EXPERT OPINION

Trends in rheumatic fever: clinical aspects and perspectives in prophylactic treatments

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Introduction: Rheumatic fever (RF), a systemic illness that may occur following Group A beta-hemolytic streptococcal (GABHS) pharyngitis in children, is a major problem in countries with limited resources. Because of its long track record and low cost, an injection of benzathine penicillin G (BPG) suspension every 3 or 4 weeks has been used as secondary prophylaxis. Despite its excellent *in vitro* efficacy, the inability of BPG to eradicate GABHS has been frequently reported.

Areas covered: This work reviews the possible causes of failure, as well as the inconvenience of the current prophylactic treatment of acute RF and suggests a new pharmacotherapeutic system that could replace the current one.

Expert opinion: RF is a major problem concerning only countries with limited resources and could be considered as a neglected disease. The dose regimen using BPG suspension results in failures, which could be avoided by the use of nanocarrier-based systems. To meet this ultimate goal, the research should be transposed from the laboratory scale to an industrial and clinical application level. This research should be conducted to produce a pharmaceutical dosage form that will be commercially available, consumed by and affordable for patients. However, health, environmental and socioeconomic hazards should be considered.

Keywords: benzathine penicillin G, microemulsion, nanotechnology, rheumatic fever

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1. Introduction

Rheumatic fever (RF) is a multisystem inflammatory disease process that follows upper airway infection with Group A streptococci (GAS). It is a non-suppurative sequel of Group A beta-hemolytic streptococcal (GABHS) pharyngitis, but the exact mechanisms by which it occurs remain to be elucidated. RF is said to be a disease that 'licks the joints and bites the heart'. This underlines the fact that cardiac involvement is the most serious manifestation of RF. The acute attack of RF may be associated with severe heart failure, which may be life threatening if appropriate medical and surgical therapy is not instituted [1-3].

Considering the severity of the conditions associated with RF, it is important to diagnose it quickly and accurately. The diagnosis is based on clinical findings and supportive laboratory studies. The current trend in the diagnosed cases is an aspect that requires further attention, but the incidence of RF has declined significantly since its peak in the 1940s [4] and it still remains a major cause of acquired heart disease in developing countries. However, in the developed world, only 3% of streptococcal pharyngitis patients develop RF [5]. In fact, RF is now a rare disease in America. The high prevalence of RF in developing communities is undoubtedly related to poverty and overcrowding, factors which favor the transmission of streptococci, and its

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Article highlights.

- Rheumatic fever (RF) is a major problem in countries with limited resources.
- The incidence of rheumatic heart disease (RHD), which is the most common form of pediatric heart disease in the world, is said to exceed 50 per 100,000 children.
- The mainstays of treatment for acute attacks of Group A beta-hemolytic streptococcal (GABHS) are bed rest until signs of activity have subsided and adequate doses of penicillin to maintain bactericidal blood levels for 10 days in order to eradicate the infecting streptococci.
- The inconvenience of the current prophylactic treatment of acute RF resides not only in the poor penetration of penicillin into the tonsillar tissues and tonsillar surface fluids, but also in the microbiological interactions between GABHS and other pharyngotonsillar flora.
- The pain experienced during the treatment with benzathine penicillin G (BPG) reduces the patient's compliance.
- Despite its excellent *in vitro* efficacy, BPG's inability to eradicate GABHS is frequently reported.
- New pharmacotherapeutic systems, such as microemulsion, could replace the current one.
- The development of nanocarrier devices to treat RF provides opportunities for further research in this field.

This box summarizes key points contained in the article.

reduction in more well-to-do populations has been linked to improved living conditions and hygiene [4,5].

Prevention of RF should be focused, as primary prophylaxis, on the prevention of the initial attack by using benzathine penicillin G (BPG) to treat sore throat in order to prevent acute RF. On the other hand, secondary prophylaxis is the use of long-term penicillin in a patient with a history of RF or rheumatic heart disease (RHD) to prevent a recurrence of RF [6]. In the countries where the disease is most prevalent, antibiotic regimes for primary and secondary prevention can be effective and a vaccine may ultimately be developed [7-9], but it is unfortunate that the most important step in the eradication of RF – the improvement in living conditions and reduction of overcrowding – requires means that these countries cannot afford [10]. Therefore, RF accounts for most cases of acquired heart disease in children and young adults, causing considerable suffering, serious disability and premature death [11,12]. The social impact, in terms of hospitalization costs and clinic visits, is significant. Most of the countries in which RF is prevalent do not have the financial resources or the sophisticated medical services required to treat the long-term sequelae of chronic valvular heart disease [10].

