The revolving door: antibiotic allergy labelling in a tertiary care centre

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Acknowledgements: none

ABSTRACT

Background: Patients frequently report antibiotic allergies, however only 10% of labelled patients have a true allergy.

Aim: We investigated the documentation of antibiotic "allergy" labels (AALs) and the effect of labelling on clinical outcomes, in a West Australian adult tertiary hospital.

Methods: Retrospective cross-sectional analysis of patients captured in the 2013 and 2014 National Antimicrobial Prescribing Surveys. Data was collected on documented antibiotic adverse drug reactions, antibiotic cost, prescribing appropriateness, prevalence of multi-drug resistant organisms, length of stay, intensive care admission, and readmissions.

Results: Of 687 patients surveyed, 278 (40%) were aged 70 or above, 365 (53%) were male and 279 (41%) were prescribed antibiotics. AALs were recorded in 122 (18%) patients and the majority were penicillin labels (n=87; 71%). Details of AALs were documented for 80 of 141 (57%) individual allergy labels, with 61 describing allergic symptoms. Patients with beta-lactam allergy labels received fewer penicillins (p=0.0002) and more aminoglycosides (p=0.043) and metronidazole (p=0.021) than patients without beta-lactam labels. Five patients received an antibiotic that was contraindicated according to their allergy status. Patients with AALs had significantly more hospital readmissions within 4 weeks (p=0.001) and 6 months (p=0.025) of discharge, compared with unlabelled patients. The majority (81%) of readmitted labelled patients had major infections.

Conclusions: AALs are common but poorly documented in hospital records. Patients with AALs are significantly more likely to require alternative antibiotics, and hospital readmissions. There may be a role for antibiotic allergy delabelling to mitigate the clinical and economic burdens for patients with invalid allergy labels.

Key words: antibiotic, allergy, hypersensitivity, delabelling, penicillin

The revolving door: antibiotic allergy labelling in a tertiary care centre

MAIN TEXT

INTRODUCTION

Up to 20% of patients report one or more antibiotic allergies (antibiotic "allergy" labelled) (1-3). However, the majority of antibiotic allergy labels (AALs) are invalid (4-6). Drug allergy specialists can assist clinicians by delabelling many patients with alleged antibiotic allergies. For example, almost 90% of beta-lactam labels can be safely removed after thorough assessment (5,6).

Beta-lactams, which comprise penicillins, cephalosporins, monobactams and carbapenems, currently account for 60% of antibiotic prescriptions in Australian hospitals (7). Avoiding beta-lactam or other antibiotics in patients with alleged allergy often necessitates prescription of second-line antibiotics which may be less effective, more expensive and lead to higher rates of adverse effects and multi-drug resistance (MDR) pathogens (4,8,9). International observational studies have shown that patients with AALs have increased hospital utilization and poorer clinical outcomes (10,11). Unverified antibiotic allergy labelling is a significant and growing public health problem resulting in unnecessary adverse outcomes. Whether systematic antibiotic allergy delabelling can mitigate these clinical and economic burdens remains to be seen.

These issues have not been broadly addressed in an Australian context, apart from case series focusing on specific patient groups (12,13,14). We sought to investigate the frequency of reported AALs, the accuracy of allergy documentation, appropriateness of antibiotic prescribing and the effect of labelling on clinical outcomes in an adult tertiary hospital in Western Australia.

METHODS

We performed a retrospective single-centre cross-sectional analysis of 775 inpatients in a 600-bed adult tertiary care teaching hospital in Perth, Western Australia. All patients were captured in the 2013 and 2014 National Antimicrobial Prescribing Survey (NAPS), which was performed during "Antimicrobial Awareness Week" in November. NAPS is a voluntary annual audit of Australian health services, led by The Australian Commission

on Safety and Quality in Health Care (ACSQHC) which provides a point prevalence of hospital inpatient medication charts to assess volume and appropriateness of antimicrobial prescribing (15).

