A programme to increase appropriate usage of benzathine penicillin for management of streptococcal pharyngitis and rheumatic heart disease in Zambia

Aidan Long, Joyce Chipili Lungu, Elizabeth Machila, Sherri Schwaninger, Jonathan Spector, Brigitta Tadmor, Mark Fishman, Bongani M Mayosi, John Musuku

Abstract

Rheumatic heart disease is highly prevalent and associated with substantial morbidity and mortality in many resource-poor areas of the world, including sub-Saharan Africa. Primary and secondary prophylaxis with penicillin has been shown to significantly improve outcomes and is recognised to be the standard of care, with intra-muscular benzathine penicillin G recommended as the preferred agent by many technical experts. However, ensuring compliance with therapy has proven to be challenging. As part of a public–private partnership initiative in Zambia, we conducted an educational and access-to-medicine programme aimed at increasing appropriate use of benzathine penicillin for the prevention and management of rheumatic heart disease, according to national guidelines. The programme was informed early on by identification of potential barriers to the administration of injectable penicillin, which included concern by health workers about allergic events. We describe this programme and report initial signs of success, as indicated by increased use of benzathine penicillin. We propose that a similar approach may have benefits in rheumatic heart disease programmes in other endemic regions.

Keywords: rheumatic fever, rheumatic heart disease, benzathine penicillin, pencillin allergy

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Massachusetts General Hospital, Boston, USA
Aidan Long, MD, aalong@mgh.harvard.edu

University Teaching Hospital, Lusaka, Zambia
Joyce Chipili Lungu, RN
Elizabeth Machila, RN
John Musuku, MD

Novartis Institutes for BioMedical Research, Cambridge, USA
Sherri Schwaninger, MBA
Jonathan Spector, MD
Brigitta Tadmor, PhD

Harvard Stem Cell and Regenerative Biology Department, Harvard University, Cambridge, USA
Mark Fishman, MD

Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa
Bongani M Mayosi, MD

Rheumatic heart disease (RHD) is a major cause of morbidity and mortality in sub-Saharan Africa (SSA).[1,2] Up to 3% of school-aged children have definite or borderline RHD,[3-5] and congestive heart failure stemming from valve damage in RHD patients is a leading non-infectious cause of death in young adults.[6,7] Acute heart failure from RHD in SSA has been associated with a 35% one-year mortality rate.[8]

Yet RHD is preventable and, to some degree, treatable. Evidence generated more than 60 years ago demonstrated that antibiotic treatment of group A *Streptococcus* (GAS) pharyngitis, a practice known as 'primary prevention', significantly reduced the risk of rheumatic fever (RF).[9-11] Shortly thereafter, it was shown that 'secondary prevention', in which antibiotics are administered continuously for a period of many years to patients with RHD, was effective at suppressing new streptococcal infections and decreased the incidence of recurrent RF.[10,12-14] The initial RF and RHD studies used penicillin as the antibiotic of choice and, to this day, GAS remains exquisitely sensitive to penicillin treatment.[15-17] Penicillin continues to be the standard of care for primary and secondary prevention of RHD globally in non-allergic individuals.[2]

In resource-constrained parts of the world where RHD is still endemic, including SSA, the use of penicillin for RHD prevention and treatment is widely recognised to be suboptimal.[18-20] The reasons for this are complex and related to a multitude of interacting factors, including drug supply, pharmaco-economics, health service infrastructure and possibly socio-cultural drivers.[21] Indeed, a recent high-level report outlining the key actions required to eradicate RHD in Africa identified variable supply and suboptimal quality and use of penicillin as some of the major barriers to achievement of this goal,[22] a position endorsed by the World Heart Federation.[23]

Penicillin comes in various formulations. Benzathine penicillin G (BPG), a World Health Organisation essential medicine, is an intramuscular injectable form with a long half-life, such that only a single dose is required for primary prevention (in contrast to a 10-day course of oral pills taken twice daily), and a single monthly dose is needed for secondary prevention (compared with a regimen of oral pills taken twice daily).[10]

In SSA, leading technical authorities, including the Pan-African Society of Cardiology (PASCAR), have advocated the use of BPG for the treatment of streptococcal pharyngitis and the management of RHD to maximise the likelihood of patient compliance with recommended regimens, an approach that has met with success in other low-resource settings.[22,24,25] There is also evidence that BPG may be more effective than oral penicillin for secondary prophylaxis of RHD and, consequently, it is a commonly recommended therapy.[14,26,27]

In 2012, a public–private partnership was launched in Zambia with the goal of reducing and ultimately eliminating RHD.[28] This

multi-faceted initiative (called 'BeatRHD Zambia') is centred out of the University Teaching Hospital (UTH) in Lusaka, Zambia, and includes operational research (for example, to measure disease prevalence), public awareness, and health system-strengthening activities – in particular, efforts to increase appropriate BPG usage for primary and secondary prevention of RHD in government health facilities according to national guidelines.

