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Abstract

Objective:

Introduction:

The potential benefits to removing erroneous penicillin allergy labels (de-labeling) are wide ranging. Penicillin allergy assessment and de-labeling is an antibiotic stewardship priority. Delivery of such assessment and de-labeling by non-allergy specialists has been reported in several studies but the effectiveness and safety has not been formally synthesised. This is a necessary step in the upscaling of penicillin allergy assessment services.

Inclusion criteria: quantitative studies using appropriate designs that include adults and pediatric patients who have undergone penicillin allergy assessment and de-labeling delivered by non-allergy specialists in any healthcare setting.

Methods

A range of databases will be searched to identify studies published in the English language. Unpublished studies and the grey literature will also be searched.

Identified studies will be assessed for methodological quality using the standardised critical appraisal instruments and data extracted using tools from the Joanna Briggs Institute (JBI).

Data from included studies will be categorised using the EPOC taxonomy and effectiveness and safety of the intervention determined. Data will be pooled, where possible, to facilitate meta-analysis, whilst data from heterogeneous studies will be reported narratively.

Systematic review registration number: CRD42020219044

Keywords:

"antimicrobial stewardship"; "penicillin allergy assessment" "penicillin allergy de-labeling";

Introduction

Approximately 6% of the general population in England[1] and 15% of hospital inpatients in England, and elsewhere,[2-4] have a record of penicillin allergy. Penicillin-based antibiotics are first-line treatment for many common infections but patients with penicillin allergy labels are usually treated with second line antibiotics rather than first line penicillin antibiotics.[2] Second line, non-penicillin, antibiotics are often more costly,[5-7] can be less effective in certain clinical circumstances,[1,8-10] and

more toxic.[5] Second line antibiotics are often broader spectrum, potentially increasing a patient's risk of future infections with resistant bacteria. [5,11] Patients with penicillin allergy records are also associated with exposure to a greater number of antibiotics, increased length of hospital stay[2,4] higher hospital readmission rates,[12] all of which increase costs to healthcare systems.

However, more than ninety per cent of individuals with a penicillin allergy label are not allergic to penicillin.[13] Assessing patients with penicillin allergy labels to identify those who are not allergic to penicillin, and to de-label them, has the potential to reduce second line antibiotic use in favor of penicillins, thus reducing the unintended consequences associated with second line antibiotics.

Penicillin allergy assessment of patients with a reported penicillin allergy has traditionally been the role of allergy experts. Allergy services in the UK, and elsewhere, are limited[14] and many hospitals do not have direct access to allergy services. Furthermore, allergy services do not have capacity to assess and de-label the potentially large number of patients with reported allergies to penicillin. Traditional penicillin allergy testing requires skin testing prior to an oral challenge test, and is still the main testing method in UK allergy centres, and therefore penicillin allergy testing is resource intense. A less resource intense penicillin allergy de-labeling method uses a direct oral penicillin challenge in patients with a history consistent with low risk of future penicillin allergy, forgoing the need for skin testing.

Direct oral challenge testing makes allergy assessment possible outside allergy centres because it is quicker and less resource intensive than the traditional skin test method. Non-allergy specialist researchers have explored penicillin allergy assessment and de-labeling of hospitalized patients[15,16] and found it to be safe and effective; increased use of penicillin antibiotics instead of second line antibiotics and with minimal evidence of side effects. Two systematic reviews have confirmed the safety and efficacy of a direct oral challenge as a method of de-labeling adults when delivered by allergists and non-allergists.[17,18] Other non-allergist delivered methods of allergy assessment and de-label, such as skin testing methods, have also been successfully delivered in the inpatient and outpatient setting.[19,20] Leading allergists in the US have suggested that every physician needs to get an accurate drug intolerance history before avoiding a beta-lactam (the broader antibiotic group name that includes the penicillin antibiotic group) when it is the drug of choice, and they postulate that addressing unconfirmed beta-lactam allergy on a large scale would lead to a dramatic reduction in the morbidity and mortality associated with unconfirmed beta-lactam allergy and reduce healthcare associated costs. [21] In September 2020 the American Academy of Allergy Asthma and Immunology with the Infectious Diseases Society of America wrote to the Centers for Medicare and Medicaid Services to urge US hospitals to include verification of penicillin allergy as part of its

mandatory antibiotic stewardship programs.[22] More recently the World Health Organisation have recommended antibiotic de-labeling as an effective antimicrobial stewardship strategy[23] but knowledge of the epidemiology of penicillin allergy labels and their association with antimicrobial resistance in low and middle-income countries is sparse, as is the evidence for established antibiotic de-labeling pathways,[24] with the majority of studies in high-income countries.