NAPS data was collected from patients' medication charts, by ward pharmacists. The audit captured data on all patients admitted to hospital wards (including all medical and surgical specialties, intensive care unit, psychiatry and rehabilitation wards, but excluding the emergency department and day admission wards). Data collected included patient demographics, antibiotics prescribed (at time of audit) and documented AALs. AAL is a blanket term to denote any antibiotic recorded in the "allergies and adverse drug reaction" section of the patient's medication chart. Patients were excluded from the study if there was no NAPS documentation to indicate either the presence or absence of antibiotic adverse drug reactions. For AALs, the culprit medication and alleged symptoms (if documented in the medication chart) were captured. Documented AAL symptoms were classified as (1) anaphylaxis, (2) angioedema, (3) rash or unspecified swelling, (4) gastrointestinal upset, or (5) non-specific symptoms (e.g. headache). Groups 1, 2 and 3 represent allergic-type symptoms (graded according to severity) and groups 4 and 5 represent probable non-immunological intolerances. The daily costs of antibiotics were calculated, per patient, using the hospital pharmacy formulary. NAPS prescribing scores are graded based on the degree of appropriateness (1 optimal; 2 adequate; 3 suboptimal; 4 inadequate; 5 not assessable) of antibiotic choice as assessed by an infectious diseases pharmacist or physician using an internally validated scoring system (15). For the purposes of this study, scores of 1 or 2 were considered appropriate and 3 or 4 as inappropriate. Patient allergies were accounted for in the appropriateness scoring algorithms. Indications for each antibiotic prescription were classified as bacterial infection (specified), prophylaxis, or indication unclear.

NAPS data was supplemented with electronic records and discharge summaries to record principal diagnosis of admission, admitting specialty unit, intensive care admissions, death during admission, hospital length of stay and readmissions within 4 weeks and 6 months of discharge. The overall follow-up period for each patient, was 6 months from inclusion (NAPS audit) date. Direct hospital transfers, day procedures and review in the emergency department were not considered readmissions. Patient electronic microbiology records were reviewed to capture any *Clostridium difficile* toxin, Methicillin-resistant *Staphylococcus aureus* (MRSA) and/or Vancomycin-resistant *Enterococcus* (VRE) positive screening or diagnostic microbiological samples.

Study groups were classified based on the presence or absence of an AAL in the medication chart. We further classified patients with an AAL into "beta-lactam" and "non-beta-lactam" labels. We sub-classified "beta-lactam" labels as "penicillin group", "cephalosporin", "carbapenem" or "monobactam" labels. Patients were classified as non-allergic (no antibiotic allergy label; NAAL) if they had no known AAL or an allergy to a non-antibiotic drug or non-drug allergen. This study was approved through the Sir Charles Gairdner Group Human Research Ethics Committee (quality activity #8380).

Statistical analysis

Data were analysed using the R environment for statistical computing (16). Medians and interquartile ranges (IQR) are presented for continuous variables whilst counts and percentages are presented for categorical variables, unless otherwise stated. Chi-squared tests (Fisher's exact tests where appropriate) were used to compare specific antibiotics prescribed and infections between beta-lactam allergic labelled patients and non-beta-lactam allergic labelled patients. Initially, binary logistic regression was used to analyse the relationships between demographic patient variables and any allergy label (event='Yes'). Subsequently, multivariate models were conducted to investigate the effect of antibiotic allergy labelling on prevalence of highly resistant bacteria, intensive care admission, patient death in hospital and four-week readmission rate (logistic regression; event='Yes'); the number of readmissions within six months and NAPS prescribing score (ordinal logistic regression); hospital length of stay (Cox proportional hazards regression; event="leaving hospital" where those who died during their hospital stay are censored at their date of death); cost of antibiotics (linear regression, log-transformed response); and the number of antibiotics prescribed (Poisson regression). Patient age, gender, admitting team, antibiotic use and audit year were adjusted for in all models and backwards model selection was performed such that variables significant at a 5% level were retained for the final models.

