Benzathine Penicillin G for the Management of RHD

Concerns About Quality and Access, and Opportunities for Intervention and Improvement

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ABSTRACT

Benzathine penicillin G is an important antibiotic for the treatment and prevention of group A streptococcal infections associated with rheumatic fever and rheumatic heart disease. However, as rheumatic heart disease has receded as a public health priority in most high-income settings, attention to the supply, manufacture, and accessibility of benzathine penicillin G has declined. Concerns about the quality, efficacy, and innovation of the drug have emerged following plasma analysis and anecdotal reports from low-resource settings. This review collates core issues in supply and delivery of benzathine penicillin G as a foundation for concerted efforts to improve global quality and access. Opportunities for intervention and improvement are explored.

Rheumatic fever (RF) and rheumatic heart disease (RHD) are an autoimmune sequel of group A streptococcal (GAS) infections. Recurrences of RF accelerate progression of cardiac valve damage, culminating in heart failure, arrhythmias, and often fatalities. The global burden of RF/RHD is significant—conservatively estimated at 471,000 cases of RF annually and 233,000 deaths per year. At least 15.6 million people suffer from RF/RHD worldwide. RF/RHD is a neglected disease of poverty endemic in low-resource settings and some subpopulations in high-income countries [1].

Antibiotics are essential for prophylaxis to prevent recurrences of RF (secondary prophylaxis) and for treatment of symptomatic GAS infections (primary prevention). Since the 1950s, prophylaxis has been achieved via intramuscular (IM) administration of benzathine penicillin G (BPG) [2]. Although other antibiotics have been used, BPG is a particularly effective agent for primary and secondary prevention because its long half-life provides prolonged bactericidal protection from GAS infection. With effective secondary prophylaxis recurrence, the progression of RF to RHD can be prevented [3,4]. A small number of oral alternatives for RF secondary prophylaxis have been used; these are all less effective than IM BPG in preventing recurrences of RF [3,5,6]. Alternative regimes for individuals with severe penicillin allergy or intolerance are addressed in most RF/RHD treatment guidelines but are outside the scope of this review [5,7—11].

This review presents an overview of the current issues surrounding BPG for the management of RHD and RF. A systematic search of peer-reviewed literature identified a small number of basic science articles and commentaries on BPG. Expanding bibliographic review identified a range of other articles documenting concerns about supply, quality, and access. These issues were explored with targeted searches of public records revealing patent information, commercial details, and correspondence.

PHARMACOLOGY OF BPG

Benzathine penicillin G is a crystalline powder formed through the fusion of 2 penicillin G molecules and characterized by very low solubility and in vivo hydrolysis [2,12—14]. These features are associated with slow absorption from IM injection, producing prolonged therapeutic serum concentrations [12,15]. Prolonged concentration in serum provides excellent protection from GAS infection. No GAS resistance to BPG has been documented in vitro [16]. The mechanism for the apparent persistent susceptibility of GAS to BPG is relatively poorly understood [15,17,18].

DISEASES, DOSES, AND DEMANDS FOR BPG

From the 1950s, BPG was widely used as the first list drug for an array of conditions: syphilis, yaws, Lyme disease, and pneumococcal prophylaxis in sickle cell disease [19—21]. However, development of new antibiotics has narrowed the clinical indications for BPG. Conditions requiring BPG treatment have also become less common in high-resource settings, further shrinking demand. This section profiles the existing indications for BPG, providing a foundation for much-needed research work on the potential size of commercial markets.

Secondary prophylaxis for RHD

The World Health Organization (WHO) defines secondary prophylaxis as "the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or well-documented rheumatic heart disease. The purpose is to prevent colonization or infection of the upper respiratory tract with group A beta-hemolytic streptococci

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and the development of recurrent attacks of rheumatic fever" [9]. The internationally accepted dose for secondary prophylaxis with BPG in adults is 900 mg (1.2 million IU) intramuscularly. There is some uncertainly over the optimum frequency of administration; some papers suggest 2-weekly administration [22], others report very good outcomes on a 3-weekly regime [23,24]. Most guidelines recommend 4-weekly administration as a pragmatic choice, with an option to escalate to 3-weekly administration if there are unexplained recurrences or very high risk [3,5,9,10,25]. The recommended BPG dose for children varies between guidelines: 450 mg (0.6 million IU) up to 20 kg in Australia; 450 mg up to 27 kg in American Heart Association guidelines; and 450 mg up to 30 kg in WHO guidelines [5,9,10].

