Article Comment

Title: Penicillin reactions with severe RHD – is severe pulmonary hypertension the mediating factor?

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.[1]

In 2019 Marantelli reported a series of 10 cases of sudden death following benzathine penicillin G (BPG) injection. [2] The authors postulated that these deaths were triggered by a vasovagal reaction leading to cardiac compromise. This series and other case reports has led to an AHA advisory [1] to recommend that nearly all types of severe rheumatic heart disease (RHD) should be categorised as "elevated-risk" and patients changed to oral penicillin rather than the evidence-based and more efficacious BPG. The data to support a causal relationship was lacking.

A description of the RHD subtype, presumably based on echocardiography, was not included for 5 of the 10 cases in the Marantelli paper, [2] nor that of the cases by Ali et al and Berkovitz et al, both cited in the Advisory [1]. Unfortunately, the estimate of pulmonary hypertension or presence of right heart failure was not stated in these reports. [1,2]

Severe valvular heart disease, especially mitral stenosis, is frequently associated with significant pulmonary hypertension which is usually an indication for operation.[3] Severe rheumatic mitral regurgitation with NYHA class III or IV symptoms also may lead to secondary pulmonary hypertension.[3] Mitral regurgitation with cachexia was highlighted in the Advisory [1] as being at elevated risk, reflecting more advanced heart failure.

Vasovagal syncope typically results in transient bradycardia and peripheral vasodilatation and is generally associated with a benign prognosis.[4] A reduction in cardiac preload is usually tolerated in regurgitant valve lesions. However, when there is co-existing severe pulmonary hypertension, right ventricular hypertrophy develops to compensate for the increase in afterload. A non-compliant right ventricle is sensitive to both reduction in preload and increase in afterload, and may not recover following vasovagal syncope.[5]

We strongly recommend that the authors seek all available data pertaining to pulmonary hypertension and all clinical findings from the original sources. Until this is undertaken, the Advisory [1] appears premature to generalise all RHD subtypes listed as "elevated risk".

The Advisory recommendation to consider all severe RHD be at elevated risk for an adverse or fatal event from benzathine penicillin G injection has significant implications for RHD programmes worldwide, with the risk that secondary prophylaxis is withheld due to fears of a rare adverse event. Valve disease must not be considered in isolation, but together with all clinical information. Heart disease management should be directed by international guidelines to reduce adverse events.[3]

Underlying severe pulmonary hypertension may have been a common factor in the published cases of fatality, and until further clinical information is provided to establish underlying causes of death, there is a risk benzathine penicillin is inappropriately withheld in the most vulnerable group of RHD where a further recurrence of rheumatic fever may prove fatal.

A major typographical error is also noted in the Abstract [1]: 'and those with *no* symptoms.'

We recommend the abstract is corrected to '*those with NYHA class III and IV symptoms'* as per their Table 1. [1]

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Dear Dr. Wheeler and Team,

Thank you for your thoughtful comment on the recent AHA advisory, “Penicillin reactions in patients with severe rheumatic heart disease (RHD).” Increased dialogue is essential to inform global application and modification of this guidance. We acknowledge that there is a critical gap in our understanding of deaths that shortly follow the administration of Benzathine Penicillin G (BPG) RHD prophylaxis. In fact, the mechanism of an AHA Advisory, rather than a scientific statement or guideline, is intended to exist in this space of uncertainty, addressing an issue of high importance, even as more evidence is being gathered.

We do agree that pulmonary hypertension could be an important component of BPG-related sudden deaths. In RHD, pulmonary hypertension nearly exclusively results from left atrial hypertension, secondary to mitral stenosis or in some cases severe mitral regurgitation, which we account for in the advisory.

We know that deaths following BPG are occurring among patients with severe RHD. Most lack features of classical anaphylaxis. These deaths are often sentinel events that lead to widespread fear around BPG, both provider reluctance to administer BPG and patient reluctance to receive it. The intent of this advisory was to highlight these events, identify the patients who appear to be at highest risk, prevent BPG-related deaths, and keep more RHD patients on secondary prophylaxis.

After careful evidentiary review, the unanimous conclusion of the writing group was to recommend consideration of oral penicillin prophylaxis among the highest risk RHD patients. This decision weighed the severity of the reaction (death), the relative weakness of evidence on BPG superiority, and the benefit of oral penicillin as compared to no prophylaxis (both individually and at a community level, given fear that follows sentinel BPG-related deaths). In fact, the small number of trials that support BPG superiority are of low quality, predate echocardiography, and do not include the clinical endpoints of RHD progression or mortality. Further, oral penicillin given in these studies was less bioavailable than contemporary penicillin. A single study reporting outcomes of RHD patients prescribed Pen V (vs. Pen G) reported a low frequency of ARF recurrence comparable to IM BPG, again questioning the certainty of historical trials.

We disagree that this advisory recommends oral prophylaxis for “all” patients with severe RHD. In the REMEDY study (1), a cohort with predominately advanced RHD, we estimate that only one-fourth of patients could be considered for oral prophylaxis. This proportion would be far less outside of tertiary centers, where most patients have mild and moderate RHD.

We want to thank the authors of the editorial comment again for continuing this important discussion. It is our hope that these dialogues will motivate further research and generate critical data for evidence-based guidelines. For now, we stand behind this advisory as a stopgap, intended to prevent RHD deaths both through direct prevention of BPG-related events in those with severe RHD and by bolstering confidence to keep patients on secondary prophylaxis.

*The abstract has been corrected to read, “those with NYHA class III and IV symptoms.”

Sincerely,
Amy Sanyahumbi
Liesl Zuhlke
Andrea Beaton
On behalf of all of the authors of the advisory

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