International Journal of Scientific Reports
Zafar M et al. Int J Sci Rep. 2025 Feb;11(2):88-96
http://www.sci-rep.com
pISSN 2454-2156 | eISSN 2454-2164
DOI: https://dx.doi.org/10.18203/issn.2454-2156.IntJSciRep20250061

Review Article

Revolutionizing rheumatic heart disease prevention: the potential of high-dose subcutaneous benzathine penicillin G: a narrative review

Mahtab Zafar[1], Vaneesa Ali[2], Aysha Asif[3], Shanza Shakir[4], Farina Bari[5], Hira Shakeel[6], Suhaina Amir[7]*, Muhammad Umar[2]

[1]Rahbar Medical and Dental College, Lahore, Pakistan
[2]Khairpur Medical College, Khairpur Mir's, Pakistan
[3]Jinnah Sindh Medical University, Karachi, Pakistan
[4]Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[5]King Edward Medical University, Lahore, Pakistan
[6]Shaikh Zayed Hospital, Lahore, Pakistan
[7]Dow University of Health Sciences, Karachi, Pakistan

Received: 30 September 2024
Revised: 15 December 2024
Accepted: 16 December 2024

***Correspondence:**
Dr. Suhaina Amir,
E-mail: Suhainaamir1703@gmail.com

ABSTRACT

Rheumatic heart disease (RHD) is a severe, chronic condition arising from acute rheumatic fever (ARF), a complication of untreated group A - *Streptococcus* infections. RHD results in progressive damage to the heart valves, leading to significant morbidity and mortality. While RHD has declined in high-income countries due to effective prophylaxis, it remains a major health issue in developing regions. Approximately 15 million people worldwide are affected by RHD, impacting quality of life and healthcare systems. This narrative review evaluates the efficacy and safety of high-dose subcutaneous benzathine penicillin G (BPG) injections as a preventive strategy for RHD. Traditionally administered intramuscularly, the review explores the subcutaneous route's benefits. Subcutaneous BPG is effective in preventing ARF recurrences and managing RHD progression. It maintains therapeutic penicillin levels over extended periods, potentially reducing injection frequency. This method is associated with less pain and improved patient adherence compared to intramuscular injections. However, subcutaneous BPG administration has challenges. Adverse effects, such as allergic reactions and anaphylaxis, though infrequent, require careful management. Consistent drug supply is also essential. Future research should explore innovative delivery methods, such as implantable devices or transdermal systems, to further improve patient outcomes. In conclusion, high-dose subcutaneous BPG injections offer a promising option for RHD prophylaxis, combining efficacy with a favorable safety profile. Addressing administration and side effect challenges is crucial for optimizing treatment effectiveness.

Keywords: Rheumatic heart disease, Acute rheumatic fever, Benzathine penicillin G, Subcutaneous injection, Prophylaxis, Pharmacology

INTRODUCTION

Acute rheumatic fever (ARF) arises from an abnormal immunological response to untreated group A *Streptococcus* (*Streptococcus pyogenes*) skin or throat infections, manifesting in joint, cardiac, skin, and neurological symptoms. Rheumatic heart disease (RHD) is a dangerous illness that causes irreversible damage to the heart valves and may result in early death. It can be brought on by one or more ARF episodes.[1-3]

An aberrant immunological reaction to a group A streptococci infection in genetically susceptible individuals causes RHD. Although ARF and RHD have

become less common in affluent countries since the early 1900s, they are still leading causes of illness and death for youth in underdeveloped countries. RHD is thought to affect about 15 million people worldwide accounting for 282,000 new cases and 233,000 fatalities per year.[5,6] A systematic review of 25 studies from Bangladesh, India, Pakistan, and Nepal found that while RHD is decreasing in Bangladesh, India, and Pakistan, it is rising in Nepal, with a higher prevalence in rural areas compared to urban ones.[7] Heart failure, arrhythmias, stroke, embolisms, and eventually premature death are among the serious health consequences that can arise from RHD.[8]

Secondary antibiotic prophylaxis (SAP) with benzathine penicillin G (BPG) has been demonstrated to effectively lower the incidence of ARF recurrences and the onset or aggravation of RHD.[9-11] Recent investigations on the pharmacokinetics (PK) of teenagers with ARF have revealed that overweight people have unintentionally received subcutaneous administration, which has a favorable absorption profile but no evident negative effects.[2,12]

For many GAS infections, β-lactam penicillin is still the most effective antibiotic.[13] Penicillin-binding proteins (PBPs) are the target of β-lactam antibiotics, which prevent peptidoglycan cross-linking in metabolically active bacteria and cause bacterial death as shown in Figure 1.[14,15] For most GAS infections, one of the few reasons to think about trying a different medication is a penicillin allergy.[14]

Pain is one of the major problems when intramuscular BPG is given.[2] There have been suggestions for developing better long-acting penicillin formulations to prevent RHD because injection frequency and pain are the main obstacles to adherence. It is suggested that subcutaneous benzathine penicillin may resolve these issues as it slows absorption, increases half-life, and reduces dosing frequency. It is also suggested to cause less pain as compared to IM penicillin.[2]