Accurate identification and treatment of tonsillopharyngitis caused by GABHS, with lifetime follow-up of patients with a history of RF, continues to be an important concern for medicine today [13-15]. Since RF remains endemic in many countries where it is a major cause of morbidity and mortality, it is vital to understand the epidemiology, clinical aspects and treatment strategies for this disease process [14,16,17]. This will be the focus of the next sections. The aim of this review was, therefore, to study the possible causes of failures, as well as the inconvenience of the current prophylactic treatment of RF, and propose a new pharmacotherapeutic system that could replace the current one.

2. Epidemiology

GABHS is among the most ubiquitous and versatile of human bacterial pathogens [18]. Although GABHS can cause serious invasive diseases, pharyngitis is by far the most common infection [19]. For example, 15 million cases of streptococcal pharyngitis occur annually in the USA alone, resulting in an estimated US$2 billion of direct healthcare costs [20,21]. However, despite decades of research, knowledge of the precise molecular events mediating GABHS pharyngitis remains rudimentary [22,23].

In a five-state laboratory and population-based surveillance study between 1995 and 1999, invasive GABHS infections were found to occur at a rate of 3.6 per 100,000 population annually in the USA, accounting for 9600 – 9700 cases and 1100 – 1300 deaths. Case-fatality ratios for pneumonia, necrotizing fasciitis and central nervous system infections exceeded 20%, while the ratio for streptococcal toxic shock syndrome was 44.5%. Equally remarkable is the propensity of GABHS to elicit two delayed, non-suppurative sequels: acute RF and acute post-streptococcal glomerulonephritis [24]. The latter is beyond the scope of this review.

The incidence of RF began to decline in developed countries in the second half of the 19th century [25]. The advent of antibiotics in the 1950s accelerated this decline [26,27]. For example, in the USA the incidence of RF has fallen from 100 per 100,000 population at the turn of the century to 45 ~ 55 per 100,000 between 1935 and 1960, and further to 2 per 100,000 currently [28]. This contrasts sharply with the reported incidence in the developing world, where the incidence of RF has been reported to be as high as 21 per 1000 [2]. According to the World Health Organization (WHO) [29], about 0.5 million individuals acquire RF each year, most of them in developing countries. However, epidemiological data from many developing countries are poor and these values are very likely to be underestimated [2,30].

A recent review of the global burden of GABHS-related disease has estimated that there are at least 15.6 million people with RHD, another 1.9 million with a history of RF but no carditis (still requiring preventive treatment), 470,000 new cases of RF each year, and over 230,000 deaths due to RHD annually [4]. Sub-Saharan Africa is most severely burdened by this disease with 5 – 7 cases per 1000. Within-country variation is evident in Australia, with the indigenous population accounting for 94% of all deaths due to RF [22].

Because of its high prevalence in developing countries, RHD is the most common form of pediatric heart disease in the world [31,32]. The incidence of RF is said to exceed 50 per 100,000 children [33,34]. In many countries, it is the

most common cause of cardiac mortality in children [3]. First attacks are uncommon in the very young (under the age of 5 years) with the peak incidence occurring in those aged 5 – 15 with a decline thereafter and are rare in adults over the age of 35. Recurrent attacks are most frequent in adolescence and young adulthood and are not often diagnosed after the age of 45 [2].

3. Clinical aspects

A positive diagnosis of RF requires the presence of one or a combination of the following clinical features: carditis, migrating polyarthritis of the big joints, chorea, erythema marginatum (EM) and subcutaneous nodules, which represents the Jones Criteria.

3.1 Clinical features related to the major criteria of Jones

In 1944, T. Duckett Jones initially attempted to render the diagnosis and management of RF systematic. His description of a constellation of symptoms most often associated with clinical RF enhanced diagnostic accuracy and understanding (**Table 1**). The important addition in 1965 of a requirement for evidence of a streptococcal infection refined the criteria. However, even after this modification, diagnostic (and therapeutic) problems remain [35,36]. RF/RHD remains a global problem [2,37,38].

The clinical features of active RF include any one or a combination of the following: i) carditis, ii) polyarthritis, iii) chorea, iv) subcutaneous nodules and v) EM. These symptoms constitute the major criteria of Jones and are discussed below. Minor criteria are: i) an elevated erythrocyte sedimentation rate, ii) positive C-reactive protein, iii) raised white cell count, iv) prolonged PR interval on echocardiography (not valid if there is clinical carditis), v) arthralgia (not valid if there is clinical arthritis), vi) pyrexia and vii) a previous history of RF [5,39].