RESULTS

A total of 775 patients were captured in the NAPS database (374 in 2013, 401 in 2014). Based on the maximum available overnight hospital beds available, the capture rate was 79% in 2013 (374 out of 476 beds) and 89% in 2014 (401 of 453 beds). This is likely to be an underestimate, as not all beds were occupied at the time of the NAPS audits. There were 38 instances where the same patient was recaptured due to ward transfer during the audit period. The earliest capture date was used for these patients and an additional 50 patients were excluded because allergy status was not recorded in NAPS documentation. The final cohort of 687 patients reflected the

expected demographics in the tertiary care centre. From 2013 to 2014 the mean age of all hospitalised patients was 61 years and 53% of patients were male. In the final audit cohort, mean age was 62 years, 278 (40%) patients were aged 70 or above, 365 (53%) were male and 279 (41%) were prescribed antibiotics at the time of the audit (Table 1). The major indications for antibiotics were pneumonia (n=74, 28%), genitourinary (n=44; 17%), skin and soft tissue (n=42; 16%), intra-abdominal or gastrointestinal infections (n=34, 13%), and prophylaxis (n=26; 10%) (Table 2). Prescribing scores were judged as appropriate for 176 of 279 prescriptions (63%), inappropriate for 84 (30%) and indeterminate for 19 (7%).

Females and older patients were significantly more likely to have an AAL (gender: OR=2.54, 95% CI=1.69-3.82, p<0.001; for a one standard deviation (19.6 years) increase in age: OR=1.31, 95% CI=1.06-1.60, p=0.007). The same was also true for beta-lactam AALs alone (gender: OR=2.28, 95% CI=1.46-3.54, p<0.001; for a one standard deviation increase in age: OR=1.33, 95% CI=1.07-1.67, p=0.011). Patient admitting team (by individual specialties), audit year and prescription of antibiotics at the time of audit were not significantly associated with presence of AALs or, more specifically, beta-lactam AALs.

Antibiotic allergy "labels"

One or more AALs were recorded in 122 (18%) patients, with NAAL recorded for the remaining 565 (82%) patients. The majority of AALs were beta-lactam labels (n=101; 83%), of which most were in the "penicillin group" (n=87; 71% of "allergic" cohort; 13% of whole cohort). The specific AALs comprising the beta-lactam group were "penicillin (not otherwise specified)" (n=76; 75%), "cephalexin" (n=7), "amoxicillin" (n=5), "amoxicillin/clavulanic acid" (n=3), "piperacillin/tazobactam" (n=2) and "cephazolin" (n=2). The majority of non-beta-lactam labels comprised the sulfamethoxazole/trimethoprim (n=11), macrolide (n=7) and glycopeptide (vancomycin) (n=7) groups. In the AAL group, 108 (89%) patients had a single allergy, 10 (8%) had two documented AALs, and 4 (3%) had three or more labels.

Descriptions of reactions to the culprit antibiotic were documented for 80 of 141 (57%) individual AALs. For the remaining 61 (43%) labels there was no documentation of symptoms. Of the 80 AALs with documentation, 61 described symptoms consistent with allergy and 19 were non-specific (non-allergic) intolerances (Figure 1). Non-specific symptoms were more frequently recorded for non-beta-lactam labels.

Five patients, among a group of 33 penicillin-labelled patients prescribed antibiotics (6% of the 87 penicillin labelled patients in total), were receiving an antibiotic that would be considered contraindicated according to their allergy status. Two patients with a history of unspecified penicillin-induced anaphylaxis received a penicillin (piperacillin/tazobactam; amoxicillin/clavulanic acid). One patient with unspecified penicillin-induced "rash" received piperacillin/tazobactam. Two patients with AAL documented as "unknown reaction" (one to an unspecified penicillin, the other to amoxicillin/clavulanic acid), received amoxicillin. There were no adverse events captured as a result of these prescriptions, although this study was not designed to assess outcomes of prescribing errors.

Impact of antibiotic allergy label on choice of antibiotics

The impact of antibiotic allergy labels on antibiotic prescriptions is summarised in Table 2. As expected, patients with beta-lactam AALs were prescribed significantly fewer penicillins (p=0.0002) and significantly more alternative antibiotics such as aminoglycosides (p=0.043) and metronidazole (p=0.021), than non-beta-lactam labelled patients. Although there was increased use of 3rd and 4th generation cephalosporins, quinolones, clindamycin, fusidic acid and daptomycin, among beta-lactam labelled patients, this did not reach statistical significance.