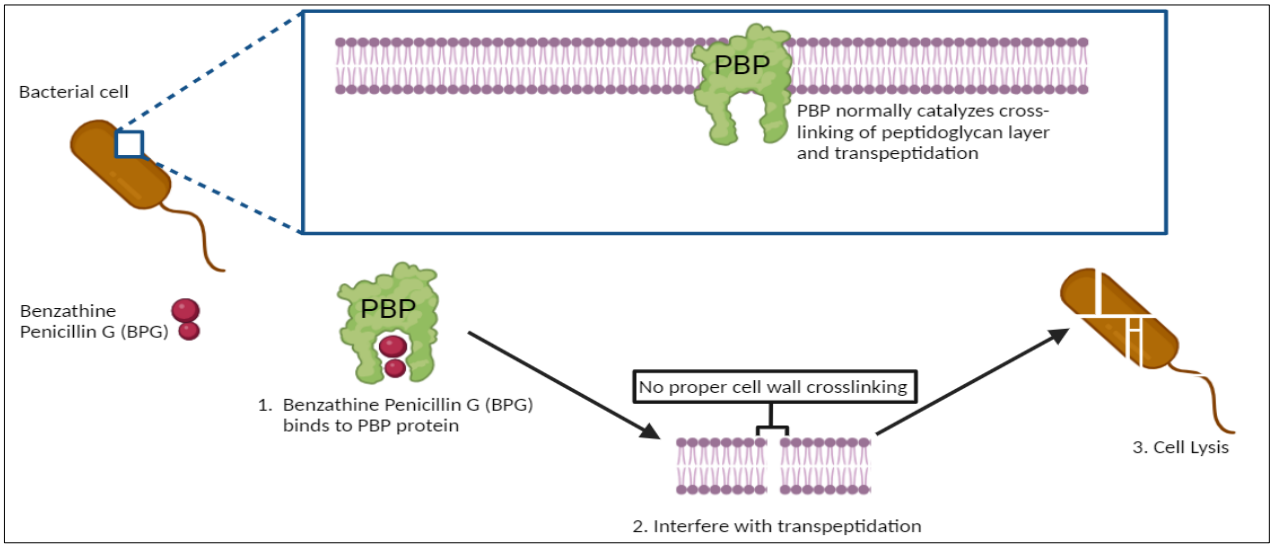

Figure 1: Mechanism of action of benzathine penicillin G on bacterial cells: BPG binds to the PBP on the bacterial cell wall. PBP normally catalyzes the cross-linking of the peptidoglycan layer, a critical process for maintaining cell wall integrity. Binding to PBP, BPG interferes with transpeptidation, resulting in improper cell wall crosslinking. This disruption leads to cell lysis and ultimately the death of the bacterial cell.

This narrative review aims to examine the efficacy and safety of high-dose subcutaneous injections of BPG as a preventive measure against RHD. By synthesizing existing research, we seek to provide a comprehensive overview of the benefits, potential risks, and practical considerations associated with this intervention.

PHARMACOLOGY OF BENZATHINE PENICILLIN G

For the secondary prevention of patients with rheumatic fever it is recommended to use intramuscular injections of 1.2 million IU (MIU; 900 mg) of BPG every 3 or 4 weeks.[16] It is established that BPG is superior to oral penicillin and non-penicillin antibiotics in preventing infections caused by *Streptococcus pyogenes* as shown in Figure 2.[17] Intramuscular injection, it is hydrolyzed to benzylpenicillin and absorbed from the depot site into the plasma. Penicillins work by binding to PBPs, which are present in the cell membrane of bacteria. This process prevents the last step of peptidoglycan formation, causing osmotic lysis of the bacterial cells, thus resulting in a bactericidal action.[18]

BPG is easily absorbed following intramuscular or subcutaneous injection, oral absorption is poor because it is susceptible to hydrolysis by gastric acid. Once BPG is intramuscularly injected, the drug is slowly released from the muscle into the systemic circulation, where it is

activated via *in-vivo* hydrolysis and produces prolonged serum concentrations of benzylpenicillin.[19]

Absorption mainly depends on body composition, formulation, and dose. Delayed absorption in obese or overweight patients highlights the potential for wide variability in BPG PK in patients with different body compositions. Furthermore, differences in BPG crystal sizes within and between different formulations may also influence absorption kinetics.[2,12,20] Like most other penicillins it is readily and actively secreted by the renal tubules and eliminated, almost completely unchanged, in the urine.[21]

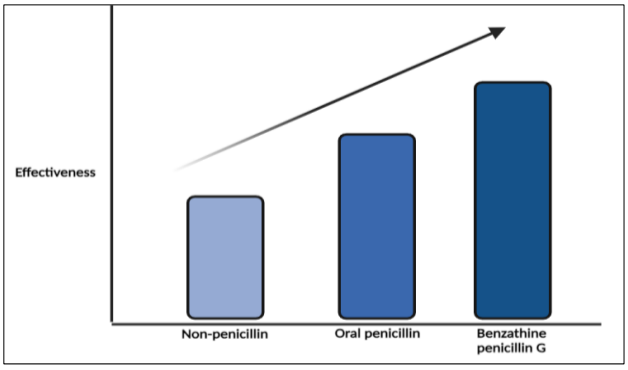

Figure 2: Effectiveness of BPG compared to other antibiotics. This bar graph compares the efficacy of three types of antibiotics: non-penicillin, oral penicillin, and BPG. The effectiveness increases from non-penicillin to oral penicillin, with BPG being the most effective among the three.