The optimal duration of secondary prophylaxis is controversial. In most guidelines, duration depends on the initial presentation of RF and location within a high-risk population [5,10]. An array of anecdotal factors have been distilled into consensus guidelines for local implementation [7,10]. Exploring the indications for prolonged prophylaxis is outside the scope of this review. However, it is noteworthy that the minimum duration of secondary prophylaxis in most guidelines is 10 years [5,7,9–11]. In severe cases, lifelong regular BPG administration may be recommended [5,10]. Missing even a single dose of BPG raises the risk of recurrent RF and can undermine entire secondary prophylaxis programs. Stability of supply is a critical issue for programmatic success.

Primary treatment of group A streptococcal pharyngitis

Antibiotic treatment of symptomatic GAS pharyngitis is widely recommended [5,7,9,10]. However, access to culture or rapid antigen tests is limited in low-resource settings, and may delay treatment. Evidence for empiric treatment of childhood sore throats according to a clinical decision rule in high-risk populations has recently been published [26]. A single dose of BPG (between 225 g and 900 g depending on weight) is recommended in high-risk settings or where oral compliance is challenging [7,10]. Treatment of asymptomatic GAS carriers is not routine but may be considered in rare circumstances, such as disease outbreaks in closed communities [5,27,28].

Syphilis

An estimated 12 million people are infected with the spirochete *Treponema pallidum* [29]. *T. pallidum* is particularly responsive to penicillin in the form of BPG [30]. The recommended dose is double the RF/RHD prophylaxis dose at 1.44 g (2.4 million IU) as a single immediate dose for primary syphilis or 3 doses for late syphilis [31]. There is some evidence that use of oral azithromycin is comparable to a single dose of BPG for treatment of early syphilis [32]. However, BPG remains the only agent suitable for treating pregnant women to prevent transmission to the fetus and avert congenital syphilis in neonates [30,31].

Yaws

Yaws is a skin infection caused by the spirochete bacterium *Treponema pallidum* subspecies *pertenue*, which is related to the causative organism of syphilis. The disease is estimated to affect approximately half a million people, predominantly children in low-resource rural areas [33]. The burden of yaws in Africa, South East Asia, and the Pacific Islands parallels the particular persistence of RF/RHD in resource-limited settings. Treatment of yaws has traditionally been with 1.2 MU of IM BPG for adults and 0.6 MU IM BPG for children [34]. Evidence for the role of oral azithromycin as a treatment of choice for yaws is emerging, potentially reducing demand in the BPG market [35]

PAST AND PRESENT BPG SUPPLIES

BPG was developed by J. Lester Szabo in 1951, and the first BPG patent appears to have been held in the United States in 1953 by Bruce [2,36,37]. Advances in stabilizing this original powdered formulation were patented in subsequent years [37]. Initial clinical application was for the treatment of syphilitic infections, spurring considerable demand, commercial interest, and a variety of branded products throughout the 1950s [36,38]. The patents, production, and formulation of powdered BPG over the last 60 years is difficult to track amid a crowded manufacturing market, frequent stock outages, and changes in suppliers [39–43].

A pre-mixed liquid formulation of BPG has been developed, eliminating the need for a dilutant, but requiring refrigeration. The initial patent on this new product was first held by Wyeth under the brand name Bicillin L-A, a 2-ml formulation distributed in a Bicillin Tubex injector [15]. Wyeth's Bicillin L-A, distributed by Aspen Pharmaceuticals, was introduced into the Australia market in 1995 and became the sole source of BPG to the country [44]. Industry statements suggest that global rights to Bicillin L-A were transferred to U.S.-based King Pharmaceuticals (reportedly owned by Monarch at this time) in August 2005 [39,45,46]. Some conflicting reports suggest that the patent rights had been transferred years earlier, but that Wyeth had continued to produce for King under contract [47]. In 2007, the U.S. Food and Drug Administration approved King Pharmaceutical to produce Bicillin L-A at a new manufacturing and production facility in Michigan, USA [48]. A company press release from that time records King Pharmaceuticals as the only manufacturer of Bicillin L-A in the United States [48]. Pfizer acquired King/Monarch Pharmaceuticals in 2010 and Wyeth in 2009 and now appears to be the sole provider of the suspension formulation of BPG in high-resource settings [49].

