

Global Status Update on Benzathine Penicillin G

Rosemary Wyber¹, Timothy Johnson¹, Shannon Marantelli², Jonathan Carapetis¹

¹Telethon Kids Institute, University of Western Australia. ²University of Western Australia

BACKGROUND

Benzathine penicillin G (BPG) is an injectable antibiotic which provides prolonged levels of penicillin in the blood. BPG appears on the World Health Organization's Essential Medicines List but is subject to frequent stock outs and shortages. In addition, some clinicians report anecdotal concerns about the quality of some formulations of BPG. Understanding the stock outs, quality, safety and supply of BPG is critical for efforts to control rheumatic heart disease, syphilis and other diseases. This semi-structured review identifies the key global indications for BPG, collates information about supply issues and provides preliminary recommendations to improve supply.

METHODS

A review of major clinical guidelines was conducted to identify doses and indications for BPG globally. Peer reviewed and grey literature was reviewed for evidence of BPG shortages. Statements from stakeholders and the World Health Organization informed the development of recommendations, along with a focused review of literature on antibiotic reformulation.

RESULTS

There are two major global indications for BPG and a number of minor indications:

Major indications for BPG

The clinical demand for BPG is unequivocal: no equally efficacious alternative antibiotics exist, global disease burden is high and clinical outcomes of untreated disease are severe.

- Treatment of syphilis, particularly in pregnant women
- Prophylaxis against rheumatic fever to prevent rheumatic heart disease

Minor indications

The clinical demand for BPG is equivocal or varies by setting: BPG is indicated but alternative antibiotics exist, morbidity/mortality from the disease is low, systems for delivering the intervention are inadequate or use of BPG is under investigation for novel indications.

- Primary prevention of rheumatic fever
- Treatment of skin sores and pyoderma
- Treatment of yaws, bejel & pinta
- Prophylaxis in sickle cell disease
- Prophylaxis following splenectomy
- Prophylaxis of recurrent cellulitis

High quality BPG is a safe, effective and affordable antibiotic for which there are decades of clinical experience. BPG remains the drug of choice for major indications because the target organisms – *Treponema pallidum* and group A streptococci - remain exquisitely susceptible.

Despite considerable clinical need BPG has been subject to widespread global shortages in recent years. Shortages have largely been attributed to difficulty securing quality assured active pharmaceutical ingredient (API) for the manufacture of formulated product. Shortages of API reflect the vulnerabilities of the global BPG market: procurement is fragmented by clinical indication, the number of manufacturers is small and total price of the drug is low.

BPG shortages interrupt treatment regimens and increase the use of more expensive, less effective drugs which may accelerate development of resistance in other organisms. A reliable supply of high quality BPG is urgently needed to provide gold standard care and to support rational use of antibiotics. However, BPG and other older, off-patent antibiotics have been licenced on historic data which is insufficient for contemporary regulatory standards. Improving the quality and supply of BPG requires collective global action to redevelop the drug: answering outstanding scientific questions, integrating new data in regulatory bodies and communicating clearly about how, when and why the drug should be used.

CONCLUSION

BPG remains an essential medicine and tangible, multi-stakeholder, steps are needed for it to be made safe and available to the vulnerable populations who need it most. At a global level, stakeholders in the global BPG market should convene to develop a joint strategy to revive and re-develop the drug. Input from clinicians, consumers, scientists, procurement agencies, manufacturers, multinational agencies and governments is needed to tackle outstanding questions about BPG. Market demand, product acceptability, regulatory requirements and scope for novel indications should be explored by this group. Nationally, strong pharmacovigilance programs, clear clinical guidelines and training for health workers administering BPG should be prioritized. With collective action this safe, effective, affordable medication can become a cornerstone of global disease control.

