

Journal Pre-proof

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PII: S1081-1206(19)31494-2

DOI: <https://doi.org/10.1016/j.anai.2019.12.016>

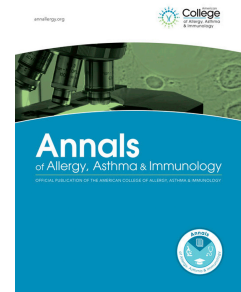
Reference: ANAI 3108

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 4 October 2019

Revised Date: 4 December 2019

Accepted Date: 16 December 2019



Please cite this article as: Macy E, Addressing the epidemic of antibiotic “allergy” over-diagnosis, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2019.12.016>.

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Addressing the epidemic of antibiotic “allergy” over-diagnosis

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Funding: EM received a \$1200 honorarium from the Annals of Allergy Asthma and Immunology for writing this CME manuscript.

Disclosures: EM is a partner in the Southern California Permanente Medical Group. He is a member of the American Academy of Allergy, Asthma, and Immunology Ask an Expert panel. He has received research grants from ALK Abello, Inc. to study adverse drug reactions and has served on clinical trial safety and monitoring committees for BioMarin, Ultragenyx, and Audentes.

Abbreviations

EBV	infectious mononucleosis
ED	emergency department
EHR	electronic health record
KPSC	Kaiser Permanente Southern California
MDIS	multiple drug intolerance syndrome
SJS/TEN	Stevens-Johnson syndrome / toxic epidermal necrolysis

The word “*allergy*” will be used to describe what is entered in the medical record. The word “allergy” will be reserved to describe a confirmed clinically-significant acute-onset IgE-mediated hypersensitivity.

Key words: Adverse drug reaction, Allergy, Antibiotic, Hypersensitivity, Incidence, Prevalence, Over-diagnosis, Stewardship

Manuscript word count: 4,361

Tables: 2

Figures: 2

Abstract: 19-10-0505R1

Objective There is an epidemic of antibiotic allergy.

Data Sources Articles published since 2008.

Study Selections Articles on antibiotic allergy and stewardship.

Results A number of overlapping factors contribute. The most important factor is antibiotic overuse. Antibiotics are commonly used in situations where no antibiotics are indicated. Thirty to 50% of ambulatory antibiotic use may be inappropriate. The duration of indicated antibiotic use is often excessive, which leads to more side-effects. All antibiotic use can result in adverse reactions and a fraction of these will be dutifully recorded as an allergy in the electronic health record (EHR). Most EHRs are not well structured to accurately convey information on expected side-effects that have occurred, metabolic or other contraindications, dose-related or situational toxicities, personal preferences, clinically-significant immunologically-mediated hypersensitivity, and other reasons a particular patient may not want or should not be given a specific drug or type of drug in the future. As populations age, their accumulated baggage of reported antibiotic allergies increase. Suspected antibiotic allergy is rarely confirmed with appropriate testing or rechallenge. Patients then receive sub-optimal antibiotic therapy and experience more side-effects, treatment failures, and serious antibiotic-resistant infections. Reporting an antibiotic allergy in the EHR is nominally done to improve patient safety, but unfortunately, this is often not the actual result.

Conclusion Audit and feedback, to help ensure adherence to Choosing Wisely® recommendations and good antibiotic stewardship practices, can help reduce inappropriate antibiotic use. Restructuring EHRs to facilitate correct drug intolerance reporting, along with active antibiotic allergy delabeling programs, can help stem this epidemic.

1 Introduction

2
3 An *allergy* is commonly noted on more than 20% of all electronic health records of
4 unselected individuals using health care in developed countries.^{1,2} Antibiotic *allergies*
5 are the most common class of drug *allergy* reported.^{3,4} Antibiotic *allergies*, though
6 almost always shown to be inaccurate when adequate testing is performed, are rarely
7 confirmed and can lead to less effective subsequent antibiotic therapy and increased
8 patient morbidity.^{5,6} The most commonly reported antibiotic *allergy* is still penicillin,
9 typically accounting for more than half of all antibiotic *allergies*.^{1,3} This high rate of
10 labeling persists despite good evidence that rate of IgE-mediated hypersensitivity to
11 penicillin as documented by properly performed positive penicillin skin test results has
12 been falling over the past 30+ years.⁷ The true rate of clinically-significant acute-onset
13 penicillin hypersensitivity confirmed by the reference standard test, an oral amoxicillin
14 challenge and 1 hour of follow-up, is even lower.^{8,9}

15
16 There are a variety of factors leading to a high population prevalence of antibiotic
17 *allergy*, inaccurate labeling, and then inappropriate responses to these inaccurate
18 labels. Very few healthcare systems have a culture of confirming *allergy* reports, they
19 are just generally accepted as correct. *Allergy* reports are presumed to improve patient
20 safety by leading to avoidance of re-exposure, with an assumed recurrence of an
21 equivalent or worse reaction.¹⁰ This however is often not true.¹¹

22

Epidemiology of antibiotic *allergy*

All reports of antibiotic *allergy* prevalence have significant biases based on the specific populations examined.¹⁻⁴ In order to even have a record of an antibiotic *allergy* that can be tracked, one needs to have access to healthcare and have a healthcare record. In the United States in 2018 about 27.5 million people (8.5%) did not have health insurance at any point during the year.¹² Fortunately, this is much less of an issue in Canada and the European Union. Even in individuals with essentially no barriers to accessing healthcare, such as is the case with Kaiser Permanente Southern California (KPSC) members, only 6,144,422 (82.5%) of 7,449,079 unique individuals with any KPSC healthplan coverage between 2009 and 2017 used any KPSC healthcare services.¹³ Thus, when a paper notes an antibiotic *allergy* prevalence, it is critical to know the characteristics of the population under consideration, and those segments of the population that were excluded.

In a cohort 2,375,424 KPSC healthplan members, which had an entry criteria of at least one healthcare visit and at least 11 months of healthplan coverage during 2009, there were 478,283 (20.1%) who had at least one drug *allergy* reported and 310,768 (13.1%) had at least one antibiotic *allergy* reported.¹ There was a marked gender difference with 16.7% of females and only 8.8% of males noting any antibiotic *allergy*. A penicillin *allergy* was noted by 9.46% of females and 5.93% of males in this cohort. Individuals with any drug *allergy* compared to healthplan members with no drug *allergy* were more likely to be female, 68.0% versus 51.2%; older, mean ages 52.0 ± 20.6 versus $35.7 \pm$

22.1 years; heavier, mean BMI 28.3 ± 7.1 versus 26.3 ± 7.2 ; and more likely to have ever been seen in Psychiatry, 31.4% versus 20.1%. Cumulative data on all 6,144,422 KPSC healthplan members who had at least one visit between 2009 through 2017 showed a penicillin *allergy* population prevalence of 10.9% in females and 7.3% in males and a total of 9.2%.¹³

Zhou and coworkers from Boston reported in 2016 on a cohort of 1,766,328 individuals who were hospitalized at least once between 1990 and 2013.¹⁴ They noted that 35.5% had at least one drug *allergy*, with 15.2% of females and 9.5% of males reporting a penicillin *allergy*. Their cohort was 59% female and they did not report mean ages, but being a hospitalized cohort it would be expected to be significantly older than the KPSC cohort.