In this complicated patent and manufacturing landscape, shortages of BPG have occurred. Details of stock outages have been best documented in high-resource settings with pockets of endemic RF/RHD in vulnerable

populations. Supply of BPG for secondary prophylaxis was limited in countries of the former Yugoslavia in the early 1990s [50]. Shortages have occurred in North America from 2002 when Wyeth-Ayerst stopped producing BPG from a Canadian plant [51,52]. Liquid Bicillin-LA stock outages occurred in Australia and New Zealand between 2001 and 2008 [15,53]. In the United States, shortages were notified to the Center for Disease Control in 2005; by 2010, 15% of 353 surveyed directors of pharmacy were still dealing with shortages in America [54,55]. A World Heart Federation survey of healthcare providers who treat patients with RF/RHD prophylaxis collected data from 24 countries in Africa, the Asia-Pacific region, and Central and South America in 2011 [56]. Minimal access to BPG was reported in almost all settings, with some respondents indicating no access to BPG at all [56]. Of 39 respondents, 35% indicated that their BPG supply is inadequate to treat all of their patients using recommended prophylaxis schedules [56].

COST OF BPG

Reliable data on the purchase price of BPG is difficult to secure. Powdered BPG is available to some providers through the support of the United Nations Children's Fund pooled procurement [57]. A 2010 report from the United Nations Children's Fund records 2.4 million IU vials of powdered benzathine benzylpenicillin at a median of US$0.31 per dose. A 2010 human immunodeficiency virus guide for Zambia documents Monarch-branded 1.2 million IU of pre-mixed BPG priced at $57.60 [58]. South African researchers used a value of US $1 in 2010 (sensitivity range 0 to 13), for a single vial of powdered BPG in a recent cost-effectiveness analysis guided by local pharmacy data [26]. A recent newspaper report from Kenya suggests the cost of a single dose of BPG costs Sh250, approximately US$2.90 [59]. In Australia, a 900-mg dose of Pfizer-branded Bicillin L-A is listed in the Pharmaceutical Benefits Scheme at a cost of AU$29.32 (US$29.85) per dose [60]. This is comparable with the same product in the New Zealand Pharmaceutical Schedule, which indicates a price of NZ $31.50 (US$25.03) (http://www.pharmac.health.nz/ckeditor_assets/attachments/15/sched.pdf).

Finally, understanding the uses and supply of BPG has been confused by a number of similarly named products. In particular, Bicillin C-R (controlled release) and Bicillin A-P (all purpose) [15,61,62]. These formulations contain procaine penicillin G and/or aqueous penicillin, which achieve higher and shorter serum concentration levels after IM administration. Combinations of BPG and procaine penicillin G have been proposed for the treatment of respiratory tract infections, scarlet fever, and skin infections, but they are not suitable for RF secondary prophylaxis [63].

BPG QUALITY

The paucity of readily accessible quality control guidelines in BPG manufacturing has been a source of concern within the RHD community for some years [46,64,65]. Attempts to obtain process information from manufacturers have been unsuccessful despite a number of concerted efforts [46,66]. In Canada, 2 "notice of compliance" documents have been issued for branded, liquid formulation Bicillin L-A (Pfizer and King); those documents represent compliance with local Food and Drug Regulations [67]. The need for continuous quality improvement activities to address different preparations of BPG has also been identified by WHO with little effect [68].

Efficacy

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 [69]. This is important for U.S. Food and Drug Administration licensing of generic medications, which evaluates bioequivalence via a plasma concentration-time curve from zero to complete drug excretion [69,70].