Impact of antibiotic allergy label on hospital outcomes

Of the 663 discharged patients (excluding 24 patients who died in hospital), 129 (19.5%) were readmitted within four weeks. Patients with an AAL were significantly more likely to be readmitted within four weeks than NAAL patients (OR=2.16, 95% CI=1.34-3.46, p=0.001) (Table 3). Of the 35 AAL patients readmitted within four weeks, 29 (81%) had infections in the first and/or second admission (captured as principal diagnosis or NAPS antibiotic prescription). Five patients (14%) were readmitted with recurrence of the same infection (urosepsis, pneumonia, wound and ocular infections). Limiting the cohort to patients with a principal diagnosis of infection, 9 of 30 (30%) AAL patients were readmitted within four weeks, compared with 24 of 136 (18%) NAAL, although this did not reach statistical significance, and was therefore not included in the final multivariate model.

Patients with an AAL also had significantly more readmissions within six months compared to NAAL patients (OR=1.55, 95% CI=1.06-2.27, p=0.025) (Table 3). Specifically, 58 of 121 (48%) AAL patients were readmitted in six months compared with 200 of 542 (37%) NAAL patients. Furthermore, 34 (28%) AAL patients were readmitted twice or more in this period, compared with 102 (18%) NAAL patients.

Further analysis focussing on beta-lactam labelled patients yielded corresponding results. Beta-lactam labelled patients were significantly more likely to require readmission within 4 weeks with 29 of 101 (29%) beta-lactam AAL patients readmitted, compared with 100 of 562 (18%) of non-beta-lactam AAL patients (OR=2.03, 95% CI=1.23-3.35, p=0.006). The length of readmissions ranged from 2 to 22 days. Beta-lactam AAL patients also had significantly more readmissions within 6 months (OR=1.51, 95% CI=1.00-2.27, p=0.049). Thirty of 101 (30%) beta-lactam AAL patients had two or more readmissions within 6 months, compared with 106 of 562 (19%) of non-beta-lactam AAL patients.

These results were adjusted for patient age, gender, admitting team and intensive care admissions and no specific chronic diseases (e.g. cystic fibrosis, malignancy, transplant recipients) appeared overrepresented among readmitted allergy labelled patients. There were no significant differences in the following variables between patients with and without any antibiotic allergy labels: antibiotic costs, appropriateness of antibiotic prescribing, prevalence of multi-drug resistant organisms on microbiological follow-up, hospital length of stay, patient death in hospital and intensive care admissions (Table 3).

DISCUSSION

This study provides a snapshot of antibiotic allergy labelling in a metropolitan tertiary care centre. Eighteen per cent of hospitalized patients reported at least one AAL, the majority to penicillin (72%). This equals the national average (18%) and is toward the upper range of reports in the international literature (1-3,8).

Documentation of "allergic" symptoms was frequently missing from patient medication charts, despite inpatient status and ward pharmacist review. Furthermore, five (6%) penicillin labelled patients received antibiotics which would be considered contraindicated, according to their allergy status. A recently published Australian study reported a similar rate of inadvertent antibiotic rechallenge (7%) in a general medical cohort (14). This is

concerning in light of reports of increasing medication-related anaphylaxis and mortality in adult Australian hospitals (17,18). The ACSQHC medication safety standards state such medication errors are "highly preventable" through effective use of allergy alert systems (19). However, allergy alert systems rely on accurate allergy documentation and correct clinical decision making: deficits in both areas have been highlighted in previous studies (20,21). None of the five patients had adverse reactions following penicillin re-challenge. Multiple factors (including loss of IgE-mediated allergy reactivity over time and labelling non-immunological ADRs or viral-induced exanthems) explain why many labelled patients tolerate future penicillin use (4,5,6). However, appropriate risk stratification is essential to avoid preventable prescribing errors and harm to truly allergic patients. It is not clear whether further (undocumented) history guided clinical decision-making for the five patients highlighted in this study.

Drug allergy specialists can safely investigate IgE-mediated (Type I) allergy labels through thorough clinical assessment with skin-prick/intradermal testing, and observed oral challenges for selected cases (22,24). This enables confirmation or, in most cases, exclusion (i.e. delabelling) of AALs. There is evidence supporting the safety of supervised graded oral amoxicillin challenges for children with historical immediate or non-immediate reactions to penicillin, but this approach remains to be fully investigated in the adult population (25). In the acute setting, desensitization may be indicated to induce temporary drug tolerance for patients with true IgE-mediated antibiotic allergy, where no acceptable alternative antibiotic exists (23). Testing strategies for delayed T cell mediated (Type IV) reactions include patch testing (which is only available at select drug allergy clinics in Australia) and oral challenges on a case-by-case basis (22,24).