McConeghy and coworkers in 2017 reported on 2,9948,543 unique patients who had a total of 10,858,398 hospital admissions at Veterans Affairs Medical Centers from 2000 to 2014.¹⁵ Not surprisingly, this cohort was 95.2% male with a mean age of 63 ± 14 years. The most common *allergy* recorded was to penicillins, with 1,410,080 (13%) individuals so labeled, and the prevalence of penicillin *allergy* was very stable over the study interval, with essentially no delabeling.

Reports on most hospitalized populations are significantly enriched for older individuals and women, both groups more likely to have a reported antibiotic *allergy*. We reported in 2009 on a KPSC cohort studied in 2007, that 21.4% of women age ≥ 80 years had a

penicillin *allergy* and 19.3% had a sulfonamide antibiotic *allergy* noted.⁴ Only 14.3% of males age ≥ 80 years in the same cohort had a penicillin allergy with only 7.8% noting a sulfonamide antibiotic allergy. Individuals with a cancer diagnosis have higher reported rates of antibiotic *allergy*.¹⁶ There is a 10% increase in the adverse drug reaction rate for each additional drug administered in hospitalized patients and often 60% of hospitalized individuals receive at least one antibiotic.¹⁷ Women, on average, receive more antibiotics per year than men.¹ Women report more drug *allergies* per exposure than men.¹ Individuals with a history of one antibiotic *allergy* report more new antibiotic *allergies* at higher rates after each antibiotic exposure.¹

Most of the allergies reported in individuals with multiple drug intolerance syndrome (MDIS), defined as having at least 3 unrelated drug class *allergies*, are to antibiotics.^{1,2} The prevalence of MDIS increases with increasing age and is much more likely to occur in females. Individuals with MDIS are no more likely to be confirmed to have immunologically-mediated hypersensitivity than individuals with a single drug intolerance. Just like individuals with any drug *allergies*, individuals with MDIS report new *allergies* at higher rates than individuals with no *allergies*, and the rate increasing with each new *allergy* reported. Interestingly, despite multiple drug intolerances, they still use drugs at higher rates than age and gender matched controls without MDIS. Individuals with anxiety and depression are more likely to report MDIS.² MDIS has been reported to occur in 2.1%, 4.9%, and 7.1% of 3 completely different cohorts.^{1,18,2} The lowest rate was noted in the 2,375,424 KPSC healthplan members studied during 2009 commented on above.¹ The intermediate rate was noted in a British cohort of

25,695 hospitalized individuals with an entry criteria of at least one reported drug allergy studied between 2009 and 2013.¹⁸ The highest rate was noted in a cohort of 746,888 individuals in the Boston area which had an entry criteria of at least 4 healthcare visits over a 8+ year period from prior to 2008 through 2015.²

There are no published reports from any healthcare program that has comprehensively attempted to delabel individuals with penicillin or any other antibiotic *allergy*. Even in KPSC, where we have a very active penicillin *allergy* delabeling program, we generate many fold more new penicillin *allergies* annually than we delabel.^{9,13}

In summary, antibiotic *allergy* labels are currently very prevalent, particularly in females, the elderly, and in hospitalized populations. They are baggage that accumulate with time and are rarely reconciled, re-evaluated, or removed.

Factors resulting in over-reporting and inaccurate reporting of antibiotic *allergies*

Morgan and coworkers reported in 2019 on medical overuse articles published in 2018.¹⁹ They selected what they felt were the 10 most clinically relevant articles and 2 (20%) were related to antibiotic over-use. They noted that procalcitonin measurements did not reduce antibiotic duration in a real-world setting, showing how hard it can be to change clinical practice with data. They also noted that antibiotics were over-used in Urgent Care centers between 2010 and 2011, with 45.7% of individuals seen for a viral illness receiving antibiotics. This compared to 24.6% for equivalent patient seen in Emergency Departments and only 17% of those seen with the same symptoms in Primary Care offices.¹⁹ Antibiotics were prescribed to 39% of all individuals seen in Urgent Care centers.¹⁹ Higher levels of antibiotic use and overuse are associated with a greater incidence of new antibiotic *allergies*.¹ Countries with lower rates of antibiotic use have lower prevalences of antibiotic *allergy*.

Skin rashes in the setting of febrile illnesses are often secondary to the underlying viral or bacterial infection and are commonly mistaken for an *allergy* to any antibiotic given concurrently.²⁰ Acute idiopathic urticaria is commonly noted after infections and may be mistaken for an antibiotic-associated reaction.

Thompson and Ramos in 2017 reviewed English-language primary literature, case reports, review articles, and mechanistic articles relating to the epidemiology and the underlying mechanism of antibiotic-associated skin rashes in patients with

concurrent infectious mononucleosis (EBV) and found much lower rates than previously believed.²¹ The top 3 antibiotics inappropriately used in the setting of acute EBV infections were ampicillin, azithromycin, and amoxicillin. EBV and antibiotic-associated rashes were more commonly noted in the 1960s, 33 to 55.6%, than in 2013, 15 to 33%. They proposed that the mechanism is a transient virus-mediated immune alteration that sets the stage for loss of antigenic tolerance and the development of a reversible, delayed-type hypersensitivity reaction to the antibiotic, though this has not been confirmed or validated. When these individuals are challenged with amoxicillin 6 months later, the vast majority are tolerant.

Misirlioglu and coworkers in 2018 reported on a cohort of 221 children, seen between 2013 and 2016, diagnosed with an acute EBV infection, of whom 120 (54.3%) were mistreated with antibiotics.²² Overall rashes developed in 41 (18.6%). Interestingly in the 120 inappropriately treated with antibiotics, mostly with aminopenicillins, only 20 (16.6%) developed rashes, $p = 0.43$.

Topaz and coworkers reported in 2015 on the rising rates of drug *allergy* alert overrides in EHRs from 2004 through 2013.²³ They noted that the most common reasons for the overrides were a combination of the patient previously tolerating the medication or the patient stating that they did not have the *allergy* reported. Antibiotic *allergy*-related alerts only accounted for 10% of the 611,192 alerts reviewed. Penicillin *allergy* alerts were one of the least overridden, less frequently than 1st generation cephalosporins or sulfonamide antibiotics, but were still overridden 74.3% of the time. Providers were also

152 noted to repeatedly override the alerts as opposed to just removing the proven
153 inaccurate *allergy* reports.

