Availability and administration of benzathine penicillin G for the prevention of rheumatic fever in Africa: report of the Working Group on Penicillin, Pan-African Society of Cardiology Task Force on Rheumatic Heart Disease

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Abstract

Methods: Penicillin is the cornerstone of management for rheumatic heart disease (RHD), an important public health problem in Africa. An online survey was used to collect data from African health workers about availability and administration of penicillin.

Results: There were 30 respondents from 14 countries. Unavailability of benzathine penicillin G (BPG) was reported by 30% of respondents. Skin testing was practiced by 40% of respondents, 30% did not have administration guides and only 30% had emergency kits available. The interval of BPG for secondary prophylaxis varied between two and four weeks. Major adverse reactions were observed by 30% of respondents, including anaphylactic shock/death in six cases. Forty-three per cent of respondents reported that health workers had concerns about BPG administration, including worry about reactions, pain and the viscosity of the solution, and 50% were not confident to manage BPG allergy.

Conclusion: BPG availability should be addressed and African health workers' knowledge and practices need to be augmented.

Keywords: penicillin, Africa, availability, administration

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Rheumatic heart disease (RHD) affects about 33 million people worldwide and leads to 320 000 deaths annually; most of these cases occur in sub-Saharan Africa and Asia.[1] Penicillin is the principal antibiotic for prevention of acute rheumatic fever (ARF) and RHD. Benzathine penicillin G (BPG) is a long-acting formulation of penicillin that can be administered as a single-dose treatment for bacterial pharyngitis and as three- to four-weekly secondary prophylaxis of ARF. The four-weekly interval was found to be less effective in reducing rheumatic fever relapses when compared with two-weekly intervals, therefore some countries use a two-weekly regimen.[2] Other indications for BPG include treatment of syphilis, particularly prevention of mother-to-child transmission, and management of hyposplenism in sickle cell disease.

BPG has been included in each iteration of the World Health Organisation (WHO) Essential Medicines list since the list was developed.[3] Therefore BPG is expected to be available in most low- and middle-income countries where RHD is prevalent. However, reports of shortages are widespread and use of the drug has been further complicated by concerns about quality, adverse events and optimal administration techniques.[4]

In 2016 the Pan-African Society of Cardiology (PASCAR) initiated a broad RHD control agenda with support from the African Union, codified in the Addis Ababa Communiqué. The PASCAR approach focused on seven key actions to eradicate RHD from Africa.[5] The second of these actions was to address the issues surrounding BPG and the Penicillin Working Group was formed. The objective of the Penicillin Working Group in the long term is to help establish safe and efficacious BPG and oral penicillin supply and use at primary-care level in African countries.

This survey represents the first output of the Working Group to document penicillin availability and utility in African countries. This pragmatic approach is intended to identify priorities for improving the use of penicillin in Africa.

Methods

An online survey was designed by the Working Group and formulated in Survey Monkey. The survey questions can be viewed online at https://www.surveymonkey.com/r/PVTFGHK. The survey tool addressed five key domains: availability, brands and prices, administration, adverse reactions and health workers concerns and needs. The questionnaire was sent to the PASCAR RHD community (160 people) through e-mails and re-circulated three times. Participants were asked to invite their colleagues who work with RHD to fill in the questionnaire. Ethics approval was not considered necessary or feasible for this low-risk survey across a number of jurisdictions.

Results

The total number of respondents was 30 (18% of the people contacted), representing 14 countries (Fig. 1). Most respondents (87%) were doctors working in public referral centres. RHD was the commonest indication for BPG administration (86%); other reported clinical indications include syphilis and sickle cell disease.

BPG was reported to be not regularly available by 30% of respondents (Fig. 2). All but one respondent indicated BPG is on the national essential-drug list (96.6%) and on the free-drug list (58%). Oral penicillin is included on the essential-drug list in 65% and on the free-drug list in 40% of respondents' countries.

Most respondents recognised that one to three brands are available, but some countries reported 10 brands (Uganda), six brands (Tanzania) and five brands (Mozambique). Reported retail purchase price for a 1.2-million international unit (IU) vial ranged between US$0.5 and US$1. In 10 countries (71%) BPG was listed as a 'free drug'.

Skin testing before BPG administration is practiced by 40% of respondents' centres. Skin testing is performed prior to the first injection by 20% and before each injection by 20% of respondents (Fig. 3). Skin testing is mostly done with dilute BPG (85%). Only 30% use controls for skin testing. Positive tests were observed by 20% of respondents. Centres that perform skin testing were in Angola, Nigeria, Sudan, Egypt, Zambia and Mozambique.

Of the respondents, 30% did not have a guide to the administration of BPG in their centre. In centres with a guide, utilisation of the resource was estimated at 80%.