Carditis is the only lesion in RF that can cause death or permanent sequelae. All the other conditions resolve completely without any ill effects. The term 'carditis' implies acute, active, ongoing inflammation in cardiac tissue, whether it be pericardium, myocardium or endocardium, whereas 'RHD' denotes the resultant chronic lesion after the acute disease has subsided [5]. These conditions occur as a result of an autoimmune response against streptococcal antigens that develop cross-recognition to the human cardiac tissue. This mimicry between streptococcal antigens and heart tissue proteins, combined with the production of pro-inflammatory cytokines and reduced production of IL-4, leads to the development of cardiac tissue damage [40]. RHD affects the mitral valve in up to 50% of cases and results in mitral insufficiency, mitral stenosis or both. In young patients, mitral regurgitation is predominant, but mitral stenosis becomes progressively more common with age [27,41,42]. Regurgitant rheumatic valves are edematous with fibrous thickening and minimal calcification, non-fused commissures, annular dilatation and anterior chordal elongation, whereas stenotic rheumatic valves have stiff and restricted leaflets, commissural fusion, annular calcification and chordal fusion [41,42].

As stated above, one of the major criteria of Jones is chorea. Sydenham's or rheumatic chorea manifests as repetitive, involuntary, jerky movements involving mainly the face and limbs which may continue during sleep. Hyperextension of joints because of severe hypotonia is seen, especially involving the metacarpophalangeal joints ('dinner-fork' position, with the wrists flexed) [5]. This is usually sporadic. The large joints of elbows, wrists, knees and ankles are usually involved, with occasional involvement of smaller joints of the fingers. There is pain, tenderness, swelling and limitation of movement. The response to aspirin is dramatic: the arthritis seldom persists beyond 5 days. When any of the other major criteria co-exist, the arthritis can be confidently diagnosed as being due to RF. However, difficulties arise when only one joint is involved with no other major signs, or if there is arthralgia without objective signs of arthritis [5,27,37].

The other clinical features include subcutaneous nodules and EM, which are rare, especially in dark-skinned populations. The nodules of acute RF are never tender, and are found most commonly over the extensor surfaces of the elbows, knees, shins and over the spine [43]. EM is a transient rash in the form of wavy lines or erythematous rings with normal paler centers, occurring mostly on the trunk and proximal parts of the extremities but never the face, hands or feet [5,27,39].

4. GABHS pathogenicity

Infections have an important role in the 'mosaic of autoimmunity'. Almost every autoimmune disease investigated is linked to one or more specific infectious agents [44,45]. One of the best-recognized examples of this relationship is acute RF, which develops several weeks after infection with *Streptococcus pyogenes* [46,47].

The reaction of the immune system plays an important role in the inflammatory process during RF [45]. The inflammation caused by RF results in a characteristic histopathological picture, including the presence of Aschoff bodies and leukocyte infiltration. Although the pathognomonic Aschoff bodies are rarely seen in the valves themselves, RF does lead to an acute valvulitis with inflammation and edema of the leaflets. Fibrin–platelet thrombi occur along the leaflet contact zones. Fibrosis of the affected valves leads to deformity, stenosis and insufficiency. The progression to overt RHD, particularly the calcification that accompanies RHD, was until recently thought to be a passive process attributable to the abnormal hemodynamics caused by the deformed valves [18,23,44,46,48]. Importantly, the type of response to the infection is related to the *S. pyogenes* strain. Studies of outbreaks of streptococcal pharyngitis show that strains of certain M serotypes are strongly and repetitively associated with RF whereas strains

Table 1. Jones Criteria for guidance in the diagnosis of acute RF.

Major manifestations	Minor manifestations	
Carditis	**Clinical**	**Laboratory**
Polyarthritis	Previous RF or RHD	Prolonged PR interval
Chorea	Arthralgia	Acute phase reactants
EM	Fever	Elevated erythrocyte sedimentation rate
Subcutaneous Nodules		Positive C-reactive protein
		Leukocitosis

EM: Erythema marginatum; RF: Rheumatic fever; RHD: Rheumatic heart disease.

of other equally prevalent types do not initiate the disease or even reactivate it in highly susceptible hosts [27,49].

The propensity of a given strain to elicit RF may well depend on its phase of virulence, an indication of quantitative factors such as the reduction of M protein, hyaluronate or other less well-defined biological properties. Virulence is likely to be enhanced in epidemiological settings that favor rapid person-to-person passage [18]. Moreover, variations in the rheumatogenicity of prevalent GABHS probably account for the marked temporal and geographic fluctuations in the incidence of RF [39].