To our knowledge this is the largest Australian-based study to show that hospitalized patients carrying an AAL have poorer clinical outcomes, compared with unlabelled patients. Our study is strengthened by the unbiased selection criteria (based on the NAPS) which provided a "real life" snapshot of documentation and prescribing for patients with AALs at the time of their admission. Limitations of our study include the reliance on documentation in medical records to collect additional data. However, we used objective clinical outcomes such as in-hospital mortality, length of stay and readmissions, which are accurately reflected in medical records. Due to the cross-sectional retrospective study design it was not possible to determine the validity of reported AALs (by patient interview or specific allergy testing) to further classify via a strict immunological basis. Furthermore, we could not capture every infection or antimicrobial prescription during admission, which limited

sub-analyses in these groups. Nevertheless, the same trend towards frequent readmissions was seen when limiting the cohort to patients with a principal diagnosis of infection, or those prescribed antibiotics. Our results may have been biased by the large proportion of beta-lactam AAL patients. However, this reflects the usual composition of AALs in the hospital setting, and encouragingly, delabelling strategies have been well validated in this cohort.

We propose that the association between AALs and hospital readmissions is best explained by necessary reliance on second-line antibiotics in labelled patients with infections. Our data (Table 2) highlights the differences in antibiotic prescribing patterns between AAL and NAAL groups, with greater reliance on alternative antibiotics for AAL patients. Second-line therapies have less favourable safety profiles and can be resistance and *Clostridum difficile* generating; all of which, may necessitate hospital readmissions (6,10,26). An alternative interpretation is that patients prone to readmissions for other reasons (such as more severe disease states requiring more frequent repetitive courses or high dose parenteral antibiotics) accumulate more drug allergy labels over time. Although it is not possible to discount the latter, our statistical analysis indicated that patient age, gender, admitting specialty, intensive care admission and chronic disease states, did not affect the results.

This study adds to a growing international body of literature highlighting the significant public health implications of (frequently invalid) AALs (5,6,8-14,27). Our study complements findings from two recently published studies (14,28). A Dutch study reported a higher risk of readmissions within 12 weeks among penicillin allergy labelled patients (28). An Australian study reported poor AAL documentation, and inappropriate antibiotic prescriptions for some AAL patients (14). Both studies reported increased use of broad spectrum antibiotics (including 3rd generation cephalosporins, quinolones and macrolides) for AAL patients (14). Similar findings have been reported in the United States; Macy et al reported that patients with penicillin allergy labels spend significantly more time in hospital, with exposure to more broad-spectrum antibiotics and higher rates of *C. difficile,* MRSA and VRE (11). Another large American study reported increased lengths of stay, intensive care admission rates and higher mortality rates for patients with AALs (10). Economic modelling suggests that delabelling strategies could lead to significant health care savings (11). In our study there were no significant differences in antibiotic costs, hospital length of stay, and intensive care admissions.

This may be due to the smaller sample size and the broad inclusion of all patients rather than higher risk patient groups.

CONCLUSION

Clinicians face two conflicting issues when managing patients with AALs. In the acute setting, clinicians must pay AALs respect by carefully documenting labels and prescribing antibiotics safely. However, in the long-term, over-labelling can set up a negative cycle of restricted access to antibiotics, poorer clinical outcomes and increased hospitalisation - the "revolving door". Given that the majority of AALs are in fact, invalid, many patients may be unnecessarily suffering adverse outcomes. Clinical education in both primary care and hospital settings could lead to considerable improvements in diagnosis and management of patients with suspected drug allergy. Optimal drug allergy management relies on contemporaneous, detailed ADR reporting, to differentiate immunological (type I-IV) and non-immunological ADRs at the outset. Patients who carry a historically plausible allergy label (particularly beta-lactam labels), can be further assessed by a drug allergy specialist to confirm true allergy labels and remove invalid labels. Ultimately, a collaborative effort to improve system-wide antibiotic allergy management could lead to significant health care savings and provide patients with more timely, safe and effective care.

