ABSTRACT
Penicillin allergy is the most prevalent drug allergy. Its overdiagnosis has been associated with inappropriate antibiotic prescribing, increased antimicrobial resistance, worse clinical outcomes, and increased healthcare costs.

Methods:
403 inpatients were audited against National Institute of Clinical Excellence (NICE) Clinical Guidance 183 (CG183) on diagnosis, investigations, documentation, and management of penicillin allergy. 50 junior doctors were surveyed to explore barriers to best practice, investigating their knowledge of, and confidence using the NICE CG183 guidelines. Their views on potential solutions were also explored.

Key results:
The audit identified: 13% (54/403) of patients labelled penicillin allergic; 24% (13/54) fulfilled criteria for referral but none were referred to specialists. With regards to documentation: 33% (18/54) documented exact drug name; 72% (39/54) documented signs and symptoms; 20% (11/54) documented reaction severity; 2% (1/54) documented indication for the drug taken; 4% (2/54) documented number of doses taken or days before onset of the reaction and 0% documented route of administration.

The survey revealed barriers including: 1- lack of awareness and confidence in applying the NICE CG183 on diagnosis and management; 2- tendency to err on the side of caution when de-labelling patients. All agreed that decision support tools would address barriers to best practice and appropriate penicillin allergy de-labelling

Conclusion: The current practice of diagnosing, documenting, and managing penicillin allergies does not meet NICE CG183. A lack of awareness and confidence using NICE CG183 are the main contributing barriers to best practice. Decision support tools, including a drug allergy app, would help overcome these barriers.

Keywords:
Penicillin, NICE, Penicillin Allergy, Drug Allergy, Survey, Audit, Decision Support Tool

Impact statement:
Penicillin allergy management does not meet NICE CG183 standards, and contributing barriers include doctors' lack of awareness and confidence using CG183 standards but can be overcome through decision support tools.
INTRODUCTION

Penicillin belongs to the larger beta-lactam family (Figure 1) (1). Across the globe, penicillin allergy is the most documented drug allergy as it is reported by around 10% of the general population, and by 13.7% of the inpatient population (2, 3). A review into the Evaluation and Management of penicillin allergy by Shenoy et al. in the United States, evidenced that less than 10% of those who report a penicillin allergy are truly allergic (4). This reaction can be confirmed by skin sensitivity testing undertaken by drug allergy specialists (5). This test has a high specificity, as it can accurately identify about 90% those who do not have a true penicillin allergy (4).

The identification of those who are truly penicillin allergic has been evidenced to be highly critical. Studies show that patients with a penicillin allergy label will be treated with less effective, more toxic, broad-spectrum antibiotics, including vancomycin, clindamycin, and quinolones (6, 7). The use of these antibiotics has been evidenced to significantly increase costs of care, and the length of hospital admissions (8, 9). Research by Li et al., into the economic impact of penicillin allergy labelling, found that the total cost of antibiotics prescribed for patients with a penicillin allergy label is a 1.82-2.58 fold greater than the total cost for those without the label (9). Further to this, studies by Blumenthal et al. and Macy et al., evidenced that the use of these broad-spectrum antibiotics, largely increases patients’ risk for adverse events, while undermining the goals of antimicrobial stewardship, through significantly increasing the rates of Clostridium difficile, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant Enterococcus (6, 7). These clinical consequences of prescribing non-penicillin antibiotics make it imperative to stop penicillin allergy overdiagnosis, by ensuring that only those with a true penicillin allergy are given the label.

NICE CG183 has established standards for assessing patients with drug allergies based on their history and examination (10). The guidance advises clinicians on how to make distinctions between reactions based their characteristics, timing, systemic involvement, and severity (10). It also has clear standards on the structure of how the purported reactions should be documented, as well as the criteria of when it’s appropriate to refer patients to specialist drug allergy services (10).

The high prevalence of patients with a penicillin allergy label raises the important query into whether these standards of best practice are being met. There are numerous studies which evidence widespread inconsistency in the documentation of drug allergies, and low referral rates of patients to allergy specialist services (11-13). A study by MacLaughlin et al. included a total of 660 patients, 99 having a recorded penicillin allergy but only 33% had some form of evaluation and description of their suspected allergic reaction (12). Further to this, a study by Elkhalifa et al. found that in a UK hospital, over 60% of clinicians had not referred any patients to a specialist drug allergy service (13).