Specific areas of frequent antibiotic misuse and overuse

The Centers for Disease Control and Prevention (CDC) reported in 2019 that at least 30% of antibiotic prescriptions in the United States are unnecessary.²⁴ They noted a 2.5-fold difference in per capita antibiotic use between the lowest and highest prescribing states. On a positive note, there was a 5% decrease in per capita antibiotic use between 2011 and 2016, but there were still over 270 million courses of antibiotics prescribed annually for 323.4 million Americans.²⁴

Chua and coworkers reported in 2019 on the appropriateness of outpatient antibiotic prescribing among privately insured US patients.²⁵ They noted that for all outpatient antibiotic prescription fills by over 19 million privately insured US children and nonelderly adults in 2016, 23.2% were inappropriate, 35.5% were potentially appropriate, and 28.5% were not associated with a recent diagnosis code. They concluded that about 1 in 7 individuals filled at least one inappropriate antibiotic prescription in 2016.

Grigoryan and co-workers reviewed in 2019 the poorly studied area of antibiotic use without a prescription in the United States.²⁶ They reported an annual incidence of nonprescription antibiotic use from 1% to 66%, storage of antibiotics for future use in 14% to 48% of respondents, and prevalence of intention to use antibiotics without a prescription of about 25%. They noted that non-prescription antibiotics could be from previously prescribed courses, local markets or stores that obtain antibiotics

internationally for under-the-counter sales, and family or friends. Potential factors contributing to nonprescription antibiotic use included difficulty accessing the health care system, costs of physician visits, long waiting periods in clinics, and transportation problems.

Suda and coworkers in 2019 reported on the appropriateness of prophylactic antibiotic use prior to dental procedures in the United States between 2011 and 2015.²⁷ They determined that 80% of the antibiotics prescribed in this setting were inappropriate. They noted that Dentists prescribed about 10% of all antibiotics used in the United States. Antibiotic prophylaxis is not currently recommended in patients with prosthetic joints. Only one dose of an antibiotic, typically amoxicillin 1-2 grams is recommended 30 to 60 minutes prior to a dental procedure that involves manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa in patients with previous infective endocarditis, certain congenital heart diseases, cardiac transplant with cardiac valvopathy, or a prosthetic cardiac valve or materials used for valve repair. They noted that women were more likely to be overtreated (Odds ratio 1.21; 95% confidence interval 1.17 to 1.25). Alarminglly clindamycin was the antibiotic most likely to be overprescribed and Dentists were the top prescribers of clindamycin in the United States.²⁷

About 15% of the population is affected with migraine. Individuals with migraine often will note facial pain when they have viral infections. This facial pain is often incorrectly called "sinus", and then mis-treated with antibiotics.²⁸ There is currently a Choosing

200 Wisely recommendation not to treat acute “sinus” symptoms, namely facial pain with
201 antibiotics, yet this remains a very common practice.^{30,31}

202

Morbidity associated with antibiotic overuse

The CDC 2018 update on antibiotic use noted that antibiotic-related adverse events are a common cause of Emergency Department (ED) visits in young adults, ages 20 to 35.²⁴ Adverse drug events account for up to 16% of ED visits and 7% of hospital admissions, though only a small fraction of these are antibiotic-associated.³² Unfortunately, electronic medication reconciliation did not reduce adverse drug events.³² There are still about 70,000 children annually seen in the ED for adverse drug events and about 86% have characteristics, mostly rashes and angioedema, that then result in them frequently being labeled with a new antibiotic-allergy.²⁴ The most commonly implicated antibiotics are penicillins, cephalosporins, and sulfamethoxazole-trimethoprim. The CDC report additionally noted that the average duration of up to 70% of antibiotic prescriptions that were given for appropriate indications were longer than needed, and typically up to twice as long as needed.²⁴

Petty and coworkers in 2019 reviewed the risk factors and outcomes associated with treatment of asymptomatic bacteriuria in hospitalized patients.³³ Treatment was not associated with better outcomes and may be associated with longer hospitalizations. Stewardship efforts should be directed at avoiding unnecessary urine testing and better management strategies for elderly patients with altered mental status.³⁴

Blumenthal and coworkers in 2019 reported on hypersensitivity reactions in a safety report database at a large academic hospital between April 2006 and March 2016.³⁵

226 They noted that 26% of all hypersensitivity reactions were associated with antibiotics.
227 Beta-lactams accounted for 11% and vancomycin for 8%, despite its relatively
228 infrequent use compared to other antibiotics. They noted that overall about 1 in 5
229 adverse drug reactions was an apparent hypersensitivity reaction, though they did not
230 note how many were actually confirmed by testing or rechallenge. They commented
231 that measures that would lead to less vancomycin use, such as penicillin *allergy*
232 delabeling, could help reduce overall antibiotic-associated hypersensitivity events.³⁵

233

Ways to restructure adverse drug reaction reporting in the electronic health record

The place where drug intolerances are recorded in the EHR should not be called “allergies”. A better term would be “intolerances”.¹⁰ The term “intolerance” can cover medications that should be avoided for metabolic, genetic, or pharmacologic reasons, without ever having had an exposure resulting in an adverse drug reaction. The term “allergy” should be reserved for those rare cases where clinically-significant IgE-mediated hypersensitivity has been confirmed and desensitization is possible if the medication is needed for management of a future life-threatening condition. Delayed-type T-cell-mediated hypersensitivity should also not be mis-labeled as an *allergy*, because desensitization is not possible.³⁶ Expected antibiotic-associated side-effects such as nausea or headaches should not be noted as *allergies*.¹⁰ Presumptive antibiotic allergy, specifically in those with a convincing history, may be provisionally labeled as such, but with the recommendation for confirmation within a reasonable period of time, perhaps 6 months.¹⁰ Topaz and coworkers in 2017 noted 5 steps that can help improve drug allergy alerts.³⁷ These include capturing data on the timing of rashes after the first dose of the last course, patient engagement in drug allergy labeling and delabeling, structuring allergy alerts to be informative or interruptive, turning alerts off when there is no clear evidence of cross-reactivity, and tracking allergy alerting and override rates over time.³⁷

256 Having a warning in the EHR not to use cephalosporins in the setting of a penicillin
257 *allergy* compounds the problem of inaccurate penicillin *allergy* reporting by possibly
258 denying patients safe and appropriate exposure to cephalosporins.^{38,39} KPSC removed
259 this warning from their EHR in December 2017. An analysis of the effect this had on
260 cephalosporin-associated anaphylaxis, new antibiotic allergy reports, all cause deaths,
261 therapeutic failures, healthcare utilization, and multi-drug resistant infections is ongoing.
262

Morbidity associated with inaccurate antibiotic allergy labeling

Trubiano and coworkers in 2015 reported on patients hospitalized between 2010 and 2012 with a cancer diagnosis.¹⁶ They noted that 23 % of cancer patients (n = 198) had an antibiotic *allergy*. These patients used more antibiotics per admission (3 vs. 2, p = 0.01), had a higher fraction of fluoroquinolone use (11 % vs. 6 %, p < 0.05), trended toward longer antibiotic course durations (15 vs. 13 days, p = 0.09), had higher readmission rates (53 % vs. 28 %, p < 0.001) and poorer concordance with prescribing guidelines (47 % vs. 91 %, p < 0.001), compared to cancer patients without any antibiotic *allergies*.¹⁶

Norton and coworkers in 2018 reviewed the morbidity associated with antibiotic *allergy* labeling in children.⁴⁰ In some cohorts, 75% of children with a penicillin *allergy* were labeled prior to age 3. The usage rates for non-beta-lactam alternative antibiotics are typically 30 to 40% higher in children with suspected, but unconfirmed, penicillin *allergy*.