Penicillin allergy de-labeling is well supported by healthcare workers and accepted by patients. Healthcare workers in a UK hospital reported frequently encountering patients with penicillin allergy records they believed to be erroneous, and recognised that incorrect penicillin allergy records were a problem that required a solution.[25] An Australian study demonstrated patient acceptability for oral penicillin challenges to rule out penicillin allergy,[26] whilst a US study found that patients felt that penicillin allergy testing provided valuable medical information.[27]

Enablement of the wider healthcare workforce to assess patients with penicillin allergy records and de-label eligible patients is required in order to deliver penicillin allergy assessment and de-labeling at scale. Lin reported on a successful general physician delivered penicillin allergy de-labeling programme in hospitalized patients in the Netherlands.[28] The intervention included physician education, the handing out of pocket-sized reminder cards and utilised the electronic medical record to prompt physicians to perform the necessary assessment. Maguire reported a successful US Emergency Department physician-delivered penicillin allergy de-labeling patient pathway.[29] The intervention included the development of a penicillin and cephalosporin test dose procedure guideline, pharmacist-led education, a physician ordering of test doses, pharmacist verification and nurse administration and post-challenge dose observation.

In this review, we aim to systematically review the literature to identify and determine the effectiveness of interventions that enable non-allergy specialist healthcare workers to assess, and, where appropriate, de-label adult and pediatric patients with a reported penicillin allergy in any healthcare setting and to determine and to synthesise the components of these interventions that make them safe and effective. Non-allergy specialist is defined as a medical professional whose primary specialization is not in allergy, or who has not trained in allergy as part of their specialty.[30]

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Evidence Synthesis was conducted and no current systematic reviews on the topic were identified. However, one systematic review by Cooper *et al.*[17] synthesising the evidence for the safety and efficacy of de-labeling penicillin allergy in adults using direct oral challenge was underway, and has since been published, and shows direct oral challenge as a method for de-

labeling adults, delivered by both allergists and non-allergist, is safe and effective. The systematic review we propose is similar to that of Cooper *et al.* but will offer further insight into penicillin allergy assessment and de-labeling interventions. Our proposed review is more focused than that of Cooper *et al*, because it looks solely at non-allergists, but also broader because it is not limited by healthcare setting, it will include children and adolescents as well as adults, and will include all de-labeling methods utilised to de-label patients with incorrect penicillin allergy labels. We have narrowed our search to only non-allergists because we want to understand the wider frameworks that enable non-allergists to assess penicillin allergy records and safely de-label patients because if we are to tackle this at scale we need to mobilise the non-allergist workforce and learn how to do this safely.

The findings of this review will inform the development of a complex intervention designed to facilitate and embed penicillin allergy assessment and de-labeling delivered by non-allergy specialists as part of secondary care antimicrobial stewardship programme in a UK hospital.

We aim to systematically review and synthesise the literature evaluating the effectiveness and the safety of interventions that enable non-allergy specialist healthcare workers to remove incorrect penicillin allergy labels in adult adolescent and pediatric patients with reported penicillin allergies.

The objective of this systematic review is to (1) identify and synthesise the range of interventions and allergy testing methods used by non-allergists to enable assessment of reported penicillin allergies and subsequent de-labeling. (2) To identify which types of healthcare workers have been targeted by interventions that set out to assess and de-label penicillin allergy records in objective 1. (3) To determine the effectiveness (increases in penicillin antibiotic use) and safety (absence of adverse drug events) of strategies used to deliver non-allergy specialist inpatient de-labeling in hospitalized patients.

Review question(s)

What is the effectiveness and safety of interventions that facilitate non-allergy specialist healthcare workers' assessment of adults and pediatric patients with reported penicillin allergy records with subsequent de-labeling of erroneous records?

Inclusion criteria

Participants

This review will include studies with any patient (adults, adolescents and children) who have a penicillin allergy record, or self-reported allergy to penicillin on direct questioning, in any healthcare context from any country.

Intervention(s)

The review will also include studies reporting on penicillin allergy de-labeling using any method (direct de-label, direct oral challenge, skin testing and oral challenge) by non-allergy specialists which include, but not limited to, nurses, pharmacists and doctors.

Exclusions

Penicillin allergy assessment and de-labeling interventions delivered by immunologists, or allergy specialists will be excluded.

Comparator(s)

Adults adolescents and children who receive usual standard care and do not undergo penicillin allergy assessment. Due to the nature of the intervention there may not be a comparator group and therefore studies without comparator or control group will not be excluded.

Outcomes

This review will consider studies that include the following outcomes:

Primary outcome:

The number of adults, adolescents or children with a penicillin allergy record successfully de-labeled.

Secondary outcomes:

1. Any measured antimicrobial stewardship impact (e.g. antibiotic class prescribed, antibiotic cost, antibiotic side effects, treatment failure, health care associated infections (HCAI) and antibiotic resistant (AMR) infections).

2. Any measured healthcare system impact (e.g. length of hospital stay, healthcare resource utilization).

3. Any unintended harm associated with the de-label process (e.g. anaphylaxis, side effects of antibiotics).

Types of studies

Included

This review will include both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies as well as descriptive observational study designs.

Excluded

Case reports

Methods

The systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness,[31] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[32]

The protocol has been registered in PROSPERO CRD: 42020219044

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of EMBASE will be undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles will be used to develop a full search strategy for EMBASE (see Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information source. Backwards and forwards references searches of all included sources of evidence will be completed to identify additional studies.