The audit aimed to determine the prevalence of the penicillin allergy label among a randomly selected cohort of inpatients at Salford Royal Hospital, while also exploring if the diagnosis, documentation, investigations, and management of these penicillin allergies met the standards outlined by NICE.
CG183. The survey aimed to determine clinicians perceived barriers to best practice through assessing their knowledge of and confidence using the NICE CG183 guidelines, as well as their views on various decision support tools.

METHODS
The study was undertaken at Salford Royal Hospital and consisted of two parts:
- A Clinical audit which was registered
- A Survey undertaken by 50 junior doctors

Audit Method
Using a comprehensive electronic patient record (EPR) database, a prospective audit collected data from 403 inpatients on 26 acute medical and surgical wards at Salford Royal Hospital. The wards were randomly selected using a random number generator program on Google. This audit identified patients with a penicillin allergy label and determined if the standards outlined by NICE CG183 on drug allergy labelling, documentation, and referral are being met. (See Figure 2 for the flow chart summarising how this data was collected). The standards of the documentation of the purported reaction explored the signs, symptoms, and severity, indication for taking the drug, number of doses or days on the drug before the reaction, and its route and date of administration. The data collected remained anonymous and was documented in an excel spreadsheet.

Survey Method
A prospective survey explored the perspective of 50 junior doctors on the potential barriers preventing the best practice which is outlined by NICE CG183. The survey explored potential barriers including their confidence in taking and drawing a conclusion from a patients’ allergy history; a perceived lack of time or responsibility to take an adequate allergy history; their knowledge of, and confidence using the NICE CG183 guidance for diagnosing, de-labelling, documenting, and referring patients with penicillin allergies; and their knowledge on the negative implications of false penicillin allergy labels (See Appendix 1 for more detail). Furthermore, it also found their perspective on proposed decision support tools for removing penicillin allergies. The survey was anonymous and taken from doctors on 10 randomly selected acute medical and surgical wards in Salford Royal Hospital. The wards were randomly selected using a random number generator program on Google, and the survey was constructed using Microsoft forms. There were no partial responders to the survey.

RESULTS
Audit Results
The audit found the prevalence of penicillin allergy within this inpatient population to be 13% (54/403). It demonstrated inconsistencies in the documentation and referral of patients with purported reactions. All results, and demographic data are summarised in Figure 2. The audit found that while most purported reactions to penicillin had the drug name (Penicillin) 100% (54/54), signs and symptoms 72% (39/54), and date 100% (54/54) documented, less than 50% had the exact drug name (the type of
Penicillin) 33% (18/54), severity of reaction 20% (11/54), indication for taking the drug 2% (1/54), number of doses taken or days on the drug before onset of reaction 4% (2/54), and route of administration 0% (0/54) recorded. Therefore, the audit observed that no patient had all the recommended NICE CG183 information documented for their purported, and although 24% (13/54) of patients met criteria for referral, no patients had been referred to drug allergy services.

Survey Results
The survey was undertaken by junior doctors at various levels. 21 were at specialty trainee level (ST1+) (42%), 16 were at Foundation Year 1 (FY1) level (32%) and 13 were at Foundation Year 2 (FY2) level (26%).

The survey illustrated that a significant proportion this cohort of doctors strongly agree or agree with:
1- being confident in taking a patients allergy history and interpreting it 96% (48/50); 2- having enough time to take a detailed drug allergy history 70% (30/50); 3 - are aware of the implications of prescribing alternative antibiotics to beta-lactams in those who do not have a true penicillin allergy 78% (39/50). On the other hand, majority disagree or strongly disagree with the following: 1- It is mostly the duty of the pharmacist to take the allergy history 80% (40/50); 2 - have referred patients with a label of penicillin allergy to a drug allergy service 78% (39/50).

A heatmap with the percentage breakdown in the junior doctor’s responses to each statement is summarised in Figure 3.