Secondary prophylaxis for RF/RHD is thought to require a minimum serum concentration of 0.02 μg/ml BGP to prevent GAS infection, based on a reported minimum inhibitory concentration 90 of 0.0016 [66,71]. The oft-recommended 28-day dosing interval of BPG is calculated to keep serum concentrations above this therapeutic threshold in order to prevent GAS infection. However, there are well-founded concerns about the variability of penicillin serum concentration from an array of manufacturers over a period of some years [46,65,66]. In a recent trial, young American military recruits received a single stat dose of 1.2 MU of BPG; mean serum concentrations were less than the minimum serum concentration of 0.02 μg/ml by day 9 after administration in one-half of the subjects. Generalizing these results to the RHD secondary prophylaxis population suggests that patients may be unprotected from GAS infection for up to 19 days prior to the next dose administration [66]. A meta-analysis of 37 similar studies evaluated trends in therapeutic penicillin serum concentrations; investigators have reported that the duration of therapeutic serum concentrations is significantly shorter in studies since 1990 than it is in data from earlier decades [71]. This raises significant concerns about the effectiveness of contemporary secondary prophylaxis programs.

Safety

Generally accepted international data suggests that the incidence of allergic reactions to monthly BPG injection is 3.2% and anaphylactic reactions is 0.2% [9,72]. However, anecdotal reports of adverse reactions appear to have increased in recent years, in conjunction with concerns about medication quality. Three deaths documented in Zimbabwe in 2000 were associated with BPG from 3 different manufacturers [73]. A high frequency of anaphylaxis events has also been reported in World Heart

Federation's BPG survey; 26% of 39 clinicians reported at least 1 anaphylactic reaction, and 21% of all providers reported that they have had a patient die due to anaphylaxis after BPG injection [56]. At present, it is impossible to determine whether adverse drug reactions are caused by penicillin, reactions to other components of the medication/dilatant, unrelated to BPG administration, or misclassified reactions. The role of vasovagal reactions to IM injection, particularly in diverse cultural settings, may also be an important area for further research. A system for reporting adverse drug events is important for BPG as a way of monitoring both penicillin safety and perhaps a proxy guide to BPG quality [74].

Administration challenges

Powdered BPG forms a suspension when reconstituted prior to administration. This incomplete dissolution predisposes to precipitation and needle blockage during administration [75]. Worldwide anecdotal reports suggest this precipitation is a common problem. For example, when Australia used powdered Pan Benz during the 2006 stock outage of Bicillin L-A, up to 40% of injections of Pan Benz were affected by needle blockages. Concerns were reportedly raised to the Therapeutic Goods Administration via the Centers for Disease Control, though no record of subsequent regulatory intervention can be found [76]. Many countries are dependent on powdered BPG for the near future, and effective administration remains an unmet challenge.

BPG AS AN ESSENTIAL MEDICINE

WHO has biennially produced a list of essential drugs since 1977, forming the foundation for 156 national Essential Medicines Lists (EML) [77,78]. The success of EML spurred the development of further specific lists, including the Interagency List of Essential Medicines for Reproductive Health in 2006 and the Essential Medicines List for Children (EMLc) in 2007 [79,80]. These lists were supplemented by a WHO publication on model prescribing information for RF/RHD in 1999 [68].

The adult 1.2 million MU dose of BPG appears in the (current) 17th edition 2011 EML of WHO [81]. The pediatric EML also includes BPG but only at the standard adult dose. Theoretically, this could be problematic for countries with a high burden of RF/RHD in young children or with widespread growth stunting. The inclusion of pediatric doses for RHD prophylaxis received specific attention during the drafting of the EMLc, including in a detailed report [80,82]. Similarly, BPG appears on the Interagency List of Essential Medicines for Reproductive Health in a 1.44 g (2.4 million IU) form for treatment of syphilis [79]. It is unclear whether the recommended formulations of BPG, which appear on the WHO EML, are translated to national level EMLs. This requires a targeted investigation to evaluate which countries with a high burden of RHD have adopted the EML recommendations to national formularies.

DELIVERY MECHANISMS

Delivering each injection in secondary prophylaxis regimes is a global challenge. In many settings, far fewer than 80% of scheduled injections are delivered, significantly increasing the risk of rheumatic fever [83–87]. Although the link between the pain of BPG administration and compliance has little published support, it is reasonable to assume that discomfort is a factor for young people [10,88,89]. Adherence with secondary prophylaxis is critically low in many settings; any attempt to improve acceptability of BPG warrants vigorous investigation.

