (*IE triangle*), i.e.: a suitable anatomical substrate (including all high risk conditions specified in AHA and ESC guidelines), a trigger (bacteraemia) and modulating factors (host immune system). Although the first two elements are readily detectable, the third remains somewhat elusive. Accordingly, it has been hypothesised that fluctuations in the host immune system may underlie an irregular susceptibility to IE in the same individual when exposed to an identical situation of risk at different moments in his/her life. The latter may also explain the failure of antibiotic prophylaxis to prevent IE in up to 50% of cases. The hypothesis we put forward differs considerably from procedures implemented prior to the 2007 AHA and 2009 ESC guidelines (*prior to which a negligible heart valve defect, such as slight prolapse of the mitral valve, was deemed sufficient for the administration of IE antibiotic prophylaxis*) and following publication (*whereby only two of the three factors outlined in the IE triangle are taken into account when deciding whether to administer antibiotic prophylaxis*).

Evaluation of the hypothesis

It has been suggested that fluctuations in the immune system may potentially affect both susceptibility to develop IE and effectiveness of antibiotic prophylaxis in preventing damage to the cardiac valves.

The human immune system is a highly complex network, usually subdivided into innate and adaptive immunities. An innate immune response is implemented by means of molecules (antibodies), whereas an adaptive immune response is fostered by means of cells such as macrophages, T-lymphocytes, and natural killer cells. Adaptive immune traits are largely associated with genetic factors, whilst innate immune traits are increasingly linked to the environment[22].

The immune system however does not act consistently as an impenetrable shield against pathogens, but acts distinctively within the same individual at different times, on the basis of a circadian rhythm (*from the Latin circa diem, meaning 'for about a day'*).

The circadian rhythm, a natural, internal process, modulates a series of physiological and behavioural activities accomplished by the human body. It indeed regulates the innate immune system, undergoing recurrent oscillatory changes through a molecular feedback loop and signal amplification acting on information received from the external environment. The internal body clock likewise provides a pivotal contribution in the inflammatory process, interacting directly with inflammatory molecules, such as those belonging to the NF-ϰB protein family. However, inflammation per se may also represent a direct cause of circadian rhythm disorders[23]. Indeed, it is well known that the number of hematopoietic stem and progenitor cells, together with the majority of mature leukocytes in the bloodstream, reach a nocturnal peak in humans and a diurnal peak in rodents, subsequently decreasing during the active phase. On the contrary, glucocorticoid, epinephrine, and norepinephrine levels, together with those of pro-inflammatory cytokines including tumour necrosis factor and interleukin-1β peak during onset of the active phase, which heavily influences individual susceptibility to all infections, including IE.

Thanks to the pioneering animal model studies conducted in the 1960s and 1970s, the response of mice to numerous pathogens and bacterial endotoxins/exotoxins is known to be diurnally regulated. The findings obtained in these studies indeed demonstrate the high sensitivity of mice to infections and proneness to significantly reduced survival at the start of their active phase (i.e. the early evening)[24].

The studies also revealed how patients with unresolved infectious foci represented by chronic oral infections or poor oral hygiene, consistently featured a functional immune system phenotype characterized by deep anti-inflammatory and/or functional "anergy" ("injury-associated immunosuppression") resulting in a markedly increased susceptibility to IE[25]. Regrettably, it is currently impossible to predict individual genetically-determined biological response (inflammation) to infections. Over the years, a series of genetic factors have been identified as contributing to host-susceptibility to IE, with higher rates of infections being demonstrated in specific ethnic populations (Maori and Pacific Island people vs European; Aboriginal Australian vs Australian; Black American vs White American). Furthermore, several rare genetic conditions have also been associated with susceptibility to IE[26].

Genome-wide association studies have been set up to identify genes underlying variations in response to infections and regulation of the immune system. Accordingly, in the VIRSTA cohort study which envisaged use of a Staphylococcus aureus-induced IE model, an association was detected between four single nucleotide genetic polymorphisms located on chromosome 3 and the predisposing host to the disease in 67 patients with IE of the native heart valves versus 72 matched controls presenting with uncomplicated bacteraemia. A replication study was subsequently performed on an independent Danish patient cohort with S. aureus bacteraemia, both with and without IE[27].

Moreover, numerous clinical and pathological conditions (including age, gender, diabetes, end-stage renal disease, immunosuppressive therapies, vaccinations, antibiotic resistance, etc.) exert a significant impact on functioning of the immune system, impinging on the fluctuations of the same and thus affecting consequent susceptibility to IE[27,28].

Lastly, an additional factor with the potential to impinge on immune system response is represented by the hypothalamic-pituitary-adrenal endocrine axis. The latter regulates response to acute and chronic infection through the secretion of glucocorticoid hormones, largely cortisol. Glucocorticoid release, under control of the circadian clock, is widely implicated in response of the immune system to infections, thereby indicating a close interplay between stress and circadian systems in the regulation of immunity[29]. An association between the mortality rate in hospitalised IE patients and increased cortisol levels and lymphocytopenia has been described[31].

Over the last few months, in the context of the COVID-19 pandemic, we have witnessed a further example of how fluctuations in the innate immune system play a key role in susceptibility to infection[31,32].

Consequences of this hypothesis and discussion

Need to better define the prescription of preventive antibiotic prophylaxis

In line with the hypothesis put forward herein, a better defined, tailored approach should be implemented for use in prescribing preventive antibiotic prophylaxis for IE. Indeed, patients currently classified as moderate-risk may at some point over their lifetime display susceptibility to IE as the consequence of an unforeseen or progressive impairment in their immune system defences following onset of a range of comorbidities such as diabetes, or due to the aging process. Accordingly, when evaluating the advisability of prescribing antibiotic prophylaxis, numerous factors should be taken into account, including the presence of comorbidities, cortisol levels, and ethnicity.

Newly emerging high-risk populations

Additionally, the potential reclassification of some 'moderate-risk' subjects, such as children, into the 'high-risk' category may play a crucial role in the prevention of IE. Indeed, in children the immune system has not yet developed fully[33], which may explain the observation of high rates of IE caused by Streptococcus viridans of suspected odontological origin in young patients affected by bicuspid aortic valve and mitral valve prolapse that features a clinical course similar to that observed in high-risk IE patients[34]. Accordingly, these children probably should be deemed as being at 'high-risk' and antibiotic prophylaxis revisited.

Likewise, chronic injection drug users also constitute a newly emerging high-risk population. Staphylococcus aureus, the most common pathogen involved in the development of IE in this population, is regularly detected on the skin of injection drug users and is inoculated deeper into their bodies during injection. Compared to the healthy population, immune system defences are frequently lower in the drug user population and thus more susceptible to bacterial proliferation[35]. A percentage ranging from 30 to 90% of injection drug users are also affected by human immunodeficiency virus, in turn resulting in a compromised ability to cope with infections and increased susceptibility to IE[36].

To summarise, in the light of the above considerations, an updated approach to IE prophylaxis should be developed[37,38].

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