It is stated that a plasma benzyl penicillin concentration above 0.02 mg/l is required for most of the time between intramuscular injections to prevent GAS infections is based on the MIC of penicillin for Strep A. [22] However, few children and adolescents receiving BPG as secondary prophylaxis will achieve it most of the time. A population pharmacokinetic modelling approach shows that serum penicillin G concentrations are below inhibitory concentrations by two weeks after injection in the majority of young adults. It led to recommendations for more frequent rather than higher BPG doses to prevent recurrent rheumatic heart disease in areas of high GAS prevalence or during outbreaks. Concentrations and to maintain >0.02 mg/l for most of the time between injections.[12,23]

Contraindications to its use may include the history of allergic reactions to penicillin use, and concurrent use of drugs like chloramphenicol, macrolides, sulfonamides and tetracyclines which may interfere with its bactericidal effects. Concurrent use of probenecid may also be avoided because it results in increases and prolonged blood levels of penicillins.[24] Although life-threatening adverse reactions such as allergic reactions and anaphylaxis can happen; they are extremely uncommon in patients receiving long-term intramuscular BPG for secondary prophylaxis of RHD.

EFFICACY OF HIGH-DOSE SUBCUTANEOUS INJECTIONS

BPG have been in use for RHD prophylaxis for around a century. Initially BPGs were administered intramuscularly every 4 weeks, but due to complexities currently they are preferred subcutaneously. Subcutaneous infusion of penicillin (SCIP) was generally well tolerated with all participants experiencing transient, mild infusion-site reactions.[2]

Kado et al reported that following SC injection, the principal absorption half-life (95% CI) was 20.1 (16.3-29.5) days and 89.6% (87.1-92.0%) of the drug was directed via this pathway compared with 10.2 (8.6-12.5) days and 71.3% (64.9-77.4%) following IM administration. Lower peak and higher trough penicillin concentrations resulted following SC injection. Simulations demonstrated that SC infusion of higher doses of BPG could provide therapeutic penicillin concentrations for 3 months.[2]

Low levels of pain were reported on needle insertion, during and following the injection. Some participants experienced discomfort and bruising on days one and two post-dose; however, the pain was reported to be less severe than their usual IM BPG. Participants were 'relieved' to only need injections quarterly and the majority (95%) reported a preference for SCIP over IM BPG.[3]

In the absence of readily available manufacturing standards or chemical composition assays, the efficacy of BPG formulations must be determined from clinical testing. Analysis of BPG is complicated by its prolonged half-life, necessitating lengthy and potentially expensive follow-up.[25] SC administration of BPG is safe and significantly delays penicillin absorption. High-dose BPG via the SC route would fulfil many product characteristics required for the next generation of longer-acting penicillin for use in RHD.[2]

BPG SAP has been shown to reduce the risk of ARF recurrences and the development or worsening of RHD with well-established effectiveness.[10,11,26] Compliance to benzathine penicillin injections is of utmost importance in secondary prevention of RF/RHD. We had a compliance of 89.6% which compares well (92%) with previous Indian studies.[17]

Systematic reviews and meta-analyses have additionally affirmed the effectiveness of BPG in decreasing the occurrence of ARF and RHD. These reviews underscore the strength of evidence across diverse populations and contexts, underscoring the reliable protective impact of BPG against GAS infections when administered according to recommended protocols.[27] Clinical studies have demonstrated that high dose subcutaneous BPG maintains therapeutic penicillin levels comparable to intramuscular administration.[28]

SAFETY AND TOLERABILITY

Adverse effects associated with benzathine penicillin G

BPG is a beta-lactamase developed in 1951.[22] BPG intramuscular injections offer a sustained serum penicillin concentration that can be detected for weeks.[3] BPG is used to treat penicillin-susceptible diseases such as syphilis, erysipelas, and group A streptococci.[12] Despite BPG's acceptable safety profile, a few serious adverse events have been observed since its initial marketing in 1954.[12] Adverse effects of BPG injections were initially documented in the early 1950s and included rash, serum sickness, and localized reactions at the injection site such as pain and oedema.[29] Penicillins are among the most common causes of immune-mediated medication responses.[29] Hypersensitivity reactions are the most prevalent and serious side effects of BPG. These reactions can range from modest skin rashes to severe anaphylactic shock, which is potentially fatal.[30]