Fig. 1. Geographic location of respondents to the penicillin survey in alphabetical order: 1. Angola; 2. Egypt; 3. Ethiopia; 4. Liberia; 5. Mozambique; 6. Niger; 7. Nigeria; 8. Rwanda; 9. South Africa; 10. Sudan; 11. Tanzania; 12. Uganda; 13. Zambia; 14. Zimbabwe.

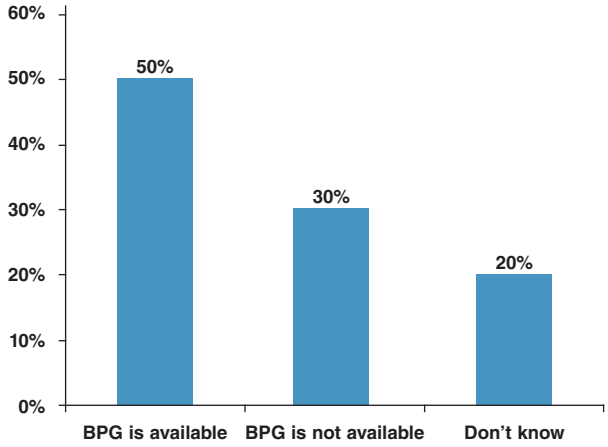

Fig. 2. Availability of benzathine penicillin (BPG).

Only 30% had emergency kits containing adrenaline available when BPG is administered.

There was a large variation between countries in interval of BPG injections for secondary prophylaxis. BPG was mostly given four weekly (60%), but 10% of respondents were administering BPG every two weeks.

Minor reactions were observed by 33% of respondents and major reactions by 30%. Major reactions included death in six cases reported from Nigeria, Zimbabwe, Rwanda, Sudan and Tanzania.

With regard to health workers' concerns and needs, 43% of respondents reported that health workers do have concerns about BPG administration. These concerns include worry about reactions, pain, viscosity of the solution and the difficulty to inject it. Twenty-three per cent of respondents reported that they had concerns about the quality of BPG.

Half of respondents reported that they do not feel confident to manage a patient with BPG allergy. Most respondents (86%) would like to have a refresher course on BPG administration and 95% would like to have an administration guide.

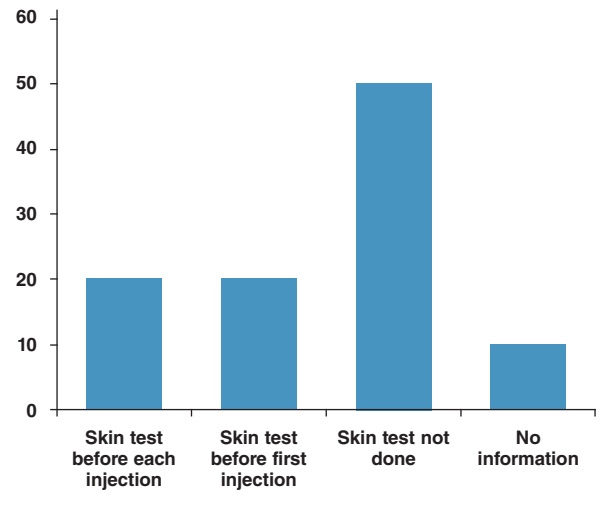

Fig. 3. Skin testing before BPG administration.

Discussion

This pragmatic survey included 14 countries with responses from North, South, East, West and Central Africa. Most respondents work in governmental hospitals that typically treat patients with RHD. This survey unmasked major barriers to the use of BPG in African countries where RHD constitutes a major public health problem and was documented to be the most common indication for BPG use.

Shortages of BPG at the point of care were reported in nearly a third of countries surveyed. This is similar to the 2013 global survey of clinicians in 24 countries when 42% (16/39) of respondents indicated problems with BPG supply.[6] Similarly, a more recent survey conducted by the WHO and the Clinton Health Access Initiative (CHAI) of 81 countries in America and Africa revealed that at least 41% of countries experienced BPG shortages, which were attributed to shortfalls in supply, demand and procurement.[6] The market analysis by CHAI highlights the perceived issues with quality and safety, leading to underutilisation of BPG by health staff.[4,6,7] Substitution behaviour may increase the use of alternative, less effective and more expensive antibiotics. In turn, orders for BPG have decreased, leading to delays in production and distribution.

The beliefs and preferences of people who provide, administer and receive BPG injections drive supply. Therefore supporting safe and appropriate use of BPG is important for stabilising demand and the market. Clinical guidelines and administration guides are important parts of supporting health workers. This survey revealed that although some countries reported that they do have BPG administration guidelines, they are not universally used. A clear need for training courses and resources was also identified. The PASCAR Penicillin Working Group is developing a task aid for BPG administration to respond to this need but ongoing support and education is needed to ensure this effective medication is safely used.

