NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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The risk of MRSA and *C difficile* in people with documented 'penicillin allergy'

A large population-based cohort study from UK general practice data found that people with a documented 'penicillin allergy' had an increased risk of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*. This increased risk was thought to be brought about by the increased use of antibiotics selected as an alternative to beta-lactams. This highlights the importance of ensuring that only 'true' penicillin allergies are documented, in line with the NICE guideline on drug allergy: diagnosis and management. NICE is currently producing a suite of antimicrobial prescribing guidelines, which should help prescribers to select the most suitable antibiotic regimens for specific conditions.

Overview and current advice

About half a million people admitted to NHS hospitals each year have a diagnostic 'label' of drug allergy, with the most common being penicillin allergy. About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood (NICE drug allergy full guideline). Fewer than 10% of people who think they are allergic to penicillin have a true allergy. Therefore, penicillin allergy can potentially be excluded in 90% of people who think they have a penicillin allergy. Studies (such as Lee et al. 2000) have shown that people with a label of penicillin allergy are more likely to be treated with broad-spectrum, non-penicillin antibiotics, such as quinolones, vancomycin and third-generation cephalosporins. However, use of these antibiotics in people with an unsubstantiated label of penicillin allergy may lead to antibiotic resistance and, in some cases, sub-optimal therapy.

Analysis of patient safety incidents reported to the National Reporting and Learning System between 2005 and 2013 identified 18,079 incidents involving any drug allergy (not just penicillins). These included 6 deaths, 19 'severe harms', 4,980 'other harms' and 13,071 'near-misses'. The majority of these incidents involved a drug that was prescribed, dispensed or administered to a patient with a previously known allergy to that drug or drug class. Therefore, it is important to remember that a true allergy can have serious consequences.

The NICE guideline on drug allergy: diagnosis and management defines drug allergy as 'any reaction caused by a drug with clinical features compatible with an immunological mechanism'. The guideline aims to make it easier for professionals to tell when someone is having an allergic reaction, by specifying the key signs and patterns to look out for. It also makes recommendations on improving people's understanding of their drug allergies, and ensuring these are recorded properly in their medical records. In addition, the NICE guideline on antimicrobial stewardship provides good practice

recommendations on systems and processes for the effective use of antimicrobials. The NICE Pathway on drug allergy and antimicrobial stewardship bring together all related NICE guidance and associated products on these topics in a set of interactive topic-based diagrams. The NICE key therapeutic topic on antimicrobial stewardship: prescribing antibiotics summarises the evidence-base in this area.

New evidence

A population-based cohort study, examined the public health consequences of having a penicillin allergy label by looking at the relationship between having a newly-recorded 'penicillin allergy' and the risk of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* (Blumenthal et al. 2018). A total of 64,141 people with a documented 'penicillin allergy' were matched with 237,258 comparators, who took penicillin but did not have a documented penicillin allergy, using data recorded on the Health Improvement Network (THIN) database between 1995 and 2015. The THIN database contains data on 11.1 million people collected from over 550 general practitioners spread over the UK. Participants were only eligible if they had no history of MRSA or *C difficile* before study entry and had been enrolled with a GP for at least a year.

People with documented 'penicillin allergy' were matched to their comparators, in terms of age, sex, body mass index, socioeconomic status, smoking status, alcohol use, various comorbidities as well as visits to a GP and hospital admissions. As might be expected, reports of allergies to other antibiotics were more common in people who had documented 'penicillin allergy'. Most of the 'penicillin allergies' were described as 'moderate severity' (86.0%) and of 'likely certainty' (73.6%). The documented 'penicillin allergies' included 'allergies' (74.4%), 'intolerances' (14.5%) and 'adverse effects' (11.1%).

Over a mean follow-up of 6 years, 1,365 people developed MRSA (442 people with 'penicillin allergy' and 923 people from the comparator group) and 1,688 developed *C difficile* (442 people with 'penicillin allergy' and 1,246 comparators). An increase in both MRSA and *C difficile* was found in people who had a 'penicillin allergy' compared with the comparators. For people with a 'penicillin allergy' the adjusted hazard ratio [HR] for MRSA was 1.69 (95 % confidence interval [CI] 1.51 to 1.90) and for *C difficile* the adjusted HR was 1.26 (95% CI 1.12 to 1.40). In addition, increased use of alternative antibiotics to a penicillin accounted for 55% of the increased risk of MRSA and 35% of the increased risk of *C difficile* found.

People with a documented 'penicillin allergy' were less likely to be prescribed a penicillin (adjusted incidence rate ratio [IRR] 0.30, 95% CI 0.30 to 0.31) and, instead, were more likely to be prescribed macrolide antibiotics (IRR 4.15, 95% CI 4.12 to 4.17), clindamycin (IRR 3.89, 95% CI 3.66 to 4.12), fluoroquinolones (IRR 2.10, 95% CI 2.08 to 2.13), tetracyclines (IRR 1.75, 95% CI 1.73 to 1.76) and sulphonamide antibiotics (IRR 1.26, 95% CI 1.25 to 1.27). The authors concluded that having a documented 'penicillin allergy' was associated with an increased risk of MRSA and *C difficile* that was mediated by the increased use of antibiotics that were selected as an alternative to beta-lactams.

Commentary

Commentary provided by NICE

The findings of this study (Blumenthal et al. 2018) build on previous evidence that using other antibiotics as an alternative to beta-lactam antibiotics in those with a documented 'penicillin allergy' is associated with an increased risk of MRSA and *C difficile*. This recent study (Blumenthal et al. 2018) adds to this evidence by finding such an association in people seen within a *general practice* setting.

A strength of this study (Blumenthal et al. 2018) is that it used a large sample who were registered on a UK general practice database and so the results help to reflect current clinical practice. In addition,

the authors chose to look at the first documentation of MRSA and *C difficile* to make sure that they captured only new colonisation or infection that were clinically important. Weaknesses include that this was an observational study and, whilst considerable effort to control for differences between groups in baseline characteristics was made, not all potentially confounding factors were recorded and adjusted for and some imbalances will have inevitably remained. Also, being GP-based, the dataset might have missed some inpatient cases of MRSA and *C difficile* that had been detected previously.

Despite these limitations, this study (Blumenthal et al. 2018) provides an important focus for practice. A public health strategy is underway to try and reduce the incidence of MRSA and *C difficile* in people who have been documented to have a 'penicillin allergy'. This may be aided by ensuring that only 'true' penicillin allergies are documented, in line with the NICE guideline on drug allergy: diagnosis and management, helping to reduce unnecessary prescription of broad spectrum non-beta-lactam antibiotics (and hence development of resistant organisms) in people who are not truly allergic to penicillin.

In addition, the NICE guideline on drug allergy: diagnosis and management also advises to refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service if they: need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic; **or** if they are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency). NICE is currently producing a suite of antimicrobial prescribing guidelines, which should also help prescribers to select the most suitable antibiotic regimens for specific conditions.

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References

Blumenthal KG, Lu N, Xhang Y et al. (2018). Risk of methicillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. BMJ 361:K2400

Lee CE, Zembower TR et al (2000). The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Archives of Internal Medicine 160:2819–22

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