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Low self-reported penicillin allergy in South Africa—implications for global public health response

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Objectives: In high-income countries, up to 25% of inpatients have a self-reported penicillin allergy (PA). After testing, 95% of these self-reported PAs are incorrect. These incorrectly labelled PAs increase the use of broad-spectrum antibiotics, and drive bacterial resistance. The epidemiology of PA in low- and middle-income countries is unknown. We aimed to describe the epidemiology and delabelling outcomes of self-reported PA in South African (SA) inpatients.

Methods: We conducted point prevalence surveys between April 2019 and June 2021 at seven hospitals in Cape Town, South Africa. A team trained in the PEN-FAST allergy decision tool conducted in-person interviews, and reviewed patient notes to identify and risk stratify inpatients with a self-reported PA. These patients were referred to the Groote Schuur Hospital (GSH) allergy clinic for delabelling.

Results: A total of 1486 hospital inpatients were surveyed and 3.2% ($n=48$) carried a PA label. Importantly, 64.6% ($n=31$) were classified by PEN-FAST as low risk for true penicillin hypersensitivity. Overall, 25% of the self-reported PAs received a β-lactam antibiotic in hospital and were directly delabelled. Delabelling attrition was very high, with 6.3% (3/48) of the self-reported PAs attending the GSH allergy clinic, and only one patient proceeding to a negative oral penicillin challenge.

Conclusions: Inpatient self-reported PA was lower in South Africa hospitals compared with other upper-middle-income countries, and the majority of patients carried a low-risk PA label. Linkage for delabelling with the allergy clinic was very poor, and thus strategies to improve access and delivery of delabelling remains an urgent public health issue.

Introduction

The lowest rate of self-reported penicillin allergy (PA) from a high-income country (HIC) inpatient setting is 9.9% of 1738 patients enrolled over a 1 year period in Montreal, Canada.[1] PA delabelling programmes are now considered a key pillar of antibiotic stewardship.[2,3] However, the burden of antimicrobial resistance is highest in low- and middle-income countries (LMICs).[4] The lack of data on the extent of self-reported penicillin and β-lactam allergy in LMICs is a rate-limiting factor in advancing policy discussions to incorporate delabelling approaches into stewardship programmes in these settings. In this communication we present data from the first point prevalence survey on PA conducted in hospitalized patients in Cape Town, South Africa, an upper-middle-income country (UMIC), and the first such data from Africa.

Materials and methods

We conducted a multicentre point prevalence survey of hospitalized patients between 4 April 2019 and 14 June 2021. A total of 1486 hospital inpatients were surveyed at seven hospitals in Cape Town, South Africa, including tertiary and district-level government-funded hospitals and two private hospitals. The study was approved by the Human Ethics Research Counsel of the University of Cape Town (UCT) (HREC: 417/2019) and institutions involved.

A medical team (of medical students, medical registrars, paediatric registrars, allergologists, and infectious disease specialists) trained in using the PEN-FAST tool for PA risk stratification[2] surveyed all hospitalized patients. All data were then reviewed by an Allergy Fellow. If the patient reported a PA, the PEN-FAST classification was done immediately with the patient or guardian. The PEN-FAST PA phenotype clinical decision tool (developed by Trubiano *et al.*[2]) has a high negative predictive value of 96.3%

(95% CI 94.1%–97.8%).[2,5] The major criteria for the PEN-FAST tool are: the allergy event occurring within the preceding 5 years (2 points); anaphylaxis, angioedema or severe cutaneous delayed reactions (2 points). A single minor criterion of whether the allergic reaction required treatment scores 1 point. The PEN-FAST tool has a validated area under the curve of 0.805 (for a cut-off of 3 points chosen to classify as low risk of PA).[2] We used the following cut-off points: ≤3, low risk; 4, moderate risk; 5, high risk. The novel PEN-FAST PA clinical decision mobile app was used by investigators to classify patients as low risk (1%–5%), moderate risk (20%) or high risk (50%) of a positive PA test.

All patients admitted to the hospital were surveyed; if a patient was unable to speak or answer questions (e.g. intubated or sedated patients, neonates without a parent) then the folder was reviewed and family contacted if necessary. If there was a language barrier, then a ward nurse/another investigator assisted with translation (e.g. isiXhosa, Afrikaans).

In addition, the patient's folder was reviewed for documentation of allergy (in the doctor's notes, nursing notes, and on the prescription charts) and antibiotic use was recorded. All patients who reported a PA were contacted post discharge and offered allergy testing (delabelling) at the nearby Groote Schuur Hospital allergy clinic. Patients were contacted from 1 to 3 months post discharge; each patient was contacted on three separate occasions before being assigned as uncontactable. A direct oral challenge (DOC) was performed for low-risk patients (PEN-FAST score <3) in the clinic. Per protocol, the DOC consists of administration of 500 mg of amoxicillin, followed by close monitoring of symptoms and vital signs for 1 hour. Moderate- and high-risk patients first had skin-prick testing and intradermal testing followed by a post-intradermal challenge if the skin prick tests and intradermal tests were negative.