One of the areas of greatest confusion in use of BPG centres on skin testing. In some countries there is a belief that skin testing is needed to assess for risk of penicillin allergy prior to BPG administration. This study indicates that 40% of respondents use some kind of skin testing with dilute BPG. In addition to Africa, we are aware of other countries that use dilute BPG skin testing, including Iran,[8] Nepal[9] and India (pers commun). Despite this widespread practice, there is no evidence that skin testing is useful in reducing adverse reactions to BPG. It is possible that the practice stems from the 2001 WHO guidelines on ARF and RHD, which suggest that health workers need to be trained on skin testing before giving BPG injections for secondary prophylaxis.[10] In this reference there was no specification of the type of skin test. This recommendation might explain the widely practiced use of dilute BPG for skin testing.

The standard test for BPG allergy is conducted using benzylpenicilloyl polylysine (major determinant), penicillin G diluted with normal saline to 10 000 units/ml (minor determinant), positive and negative controls.[11] It is indicated in patients with a prior history of hypersensitivity to penicillin and it is not recommended for routine use prior to BPG injection. This test is not expected to be readily available in African primary healthcare settings therefore there is no need to include it as a guideline.

In contrast to the widespread use of skin testing, emergency kits containing adrenaline were reported to be available to only 30% of respondents. Prompt administration of adrenaline is the mainstay of treating anaphylaxis. Ensuring that adrenaline and other resuscitation equipment are available when BPG is administered is important for safe use of the medication. Similarly, training of health workers on management of anaphylaxis will increase their confidence, as has been reported from the Zambian experience.[12]

The survey showed variations in BPG interval for secondary prophylaxis. Most countries follow the WHO recommendation of three- to four-weekly injections however some respondents administer BPG two weekly. This emphasises the need for standardised administration guidelines and may require conducting research to study the best interval for BPG to be effective for secondary prophylaxis.

Adverse reactions to BPG are not rare and have been one of the barriers to the use of the drug. The commonest minor adverse reaction to BPG is pain at the site of injection. There is some evidence that this can be managed by using an anaesthetic solution such as lidocaine 2% as diluent for the BPG powder.[13] However, this practice is not endorsed by manufacturers and clinical guidelines are not yet in place to support the use of local anaesthetic.

Major adverse reactions have also been reported, including deaths associated with BPG administration. A third of respondents in this survey identified major adverse reactions associated with BPG. This result is similar to the World Heart Federation survey in 2013 that included 39 physicians, where 26% reported serious adverse reactions related to BPG, including deaths.[6]

The mechanism of these deaths is not entirely understood. Anaphylaxis can cause death following injection, however other mechanisms such as inadvertent intravenous injection and arrhythmias need to be considered. Sudden deaths without signs of anaphylaxis have been reported and may be related to arrhythmias in patients who have a severe valve dysfunction.[14]

Improving health workers' knowledge and practices can largely decrease these adverse events and improve workers' confidence in dealing with them. As is seen in this report, health workers' reluctance to give BPG and the lack of confidence were common and directly related to their fear of adverse reactions. Further improvement is sorely needed in order to overcome such serious reactions.

This survey has a number of limitations. The number of participants is small. Clinicians with concerns and adverse experiences with BPG may have been more inclined to respond, leading to bias over-representing concerns. Although respondents may not have been representative, it is clear that shortages of BPG and concerns about use persist in a number of places across the African continent.

Conclusion

This survey demonstrates that shortages of BPG supply occur in Africa and this can limit use of the drug for prevention and management of RHD. Skin testing is quite widespread despite the lack of evidence that it can reduce the risk of major adverse events. In contrast, lifesaving access to emergency kits and adrenaline to manage anaphylaxis are limited. Adverse reactions do occur and health workers reported that they are not confident in managing these. Safe and reliable supplies of BPG are critical for managing the ongoing burden of RHD in Africa. Penicillin is

the only intervention proven to alter the natural history of RHD and save lives. Improving access to this essential medicine must be prioritised by governments and clinicians must be supported to use it confidently and safely.

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Commenting on the research, Professor Paul Leeson, professor of cardiovascular medicine, at the University of Oxford, said in a report in *The Daily Telegraph:* 'This study has the potential to transform how we prescribe blood pressure medication. The findings are likely to be relevant to most people who take tablets for high blood pressure.

Dr Richard Francis, head of research, Stroke Association added: 'We're pleased to see this research, which could potentially change the way we prevent strokes in the future. This is a robust study that shows that people who take their blood pressure medication at night have better blood pressure control and have reduced risk of a cardiovascular event such as a stroke or heart attack. 'Hopefully we can see studies like this recreated in the UK and combined with existing evidence, this could lead to a review of current guidelines on treating high blood pressure.'

Vanessa Smith, from the British Heart Foundation, said in a BBC News report: 'Although this study supports previous findings in this area, further research among other ethnic groups and people who work shift patterns would be needed, to truly prove if taking blood pressure medication at night is more beneficial for cardiovascular health. If you're currently taking blood pressure medication, it's important to check with your GP or pharmacist before changing the time you take it. There may be specific reasons why your doctor has prescribed medication in the morning or night.'

Source: Medical Brief 2019