REFERENCES

1. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients. Arch Intern Med. 2000 Oct;160:2819-2822.
2. Salkind AR, Cuddy PG, Foxworth JW. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA. 2001 May;285(19):2498–2505.
3. Khasawneh FA, Slaton MA, Katzen SL. The prevalence and reliability of self-reported penicillin allergy in a community hospital. Int J Gen Med. 2013 Dec;6(6):905-909.
4. Lutomski DM, Lafollette JA, Biaglow MA, Haglund LA. Antibiotic allergies in the medical record: effect on drug selection and assessment of validity. Pharmacotherapy. 2008 Nov;28(11):1348-1353.
5. Bourke K, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. J Allergy Clin Immunol Pract. 2015 May/Jun;3(3):365-374.e1
6. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. Curr Allergy Asthma Rep. 2014 Nov;14(11):476.
7. South Australian Department for Health and Ageing, Branch of Infection Control Service Communicable Disease Control. Australian National Antimicrobial Utilisation Surveillance Program Annual Report; 2013-2014 [updated 2015 Oct 20; cited 2015 Oct 15]. Available from: www.sahealth.sa.gov.au/nausp.
8. Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy. 2003 Apr;33(4):501-506.
9. Picard M, Bégin P, Bouchard H, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. J Allergy Clin Immunol Pract. 2013 May/Jun;1(3):252-257.
10. Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy. 2011 Aug;31(8):742-747.
11. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol. 2014 Mar;133(3):790-796.
12. Irawati L, Hughes JD, Keen NJ, et al. Influence of penicillin allergy on antibiotic prescribing patterns and costs. J Res Pharm Pract. 2006;36(4):286-90.

13. Trubiano JA, Leung VK, Chu MY, Worth LJ, Slavin MA, Thursky KA. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. Antimicrob Resist Infect Control. 2015;4:23.

14. Trubiano J, Mangalore R, Baey Y, Le D, Graudins L, Charles P et al. Old but not forgotten: antibiotic allergies in general medicine (the AGM study). Med J Aust. 2016 Apr 18;204(7):273.

15. Australian Commission on Safety and Quality in Health care: National Antimicrobial Prescribing Survey (NAPS) [Internet]. 2015 [cited 2015 Oct 15]. Available from: http://www.safetyandquality.gov.au/national-priorities/amr-and-au-surveillance-project/national-antimicrobial-prescribing-survey-naps/.

16. R Core Team (2015). R: *A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

17. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009 Feb;123(2):434-442.

18. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. 2015 Aug;136(2):367-375.

19. Australian Commission on Safety and Quality in Health Care. Safety and Quality Improvement Guide Standard 4: Medication Safety. [Internet]. Oct 2012 [cited 2015 Dec 01]. Available from: http://www.safetyandquality.gov.au/publications/safety-and-quality-improvement-guide-standard-4-medication-safety-october-2012/

20. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A. Survey of inpatient clinical providers' antibiotic prescribing knowledge. J Allergy Clin Immunol Pract. 2014 Jan;2(4):407-413.

21. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. Int J Qual Health Care. 2003;15(1):49-59.

22. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA et al. International consensus on drug allergy. Allergy. 2014;69:420-437.

23. Macy E, Ngor E. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol: In Practice 2013;1:258-263.

24. Romano A, Caubet JC. Antibiotic allergies in children and adults: from clinical symptoms to skin testing diagnosis. J Allergy Clin Immunol Pract. 2014 Jan-Feb;2(1):3-12.

25. Mill C, Primeau M, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. JAMA Paediatr. 2015 Apr 4 [electronic publication].

26. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013 Sep;68(9):1951-1961.

27. Trubiano J, Cairns K, Evans J, Ding A, Jguyen T, Dooley M et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. BMC Infect Dis. 2015 Dec 16;15:572.

28. van Dijk S, Gardarsdottir H, Wassenberg M, Oosterheert J, de Groot M, Rockmann H et al. The high impact of penicillin allergy registration in hospitalized patients. J Allergy Clin Immunol Pract. 2016 April 28 [electronic publication].