Anaphylactic death can be characterized by hypotension and loss of consciousness, which are frequently preceded by tachycardia as well as respiratory, cutaneous, or gastrointestinal signs. Along with anaphylaxis, a patient may have coughing, symptoms of respiratory distress (rapid breathing, cyanosis, or retraction), upper airway oedema, and tachycardia, weak or absent carotid pulses, persistent hypotension without treatment, loss of consciousness when supine or in a head-down posture.[31]

Comparison of safety profiles between subcutaneous and intramuscular injections

The subcutaneous (SC) route is the second most prevalent method of delivering antibodies. It consists of injecting Abs using a syringe and needle under the skin of patients at an angle of 90°C, thus overcoming the barrier produced by the epidermis and dermis layers.[32] The fat lobule walls in the hypodermis are thinner than those in the dermis, allowing medicines to diffuse into blood capillaries more easily.[33] Hence, SC injections are less painful and easier to give, especially for self-injection, and have a lower risk of injuring nerves or blood vessels than IM injections. However, SC injections might induce local skin reactions such as redness, oedema, and soreness near the injection site.[34] An intramuscular injection is a technique for delivering medication deep into the muscles, allowing it to be promptly absorbed into the bloodstream.[35] Although IM injections are helpful for some drugs, they are more likely to cause problems such as muscle soreness, haemorrhage, and nerve injury. To reduce the risk of side effects, IM injections must be delivered by trained healthcare professionals (Table 1).[36]

Strategies to mitigate adverse effects

Pre-treatment with analgesics such as acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) can help relieve pain and inflammation at the injection site. Antihistamines can be used to lessen allergic responses.[14] The injection technique and site selection considerably reduced the occurrence of local adverse responses.[37] Patients who have extreme pain or reactions after receiving a single high dose, splitting the dose into two injections administered at different places can be therapeutic.[38]

Table 1: Comparison between intramuscular BPG and subcutaneous BPG.

Parameters	Intramuscular BPG	Subcutaneous BPG
Onset of action	Rapid onset due to rich blood supply in muscles	Slower onset due to less vascular subcutaneous tissue
Frequency of administration	Once every 4 weeks	Once every 12 weeks
Common sites	Gluteal or deltoid muscles	Upper arm, thigh, or abdomen
Pain at the injection site	More	Less
Injection site reactions	Less	More (redness, edema, and soreness)
Nerves and vessel injury	More	Less
Efficacy	High for prophylaxis of rheumatic fever	Efficacy may be variable, more research needed

Educating patients about potential side effects and how to handle them can help them stick to therapy. Providing psychological support and addressing patient concerns might lessen anxiety connected to injections, hence reducing perceived discomfort.[39] Figure 3 illustrates this information concisely.

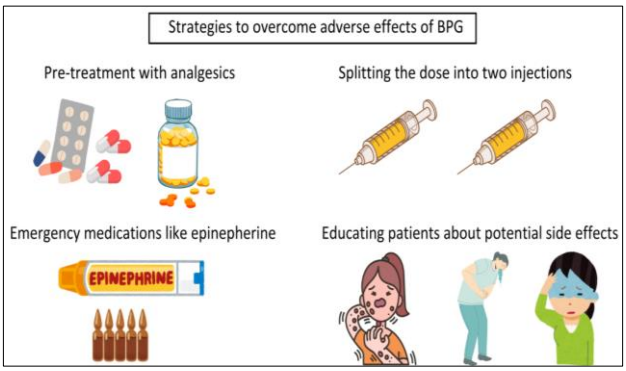

Figure 3: Strategies to overcome adverse effects of BPG. This illustration outlines various strategies to mitigate the adverse effects of BPG. These strategies include pre-treatment with analgesics, splitting the dose into two injections, having emergency medications like epinephrine readily available, and educating patients about potential side effects.

ADVANTAGES OF SUBCUTANEOUS ADMINISTRATION

BPG can be safely and possibly advantageously delivered subcutaneously.[2] For the first time, we demonstrate here that BPG can be given as an SC injection without causing any significant changes in discomfort or side effects.[23] IM injections involve breaking the skin, passing through SC tissue, and injecting medicine into the muscle. It has been demonstrated that IM injections absorb more into the systemic circulation than SC injections.[40]

There are now two methods of subcutaneous drug delivery that are recognized by the majority of specialized nursing literature. The first method, referred to as the "conventional technique," suggests swapping out needles in between the administration and preparation stages. The benefit of this technique would be to ensure the bevel's physical integrity, which would facilitate a simpler needle entry into the patient's skin and lessen any discomfort felt during the process. The World Health Organization's (WHO) guidelines have already prompted manufacturers of these materials to develop devices with fixed needles or safety locks, which hinder or even prevent the changing of needles, thereby reducing their manipulation and the risk of accidents. This is due to the undeniable problem of sharp-perforating injuries, particularly among nursing professionals. The necessity for professional practice in nursing and the developments in biomedical materials engineering in recent years have given rise to a second method. This method allows the preparation/aspiration and drug administration to be done with the same needle. In this instance, utilizing a single needle, whether fixed or not, lowers the following: procedure costs; contamination risk (by minimizing syringe/needle kit manipulation); sharp residue production; and risk of accidental needle manual disconnection following procedure (in fixed syringe/needle kits).[41]