Rheumatogenic streptococcal strains have distinct biological properties. Their M-protein molecules share a particular surface-exposed antigenic domain against which RF patients mount a strong IgG response. Surface structures of GABHS, including the family of M proteins, the hyaluronic acid capsule and fibronectin-binding proteins, allow the organism to adhere to, colonize and invade human skin and mucus membranes under varying environmental conditions. M proteins bind to complement control factors and other host proteins to prevent activation of the alternate complement pathway and thus evade phagocytosis and killing by polymorphonuclear leucocytes. Extracellular toxins, including superantigenic streptococcal pyrogenic exotoxins, contribute to tissue invasion and initiate the cytokine storm believed to be responsible for illnesses such as necrotizing fasciitis and the highly lethal streptococcal toxic shock syndrome [18,39,48,50].

Indeed, the specific biological properties of the streptococcus causing pharyngitis allow this organism to i) adhere to the pharyngeal mucosa and cause infection and ii) resist phagocytosis. Although the exact mechanism by which GABHS induces the disease remains unexplained, most attention has been focused on the aforementioned notion of autoimmunity, or, more precisely, molecular mimicry. This theory is rendered more credible by several examples of antigenic similarity between somatic constituents of GABHS and human tissues, including the heart, synovium and neurons of the basal ganglia of the brain. Taken together, these immunological cross-reactions could theoretically account for most of the manifestations of RF. As yet, however, there is no direct evidence that any of these manifestations are pathogenically significant [18,27,50,51].

5. Recommendations for treatment

There is no doubt that RF is a preventable illness and should receive high priority in primary healthcare programs in all developing countries [52,53]. Although RF is theoretically preventable through the use of antibiotic treatment for streptococcal infections [54-56], once RF has occurred, there is no therapy, apart from prevention of recurrent episodes of RF that has been shown to be able to prevent progression to valvular involvement [46,57].

Before the 1950s, when it was demonstrated that penicillin therapy could prevent acute RF, it was well known that most cases of GABHS pharyngitis were self-limiting [58]. Without antibiotic treatment, tonsils and lymph nodes did not return to their normal volume for several weeks, but the great majority of patients had resolution of their signs and symptoms within 7 days and fever usually disappeared within 3 – 5 days. For that reason, the use of clinical cure as an efficacy end point in GABHS pharyngitis is unreliable. Antimicrobial therapy is vital because without antibiotic treatment some patients develop acute RF. Indeed, the trials involving untreated streptococcal pharyngitis show that at least 2.4% of individuals receiving no antibiotic developed acute RF 1 – 2 months following a suspected streptococcal sore throat infection [59]. Robertson KA, *et al.* demonstrated that a protective effect of 80% was found with a reduction in risk of acute RF for patients with sore throat and symptoms suggestive of GAS infection when treated intramuscularly with penicillin [59]. A relationship has been established between bacterial eradication of GABHS by penicillin therapy and the prevention of acute RF [60]. Therefore, trials comparing the clinical efficacy of various antibiotic regimens use the end point of bacteriological eradication of GABHS as a surrogate marker of prevention [61]. This is reflected in the guidelines of the Food and Drug Administration and the European Medicines Evaluation Agency for the development of new antibiotics for GABHS pharyngitis, with both agencies using bacteriological eradication of the initial pathogens as the main efficacy end point [50,52,62,63].

In 1950, it was reported that acute RF could be prevented by the treatment of streptococcal pharyngitis with penicillin [64]. The next year, a new depot form of penicillin, BPG, was studied and reported to be effective in the secondary prophylaxis for prevention of recurrent RF [56,65,66]. Both the WHO and the American Heart Association recommend injections every 3 weeks of 1,200,000 units of BPG for secondary RF prophylaxis in certain high-risk patients or highly endemic areas [65]. Official recommendations include two phases: treatment of acute attacks of pharyngitis and prophylaxis, as detailed below.

The mainstays of treatment for acute RF attacks are bed rest until signs of activity have subsided and adequate doses of penicillin to maintain bactericidal blood levels for 10 days in order to eradicate the infecting streptococci. Salicylates in short courses can be used to obtain symptomatic relief from arthritic pain, but have not been shown to be of value in carditis. Corticosteroids have not proved to be effective in the management of carditis, since they neither shorten the duration of the acute attack nor have any beneficial effect on the long-term outcome. Nevertheless, some authors recommend their use in severe cases or in life-threatening situations despite the lack of evidence of benefit. In patients with heart failure, digoxin, diuretics with potassium supplementation and occasionally captopril may be indicated [3,5,27].