FIGURE LEGENDS

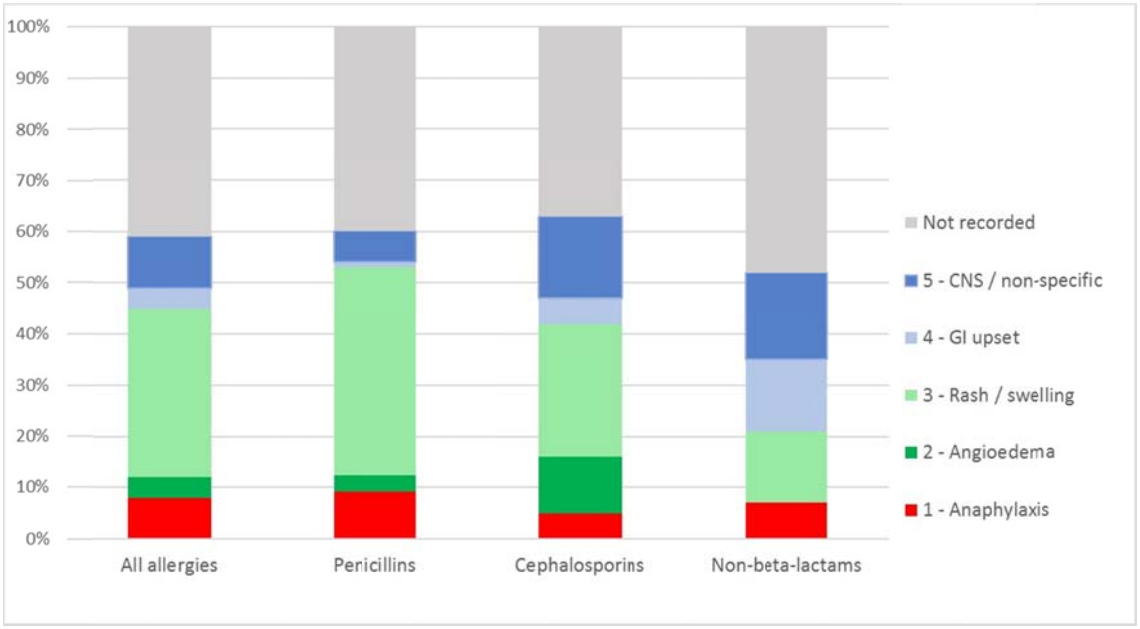

Figure 1: Documented symptoms associated with antibiotic labels, per total antibiotic allergy labels.

TABLES

Table 1: Counts and percentages of patient demographics

Demographics	Any antibiotic allergy label		All patients (N=687)
	Yes (N=122)	No (N=565)	
Age Group			
<30 yrs	9 (18%)	41	50 (7%)
30-49 yrs	14 (10%)	121	135 (20%)
50-69 yrs	37 (17%)	187	224 (33%)
70-89 yrs	54 (22%)	187	241 (35%)
> 90 yrs	8 (22%)	29	37 (5%)
Gender			
Female	80 (25%)	242	322 (47%)
Male	42 (12%)	323	365 (53%)
Admitting Team			
Medical	77 (20%)	301	378 (55%)
Surgical	32 (15%)	187	219 (32%)
ICU / Psychiatry	13 (14%)	77	90 (13%)
Principal Diagnosis			
Infection	30 (17%)	142	172 (25%)
Other (Not infection)	92 (18%)	423	515 (75%)
Prescribed antibiotics at time of audit			
No	74 (18%)	334	408 (59%)
Yes	48 (17%)	231	279 (41%)

Table 2: Counts and percentages of specific antibiotics prescribed, and documented bacterial infections, broken down by antibiotic allergy label *(note some patients received more than one antibiotic prescription or had more than infection)*