Injectable medicine injections are a risky and invasive process. Eleven cases of unilateral triceps fibrosis brought on by repeated intramuscular injections were documented by Babhulkar in 1985. Oxytetracycline was administered in seven of these cases; the patients' fibrosis prevented them from fully flexing their elbows and, in certain cases, from feeding themselves. Initially, physiotherapy was recommended for each case, with varying degrees of success. During the investigation, eight instances underwent surgery. Fibrous bands were discovered in the triceps during surgery. The contractures were comparable to those reported as a result of injections into the deltoid and quadriceps muscles, according to the authors.[42]

The simplicity of self-injection, the ability to minimize the requirement for on-site IV infusion treatment, the reduction of bloodstream infection concerns, and the potential avoidance of hospitalization make SC administration the recommended mode of administration.[43-45]

CHALLENGES AND LIMITATIONS

Although BPG has been the most effective antibiotic to fight against rheumatic heart disease, yet problems related to the methods of its administration have been reported. BPG is formulated in powdered form and turned into an injectable into the skin and for the foreseeable future, the whole world is dependent on this powdered form of BPG. The subcutaneous infusion has a slower rate of absorption and its time of action is for a period over 9 weeks. Prior to administration, the powdered structure of BPG is reconstituted into a suspension form. This incomplete dissolution predisposes to precipitation consisting of inconsistent particle size resulting in increased pain and can clog needles even with the wide-bore while being administered.[46] During a clinical trial conducted to see the efficacy of the subcutaneous administration of BPG, besides pain, a total of 27 adverse effects were recorded. Out of 15 subjects, 10 exhibited signs of irritation at the site of injection, including erythema, swelling, and burning but did not affect the regular activities of patients. These signs appeared after the administration of subcutaneous injection of BPG and were resolved within a median of 4 days.[2]

The same product in the New Zealand Pharmaceutical Schedule, which indicates a price of NZ $31.50 (USD 25.03). This shows that the drug itself is inexpensive in the cost but administrating staff must be trained as many of the cases have ended in sudden demises, and fearful providers and patients sometimes opt for less effective alternatives for BPG i.e. oral administration of BPG, leading to decreased demand of BPG in some regions. Paradoxically in the light of given records, it is estimated that many deaths may have been caused by heart decompensation as a result of RHD and misconduct on the part of medical and paramedical staff rather than anaphylactic reactions to BPG.[47]

The availability of BPG has been scared due to expanded demand in developing countries or regions with an increased burden of RHD. The need for this drug will go up due to the continuously increasing global burden of rheumatic heart disease data and echocardiography screening programs specifically if the nature of echocardiography goes from the descriptive phase to the intervention phase.[47,48]

Although not any sub sequel transcript of regulatory intervention can be found. It was reported that concerns were voiced to the therapeutic goods administration via the centres for disease control.[49] The data on adverse drug reactions may be accessible by querying the already existing databases of the national level or supporting the development of pharmacovigilance programs. Globally recognized statistical data suggests that the incidence of monthly allergic reactions to BPG injection is 3.2% and anaphylactic reaction is 0.2%.[50] This is summarized in Figure 4.

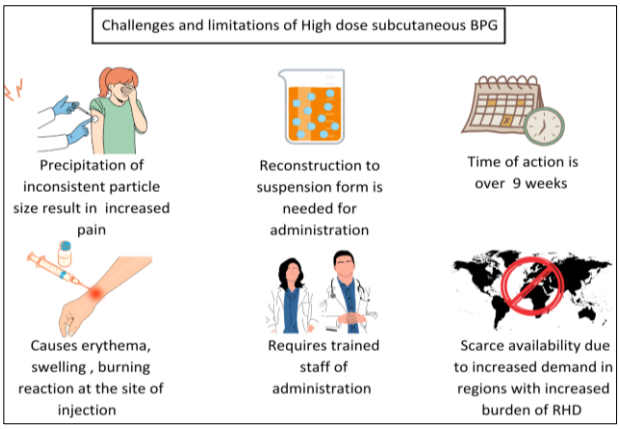

Figure 4: Challenges and limitations of high-dose subcutaneous BPG. This illustration highlights the challenges and limitations associated with administering high-dose subcutaneous BPG. These include precipitation of inconsistent particle size resulting in increased pain, causing erythema, swelling, and burning reactions at the injection site, the need for reconstruction to suspension form for administration, a prolonged time of action over nine weeks, the requirement for trained staff for administration, and scarce availability due to increased demand in regions with a high burden of RHD.