Results

A total of 1486 hospital inpatients (1166 adults aged ≥18 years and 320 children aged <18 years) were surveyed. The median (IQR) age was 40 (25–60) years, and 52.8% were female. Overall, only 48 (3.2%) patients self-reported a PA (Tables S1, S2 and S3, available as Supplementary data at *JAC-AMR* Online).

Of the 48 self-reported PA patients (Table 1, Tables S4 and S5), 60.4% were female, and the median (IQR) age was 59 (37–68) years, with no PA reported under the age of 18 years. Using the PEN-FAST classification, 64.6% ($n=31$) patients were classified as low risk, 22.9% ($n=11$) as moderate risk, and only 10.4% ($n=5$) patients as high risk for positive penicillin testing. Eight patients reported anaphylaxis (16.6%) and 10 reported angioedema (six of whom had laryngeal angioedema). The most common symptoms were a mild/self-limiting skin rash in 25% ($n=12$) of patients. The majority reported allergic reactions that had occurred more than 10 years previously (72.9%), while 12.5% could not recall the event and relied on a family history. A PA was documented in only 52.1% ($n=25$) of the patient notes/prescription charts and 22 (64.7%) patients received a β-lactam-containing antibiotic in hospital without initial screening.

There was significant loss to follow-up, with only three patients attending the allergy clinic after discharge, all of whom were moderate/high risk for PA. Skin-prick testing and intradermal testing was negative in three patients, and two patients declined a DOC. One patient was successfully delabelled by direct challenge.

Table 1. Characteristics of patients with self-reported PA

	All ($N=48$)
Female, *n* (%)	29 (60.4)
Age (years), median (IQR)	59 (38–68)
PEN-FAST classification, *n* (%)	
Low risk (score ≤3)	31 (64.6)
Moderate risk (score=4)	11 (22.9)
High risk (score=5)	5 (10.4)
Unknown	1 (2)
Questions from PEN-FAST, *n* (%)	
Penicillin allergy reported	48 (100)
5 years or less since reaction	9 (18.8)
Anaphylaxis or angioedema	10 (20.8)
Severe cutaneous adverse reaction	7 (14.6)
Required treatment	30 (62.5)
Reaction >10 years, *n* (%)	35 (72.9)
Patient can recall event, *n* (%)	31 (64.6)
Family history only, *n* (%)	6 (12.5)
Required adrenaline, *n* (%)	10 (20.8)

Discussion

These data suggest that the burden of self-reported PA is considerably lower in Cape Town, South Africa compared with HICs, with implications for policy planning in relation to antibiotic stewardship. However, the data also indicate that even though the prevalence of reported PA is lower, the majority of patients are low-risk patients for true PA, meaning rates of confirmed allergy may be even lower in this African population. There are several possible contributing factors that may explain both a lower rate of PA labels as well as a possible lower rate of true penicillin hypersensitivity in our population. Antibiotic prescribing patterns differ across the world, and involve a complex interplay of social, patient, provider and economic factors.[6] The majority of PA labels result from viral or drug-related rashes in childhood.[7] Difficulties in accessing healthcare in South Africa (particularly in rural areas) may result in fewer antibiotic exposures in childhood,[6] and difficulties in recognizing fine viral rash in pigmented skin may be important factors.[8] It is likely that these factors will also impact PA prevalence in other LMICs; however, additional research is needed to guide allergy delabelling action plans, including repeating our research in other LMIC settings.

Another important finding was that, despite several attempts to contact and assist patients to attend our allergy clinic, only 1 of 48 patients completed DOC for delabelling. Multiple factors may have contributed, including: patient-perceived lack of importance of carrying a PA label; fear of the testing and procedures or the time involved; changes in contact details and a mobile patient population; or even lack of resources to return for clinic visits.[6,9,10] This inability to have patients return and attend allergy clinics or elective procedures has been highlighted, even in HICs, and undoubtedly aggravated across the world by the COVID-19 pandemic. In paediatric patients, recommendations now exclude the use of skin-prick tests as a possible barrier to care, advocating for direct oral delabelling.[11]

Other important limitations of this study include the fact that all facilities were in the Western Cape. In addition, the surveys were conducted between COVID-19 waves at the various

facilities, which may have impacted elective admissions. This in-hospital patient cohort was younger than similar cohorts in HICs. These data are an important first step in understanding the epidemiology of PA in Africa and upper-middle-income countries/LMICs; additional research in different geographical areas and during non-COVID times is indicated.

These data support bedside direct antibiotic delabelling or challenges in low-risk patients by non-allergists as the only viable option in LMICs. The development, validation and implementation of risk-stratification tools to guide non-allergists will be critical to this effort. This includes ongoing research and validation of delabelling efforts in other LMIC inpatient settings. A comprehensive framework for incorporation of penicillin delabelling in LMICs has been recently outlined.[12]

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S5 are available as Supplementary data at *JAC-AMR* Online.

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