Trubiano and coworkers in 2018 reviewed how antibiotic *allergy* labels may be harming some of the most vulnerable patients.¹¹ They noted in older inpatients there can be as much as a 25% mismatch between reported and recorded antibiotic *allergy*. Having any antibiotic *allergy* label was associated with more antibiotic treatments per admission and more readmissions with an infective diagnosis.¹¹

Tamma and coworkers in 2017 reported on adverse events associated with antibiotic use in hospitalized patients.⁴¹ In their cohort of almost 1500 patients, 20% experienced at least 1 antibiotic-associated adverse reaction. They noted that almost 20% of the antibiotic exposures were not clinically indicated and 20% of those also had an antibiotic-associated adverse reaction. For every additional 10 days of antibiotic therapy there was a 3% increased risk of an antibiotic-associated adverse reaction.⁴⁰

There is an increasing understanding that shorter courses may be better for most common indications for antibiotic therapy.^{24,30} Longer courses of antibiotic are often directly correlated to an increase incidence of adverse events. The overuse and misuse of antibiotics not only results in an increase in acute and chronic morbidity and additional antibiotic allergy reports, it is a fundamental driver of increasing antibiotic resistance.⁴²

Possible interventions to help reduce inaccurate antibiotic *allergy* labeling

There are 34 Choosing Wisely® recommendations that address antibiotic usage.³⁰ They cover 8 general topics involving antibiotic use and abuse including antibiotic use in upper respiratory infections and otitis, urinary tract symptoms, surgical and dental prophylaxis, skin symptoms, empiric antibiotic use, *Clostridioides difficile*, using oral antibiotics when possible, and penicillin *allergy* delabeling. Adhering to Choosing Wisely® recommendations is an essential first step in reducing inaccurate antibiotic *allergy* labeling, see Figure 1.

Rowe and Lindar in 2019 reported on approaches to help reduce ambulatory antibiotic overuse.⁴³ They found that audit and feedback, telling physicians how many antibiotics they used, and for what reasons, compared to their co-workers, along with accountable justification alerts, were able to reduce inappropriate antibiotic prescribing to 5% or less. They noted that point of care testing and delayed antibiotic prescriptions were ineffective. Measures that were helpful included precommitment posters, communication training (to have those “difficult” conversations), combined patient/clinician education, and clinical decision support. Saarela and coworkers in 2019 that multiplex polymerase chain reaction respiratory virus testing did not reduce antibiotic use or length of hospital stay, even when available within 24 hours of admission.⁴⁴

Many healthcare providers may lack an adequate understanding of adverse drug reactions, and thus may be more likely to report a side-effect as an allergy. Educational campaigns that help healthcare providers differentiate between drug side-effects and non-serious and serious drug hypersensitivity reactions may be helpful. There is no published evidence that I am aware of that shows that nursing or other ancillary staff input adverse drug reaction data and better or worse than physicians, except that pharmacists with an interest in this topic probably do it better than most physicians.

Antibiotic allergy delabeling

The CDC 2018 update on antibiotic use in the United States highlighted the importance of penicillin allergy delabeling.²⁴ Avoid any testing or rechallenge, outside of a research setting, if the index antibiotic-associated reaction had the clinical characteristics of serious or systemic delayed-onset immunologically-mediated or HLA-associated antibiotic hypersensitivity syndrome.³⁶ These include acute generalized exanthematous pustulosis, drug-induced hypersensitivity syndrome also known as drug reaction with eosinophilia and systemic symptoms, drug-induced liver disease, and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). These are all very rare, occurring in typically in less than 1 in 100,000 antibiotic exposures.⁴⁵ These severe reactions are more commonly associated with sulfonamide antibiotics, vancomycin, quinolones, and certain beta-lactams, specifically flucloxacillin and amoxicillin-clavulanate, and more rarely with most other antibiotics including other beta-lactams, tetracyclines, aminoglycosides, clindamycin, nitrofurantoin, metronidazole, or macrolides.

Most delayed-onset T-cell-mediated antibiotic-associated reactions are not serious or systemic but consist of benign maculopapular rashes. The expression of chemokines and chemokine receptors in both skin biopsies and peripheral CD4(+) T cells in patients with drug-induced maculopapular rashes are consistent with a Th1 profile.⁴⁶ The complex and diverse clinical manifestations of delayed-type hypersensitivity are caused by the functional heterogeneity of T cells and systemic viral infections may increase the risk of delayed-type hypersensitivity reactions.⁴⁷ It is important to thoroughly investigate

all suspected SJS/TEN cases, because the diagnosis is often miscoded, typically being vastly over-diagnosed.⁴⁸

Penicillin is the best studied antibiotic and lessons learned about penicillin *allergy* delabeling can be directly applied to other beta-lactams.⁸ Penicillin *allergy* delabeling can effectively be done by using risk-stratification based on clinical history to target the specific testing needed.⁹ The clinical findings associated with immunologically-mediated antibiotic hypersensitivity are outlined in Table 1 and graphically displayed in Figure 2. Individuals with a convincing history of penicillin-associated anaphylaxis should undergo penicillin skin testing with penicilloyl-polylysine prior to the confirmatory oral amoxicillin 250 mg oral challenge and 1 hour of observation if skin test negative.^{8,9} Individuals with a history of benign cutaneous reactions, other benign reactions, or an unknown history, can safely be evaluated using a single dose oral amoxicillin challenge and 1 hour of direct observation and 5 days of at home observation.⁹ It is important to discuss with the patient that a challenge may result in a reaction of equivalent severity to the index reaction and the medical professionals performing the challenge need to be able to treat the potential reaction.

Sulfonamides primarily induce T-cell-mediated hypersensitivity, but only a small minority of post-sulfonamide rashes are confirmed upon rechallenge.⁴⁹ A single therapeutic trimethoprim-sulfamethoxazole dose with 5 days of at home observation is a safe and effective challenge protocol.⁵⁰

Tetracyclines rarely cause clinically significant immunologically mediated hypersensitivity, typically gastrointestinal symptoms and cutaneous photosensitivity, and rechallenges are generally uneventful.³⁶ Again, a single therapeutic dose and an at-home observation period at least as long as the time between the first dose of the index reaction course and the start of the index reaction.

Macrolides typically do not cause IgE-mediated hypersensitivity.³⁶ They are also irritating to the skin and skin testing is thus not useful.³⁶ Rechallenges are generally uneventful. Again, the observation period after a single therapeutic dose needs to be at least as long as the time between the first dose of the index reaction course and the start of the index reaction.