The survey asked doctors to respond to the statement ‘Would you feel confident using any of the following to support your decision to remove a penicillin allergy label, based on history alone’. They were able to select as few or as many of suggestions, and the responses showed the popularity of each of the choices:
- 26% (13/50) education material
- 26% (13/50) a web-based algorithm tool as a decision support tool
- 26% (13/50) a drug allergy app as a decision support tool
- 22% (11/50) a flow chart as a decision support tool

DISCUSSION OF FINDINGS
The audit demonstrated that among this cohort of patients reviewed, there are inconsistencies in the documentation of their allergy status and purported reactions to penicillin. The current practice of documenting, labelling, and referring patients with a penicillin allergy does not meet the standards of best practice, and thus may be contributing to an inappropriately high prevalence of patients with a penicillin allergy label. The survey found that the potential barriers to best practice for this cohort of junior doctors includes their lack of awareness and confidence applying NICE CG183, as well as their tendency to err on the side of caution when managing patients with a suspected penicillin allergy label.
The junior doctors showed equal popularity to using education material, a web-based algorithm tool, and a drug allergy app as decision support tools and solutions to overcome these identified barriers.

This audit provided an overview of how penicillin allergies are documented and recorded in electronic patient records at Salford Royal Hospital. The audit showed that within this inpatient population, the prevalence of those with a penicillin allergy label is 13% (54/403). This is similar to findings in a study by Baxter et al. who found its prevalence to be 13.7% (3). Further to this, the audit also found that 10.17% (41/403) inpatients had an allergy status which did not fulfil the NICE CG183 standards. Every patient in the audit with an identified penicillin allergy label did not have all the recommended NICE CG183 information documented on their purported reaction (10). This finding is supported by a study by Shah et al., which illustrated that only 22.7% of those with a beta-lactam allergy label had a documented description of their reaction (11). The audit also evidenced that no patients in this cohort had been referred to drug allergy services, although 24% (13/54) fulfilled the NICE CG183 criteria for referral (11). This supports research from a study by Elkhalifa et al. who found that in a UK hospital over 60% of clinicians had not referred any patients to a specialist drug allergy service over the last year (13). This audit therefore supports the findings of other studies, that in practice, there is a clear stray from the NICE CG183 for documenting, managing, and referring patients with penicillin allergies.

The survey provided an insight on what 50 junior doctors perceive as potential barriers preventing the best practice for diagnosing, managing, and referring patients with suspected penicillin allergies. It identified that a majority of the doctors greatly lack awareness of, and confidence in using NICE CG183. This helps to account for the absence of best practice illustrated by the clinical audit. This finding is supported by a study undertaken by Picard at al., who evidenced that a key contributing barrier to referring patients, is the clinician’s absence of awareness in the relevant criteria (14).

The survey also highlighted that within this cohort of doctors, it is a common tendency to err on the side of caution when managing patients reporting a penicillin allergy. This coupled with their reported lack of confidence to remove a patient’s penicillin allergy label based on their history alone, helps to explain the high prevalence of patients who were falsely labelled penicillin allergic. On the other hand, the survey also found that majority of the doctors in this study were confident in taking, interpreting, and drawing a firm conclusion on an allergy based on a patient’s history alone. This differs to findings by Elkhalifa et al., as this study reported that most clinicians (55.2%) believed that it not possible to use history alone to decide a patients allergy status (13). The survey also explored a number of potential solutions which may help doctors to feel more confident in appropriately de-labelling patients with an inappropriate penicillin allergy label, these include the use of educational material, or decision support tools in the form of web-based algorithm, drug allergy app or flow charts.

Limitations of the Data
The findings of the audit and survey have some possible limitations, firstly it included a small sample size, and was undertaken at a single regional centre, Salford Royal Hospital. Furthermore, the survey
is limited in its relevance, as it only explored the views of junior doctors, who are still in training, and did not include other prescribing clinicians. It found varying results to studies by Elkhailfa et al., and this may be due to the lack of role diversity in this survey, as their survey included doctors in training, consultants, and non-medical prescribers (13). The level of training may impact the results, as studies undertaken by Elkhailfa et al. and Amin et al. have correlated a lack of training to the inappropriate management of allergies (13,15).

