



STUDY PROTOCOL

The impact of a penicillin allergy label on antibiotic resistance in patients with bloodstream infections: Study Protocol

[version 1; peer review: awaiting peer review]

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Abstract

Background

Antibiotics used in place of penicillin antibiotics in patients with penicillin allergy may have a greater tendency to select for antimicrobial resistance (AMR). Therefore, patients with penicillin allergy may be at an increased risk of AMR bloodstream infections, which are associated with significant morbidity and mortality and are increasing in prevalence. This study aims to investigate whether patients with a penicillin allergy have a higher risk of AMR bloodstream infections.

Methods

This is an observational cohort study using routinely collected patient level data obtained from the Health Data Research UK acute care hub 'PIONEER'. The study will include adult patients (≥ 16 years old) admitted to the University Hospital Birmingham NHS Trust between 2015 and 2019 who had positive blood cultures during their admission. The primary outcome of interest is the presence of an AMR bloodstream infection (BSI). Associations between the primary outcome and penicillin allergy status will be investigated using multivariable logistic regression. Secondary outcomes will include rates of community and hospital acquired AMR BSIs, BSIs caused by

pathogens resistant to one or more key antibiotics or antibiotic classes, total antibiotic use, length of hospitalisation and mortality rates.

Plain Language summary

Antibiotic: A medicine used to treat infections caused by bacteria. Antibiotics work by killing bacteria.

Antibiotic resistance bacteria: Bacteria that have changed so they are no longer killed by antibiotics, for example “Superbugs like MRSA”.

Antimicrobial resistance/AMR: A term used to describe the development of antibiotic resistant bacteria.

Bloodstream Infection/BSI: A serious infection caused by bacteria in the blood.

Penicillins: A commonly prescribed group of antibiotics.

Penicillin allergy: When your immune system reacts abnormally to penicillin, wrongly thinking it is harmful.

Penicillin's are the first-choice treatment for many common infections. People who have a penicillin allergy are treated with different, non-penicillin antibiotics. People with penicillin allergy are typically prescribed more antibiotics overall, partly because the alternative antibiotics fail to clear the infection. Research has shown that although many people have penicillin allergy label, most of these people (9 in 10) do not actually have a true allergy when they are tested by a specialist, which means antibiotics are being misused and overused unnecessarily.

Penicillin allergy labels have been linked with “superbugs”, these are bacteria which are ‘resistant’ to usual antibiotic treatments and therefore these antibiotics will not work as well. People who are affected take longer to get better from common infections and are more likely to die from serious infections e.g. bloodstream infections. This problem is often called antimicrobial resistance.

The full impact of penicillin allergy on antimicrobial resistance is unknown. In particular, the impact of penicillin allergy on antimicrobial resistance and health outcomes in patients treated for bloodstream infections (which can cause life-threatening infections) is not known.

Our aim is to understand the links between penicillin allergy, antimicrobial resistance and patient health outcomes in patients who have bloodstream infections, in order to improve antibiotic use.

Keywords

Penicillin allergy, antimicrobial resistance, bloodstream infections, bacteraemia , antibiotic allergy

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Background

Escalating antimicrobial resistance (AMR) in bacteria is a global health concern which is driven in part by antibiotic misuse and overuse. It is predicted that 10 million people globally could die from AMR per year by 2050.¹ The presence of a penicillin allergy impacts on antibiotic prescribing; in particular patients with a penicillin allergy are more likely to receive broad spectrum antibiotics which are more likely to drive AMR.²⁻⁴ Additionally, patients with penicillin allergy have longer hospital stays, receive repeated courses of antibiotic and are almost twice as likely to be prescribed antibiotics compared to patients without a penicillin allergy.²⁻⁴ Consequently, incorrect penicillin allergy labels could be contributing to the emergence of AMR. In the United Kingdom, 6–8% of primary care^{2,5} and 14% of hospitalised patients^{6,7} are reported to have PenA however only around 5% of patients reporting a penicillin allergy are found to be truly allergic on further assessment.⁸

Patients with penicillin allergy have been found to have higher rates of methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE).⁹ Therefore, patients with penicillin allergy may be at risk of resistant bloodstream infections, which cause significant mortality and morbidity.¹⁰ In 2019, resistant bloodstream infections were responsible for 2.91 million deaths globally.¹¹ In England, the burden of bloodstream infections is increasing with data from the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) showing that there was a 13.6% increase in BSI compared from 2019 to 2024, and a 3.5% increase in resistant bloodstream infections.¹²

This study aims to investigate whether patients with a penicillin allergy have a higher risk of resistant bloodstream infections using data from PIONEER Health Data Research Hub, a repository of health data collected as a part of routine NHS care. This study hypothesises that patients with a penicillin allergy label will be more likely to have a resistant bloodstream infection when compared to patients without a penicillin allergy label.