To explore and address factors contributing to possible low rates of BPG use among health workers in Zambia, we undertook an assessment of health workers' attitudes and practices relating to BPG safety, appropriate use and effectiveness. The information obtained was used to inform education and training, and interventions for BPG access, which have been implemented in health centres across Lusaka, Zambia, and are now being rolled out in other provinces. This report describes the experience to date of supporting the use of BPG for primary and secondary prevention of RHD in Zambia.

Unmasking potential barriers to penicillin administration

A two-day workshop was conducted at UTH in October 2014 in order to elicit participants' knowledge, attitudes and practices relating to RHD and BPG, and to provide education and training on how to administer BPG. The workshop involved a classroom-based didactic and interactive programme directed at representatives from UTH and 20 government clinics in Lusaka. There were 29 attendees, mostly nurses and a few doctors.

Focus group discussion

An initial focus group discussion (led by AL and JM) permitted course leaders to gain insight into current patterns of penicillin usage in cases of streptococcal pharyngitis and RHD. It allowed for an informal exploration of factors that were perceived to limit the use of BPG in these clinical circumstances. All 29 workshop participants expressed awareness of the existence of RHD and the majority reported having been involved in the care of such patients. While most participants reported prior experience with administration of oral penicillin VK and intramuscular penicillin G, no participant was able to relate first-hand experience in the administration of intramuscular BPG.

Precise identification of the reasons for the non-use of BPG was challenging to ascertain but one theme appeared central: fear of penicillin allergy as a potential barrier to administration of BPG in Zambia. This concern had also been brought to light before the workshop by personal interactions between Zambian nurses and doctors and the head of Paediatrics at UTH (JM), which revealed anxiety over a perceived high risk of penicillin allergy associated with injectable penicillin (distinct from the oral form of penicillin).

During the focus group, a significant number of the participants expressed grave fear of inducing an allergic reaction, apparently based on anecdotal information they had received secondhand about such events. No participant reported directly having encountered an adverse drug reaction (including allergic or anaphylactic reactions) with administration of any formulation of penicillin. Only one participant had previous training in drug-allergy recognition and management.

There appeared to be prevalent misconceptions that anaphylactic reactions to BPG were common and were increased in individuals who were fasting or otherwise weak. Most programme participants were not aware that prior tolerance of other forms of penicillin (such as oral penicillin VK or intramuscular penicillin G) might have a bearing on the subsequent risk of anaphylaxis to BPG. A small number of participants inquired whether penicillin allergy testing would be necessary before BPG administration.

Educational session

Informed by observations in the focus group, the educational component of the workshop covered the following topics: streptococcal pharyngitis and its relationship to RF and RHD; the role of penicillin in primary and secondary prevention; review of the various forms of penicillin, including BPG, penicillin VK and penicillin G; use of penicillin in previously documented RHD control programmes; the nature and likelihood of possible adverse reactions to penicillin (including IgE-mediated type I allergic reactions and other non-allergic adverse reactions); and how to recognise and intervene in acute anaphylaxis. The educational session also reviewed evidence that supported the lack of need to conduct penicillin allergy testing (often simply called 'skin testing' locally) before BPG administration to a patient in whom there was no prior history of adverse reaction to penicillin.

Following the didactic programme, a hands-on, role-playing exercise was undertaken to teach recognition and management of acute anaphylaxis in a simulated patient (Fig. 1), based on algorithms developed by the World Allergy Organisation.[29] Skills imparted included placing the patient in the supine position with the legs elevated, proper assessment of the patient's airway, correct administration of intramuscular epinephrine, and determination of the potential need for additional medications such as antihistamines and bronchodilators.

Educational activities were evaluated by pre- and post-testing of knowledge and skills. All participants demonstrated significantly improved anaphylaxis management skills, and in an anonymous post-course evaluation, every participant reported that their clinical practice would change as a result of the course.

Workshop learnings

Important lessons learned from the initial educational workshop guided future programme activities. First, it was clear that health workers in Zambia had had misconceptions about the true frequency of severe penicillin allergic reactions. Second, health workers received scant, if any, training in drug-allergy recognition and management; therefore there was a need for programmes to improve health workers' confidence in managing patients with drug allergy. Third, health workers were unclear about the precise indications and dosing for administering BPG, and were eager for opportunities to improve their diagnostic and treatment skills. These were each felt to be remediable contributory factors to the suboptimal use of BPG for primary and secondary prevention of RHD in Zambia.