Additionally, the survey results need to be analysed with caution as it is limited by not clarifying the accuracy of what the doctors reported. For example, a majority of doctors reported understanding the implications of prescribing alternative antibiotics to patients with a penicillin allergy, but still believed it was best to err on the side of caution and avoid using beta-lactams in those reporting a penicillin allergy. This leads to querying whether they truly understand the negative implications of prescribing alternative antibiotics. A study by Amin et al. evidenced that many clinicians had misconceptions surrounding the characteristics of an allergic reaction and difficulty in distinguishing them from an intolerance (15). In this study, a survey of hospital staff found that only 63% of the doctors were aware of the defining characteristics of a true allergic reaction, while 23% incorrectly labelled antibiotic side effects as characteristics of an allergic reaction (15). Further to this, although the survey found that most doctors did not lack confidence to draw a firm conclusion on an allergy, it did not investigate whether they were able to accurately identify the characteristics of an allergic reaction. Further studies, for instance using case vignettes, could explore the clinician’s ability to accurately identify characteristics of an allergic reaction. However, the study mitigated the risks of any sampling bias through using a random number generator to select the wards in the audit and survey, while also collecting data for the survey from doctors at various training levels.

**Potential Solution**

The survey found that a number of decision support tools would greatly improve this cohort of doctors’ confidence in appropriately de-labelling patients with a penicillin allergy label. Elkhailfa et al., designed and developed a drug allergy mobile application to support clinicians in accurately diagnosing and referring patients with drug allergies (13). This would potentially help to reduce the number of patients with a false penicillin allergy label, and the negative consequences of prescribing alternative antibiotics. Furthermore Elkhailfa et al., have proposed incorporating a clinical flowchart (Figure 4) to the drug allergy app, thus making it a useful tool to empower clinicians to accurately diagnose drug allergies, appropriately prescribe antibiotics, i.e., penicillin, and refer patients to drug allergy services (13). However, through using the allergy app to empower clinicians, this will inevitably increase the number of referrals to specialist services, thus making it necessary to increase the capacity within such services. This would most definitely increase costs in the short term, but they are likely to be offset by the future benefits of attempting to address antimicrobial stewardship.

This proposed pathway of using a drug allergy app will address some of the barriers to best practice, such as the clinician’s lack of awareness and use of NICE CG183, but is limited in its benefit, as it does
not address all contributing barriers, including: the greater need for funding into this area and the patient’s perspective of penicillin allergies. A study by Gerace et al. found that after removing the allergy label from adult patients, 41% continued to be fearful and avoid all penicillin’s (16). This may be due to patient’s requiring greater effort in convincing that they do not need to avoid the drug and may be overcome by educating patients with leaflets or websites. Further to this, studies by Diwakar et al. evidenced that a reluctance of investing funds into these allergy services is hindering the improvement of the drug allergy services and is responsible for creating an unmet demand of these services (17). The review highlighted that globally, there is evidence of increasing incidence and prevalence of drug allergies, however the current allergy services are unable to keep up with this demand (17).

Other proposed solutions include a risk-based algorithm piloted by the Scottish Antimicrobial Group (SAPG) (18). This algorithm was used in supporting non-specialist clinicians remove unverified penicillin allergy labels from patients with a penicillin allergy label (18). This algorithm was successful in safely supporting clinicians remove a penicillin allergy label from 80% of the adult patients involved in the study (18). However, this support tool was limited in its success, as even after formally removing a penicillin allergy label, many patients and clinicians continued to experience concerns over the safety of prescribing or taking penicillin (18). This highlights the limitation of this solution in not addressing the all the barriers to best practice.

To conclude, this study demonstrated that the current practice of diagnosing, managing, and referring inpatients with a penicillin allergy at Salford Royal Hospital does not meet the standards of best practice outlined by NICE CG183. The survey identified that this stray from best practice occurs due a junior doctors lack of awareness and confidence in using these guidelines, as well as their tendency to err on the side of caution when dealing with patients reporting a penicillin allergy. A proposed decision support tool would help clinicians to accurately identify when it is appropriate to de-label patients with a penicillin allergy. However, although these support tools may help to address the clinicians lack of awareness in these guidelines, it fails to address barriers such as the lack of funding into these allergy services, and the patient’s perspective. Further research is required to explore how these specialist drug allergy services may be funded to meet their growing demand and validate such tools of penicillin allergy de-labelling, so they may be used in clinical practice.