Quinolones are direct mast cell activators.³⁶ Rechallenges remain the reference standard to confirm current tolerance, but given the known side-effect profile of quinolones, these are often among the more dangerous antibiotic rechallenges.³⁶

We have noted that annually, over the past decade, about 2% of KPSC healthplan members who have a penicillin *allergy* receive a penicillin-class antibiotic. In 2018 there were 7,281 individuals with a penicillin *allergy* who received a penicillin and though only 82 had a new reaction after the exposure reported in their EHR, only 1,228 had their penicillin *allergy* delabeled. We routinely use an oral amoxicillin challenge to confirm current penicillin class antibiotic tolerance in our delabeling protocol, so almost 6,000 additional members could have been delabeled if they actually took the penicillin-class

399 antibiotic dispensed and had no reaction. This could be confirmed by contacting these
400 individuals and, if appropriate, delabel their penicillin *allergy* and inform them that this
401 has been done and that they can now safely use penicillins. We are now attempting to
402 establish this protocol in KPSC.

Benefits associated with antibiotic allergy delabeling

We reported a matched cohort study in 2017 involving 308 KPSC penicillin *allergic* members who had penicillin *allergy* testing, 98.7% negative, and at least 2 healthcare visits between 2010 and 2012 along with at least 1 year of continuous healthplan coverage during the year prior to their index visit.⁵¹ They were matched to 1251 non-tested penicillin *allergic* control subjects on the basis of age, sex, weighted Charlson comorbidity index, drug class *allergies*, healthcare visits and hospital days during the year prior to their index visit. There was at least 3.6 years of follow-up for both groups. The key finding was 0.55 fewer hospital days per subject per year of follow-up in those who had penicillin allergy testing. The cost savings on the 308 tested subjects was estimated to be over 2 million dollars over the 3.6-year follow-up period.

Li and coworkers in 2019 reported on the benefits of penicillin *allergy* delabeling in hospitalized Australian patients from April 2017 through April 2018 at a single medical center.⁵² Compared to matched control patients the 70 penicillin allergy tested patients had a 6-day reduction in the mean length of stay. They noted in their population that typically 45% of 7000 hospitalized patients they see annually require a penicillin-class antibiotic during admission. Disappointingly 67% of the patients they delabeled in the hospital did not have their outpatient record corrected.⁵²

Ramsey and Staicu commented in 2019 on the benefits of penicillin *allergy* delabeling in cancer patients and concluded it should be a routine component of comprehensive

cancer care.⁵³ The penicillin allergy antibiotic resistance workgroup of the American Academy of Allergy, Asthma, and Immunology took it one step further and concluded that penicillin *allergy* delabeling be considered in all patients with a penicillin *allergy*.^{54,55}

Conclusion

Antibiotic *allergy* overdiagnosis is most problematic in hospitalized individuals and the elderly. These groups are likely to need antibiotic therapy, and inaccurate reporting of antibiotic *allergy* leads to significant morbidity. The key interventions needed to address the epidemic of antibiotic *allergy* over-diagnosis are minimizing inappropriate antibiotic use, accurate recording of antibiotic intolerances in the EHR, delabeling antibiotic *allergy* whenever possible, and adhering to all of the eight essential elements of effective antibiotic stewardship, see Table 2. The epidemic of antibiotic *allergy* over-diagnosis is a solvable problem, but will require a concerted effort from all physicians, other health-care providers, and the developers and managers of electronic health record systems.

References

- 1 Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol.* 2012;108:88-93.
- 2 Blumenthal KG, Li Y, Acker WW, Chang Y, Banerji A, Ghaznavi S, Camargo CA Jr, Zhou L. Multiple drug intolerance syndrome and multiple drug allergy syndrome: epidemiology and associations with anxiety and depression. *Allergy.* 2018;73:2012-23.
- 3 Wong A, Seger DL, Lai KH, Goss FR, Blumenthal KG, Zhou L. Drug hypersensitivity reactions documented in electronic health records within a large health system. *J Allergy Clin Immunol Pract.* 2019;7:1253-1260.e3.
- 4 Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med.* 2009;122:778.e1-7.
- 5 Macy E, Khan DA, Castells MC, Lang DM. Penicillin allergy testing: a key component of antibiotic stewardship. *Clin Infect Dis.* 2017;64:531-2.
- 6 Blumenthal KG, Acker WW, Li Y, Holtzman NS, Zhou L. Allergy entry and deletion in the electronic health record. *Ann Allergy Asthma Immunol.* 2017;118:380-381.

- 7 Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J*. 2009;13:12-8.
- 8 Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321:188-99.
- 9 Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. *Curr Allergy Asthma Rep*. 2019;19:27.
- 10 Blumenthal KG, Park MA, Macy EM. Redesigning the allergy module of the electronic health record. *Ann Allergy Asthma Immunol*. 2016;117:126-31.
- 11 Trubiano JA, Grayon ML, Thursky KA, Phillips EJ, Slavin MA. How antibiotic allergy labels may be harming our most vulnerable patients. *Med J Aust*. 2018;208:469-70.
- 12 Health Insurance Coverage in the United States: 2018
<https://www.census.gov/library/publications/2019/demo/p60-267.html> Accessed 9-21-2019.
- 13 Liand EH, Checn LH, Macy E. Indications for usage and adverse reactions associated with penicillins carbapenems, monobactams, and clindamycin; a

retrospective population-based study. *J Allergy Clin Immunol Pract.* 2019 (under review)

14 Zhou L, Dhopeswarkar N, Blumenthal KG, Goss F, Topaz M, Slight SP, Bates DW. Drug allergies documented in electronic health records of a large healthcare system. *Allergy.* 2016;71:1305-13.

15 McConeghy KW, Caffrey AR, Morrill HJ, Trivedi AN, LaPlante KL. Are non-allergic drug reactions commonly documented as medication “allergies”? A national cohort of Veterans’ admissions from 2000 to 2014. *Pharmacoepidemiol Drug Saf.* 2017;26:472-6.

16 Trubiano JA, Smibert O, Douglas A, Devchand M, Lambros B, Holmes NE, Chua KY, Phillips EJ, Slavin MA. The safety and efficacy of an oral penicillin challenge program in cancer patients: a multicenter pilot study. *Open forum Infect Dis.* 2018;5:ofy306.

17 Ribeiro MR, Motta AA, Marcondes-Fonseca LA, Giavina-Bianchi P. Increase of 10% in the rate of adverse drug reactions for each drug administered in hospitalized patients. *Clinics (Sao Paulo).* 2018;73:e185.

18 Omer HM, Hodson J, Thomas SK, Coleman JJ. Multiple drug intolerance syndrome: a large-scale retrospective study. *Drug Saf.* 2014;37:1037-45.