Prophylaxis can be classified as either primary or secondary (**Table 2** and **Table 3**). Primary prophylaxis refers to antibiotic treatment of GABHS pharyngitis to prevent subsequent RF [15]. A single intramuscular injection of 1,200,000 units of BPG or 10 days of penicillin V is recommended [39]. Efforts at primary prevention are confounded by the fact that many patients who develop RF are not aware of a preceding sore throat. There are no simple specific clinical signs diagnostic of streptococcal pharyngitis, and throat swabs and cultures are expensive. However, antibiotic treatment for suspected streptococcal sore throat is effective in reducing the occurrence of subsequent attacks of RF by 70 – 80% of the cases, and this may be affordable for developing countries as a strategy for preventing RF [3].

Secondary prophylaxis, the long-term administration of antibiotics to prevent recurrence, is of proven benefit and is cost-effective [2]. It has been advised until age 21 or at least 5 years after the last attack of RF, whichever is the longer. The WHO points out that it is not possible to generalize and the duration of secondary prophylaxis should be individualized, taking into account factors influencing the risk of recurrence. Lifelong prophylaxis is recommended for patients with severe valve disease or after valve replacement surgery [2].

For almost five decades, penicillin has been the drug of choice for the treatment of streptococcal pharyngitis [67,68]. This antibiotic has proven efficacy and safety with a narrow spectrum of activity and low cost. However, the correct dose and time intervals remained controversial for a long time. Some authors, like Kafetzis *et al*. emphasized that for the long-term prophylaxis, 2 or 3 weekly injections were more effective, but may be more difficult to implement [50]. Penicillin V 250 mg orally twice daily is recognized to be less effective, but may be preferred by some practitioners, particularly in very thin patients who are on warfarin anticoagulation therapy after valve replacement surgery when deep intramuscular injections may be undesirable [50]. The drawbacks and limitations of this 10-day penicillin V regimen have initiated a study of other antibiotic compounds for the treatment of GABHS pharyngitis. The aim of these therapies is to achieve equivalent (or improved) bacteriologic and clinical cure rates compared with penicillin V [50]. On the other hand, a systematic review of the correct regimen for penicillin use concludes that intramuscular penicillin seemed to be more effective than oral penicillin in preventing RF recurrence (87 – 96%) and streptococcal throat infections (71 – 91%). Additionally, this study demonstrated that 2 weekly or 3 weekly injections appeared to be more effective than 4 weekly injections [6]. The evidence in favor of 2 weekly injections is strong, with an almost 50% reduction in the risk of RF recurrence and a 40% reduction in streptococcal throat infections compared with 4 weekly injections [69].

Many other drugs, for example, cephalosporins, have been used successfully for the treatment of GABHS tonsillopharyngitis since the early 1970s [70]. Several compounds with simple and shorter dosing regimens (amoxicillin, cefadroxil, cefuroxime, cefpodoxime, cefixime, cefotiam, cefdinir, azithromycin, clarithromycin) can provide similar or better results than 10-day penicillin V in terms of GABHS eradication [71,72]. Probably because of its pharmacokinetic properties, azithromycin is the most extensively studied drug in the setting of pediatric GABHS pharyngitis [50,63,73,74].

In addition to the regimens consisting of the administration of penicillin or cephalosporins, another therapeutic approach involves a slight physico-chemical modification of penicillin that resulted in the introduction of BPG some decades ago [74]. This provides a depot form of the antibiotic that remains the drug of choice for prevention of RF. The standard recommendation is 1,200,000 units of BPG intramuscularly every 4 weeks. Pharmacokinetic studies indicated that serum penicillin levels exceeded the minimal inhibitory concentrations (MIC) of GAS for 4 weeks after intramuscular injection of 1,200,000 units of BPG [75]. The MIC of penicillin reported against GABHS is estimated to be between 0.01 and 0.03 μg/ml [74]. A level of 25 ng/ml was chosen to indicate an adequate protective penicillin level and there was a consistent, but not a statistically significant, trend of higher proportions of patients with plasma penicillin levels above 25 ng/ml with higher BPG doses each week. The choice of 25 ng/ml as a protective level of serum or plasma penicillin is based on published penicillin MICs for *S. pyogenes*, with the vast majority of organisms having MICs below 20 ng/ml. One study found that over 80% of samples from 21 days after 1,200,000 units of BPG had penicillin levels greater than 20 ng/ml [65,74].

However, data challenging the 4-week schedule have been published. It was reported that very low or non-detectable values were obtained after administration of 1,200,000 units of BPG, and that injections given at 3-week intervals resulted in fewer recurrences than injections given at 4-week intervals. The recurrence rates were 3.0 and 9.7%, respectively. More recent studies reported that intramuscular injection of BPG did not produce serum values above the MIC by week 3 in a significant proportion of patients [75]. Further pharmacokinetic studies after the administration of BPG investigated penicillin concentrations in tonsils. They indicate maintenance of consistent concentrations for 2 weeks after

Table 2. Treatment of GABHS pharyngitis (primary prevention of RF)*.