Only studies published in English will be included due to a lack of funding for translation services. No date limit will be set for included studies because this is a relatively new antimicrobial stewardship intervention and studies are only expected to be identified from 2010 onwards.

Information sources

The databases to be searched from their inception to present day include EMBASE (Ovid), MEDLINE (Ovid), CINAHL (Ovid), PsycInfo, Web of Science and Cochrane CENTRAL. Sources of unpublished studies/ grey literature to be searched include WHO Library database, key organisation websites and conference proceedings (ESCMID, Society for Healthcare Epidemiology of America, Healthcare

Infection Society and Infection Prevention Society), registered Controlled Trial Registers, technical or research reports from government agencies and the British Library (Ethos) Collection of PhD dissertations.

We will contact known experts in the topic regarding any unpublished work and to ensure we have not overlooked relevant literature.

Study selection

Following the search, all identified citations will be collated and uploaded into Endnote Note v.X9.2 (Clarivate Analytics, PA, USA)[33] and duplicates removed. Following a pilot test, titles and abstracts will then be screened by at least two independent reviewers for assessment against the inclusion criteria for the review using RAYYAN software.[34] Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia).[35] The full text of selected citations will be assessed in detail against the inclusion criteria by at least two independent reviewers using RAYYAN software.[34] Reasons for exclusion of papers at full text that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer. The results of the search and the study inclusion process will be reported in full and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[32]

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental, quasi-experimental, observational and descriptive studies.[31] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Studies will not be excluded on the grounds of their risk of bias, but the risk of bias will be reported when presenting the results. The risk of bias judgments will be summarized across different studies for each of the domains listed using the risk of bias graph and the risk of bias summary. Therefore, all studies, regardless of the results of their methodological quality, will undergo data extraction, and synthesis (where possible).[31]

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized data extraction tool.[31]

The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objectives and interventions categorised using the Effective Practice and Organisation of Care (EPOC) taxonomy of health interventions.[36] Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Studies will, where possible, be pooled in statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) or weighted (or standardized) final post-intervention mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and I squared tests and reasons for heterogeneity will be explored using subgroup and/or sensitivity analyses. Statistical analyses will be performed using the random effects model, or if study numbers are small, the fixed effects model.[37] Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test)[38-40] will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed[41] and a Summary of Findings (SoF) table will be created using GRADEPro GDT 2020 (McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be: the proportion of adults adolescents or children with a penicillin allergy record successfully de-labelled, any measured antimicrobial stewardship impact, any measured healthcare system impact, any unintended harm associated with the de-label process.

Funding

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Conflicts of interest

There is no conflict of interest in this project.

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Appendix I: Search strategy

EMBASE (OVID) searched 16th October 2020

1. (penicillin adj2 allerg*).tw.
2. (penicillin adj2 hypersensitiv*).tw.
3. (penicillin adj2 anaphylaxis).tw.
4. (beta-lactam adj2 allerg*).tw.
5. (beta-lactam adj2 hypersensitiv*).tw.
6. (beta-lactam adj2 anaphylaxis).tw.
7. ("betalactam" adj2 anaphylaxis).tw.
8. ("betalactam" adj2 hypersensitiv*).tw.
9. ("betalactam" adj2 allerg*).tw.
10. ("*lactam" adj2 allerg*).tw.
11. ("*lactam" adj2 hypersensitiv*).tw.
12. ("*lactam" adj2 anaphylaxis).tw.
13. ("antibiotic" adj2 anaphylaxis).tw.
14. ("antibiotic" adj2 hypersensitiv*).tw.

15. ("antibiotic" adj2 allerg*).tw.

16. ("antimicrobial" adj2 allerg*).tw.

17. ("antimicrobial" adj2 hypersensitiv*).tw.

18. ("antimicrobial" adj2 anaphylaxis).tw.

19. "PENICILLIN DERIVATIVE"/

20. "DRUG HYPERSENSITIVITY"/ or ANAPHYLAXIS/

21. 19 and 20

22. "PENICILLIN ALLERGY"/

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18or 21 or 22

24. "clinical decision tool".tw.

25. "clinical decision making".tw.

26. "clinical assessment tool".tw.

27. direct.tw.

28. challenge.tw.

29. de-label*.tw.

30. 27 and 28

31. delabel*.tw.

32. "interview".tw.

33. "antibiotic stewardship".tw.

34. "antimicrobial stewardship".tw.

35. test*.tw.

36. "allergy assess*".tw.

37. "oral challeng*".tw.

38. "ANTIMICROBIAL STEWARDSHIP"/

39. "SKIN TEST"/

40. "PROVOCATION TEST"/

41. "ALLERGY TEST"/

400 42. "CLINICAL EVALUATION"/

401 43. ALGORITHM/

402 44. "RISK ASSESSMENT"/

403 45. 24 or 25 or 26 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
404 or 43 or 44

405 46. 23 and 45

406 No limits set, number of returns 3188.