- 19 Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D. 2019 update on medical overuse. *JAMA Intern Med.* 2019 doi:10.1001/Jamainternmed.2019.3842.
- 20 Kang JH. Febrile illness with skin rashes. *Infect Chemother.* 2015;47:155-166.
- 21 Thompson DF, Ramos CL. Antibiotic-induced rash in patients with infectious mononucleosis. *Ann Pharmacother.* 2017;51:154-162.
- 22 Dibek Misirlioglu E, Guvenir H, Ozkaya Parlakay A, Toyran M, Tezer H, Catak AI, Kocabas CN. Incidence of antibiotic-related rash in children with Epstein-Barr virus infection and evaluation of the frequency of confirmed antibiotic hypersensitivity. *Int Arch Allergy Immunol.* 2018;176:33-38.
- 23 Topaz M, Seger DL, Slight SP, Goss F, Lai K, Wickner PG, Blumenthal K, Dhopeswarkar N, Chang F, Bates DW, Zhou L. Rising drug allergy overrides in electronic health records: an observational retrospective study of a decade of experience. *J Am Med Inform Assoc* 2016;23:601-8.
- 24 CDC. Antibiotic use in the United States, 2018 update: progress and opportunities. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

- 25 Chua KP, Fischer MA, Linder JA. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. *BMJ* 2019;364:k5092.
- 26 Grigoryan L, Germanos G, Zoorob R, Juneja S, Raphael JL, Paasche-Orlow MK, Trautner BW. Use of antibiotics without a prescription in the U.S. population. *Ann Intern Med* doi.10.7326/M19-0505.
- 27 Suda KJ, Calip GS, Zhou J, Rowan S, Gross AE, Hershow RC, Perez RI, McGregor JC, Evans CT. Assessment of the appropriateness of antibiotic prescriptions for infection prophylaxis before dental procedures, 2011 to 2015. *JAMA Network Open*. 2019;2:e193909.
- 28 Macy E. A rhinitis primer for family medicine. *Perm J*. 2012;16:61-6.
- 30 Choosing Wisely® <https://www.choosingwisely.org/> Accessed 9-25-2016.
- 31 Sharp AL, Klau MH, Keschner D, Macy E, Tang T, Shen E, Munoz-Plaza C, Kanter M, Silver MA, Gould MK. Low-value care for acute sinusitis encounters: who's choosing wisely? *Am J Manag Care*. 2015;21:470-85.
- 32 Tamblyn R, Abrahamowicz M, Buckeridge DL, Bustillo M, Forster AJ, Girard N, Habbib B, Hanley J, Huang A, Kurteva S, Lee TC, Meguerditchian AN, Moraga T,

Motulsky A, Petrella L, Weir DL, Winslade N. Effect of an electronic medication reconciliation intervention on adverse drug events. A cluster randomized trial. JAMA Netw Open. 2019;2:e1910756.

33 Petty LA, Vaughn VM, Flanders SA, Malani AN, Conlon A, et al. Risk factors and outcomes associated with treatment of asymptomatic bacteriuria in hospitalized patients. JAMA Intern Med. 2019 doi:10.1001/jamaingternmed.2019.2871.

34 Leis JA, Soong C. De-adoption of routine urine culture testing – a call to action. JAMA Intern Med. 2019 doi:10.1001/jamainternmed.2019.4515.

35 Blumenthal KG, Wolfson AR, Li Y, Seguin CM, Phadke NA, Banerji A, Mort E. Allergic reactions captured by voluntary reporting. J Patient Saf. 2019 doi:10.1097/PTS.0000000000000568.

36 Macy E, Romano A, Khan D. Practical management of antibiotic hypersensitivity in 2017. J Allergy Clin Immunol Pract. 2017;5:577-586.

37 Topaz M, Goss F, Blumenthal K, Lai K, Seger DL, Slight SP, Wickner PG, Robinson GA, Fung KW, McClure RC, Spiro S, Acker WW, Bates DW, Zhou L. Towards improving drug allergy alerts: multidisciplinary expert recommendations. Int J Med Inform. 2017;97:353-355.

- 38 Vyles D, Macy E. Self-reported beta-lactam intolerance: not a class effect, dangerous to patients, and rarely allergy. *Expert Rev Anti Infect Ther*. 2019;17:429-35.
- 39 Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol Pract* 2018;6:82-9.
- 40 Norton AE, Konvinse K, Phillips EJ, Broyles AD. Antibiotic allergy in pediatrics. *Pediatrics*. 2018;141:e20172497.
- 41 Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177:1308-15.
- 42 Lesho EP, Laguio-Vila M. The slow-motion catastrophe of antimicrobial resistance and practical interventions for all prescribers. *Mayo Clin Proc* 2019;94:1040-7.
- 43 Rowe TA, Linder JA. Novel approaches to decrease inappropriate ambulatory antibiotic use. *Expert Review of Anti-infective Therapy*. doi:10.1080/14787210.2019.1635455.
- 44 Saarela E, Tapiainen T, Kaupila J, Pokka T, Uhari M, Kauma H, Renko M. Impact of multiplex respiratory virus testing on antimicrobial consumption in adults in

acute care: a randomized clinical trial. Clin Microbiol Infect 2019

doi.org/10.1016/j.cmi.2019.09.013

45 Pavlos R, Malla S, Ostrov D, Buus S, Metushi I, Peters B, Phillips E. T cell-mediated hypersensitivity reactions to drugs. Annu Rev Med. 2015;66:439-54.

46 Fernandez TD, Mayorga C, Torres MJ, Cornejo-Garcia JA, Lopez S, Chaves P, Rondon C, Blanca M. Cytokine and chemokine expression in the skin from patients with maculopapular exanthema to drugs. Allergy. 2008;63:712-9.

47 Pichler WJ, Adam J, Watkins S, Wullemmin N, Yun J, Yerly D. Drug hypersensitivity: how drugs stimulate T cells via pharmacological interaction with immune receptors. Int Arch Allergy Immunol. 2015;168:12-24.

48 Davis RL, Gallagher MA, Asgari MM, Eide MJ, Margolis DJ, Macy E, Burmester JK, Selvam N, Boscarino JA, Cromwell LF, Feigelson HS, Kuntz JL, Pawloski PA, Penfold RB, Raebel MA, Sridhar G, Wu A, La Grenade LA, Pacanowski MA, Pinheiro SP. Identification of Stevens-Johnson syndrome and toxic epidermal necrolysis in electronic health record databases. Pharmacoepidemiol Drug Saf. 2015;24:684-92.

49 Khan DA, Knowles SR, Shear NH. Sulfonamide hypersensitivity: fact and fiction. J Allergy Clin Immunol Pract. 2019;7:2116-23.

- 50 Krantz MS, Abreo A, Phillips EJ. Oral challenge with trimethoprim-sulfamethoxazole in patients with a “sulfa” antibiotic allergy. *J Allergy Clin Immunol Pract.* 2019 doi.org/10.1016/j.jaip.2019.07.003
- 51 Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract.* 2017;5:706-10.
- 52 Li J, Shahabi-Sirjani A, Figtree M, Hoyle P, Fernando SL. Safety of direct drug provocation in adults with penicillin allergy and association with health and economic benefits. *Ann Allergy Asthma Immunol* 2019 doi.org/10.1016/j.anai.2019.08.005
- 53 Ramsey A, Staicu ML. Penicillin allergy evaluations: an emerging component of comprehensive cancer care. *J Allergy Clin Immunol Pract.* 2019;7:2192-3.
- 54 Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract.* 2017;5:333-4.
- 55 Macy E, Khan DA, Castells MC, Lang DM. Penicillin allergy testing: a key component of antibiotic stewardship. *Clin Infect Dis.* 2017;64:531-2.