Antibiotic	Route	Patient	Dose	Duration
For non-penicillin-allergic patients				
Benzathine penicillin G	i.m.	< 30 kg	600,000 IU	A single injection
		> 30 kg	1,200,000 IU	
Phenoxymethylpenicillin (penicillin V)	Oral	< 30 kg	250 mg 2 or 3 times daily	10 days
		> 30 kg	500 mg 2 or 3 times daily	
For penicillin-allergic patients				
Erythromycin ethylsuccinate	Oral	Not specified	40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days
Erythromycin estolate	Oral	Not specified	20 – 40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days

*Applied by WHO [101].

GABHS: Group A beta-hemolytic streptococcal; RF: Rheumatic fever; WHO: World Health Organization.

Table 3. Prevention of GABHS infections in individuals who have had an initial attack of RF (secondary prophylaxis of RF)*.

Antibiotic	Route	Patient	Dose
Benzathine penicillin G	i.m.	For children < 30 kg	600,000 IU every 3 – 4 weeks
		For children > 30 kg and adults	1,200,000 IU every 3 – 4 weeks
Phenoxymethylpenicillin	Oral	Not specified	250 mg 2 or 3 times daily
Sulfonamide	Oral	< 30 kg	500 mg/day
		> 30 kg	1 g/day
Erythromycin	Oral	Not specified	250 mg 2 times daily

*Applied by WHO [101].

GABHS: Group A beta-hemolytic streptococcal; RF: Rheumatic fever; WHO: World Health Organization.

administration followed by a significant reduction in values at day 21. These findings provide additional data on why recurrences of RF are observed in patients treated with the monthly schedule for prophylaxis. The results of these studies indicate that penicillin concentrations in serum and tonsils may be inadequate for prevention of RF by week 3 of administration in most children after 40,000 IU/kg BPG dose treatment [75,76].

Several reports have recently appeared in the literature questioning the persistence of effective penicillin levels beyond the third week after the BPG injection [77]. The recommendation of the American Heart Association of monthly injections is now being questioned by physicians in developing countries. In India, a prophylaxis regimen based on injections every 3 weeks was used during the 1980s [40]. In other countries, two modified regimens were proposed, one of which consisted of a regular injection every 2 weeks for all ages [69]. Furthermore, Cunningham suggested that a logical approach for secondary prevention would be a 3-week program in areas where the risk of RF recurrences is high [40].

Other studies have focused on the pharmacokinetic profiles obtained from BPG preparations from different suppliers [78]. Although the vials of the two analyzed products were found to be chemically equivalent (1,200,000 units of BPG), a remarkable difference between them was confirmed. This difference might be due to the physical properties of BPG, the degree of solubility and hence, the rate of release of penicillin from the site of injection [69,79].

In addition to the influence of the physical properties of BPG, the limited success in preventing streptococcal infections could be attributed to several interacting factors, including the compliance of patients, the chronically inflamed tonsillar tissue that hinders the penetration of penicillin and the coexistence of GABHS with other penicillinase-producing organisms. Further investigations are needed to elucidate this problem [69,80].

Other explanations could lie in the interactions between GABHS and other members of the pharyngotonsillar bacterial flora. For example, it is hypothesized that β-lactamase secreted by β-lactamase-producing bacteria, which colonize the pharynx and tonsils, may 'shield' GABHS from penicillin. Another possibility is the coaggregation of *Moraxella catarrhalis* and GABHS, which can facilitate colonization by GABHS. Normal bacterial flora can interfere with the growth of GABHS, and the absence of such competitive bacteria makes it easier for GABHS to colonize and invade the pharyngotonsillar area [81].

The inconvenience of the current prophylactic treatment of acute RF resides not only in the poor penetration of penicillin into the tonsillar tissues and tonsillar surface fluids, but also in the microbiological interactions between GABHS and other pharyngotonsillar flora, which can account for penicillin failure in eradicating GABHS [81].

Furthermore, the pain experienced during the treatment with BPG reduces the patient's compliance. In order to overcome these difficulties, innovative approaches are required.

6. Perspectives in prophylactic treatments

The delivery of BPG in a nanocarrier-based system, and in particular a microemulsion, could be a plausible and innovative alternative to the current treatment.