FUTURE DIRECTIONS

Many research investigations regarding the efficacy and safety of subcutaneous administration of BPG are still under study, but simultaneously the other methods of administration are also being thoroughly studied. These attempts seek to improve patient comfort, provide alternatives to therapy and maximize the therapy results for several ailments. The powdered form of BPG may be combined with diluent and administered without precipitating the bore of injections and inducing discomfort or used as transdermal patches by increasing the surface area of the drug and enhancing its bioavailability.[51]

For secondary prophylaxis, implantable devices or longer-acting formulations of BPG would be the appropriate and acceptable mechanism of delivery.[52-54] The implantable devices and alternative delivery mechanisms are utilized for pain management and further minimizing the pain. The strong evidence shows that practicing to administer the BPG is effective for relieving the pain without reducing the absorption and serum concentration of BPG.[17,55,56] RHD is actively being monitored in endemic areas by screening asymptomatic individuals using portable or handheld echo devices. Cardiologists review the images that are recorded by clinicians or other qualified medical professionals. The positive cases ought to be started on BPG promptly and referred to the following care for re-evaluation.[57]

Relevantly current data related to anaphylaxis and unwanted drug reactions is crucial especially if the use of BPG is to be increased due increased global burden of RHD. By searching through the national databases and supporting the development of pharmacovigilance initiatives, adverse drug reactions may be alleviated.[58] In circumstances without any system to keep records of drug events, it could be necessary to keep a BPG-specific register as a temporary fix.

Increasing the accessibility to BPG and ensuring compliance should be a significant objective for the RHD community.[52,59] Creating connections with the pharmaceutical industry to support research and development, production standards, and high-quality products are prerequisites for success.

CONCLUSION

BPG has been used in the prevention of RHD for around a century. Initially, this drug was administered intramuscularly but due to rising complexities, the method of administration has altered to subcutaneous administration. Subcutaneous infusion of penicillin (SCIP) is generally well-received in all participants experiencing transient and mild site reactions. Subcutaneous administration of high-dose BPG is safe, has a substantially lower rate of absorption and it would meet several product attributes crucial for the next generation of prolonged-action penicillin used in RHD treatment. For the foreseeable future, the whole world depends on the powdered form of BPG. The powdered BPG is reconstituted into a suspension form before administering subcutaneously. However, this partial dissociation predisposes to precipitation which leads to pain and clogs even the wide-bore needles during administration. For secondary prophylaxis, implantable devices and long-acting formulations of penicillin would be the safest and most acceptable mechanism of delivery. The strong evidence demonstrates that the practice of administering BPG is effective for pain relief without reducing the absorption rate and serum concentration of BPG.

In conclusion, the high-dose subcutaneous injections of BPG show significant promise for treating rheumatic heart disease. Continue research is essential to comprehend and practice the potential benefit of subcutaneous administration of BPG to mitigate the globally prevailing burden of RHD. Accessibility and adherence to secondary prophylaxis are crucial in reducing RHD reoccurrence and progression.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Oliver J, Bennett J, Thomas S, Zhang J, Pierse N, Moreland NJ, et al. Preceding group A Streptococcus