Figure 1: Three important ways to avoid inappropriate antibiotic use.

Figure 2: Elements in the antibiotic-associated adverse reaction history suggestive of immunologically-mediated hypersensitivity where testing is indicated.

1 Table 1: Clinical findings associated with antibiotic-associated potentially
2 immunologically-mediated hypersensitivity that warrant testing or rechallenge to confirm

3

Category	Specific syndromes	Clinical findings and diagnostic criteria
IgE-mediated acute onset allergy	Urticaria	Hives within 6 hours (typically 1 hour) of the first dose of the last course
	Anaphylaxis	Drop in blood pressure or at least two affected systems within 6 hours (typically 1 hour) of an oral exposure or 1 hour (typically minutes) after a parenteral exposure
T-cell-mediated delayed-onset hypersensitivity	Benign T-cell-mediated rashes	Diffuse maculopapular (flat red areas covered in confluent bumps) rash starting at least 6 hours after the first dose of the last course, but often within 2 days

4

5 Table 2: Eight essential elements of effective antibiotic stewardship

6

Diagnosis	Obtain appropriate tests Obtain appropriate consultations Obtain appropriate microbiological samples prior to any antibiotic use
Delabel	Evaluate all penicillin <i>allergies</i> and perform appropriate testing based on history Evaluate all other relevant antibiotic <i>allergies</i> when a possible antibiotic of choice is one of the reported <i>allergies</i> and perform appropriate testing based on the history
Desensitize	Desensitize when an IgE-mediated allergy has been confirmed to the antibiotic of choice and then use the antibiotic of choice
Debride or Drain	Consult surgery if needed
Drug	Use the most appropriate guideline-based antibiotic Use the least toxic narrowest-spectrum antibiotic based on the culture results

Dose and Distribution	Use the appropriate dose based on the site of infection, renal and hepatic function, and obesity
Deescalate	Reevaluate all empiric antibiotic therapy daily based on clinical findings and culture results striving for the narrowest-spectrum antimicrobial exposure spectrum
Duration	Follow current guidelines Shorter is often better

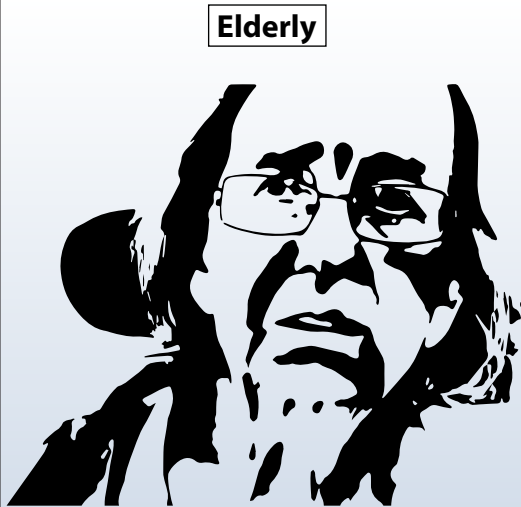
Three important ways to avoid inappropriate antibiotic use

Facial / Ear Pain



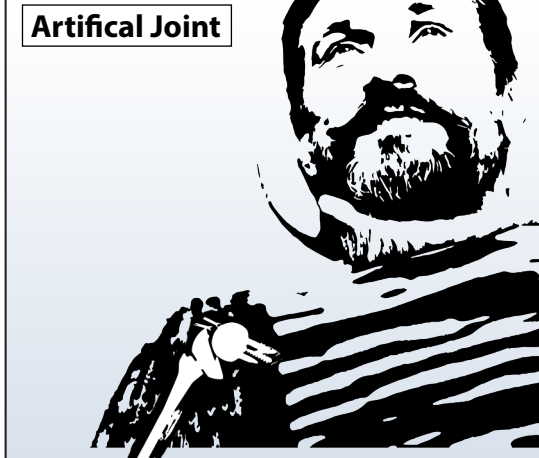
Do not give antibiotics for individuals with recurrent facial pain or acute ear pain in the setting of a probable viral infection. Consider migraine as a possible cause for facial pain. Treat the facial and ear pain symptomatically

Elderly



Do not give antibiotics for asymptomatic bacteriuria. Do not do screening urine tests in asymptomatic institutionalized elderly individuals

Artificial Joint

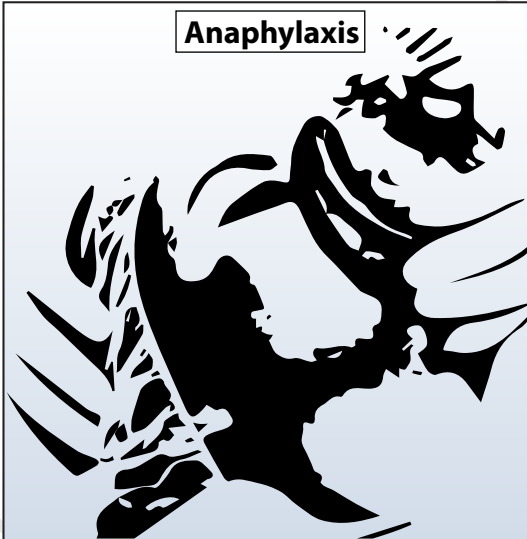


Follow current international recommendations when considering or using antibiotic prophylaxis prior to dental procedures. Do not give antibiotic prophylaxis for artificial joints

Elements in the antibiotic-associated adverse reaction history suggestive of immunologically-mediated hypersensitivity where testing is indicated

Hives

Hives within 1 hour of the first dose of the last course

Anaphylaxis

Anaphylaxis within 1 hour of the first dose of the last course

Maculopapular Rash

Total body benign maculopapular rash starting 2-5 days after the first dose of the last course

Learning Objectives: At the conclusion of this activity, participants should be able to:

- Understand the expected and avoidable causes of inaccurate antibiotic allergy reports in the medical record.
- Understand specific steps each physician can use to reduce the number of avoidable and/or inaccurate antibiotic allergy reports in the medical record.

Q1. The principle factor(s) associated with a higher population-based prevalence of antibiotic allergies are:

- 1: An older mean population age
- 2: Higher lifetime rates of antibiotic exposures in the population
- 3: Higher prevalence of food or environmental allergy in the population
- 4: Higher fraction of females in the population

- A. 1 and 4
- B. 3
- C. 1 and 2
- D. 1, 2, and 4
- E. All of the above

Q1 ANS: D. 1, 2, and 4.