Some centers employ techniques to reduce the pain of IM injections, such as use of smaller gauge needles, direct pressure, slow injections, and distractions [10]. In some programs, local anesthetic is routinely used as a dilutant for powdered BPG to reduce injection pain [90]. There is good evidence that the practice is effective at relieving pain, without reducing absorption or serum concentration of BPG [10,91,92]. However, pain could be further minimized by alternative delivery mechanisms, potentially an implantable device.

An implantable or longer acting BPG delivery device would be a more appropriate and acceptable mechanism for delivering secondary prophylaxis [64,93,94]. Although this is a conceptually promising approach, there has been little reported innovation in this field.

IMPROVING BPG ACCESS

Control of RF and RHD depends on supply, procurement, and delivery of BPG. Vaccine prospects remain years from clinical implementation, forcing primary and secondary prevention activities to the fore [95]. Improved global burden of disease data and echocardiographic screening programs are likely to expand demand for BPG, particular if echocardiography moves from a descriptive to an interventional phase [95,96]. Thus, improving access to BPG and supporting compliance should be a key priority for the RHD community [64,95]. Three domains of intervention are required.

Technical and clinical research interventions

Technical manufacturing standards or specifications for BPG have not been located during this review, nor in earlier attempts by other investigators [64]. Some specifications may reside with patent holders for pre-mixed BPG. Older standards for powdered formulations may be held by regulatory agencies that are inaccessible to electronic review. Locating and distributing of nonproprietary standards is needed in order to evaluate generic formulations and ensure standardization. Simple assays for establishing the quality and purity of BPG may also need to be developed to assist procurement agencies in purchasing decisions.

Updated data for anaphylaxis and adverse drug reactions is essential, particular if use of BPG is to be expanded. Adverse drug reaction data may be accessible by interrogating existing national level databases or supporting the development of

pharmaco-vigilance programs [97]. In settings without any mechanism for reporting drug events, a BGP-specific register may be needed as an interim measure.

Market interventions and research partnerships interventions

Increasing attention to the market dynamics of pharmaceutical products in low- and middle-income countries has emerged in recent years. Organizations such as the United Nations Children's Fund, UNITAID, Drugs for Neglected Diseases Initiative, and the Medicines Patent Pool illustrate new ways of tackling access to medicines barriers [98—101]. The RHD community should seek engagement with these kinds of organizations to tackle BPG supply and provide ongoing, disease-specific, technical support. Partnerships with other diseases still using BPG—yaws and congenital syphilis—are also likely to be important opportunities for strengthening an economically viable BPG market. Developing relationships with the pharmaceutical industry to foster research, development, manufacturing standards, and quality outcomes is a likely prerequisite for success.

Systems, policy, and applied research interventions

BPG is already incorporated in the core and subsidiary WHO EML. Further research is needed to compare national formularies against the EML; if BPG has been omitted, advocacy for inclusion and supply will be needed at a national level. At a local level, documenting costs, stock outages, and administration challenges will be a critical metric of success for global level advocacy and partnerships. Innovative inclusion of people living with RF/RHD may be possible. For example, Stop Stock-outs! is a campaign for consumers to report medication shortages by text message in Kenya and Uganda [102]. Constructive, sustainable improvements at a local level require a health systems approach. A systems framework allows consumers, prescribers, and procurers to address forecasting, purchasing, delivery, cost, and other macrodeterminants of actual medication uptake [103].

SUMMARY

Securing and delivering high-quality supplies of BPG is a surmountable challenge; powdered formulations are off-patent, fixed-dose, do not require a cold chain, and demand can be forecast in predictable volumes for many years. In comparison to the complexities of early antiretroviral regimes and vaccination efforts, universal access to BPG is eminently achievable. Working with novel partners provides an opportunity to foster integration, avoiding the development of "unsustainable monolithic programs" for RHD control [9]. This review and commentary provides a compilation on the historic and existing issues for BPG supply and delivery. Global institutional leadership will be required to move forward on priority issues for improving access [95].

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