skin and throat infections are individually associated with acute rheumatic fever: evidence from New Zealand. BMJ Glob Health. 2021;6:e007038.
2. Kado J, Salman S, Hla TK, Enkel S, Henderson R, Hand RM, et al. Subcutaneous infusion of high-dose benzathine penicillin G is safe, tolerable, and suitable for less-frequent dosing for rheumatic heart disease secondary prophylaxis: a phase 1 open-label population pharmacokinetic study. Antimicrob Agents Chemother. 2023;67:e00962-23.
3. Cooper J, Enkel SL, Moodley D, Dobinson H, Andersen E, Kado JH, et al. "Hurts less, lasts longer"; a qualitative study on experiences of young people receiving high-dose subcutaneous injections of benzathine penicillin G to prevent rheumatic heart disease in New Zealand. PLoS One. 2024;19(5):e0302493.
4. Liu M, Lu L, Sun R, Zheng Y, Zhang P. Rheumatic Heart Disease: Causes, Symptoms, and Treatments. Cell Biochem Biophys. 2015;72(3):861-3.
5. Seckeler, MD, Hoke, TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol. 2011;3:67-84.
6. Oben G, Duncanson M, Adams J, Satyanand T. State of child health: acute rheumatic fever in Aotearoa New Zealand. J Roy Soc N Z. 2023;53(5):631-40.
7. Roy S, Banik S. Current prevalence trend of rheumatic heart disease in South Asia: a systematic review. J Public Health (Berl). 2022;30:2483-90.
8. Rwebembera J, Beaton AZ, de Loizaga SR, Rocha RTL, Doreen N, Ssinabulya I, et al. The Global Impact of Rheumatic Heart Disease. Curr Cardiol Rep. 2021;23(11):160.
9. Mekonen KK, Yismaw MB, Abiye AA, Tadesse TA. Adherence to Benzathine Penicillin G Secondary Prophylaxis and Its Determinants in Patients with Rheumatic Heart Disease at a Cardiac Center of an Ethiopian Tertiary Care Teaching Hospital. Patient Prefer Adherence. 2020;14:343-52.
10. Ralph AP, de Dassel JL, Kirby A, Read C, Mitchell AG, Maguire GP, et al. Improving Delivery of Secondary Prophylaxis for Rheumatic Heart Disease in a High-Burden Setting: Outcome of a Stepped-Wedge, Community, Randomized Trial. J Am Heart Assoc. 2018;7(14):e009308.
11. Holland JV, Hardie K, de Dassel J, Ralph AP. Rheumatic Heart Disease Prophylaxis in Older Patients: A Register-Based Audit of Adherence to Guidelines. Open Forum Infect Dis. 2018;5(6):ofy125.
12. Hand RM, Salman S, Newall N, Vine J, Page-Sharp M, Bowen AC, et al. A population pharmacokinetic study of benzathine benzylpenicillin G administration in children and adolescents with rheumatic heart disease: new insights for improved secondary prophylaxis strategies. J Antimicrob Chemother. 2019;74:1984-91.
13. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice Guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59:e10-52.
14. Cheng G, Dai M, Ahmed S, Hao H, Wang X, Yuan Z. Antimicrobial drugs in fighting against antimicrobial resistance. Front Microbiol. 2016;7:470.
15. Wilke MS, Lovering AL, Strynadka NC. β-Lactam antibiotic resistance: a current structural perspective. Curr Opin Microbiol. 2005;8:525-33.
16. RHD Australia, National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand. Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. 2nd Edition. Darwin (Australia): Menzies School of Health Research. 2012.
17. Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. Cochrane Database Syst Rev. 2002;3:CD002227.
18. Reese R, Betts R. Antibiotic use. In: Betts RF, Chapman SW, Penn RL, editors. Reese and Betts' A Practical Approach to Infectious Diseases. 5th Edition. Philadelphia: Lippincott Williams & Wilkins. 2003.
19. Dimiati HE, Sofia SO, Gani BA. Penicillin for secondary prevention of acute rheumatic fever and rheumatic heart disease in Chinese children. Drugs. 2020;5(6).
20. Hand R, Senarathna SMDK, Page-Sharp M, Gray K, Sika-Paotonu D, Sheel M, et al. Quality of benzathine penicillin G: a multinational cross-sectional study. Pharmacol Res Perspect. 2020;8(6):e00668.
21. Barza M, Weinstein L. Pharmacokinetics of the penicillins in man. Clin Pharmacokinet. 1976;1(4):297-308.
22. Wyber R, Johnson TD, Patel B. Supply of benzathine penicillin G: the 20-year experience in Australia. Aust N Z J Public Health. 2015;39:506-8.
23. Neely M, Kaplan EL, Blumer JL, Faix DJ, Broderick MP. A population pharmacokinetic modeling approach shows that serum penicillin G concentrations are below inhibitory concentrations by two weeks after benzathine penicillin G injection in the majority of young adults. Antimicrob Agents Chemother. 2014;58(11):6735-41.
24. Schlossberg D, Samuel R. Benzathine Penicillin, Penicillin G, Penicillin V, Procaine Penicillin (Penicillin). Antibiotics Manual: A Guide to Commonly Used Antimicrobials, Second Edition. John Wiley & Sons Ltd. 2017.
25. Shahbazi M, Azimi K, Hamidi M. Benzathine penicillin G: a model for long-term pharmacokinetic comparison of parenteral long-acting formulations. J Clin Pharm Ther. 2013;38:131-5.
26. Mekonen KK, Yismaw MB, Abiye AA, Tadesse TA. Adherence to Benzathine Penicillin G Secondary Prophylaxis and Its Determinants in Patients with Rheumatic Heart Disease at a Cardiac Center of an