Design and deployment of subsequent tailored interventions

A core activity of the BeatRHD Zambia initiative is to work to help strengthen the Zambian health system in order that services for

Fig. 1. A skills-building, role-playing exercise was conducted at the Lusaka workshop to help nurses and doctors build confidence in their ability to successfully recognise and manage medication-induced allergy. Placing the patient on the back and elevating the lower extremities is recommended for management of anaphylaxis, in addition to the immediate administration of adrenaline.[31]

primary and secondary prevention of RHD are reliably delivered. To achieve this, an RHD control programme was developed for implementation in individual health facilities, which includes an introductory on-site training workshop, dissemination of educational materials for staff and patients, ongoing supportive supervisory visits by UTH staff, and assessment of BPG stocks. Largely as a result of the lessons learned in the initial workshop described above, four main interventions were incorporated into the RHD control programme in Zambia.

Creation of durable and accessible educational materials

A user-friendly allergy-focused educational module, based on presentations delivered in the original workshop, was developed into a laminated paper flipchart format for subsequent teaching and reference in the field without need for electronic audiovisual support (Fig. 2). The flipchart reviews the topic of drug allergy; how to recognise and manage a severe allergic reaction; how the allergy kit is used (see below for description of allergy kit); and which medicines are indicated for patients with a known allergy to penicillin. A professionally produced video recording of the allergy module content was also developed for free electronic distribution, and a link to the video file was posted to the PASCAR website for educational purposes.[30]

Compilation and provision of penicillin allergy kits

Every health centre that is enrolled in the RHD control programme is provided with a bundled 'penicillin-allergy kit' that contains the key materials needed to initiate management of a penicillin-induced allergic reaction (Fig. 3). The allergy kit was conceived to be an additional mechanism that complements

Fig. 2. The BeatRHD Zambia team conducts an on-site introductory workshop during enrollment of new health centres into the RHD control programme. The educational session was flipchart based and included allergy training as a core component.

training, to help physically prepare health workers to manage drug allergy, to help build their confidence so that they could successfully manage an allergic event, and to ultimately reduce barriers to the administration of injectable penicillin.

The allergy kit contains a set of medications consistent with World Allergy Organisation guidelines for treating drug allergy,[29] including injectable epinephrine with a sterile syringe and alcohol wipes; an oral non-sedating antihistamine; a short-acting beta-agonist bronchodilator inhaler; and oral prednisone tablets. These kits also include concise instructions for emergency steps to be taken in the event of a serious allergic reaction, a photocopy of figures from the World Allergy Organisation guidelines, a data sheet to record clinical events, a pen to complete the data sheet, and a patient handout. The components are packaged together in a locally procured, conspicuously labelled plastic box that was designed for ready availability and ease of transport. The

Fig. 3. A specially designed, bundled allergy kit was assembled and distributed to each health centre enrolled in the RHD control programme. The kit contains key medicines and other materials, including pictorial instructions, needed to initiate management of a severe drug-allergy event.

medicines in the allergy kit are clearly displayed and labelled to facilitate quick and proper use.

Ongoing supportive supervision in clinics

Nurses from UTH provide on-site supportive supervision once or twice monthly to each clinic enrolled in the RHD control programme. These visits have been determined to be necessary in order to provide regular refresher education and training relating to drug allergy and other aspects of the RHD control programme (for example, primary and secondary prevention); to answer questions and help solve problems that invariably arise at the point of care; to check and re-stock the allergy kit as necessary; and to confirm that each health centre's pharmacy has an adequate stock of penicillin, including BPG.

Assessment of BPG availability

Through the RHD control programme, free penicillin treatment is offered to patients for primary and secondary prevention of RHD. To help ensure availability of high-quality medicine, in-country stocks of penicillin were augmented by a product grant of 25 000 doses from Sandoz, in accordance with World Health Organisation guidelines for medicine donations.[31] The product grant was a supplement; we found that BPG procured through normal government processes was virtually always also available in enrolled clinics.

Training followed by supportive and mentorship visits have also been commenced in provinces outside Lusaka, with the first one being in Choma (Southern Province), where ongoing supportive supervision in clinics and assessment of BPG availability will be replicated.

Initial outcomes

Baseline information obtained from the initial workshop indicated an extremely low (and perhaps even zero) rate of usage of BPG for primary and secondary prevention of RHD among health workers at UTH and Lusaka area government health facilities. Now, two years later, we have observed substantial changes in the pattern of BPG usage as a result of the programme's interventions.