6.1 Trends in nanocarrier-based systems for non-ideal drugs

Over the last three decades, colloidal vehicles have been explored and have emerged as interesting potential systems for drug delivery. These self-organizing systems often lead to improvement in the therapeutic index of the lipophilic drugs through increased solubilization and modification of their pharmacokinetic profiles [82-86]. The potential applications of colloidal drug carriers by the intravenous route can be summarized in terms of the concentration of drugs in accessible sites, the rerouting of drugs away from sites of toxicity and the increase in the circulation time of labile or rapidly eliminated drugs [83]. Carriers may extravasate into inflamed or infected sites, where the capillary endothelium is defective. Some formulations already on the market are able to reduce the side effects and control the release of the encapsulated drugs [87]. Colloidal drug carriers are particularly useful for the formulation of new drugs produced by biotechnology (proteins and nucleic acids) because they can provide protection from degradation in biological fluids and promote their penetration into cells [88]. They also have applications with respect to small hydrophobic molecules by providing an ultradispersed form without the use of irritating solvents and allowing rapid drug dissolution. Therefore, it is likely that colloidal systems will be able to improve the efficacy of both established drugs, such as BPG, and new molecules [82,89,90].

6.2 Microemulsions: the innovative alternative for the RF treatment

Microemulsions are an example of colloidal carriers that are spontaneously forming single-phase colloidal dispersions of either oil-in-water or water-in-oil stabilized by an interfacial film of surfactants and co-surfactants [90]. These self-assembled dispersions have low viscosity, ultraslow interfacial area, good shelf-life, high solubilizing capacity, macroscopic homogeneity and microscopic heterogeneity (microdomains) [82,91].

Considering all these advantages, the use of microemulsions has been reported for different fields in the literature [90,92-96]. In particular, they may have many potential applications in the pharmaceutical area, such as improving the treatment of RF. While it is true that an increase in the solubility of drugs in the microemulsion system is an important factor in their performance, another important factor is their small droplet size, resulting in a large surface area from which the drug can partition and be absorbed more regularly or permeate through membranes. Moreover, the dissolution pathway is no longer limiting. The encapsulation of drugs in a restricted microenvironment also offers protection from enzymatic degradation by the interfacial layer. Furthermore, the membrane permeability is facilitated by the presence of surfactants and co-surfactants [97]. Therefore, these systems are ideal for the controlled release of hydrophobic drugs. Another potential advantage is their transparency which allows them to be visually assessed for microorganism growth and also allows inspection for the presence of precipitated drugs. Their thermodynamic stability is also an important characteristic of these systems when compared with kinetically stabilized emulsions. In addition to that, the formation of microemulsions requires only the most basic mixing equipment. More importantly, their manufacture is not as dependent on the careful control of the manufacturing process as, for example, the preparation of emulsions [82,83,88,89,91,97,98].

The increase in the bioavailability of drugs from microemulsions compared with conventional drug dosage forms has already been described [82,99]. Several researchers have reported studies in which the drug reservoir effect of the delivery system produced sustained release [90]. Drug release from a microemulsion formulation depends on several factors, the main one being its partitioning from the oil to the water phase of the system. Other factors such as the fraction volume of dispersed droplets and droplet size, distribution of the drug in the various phases of the system, potential interaction between the vehicle and drug and the rate of the drug diffusion from the dispersed phase of the system may also play an important role in the drug release [82]. A clear understanding of these important parameters and a careful selection of the components of formulation are essential for optimizing drug release from the microemulsion system [99].

Considering the points mentioned above, microemulsions could be a very attractive system for the parenteral administration of penicillin. They may enable a sustained release, thereby reducing the frequency of administration. Patient safety would also be improved because the dose required and the plasma concentration would be stable. However, very few studies in the literature have addressed the use of nanocarriers for RF treatment. One published work reports that BPG can be incorporated into liposomes [100], and although these systems remained stable for over a year and showed *in vitro* activity against *S. pyogenes*, they were not able to encapsulate a sufficiently large amount of BPG. Nanoemulsions and nanocapsules have also been used to formulate colloidal nanosystems of BPG intended for the prophylactic treatment of RF [101]. However, the penicillin concentration in nanocapsules was about 100 times less than the therapeutically recommended dose for children. Development of polybutyl adipate (PBA) nanocapsules loaded with BPG has been reported [102]. The drug was successively encapsulated within PBA nanocapsules with high drug loading and encapsulation efficiency using the w/o/w emulsion solvent

evaporation technique, but these nanocapsules showed high burst release. Other systems, such as a micellar system of BPG, have also been reported [103]. This micellar system could incorporate up to 90% of BPG, despite the incompatibility of this molecule with water, and improve its resistance against hydrolytic and enzymatic degradation. The systems described so far indicate that there is potential for the development of colloidal drug carriers for BPG. However, further work is still needed to reach a new and therapeutically appropriate system for BPG, which could improve the conditions of treatment of patients with RF.