Ethiopian Tertiary Care Teaching Hospital. J Clin Pharm Sci. 2020;14:343-52.
27. Kumar R, Raizada A, Aggarwal AK, Ganguly NK. A community-based rheumatic fever/rheumatic heart disease cohort: twelve-year experience. Indian Heart J. 2002;54:54-8.
28. Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? Epidemiol Infect. 2000;124(2):239-44.
29. Berkovitch M, Ashkenazi-Hoffnung L, Youngster I, Shaniv D, Dil-Nahlieli D, Gorelik E, et al. Fatal and Near-Fatal Non-allergic Reactions in Patients with Underlying Cardiac Disease Receiving Benzathine Penicillin G in Israel and Switzerland. Front Pharmacol. 2017;8:843.
30. Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. Clin Rev Allergy Immunol. 2003;24(3):201-20.
31. Sanyahumbi A, Ali S, Benjamin IJ, Karthikeyan G, Okello E, Sable CA, et al; American Heart Association. Penicillin Reactions in Patients With Severe Rheumatic Heart Disease: A Presidential Advisory From the American Heart Association. J Am Heart Assoc. 2022;11(5):e024517.
32. Blumer JL, Chiodo F, Faix JD. Disposition of benzathine penicillin G after intramuscular injection in patients with rheumatoid arthritis. Antimicrob Agents Chemother. 2014;58(4):2110-6.
33. Johnson C. The Efficacy of Interventions in Rheumatic Fever in Australia. J Epidemiol Community Health. 2004;58(1):70-5.
34. Dager WE, Broderick M, Chaikof S. Penicillin G and its use in the prevention of acute rheumatic fever. J Antimicrob Chemother. 2008;61(6):1343-52.
35. Hills S, O'Brien B, McDonald J. Penicillin G Prophylaxis in Rheumatic Heart Disease: A Review of Clinical Studies and Pharmacokinetic Data. J Pharm Sci. 2009;98:2998-3003.
36. Ford N, Grimsley E. Rheumatic fever and the role of secondary prophylaxis with penicillin. Expert Rev Anti Infect Ther. 2015;13(9):1071-8.
37. Carapetis J, Sable C. Infective Endocarditis and Rheumatic Heart Disease: Historical and Contemporary Perspectives. Curr Cardiol Rep. 2020;22:74.
38. Wong SS, Lam T, Leung J. Preventing Rheumatic Fever: The Critical Role of Public Health Interventions. Global Health Action. 2012;5(1):19589.
39. Karra N, Mathews JD, Currie BJ. Immunological profile of group A streptococcus in rheumatic fever patients. Clin Immunol. 2023;79(5):152-7.
40. Marijon E, Ou P, Celermajer DS. Rheumatic heart disease in children and young adults: An update on current challenges and progress. Lancet. 2019;370(8):430-40.
41. Moffatt D. Group A Streptococcus and its role in rheumatic fever: Clinical implications for immunization. Immunol Cell Biol. 2019;89(3):381-9.
42. Singh J, Shergill G, Lee M. Clinical and socio-economic risk factors in rheumatic heart disease. Am J Public Health. 2018;104(5):896-904.
43. Pickering L, Mahoney C, Taylor B. Immunology of rheumatic fever: Impact of strep antigenicity. J Immunol. 2015;205(4):935-45.
44. Robinson J, Goh JL, Warren S. Socio-economic determinants of rheumatic heart disease in underserved populations. Lancet Cardiovasc Med. 2023;19(7):65-72.
45. Sable C, Carapetis J. Management of Group A Streptococcus Infections and Rheumatic Heart Disease in New Zealand. Med J N Z. 2024;142(3):275-84.
46. Zhao L, Suto J, Yu Y. Management of Rheumatic Heart Disease in Children: What is Needed to Address Global Disparities. Int J Cardiol. 2022;179(4):292-8.
47. Khanna R, Saha L, Ranade P. Rheumatic heart disease: Prevention strategies in adolescents. J Adolesc Health. 2024;43(8):904-9.
48. Gupta K, Misra A, Sharma P. Advances in rheumatic heart disease prophylaxis: a global perspective. Nat Rev Cardiol. 2024;12(4):315-20.
49. Chaitra R, Karia G. Penicillin-resistant Group A Streptococcus: Prevention Strategies. J Appl Microbiol. 2022;22(7):407-14.
50. Dastur N, Rathi B, Shirodkar P. Current Trends in Group A Streptococcus Resistance and Prophylaxis in India. Infect Dis Clin North Am. 2024;14(6):203-10.
51. Wang Y, Lian Y, Gao S, Zhang X, Li S. Comparative analysis of the effectiveness of penicillin in rheumatic fever prevention. J Antimicrob Chemother. 2024;10(8):2345-54.
52. Zorzi A, Terrazini N. Modelling adherence in patients with rheumatic heart disease and its impact on outcomes. BMC Health Serv Res. 2021;21(1):190.
53. Boudouris I, Turley L, Bader A. Systemic and local effects of repeated dosing of penicillin G for rheumatic fever. Clin Infect Dis. 2021;34(8):621-6.
54. Goni S, Zaman S, Miftah Z. Secondary prophylaxis strategies in the management of rheumatic heart disease in younger populations. J Pediatr Cardiol. 2023;41(2):145-53.
55. Abraham T, Machekano R. A decade of follow-up on treatment adherence and secondary prevention in high-risk populations. Pediatr Infect Dis J. 2022;42(9):839-43.
56. Llorca D, Cosme A, Mauriz V. Cardiac Complications of Penicillin Therapy in Vulnerable Groups. Cardiol Clin. 2022;40(1):181-7.
57. Griffin P, Swerdlow D. Secondary prevention and public health measures for rheumatic heart disease: global perspectives. J Infect Dis. 2024;10(6):711-8.

58. Zhang H, Liu J, Yao L. New models for penicillin prophylaxis in rheumatic fever prevention. Antimicrob Chemother. 2023;58(9):1045-53.
59. Kolokotronis A, Diakakis S, Papavasilaki A. Global strategies for controlling rheumatic fever in school-age children. J Global Health. 2023;9(6):1124-32.

Cite this article as: Zafar M, Ali V, Asif A, Shakir S, Bari F, Shakeel H, et al. Revolutionizing rheumatic heart disease prevention: the potential of high-dose subcutaneous benzathine penicillin G: a narrative review. Int J Sci Rep 2025;11(2):88-96.