We conducted structured interviews with 18 nurses, clinical officers and pharmacists in seven clinics that had been enrolled in the RHD control programme for four to six months. Ninety per cent of respondents had administered injectable penicillin since the training, and most of them reported that they had administered the medicine on many occasions. Six of the 18 participants reported that using injectable penicillin to treat pharyngitis was a new practice for them, which they had learned as a result of the programme. None of the health workers thought it was too much work to administer injectable penicillin compared with pills. Only one nurse had apprehension about giving injectable penicillin, and she requested from the programme nurses more training on allergy recognition and management; all other health workers reported that they felt comfortable recognising and managing penicillin allergy as a result of the knowledge and skills gained in the training.

All heath workers interviewed believed that patients actually preferred injections to pills due to the perception that it was a more effective treatment. Many of the respondents also reported that they preferred the 1.2 million IU formulation to the 2.4 million IU formulation, since it was easier to dose in children. While the number of participants in this pilot evaluation was small, we believe that it provides an early signal on the impact of the programme.

To date, 21 government health facilities in Lusaka have been enrolled in the RHD control programme and records indicate that more than 9 000 doses of BPG have been administered since the programme started, the majority of which was used for primary prevention of RHD (the incidence of pharyngitis was much higher than the number of patients with RHD who required secondary prophylaxis). Penicillin-allergy skin testing prior to BPG administration was not routinely undertaken. No case of anaphylaxis has been recorded. Further scale-up of the RHD control programme in Lusaka Province is underway, as is expansion to the Southern Province. Extension to additional provinces is anticipated during 2017.

Discussion

Rheumatic fever and RHD are preventable and potentially eradicable conditions that still account for significant morbidity and mortality rates in Zambia, other countries in SSA and other underdeveloped areas of the world. Low rates of penicillin use, including BPG, in appropriate clinical circumstances are likely to be a factor accounting for the continuing high prevalence of these diseases.[18]

From our experience, included among the important underlying drivers that contribute to low rates of BPG usage are a lack of appropriate knowledge regarding the confirmed benefits to be derived from its use and the fear of potential adverse events, including allergic reactions. Similar observations have also been made in other regions of the world where RHD is endemic.[32] That fear of penicillin allergy emerged as a significant barrier to BPG use, which came as somewhat of a surprise, since apprehension towards drug allergy has not been commonly described among health workers in SSA, and scant literature exists on adverse penicillin reactions in population-based studies of RF and RHD.

A multinational study in 1991 that included 32 430 BPG injections in 1 790 patients estimated the risk of anaphylaxis to be exceedingly low, at approximately one in 10 000 injections,[33] and a 2014 retrospective study of BPG treatment in RF in Turkey found confirmed allergy in one of 535 patients (0.18% of 17 641 injections) but documented no anaphylactic reactions.[34] Three fatalities that were temporally related to BPG injection were reported from Zimbabwe more than 15 years ago, although clinical details were not well described and so it is not clear that drug allergy played a role.[35]

We document here that relatively simple interventions, including appropriate education of healthcare personnel, together with confidence building around the recognition and management of allergic drug reactions, followed by a number of low-cost ongoing supportive measures have the potential to significantly improve rates of BPG usage in the primary and secondary prevention of RHD in a low-resource setting.

Our early data also suggest that there is no need to perform routine penicillin-allergy testing prior to BPG administration in patients without a prior history of adverse reactions to penicillin.

This position is supported by several large published studies that evaluated interventions with BPG in RHD patients, where large numbers of BPG injections were administered without prior penicillin-allergy testing,[33,34] and reported the incidence of adverse reactions, including anaphylaxis, was exceedingly low.[36]

A key action recommended in the plan to eradicate RHD in Africa includes appropriate training of health workers to safely and effectively deliver BPG.[22] The preliminary experience in Zambia suggests that appropriate educational interventions in the setting of drug availability and ready access to medications to treat anaphylaxis can positively impact on rates of BPG usage. Future work will involve the exploration of innovative ways to scale up the RHD control programme, such as the use of electronic training modules, and determination of the impact of these types of interventions on health outcomes, including the incidence of RF and RHD.

Conclusion

A multi-faceted effort to combat RHD in Zambia included, as a core component, a novel programme to demystify concerns and dispel fears about safe administration of BPG. It appears that this approach contributed to increases in the rate of BPG use for primary and secondary prevention of RHD in government health facilities, according to national guidelines. Lessons from this experience may be applicable to other countries where RHD is endemic.

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