REFERENCES

Conflicts of interest
All authors have declared no conflicts of interest.

Ethics
No ethical approval was necessary.

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Figure legends:

Figure 1. Beta-lactam family tree. Above is the breakdown of the beta-lactam family (1st gen. = first generation, 2nd gen. = second generation, 3rd gen. = third generation, 4th gen. = fourth generation, 5th gen. = fifth generation).

Figure 2. AUDIT METHOD AND RESULTS. The flowchart summarises the data collected in the audit, including the demographic data.

Figure 3. The heatmap visually illustrates the breakdown of the doctors’ responses to the various statements given in the survey.

The statements with a bar that is greater than 50% green illustrates that over 50% of the doctors undertaking the survey strongly agree or agree with these statements. These include Statement 1, Statement 2, Statement 10 and Statement 5.

For Statement 3, less than half of the bar is orange or red, thereby showing that less than 50% of the doctors disagree or strongly disagree with this statement.
On the other hand, the statements with over 50% of the bar orange and red highlight that a majority of the doctors in the study disagree or strongly disagree with these statements. These include Statement 4, Statement 6, Statement 7, Statement 8, and Statement 9.

Figure 4: This outlines a clinical flow chart outlining the ideal patient journey, from a patient reporting a penicillin allergy, to outlining the most appropriate treatment option. From (15). Copyright © (2021) [Rightsholder]. Reprinted and edited with permission from [rightsholder].

* In case of Penicillin allergy, use of cephalosporins with low risk of cross reactivity (e.g., ceftiraxone or ceftriaxone) or carbapenems is unlikely to result in serious allergic reactions.

** Examples included gastrointestinal intolerance, such as diarrhoea or nausea. If the suspected drug is indicated, the same medication can be given following discussion with patient. Dechallenge of drug allergy can take place at this stage of clinical consultation.

*** In case of penicillin allergy, use of alternative β-lactam antibiotics should be discussed with drug allergy or infection specialists on a case by case basis. Discussing the risks and benefits with patients is recommended.
### APPENDIX 1 – SURVEY DATA COLLECTION PROFORMA

<table>
<thead>
<tr>
<th>DOCTORS GRADE: FY1 □   FY2 □   ST1+ □   Consultant □</th>
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**STATEMENTS EXPLORING BARRIERS TO BEST PRACTICE**

<table>
<thead>
<tr>
<th>STATEMENT 1: I am confident in taking a patients allergy history and interpreting it</th>
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<tbody>
<tr>
<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 2: I feel I have enough time to take a detailed drug allergy history</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 3: I feel confident in drawing a firm conclusion about an allergy based on the patient's history alone</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 4: It is mostly the duty of the pharmacist to take the allergy history</th>
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<tr>
<th>STATEMENT 5: Regardless of the specific details in the history it is better to err on the side of caution, and avoid beta-lactams in patients reporting a penicillin allergy</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<tr>
<th>STATEMENT 6: I am aware of the NICE clinical guidance for diagnosing and managing drug allergies</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 7: I feel confident in using the NICE criteria for documenting a patients penicillin allergy</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 8: I am aware of the NICE guidance criteria for referring patients to drug allergy services</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 9: I have referred patients with a label of penicillin allergy to a drug allergy service</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 10: I am aware of the implications of prescribing alternative antibiotics to beta-lactams in patients who do not have a penicillin allergy</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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<th>STATEMENT 11: I feel confident in removing a patients label of penicillin allergy based on history alone</th>
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<td>Strongly agree □   Agree □   Neutral □   Strongly disagree □   Disagree □</td>
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**Would you feel confident using any of the following to support your decision to remove penicillin allergy label, based on history alone**

- Educational material □
- Drug allergy app □
- Flow chart □
- Web-based algorithm □