Method

Study design and data source

This is an observational cohort study using patient level data that has been routinely collected. The data will be provided by PIONEER as an anonymised export. PIONEER is a Health Data Research UK (HDR UK) Hub that collates comprehensive health data for patients admitted to hospitals within the University Hospital Birmingham NHS Trust (UHB). UHB comprises of four hospitals: Queen Elizabeth, Heartlands, Good Hope and Solihull. This study has been designed in accordance with the REporting of studies Conducted using Observational Routinely collected Data (RECORD) guideline.¹³

Study population

The study population includes adults admitted to a University Hospital Birmingham NHS Trust hospital who had a positive blood culture collected between 2015 and 2019. A *bloodstream infection* in this study is defined as the presence of a clinically significant bacteraemia as evidenced by the isolation of a pathogenic bacteria in a blood culture. A bacteraemia caused by potential skin contaminants (e.g. coagulase-negative staphylococci [CoNS], *Corynebacterium* species, *Bacillus* species, *Cutibacterium* species, and *Micrococcus* species) will be considered to be significant if isolated in two or more blood cultures within a 48 hour period.¹⁴⁻¹⁶

Inclusion criteria

- Adult (aged ≥16 years) hospital patients who were diagnosed with a bloodstream infection (BSI)

Exclusion criteria include

- Patients with a bacteraemia where the isolated organism lacks definitive identification or where susceptibility data are not available
- Patients diagnosed with mycobacterial, candida or fungal bloodstream infections
- Patients under 16 years of age

Outcomes

The primary outcome is the rate of resistant bloodstream infections in patients with a penicillin allergy versus those without. For the purpose of this study, the Magiorakos et al¹⁷ definition of resistance will be used and a bloodstream

infections will be considered to be a resistant infection if the isolated pathogen is resistant to ≥ 1 antibiotic agent in 3 or more antibiotic classes.

Secondary outcomes will include:

- Rate of community acquired resistant bloodstream infection (CA-BSI), where CA-BSI are defined as the presence of resistant bloodstream infections diagnosed within 48 hours of admission
- Rate of hospital acquired resistant bloodstream infections (HA-BSI), where HA-BSI are defined as the presence of resistant BSI diagnosed ≥ 48 hours after admission
- Rate of BSIs caused by pathogens resistant to one or more key antibiotics. Key antibiotics for important pathogens will be derived from the UK Health Security Agency (UKHSA) ESPAUR report definitions.¹²
- Bloodstream infections resistant to one or more and two or more antibiotic classes
- Total antibiotic usage
- Length of hospitalisation
- Day 30 and 90 mortality rates

Statistical analysis

Descriptive analysis will be used to compare baseline characteristics of patients with and without penicillin allergy. Categorical data will be presented as proportions (%) and continuous data as medians and interquartile ranges (IQR) or as means and standard deviations (SD).

Multivariable logistic regression will be used in primary outcome and binary secondary outcome analysis with adjustment for confounders. Survival analysis and Cox proportional hazards regression models will be used to investigate time to event secondary outcomes.

The full statistical analysis plan can be found in the supplementary material.

Ethics and approvals

Data curation and licensed access for this study through PIONEER has been approved by the East Midlands (Derby) REC (25/EM/0130) and is supported by the Confidentiality Advisory Group (Reference 20/CAG/0084). Use of the anonymised data for this study has been approved by the PIONEER Data Trust Committee (reference PDR072).

Patient and Public Involvement

Patients and the public have been involved from project inception and two patient and public involvement (PPI) contributors who have penicillin allergy sit on the Project Advisory Committee bring invaluable “lived-experiences” to the study. The study also has ongoing input from two PPIE groups: The Smile Aiders at the University of Leeds and the Fighting Infection Group at the Leeds Biomedical Research Centre.

Dissemination and impact

Results will be presented at relevant national and international conferences as well as published in peer reviewed journals. Results will also be shared with relevant stakeholders and policy makers to provide evidence to support penicillin allergy testing as an antibiotic stewardship policy to minimise the burden of AMR.

Discussion

There is a plethora of evidence which has shown the harms associated with penicillin allergy including increased broad spectrum antibiotic use, increased antibiotic consumption overall, increased risk of death, treatment failure, longer hospital stays, increased costs and an increased risk of ICU admission.^{2,7,18–20} Furthermore, while penicillin allergy has been linked to MRSA and VRE⁹, however there is limited data on how penicillin allergy impacts patients with bloodstream infections. This study will provide insight on the relationship between penicillin allergy and on antibiotic resistant BSI.

Data availability

The data used in the study contains anonymised patient-level health information and its use is governed by PIONEER's data governance procedures which are in accordance with the Research Ethics Committee approvals. Data access is provided under licence, and access is restricted to researchers who submit a formal data access request to the PIONEER team at pioneer@uhb.nhs.uk. All data requests must be approved by the PIONEER Data Trust Committee. More information on data access requests can be found on the PIONEER website: www.pioneerdatahub.co.uk/how-to-access-the-data.

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