7. Conclusion

Due to the particular location in which RF remains a serious health public problem, the developing countries, it could be considered a neglected disease. Therefore, the population cannot expect to have intensive pharmaceutical research to remedy the obstacles to its treatment. Additionally, the reasons for RF treatment failure are multifactorial and include difficulties with health service delivery and inadequate health staff numbers in addition to a mobile population and different cultural perceptions of health and sickness. Indeed, compliance depends on the length of treatment, with evidence for better compliance with shorter regimens. Drug palatability may also be one of the most important factors affecting patient compliance, and it has a major impact on the efficiency and safety of a medication. Therefore, patient compliance is an important variable to consider when selecting an antimicrobial agent.

The overall points described in this review suggest that doses larger than the currently recommended ones of BPG may be more appropriate for prevention of RF, particularly in higher-risk populations. Although early studies of BPG suggested that larger doses resulted in prolongation of the period of detectable penicillin levels, there are inadequate data on secondary prophylaxis BPG regimens with doses greater than the 1,200,000 units. Another possibility is to consider more frequent injections although this may imply increased risks of poorer compliance.

An important factor to take into account is the development of resistance to BPG. One way of combating resistance is to eradicate the microbial load rapidly, and in this respect higher doses could be advantageous. However, it is also imperative to search for new antibiotics which would be effective against GAS. By concentrating the antibiotics at the site of action and allowing controlled release, drug delivery systems can contribute to the efficacy of both old and new molecules.

8. Expert opinion

Although GABHS is among the most ubiquitous and versatile of human bacterial pathogens inducing pharyngitis around the world, the research on RF has revealed that this is a major problem concerning only countries with limited resources. Therefore, this causes RF to be a neglected disease in these countries and the population cannot expect to have intensive pharmaceutical research to remedy the drawbacks on its treatment.

The injection of BPG suspension every 3 or 4 weeks has been used as secondary prophylaxis of RF because of its long track record and low cost. Despite its excellent *in vitro* efficacy, the inability of BPG to eradicate GABHS is frequently reported. Over the past 50 years, the rate of penicillin failure has consistently increased from about 7% in 1950 to almost 40% in 2000. Therefore, more attention should be given to the BPG clinical application, which must be a site-specific treatment rather than the intramuscular application of 1,200,000 units in which a great amount is degraded on site and only around 20 ng/ml reaches the plasma level.

This aim could be achieved by the use of nanocarrier-based systems, which are able to improve the expected pharmacokinetic/pharmacodynamic activity of a desired drug. The site-specific delivery produced by such carriers is designed to minimize undesired effects caused by conventional therapy.

Microemulsions have been shown to protect labile drugs, control drug release, increase bioavailability and reduce the variability of patient outcomes. The advantages for drug delivery offered by microemulsions include improved drug solubilization and protection against enzymatic hydrolysis, as well as the potential for enhanced absorption provided by surfactant-induced membrane fluidity leading to permeability changes. Microemulsions have great potential as a parenteral vehicle for BPG aiming at the treatment of RF because they may be used for intravenous, subcutaneous or intramuscular administration. In addition, they are generally used to obtain prolonged release formulations. Another approach represented by the use of the microemulsion is that it significantly increases half-life, area under curve and mean residence time of drugs. Therefore, through a multiparticulate and novel approach such as the use of microemulsions, the delivery of BPG can be a plausible and innovative alternative for the current treatment. To meet this ultimate goal, the research should transpose the laboratory scale to an industrial and clinical application level.

Concerning the future, the ongoing research and clinical trials of BPG microemulsion systems or other multiparticulate systems will require more attention to make the treatment more approachable and affordable for patients. Research should be conducted to produce a pharmaceutical dosage form that will be commercially available, consumed by and affordable for patients. Therefore, there is a need to design and develop various simple, cost-effective, safe and efficacious devices, which can open alternative horizons to the field of RF treatment.

Another approach that should be considered during the development of nanotechnological devices such as microemulsions for BPG is the use of scaling-up manufacturing

technologies. Also, the pharmaceutical experts should refine such technology in a more economical way.

Besides the aforementioned discussion, health, environmental and socioeconomic hazards are the other concerns that should be considered as unavoidable risks in the pharmaceutical practice of nanotechnology. Moreover, all these areas, which still have not yet been fully studied, provide opportunities for further research in the field of development of nanotechnological carriers to treat RF.

Declaration of interest

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