Antibiotic prescriptions and infections by allergy label (N=279)	Any antibiotic allergy label		No antibiotic allergy label (N=231)	P-Value^
	Any beta-lactam allergy label (N=41)	Other antibiotic allergy label (N=7)		
Antibiotics prescribed at time of audit				
Penicillins (penicillin V & G)	0 (0.0%)	1 (14.3%)	9 (3.9%)	NS
Amoxycillin +/- clavulanic acid	3 (7.3%)	1 (14.3%)	31 (13.4%)	NS
Flucloxacillin	1 (2.4%)	0 (0.0%)	14 (6.1%)	NS
Piperacillin/tazobactam	5 (12.2%)	2 (28.6%)	68 (29.4%)	**0.022**
All penicillins (all above)	**9 (22.0%)**	**4 (57.1%)**	**122 (52.8%)**	**0.0002**
Carbapenems	3 (7.3%)	0 (0.0%)	9 (3.9%)	NS
1st generation cephalosporins	8 (19.5%)	2 (28.6%)	41 (17.8%)	NS
3rd / 4th generation cephalosporins	6 (14.6%)	1 (14.3%)	13 (5.6%)	NS
All beta-lactams (all above)	**26 (63.4%)**	**7 (100.0%)**	**185 (80.1%)**	**0.013**
Macrolides	3 (7.3%)	0 (0.0%)	25 (10.8%)	NS
Quinolones	7 (17.1%)	0 (0.0%)	27 (11.7%)	NS
Metronidazole	7 (17.1%)	0 (0.0%)	14 (6.1%)	**0.021**
Norfloxacin	1 (2.4%)	0 (0.0%)	10 (4.3%)	NS
Sulfonamides	0 (0.0%)	0 (0.0%)	9 (3.9%)	NS
Tetracyclines	1 (2.4%)	0 (0.0%)	5 (2.2%)	NS
Trimethoprim	2 (4.9%)	0 (0.0%)	4 (1.7%)	NS
Aminoglycosides	3 (7.3%)	0 (0.0%)	3 (1.3%)	**0.043**
Rifaximin	1 (2.4%)	0 (0.0%)	2 (0.9%)	NS
Cotrimoxazole	0 (0.0%)	0 (0.0%)	1 (0.4%)	NS
Nitrofurantoin	0 (0.0%)	0 (0.0%)	1 (0.4%)	NS
Vancomycin	2 (4.9%)	0 (0.0%)	21 (9.1%)	NS
Clindamycin	3 (7.3%)	0 (0.0%)	6 (2.6%)	NS
Fusidic acid or daptomycin	1 (2.4%)	0 (0.0%)	2 (0.9%)	NS
Anti-mycobacterial agents	1 (2.4%)	0 (0.0%)	4 (1.7%)	NS
Documented bacterial infections				
Pneumonia	12 (29.3%)	1 (14.3%)	61 (26.4%)	NS
Genitourinary	4 (9.8%)	1 (14.3%)	40 (17.3%)	NS
Skin	10 (24.4%)	0 (0.0%)	33 (14.3%)	NS
Intra-abdominal	3 (7.3%)	0 (0.0%)	20 (8.7%)	NS
Osteomyelitis / joint	2 (4.9%)	0 (0.0%)	19 (8.2%)	NS
Gastrointestinal	3 (7.3%)	0 (0.0%)	8 (3.5%)	NS
Bacteraemia	0 (0.0%)	0 (0.0%)	7 (3.0%)	NS
Febrile neutropenia	2 (4.9%)	0 (0.0%)	5 (2.2%)	NS
CNS	0 (0.0%)	1 (14.3%)	3 (1.3%)	NS
Other infection	1 (2.4%)	0 (0.0%)	8 (3.5%)	NS
Prophylaxis	4 (9.8%)	1 (14.3%)	22 (9.5%)	NS
Indication unclear	1 (2.4%)	3 (42.9%)	14 (6.1%)	NS

^Fisher's exact test: comparing beta-lactam labelled patients with all other patients

Table 3: Summary statistics of patient outcomes broken down by any antibiotic allergy label

Outcomes	Any antibiotic allergy label		P-Value
	Yes	No	
Length of stay	10 (5 – 21) days	13 (6 - 27) days	NS
Death during admission	1 (1%)	23 (4%)	NS
Readmission within 4 weeks	35 (29%)	94 (17%)	**0.001**
Readmission in 6 months	24 (20%)	98 (18%)	**0.025**
Cost of prescribed antibiotics per patient day*	$5 ($1-$32)	$10 ($1-$28)	NS

*279 patients were on antibiotics; NS – not significant