Rationale:

Antibiotic allergy reports are more common in females and accumulate with increasing age. There is no evidence underlying food or environmental atopy is a contributing factor. There is a predictable rate of new antibiotic allergy reports with each therapeutic antibiotic exposure, thus higher lifetime rates of antibiotic exposures are associated with a higher population prevalence of antibiotic allergies.

References:

1. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol.* 2012;108:88-93.
2. Blumenthal KG, Li Y, Acker WW, et al. Multiple drug intolerance syndrome and multiple drug allergy syndrome: epidemiology and associations with anxiety and depression. *Allergy.* 2018;73:2012-2023.
3. Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med.* 2009 Aug;122(8):778.e1-7.

Q2. Which of the following statements about rashes associated with Epstein-Barr virus infections are true?

- A. Rashes within 2 weeks of the onset of a primary Epstein-Barr virus infection are more common in adults than children
- B. Less than half of individuals given an antibiotic during an acute Epstein-Barr virus infection will have a rash
- C. Most children with a primary Epstein-Barr virus infection will have a rash within 2 weeks of onset, independent of antibiotic exposure
- D. Rashes occur in most children given antibiotics, particularly aminopenicillins, during an acute Epstein-Barr virus infection
- E. Rashes are more common in individuals with an acute Epstein-Barr virus infection who are given antibiotics than in those not given antibiotics.

Q2 ANS: B. Less than half of individuals given an antibiotic during an acute Epstein-Barr virus infection will have a rash

Rationale:

A recent review noted that, over the past 20 years, only 15 to 33% of individuals with an acute Epstein-Barr virus infection erroneously given an antibiotic will have a rash. A recent study noted about 20% of children with an acute Epstein-Barr virus who are not given any antibiotics will have a rash and the rate is no higher when given antibiotics. There is no data that has shown that adults are more likely to get primary Epstein-Barr virus infection-associated rashes than children.

References:

1. Thompson DF, Ramos CL. Antibiotic-induced rash in patients with infectious mononucleosis. *Ann Pharmacother*. 2017 Feb;51(2):154-162.
2. Dibek Misirlioglu E, Guvenir H, Ozkaya Parlakay A, Toyran M, Tezer H, Catak AI, Kocabas CN. Incidence of antibiotic-related rash in children with Epstein-Barr virus infection and evaluation of the frequency of confirmed antibiotic hypersensitivity. *Int Arch Allergy Immunol*. 2018;176(1):33-38.

Q3. Which of the following statements about antibiotic allergy reporting in electronic health records is correct?

- A. Most antibiotic allergy reports in electronic health records are correct and all individuals with an antibiotic allergy noted in their medical record can be desensitized to that antibiotic if needed.

- B. Isolated antibiotic-associated nausea and vomiting are valid reasons to note a new allergy to the implicated antibiotic.
- C. Only about 5-10% of penicillin-class antibiotic allergies can be confirmed by the reference standard test, an oral challenge with a therapeutic dose.
- D. An episode of amoxicillin/clavulanate-associated *Clostridioides difficile* is a valid reason to list a new penicillin class antibiotic allergy in the medical record.
- E. Most individuals with a history of hives starting within 1 day of a penicillin exposure will be confirmed to be hypersensitive upon rechallenge.

Q3 ANS: C. Only about 5-10% of penicillin-class antibiotic allergies can be confirmed by the reference standard test, an oral challenge with a therapeutic dose.

Rationale:

Only a small fraction of antibiotic allergies noted in the medical record can be confirmed to be a clinically significant IgE-mediated acute hypersensitivity or a delayed-onset T-cell-mediated hypersensitivity by appropriate testing, and with penicillins this is only about 5%. It is not possible to desensitize an individual with a clinically significant T-cell-mediated delayed-type hypersensitivity, though rechallenge several years later is sometimes tolerated and it may be possible to treat through mild recurrent reactions.

References:

1. Blumenthal KG. The role of the clinical history in drug allergy predication. *J Allergy Clin Immunol Pract.* 2018;6:149-150.
2. Goss FR, Lai KH, Topaz M, et al. A value set for documenting adverse reactions in electronic health records. *J Am Med Inform Assoc.* 2018;25:661-669.
3. Blumenthal KG, Park MA, Macy EM. Redesigning the allergy module of the electronic health record. *Ann Allergy Asthma Immunol.* 2016;117:126-31.

Q4. Which of the following statements about antibiotic allergy reports in the electronic health record are correct?

- A. Most antibiotic allergy reports are incorrect.
- B. Most antibiotic allergy reports improve patient safety.
- C. Having an antibiotic allergy is associated with less antibiotic use.
- D. Most children with a penicillin allergy are labeled after age 3 and should also avoid all other beta-lactams.
- E. Individuals with multiple drug intolerance syndrome are less likely to use medications.

Q4 ANS: A. Most antibiotic allergy reports are incorrect.

Rationale:

Most antibiotic allergy reports can not be confirmed by the reference standard test for current intolerance, rechallenge. Norton and coworkers in 2018 noted that up to 75% of children with a penicillin allergy were labeled prior to age 3. Trubiano and coworkers in 2018 noted that having an antibiotic allergy label was associated with more antibiotic treatments per admission and more readmissions with an infective diagnosis. Non-penicillin beta-lactams are widely, safely, and appropriately used in individuals with confirmed penicillin allergy or unconfirmed penicillin allergy.

References:

1. Vyles D, Macy E. Self-reported beta-lactam intolerance: not a class effect, dangerous to patients, and rarely allergy. *Expert Rev Anti Infect Ther.* 2019;17:429-35.
2. Norton AE, Konvinse K, Phillips EJ, Broyles AD. Antibiotic allergy in pediatrics. *Pediatrics.* 2018;141:e20172497.
3. Trubiano JA, Grayon ML, Thursky KA, Phillips EJ, Slavin MA. How antibiotic allergy labels may be harming our most vulnerable patients. *Med J Aust.* 2018;208:469-70.

Q5. Which of the following measures relating to antibiotic intolerance reporting in the electronic health record will not improve patient safety?

- A. Only use the word “allergy” to note a confirmed antibiotic-specific clinically-significant IgE-mediated hypersensitivity.
- B. Skin test all individuals with an unconfirmed penicillin allergy with a complete set of reagents including penicilloyl-polylysine, penilloate, penicilloate, and high-dose amoxicillin.
- C. Do not label individuals with antibiotic-associated headaches, nausea, or vomiting as having an antibiotic allergy.
- D. Ideally label individuals with a possible antibiotic-associated serious cutaneous adverse reaction (SCAR), such as Stevens-Johnson syndrome, as having the specific SCAR, Stevens-Johnson syndrome, only if the diagnosis has been confirmed by both clinical findings and biopsy.
- E. Remove warnings not to use cephalosporins in individuals with confirmed or unconfirmed penicillin allergy.

Q5 ANS: B. Skin test all individuals with an unconfirmed penicillin allergy with a complete set of reagents including penicilloyl-polylysine, penilloate, penicilloate, and high-dose amoxicillin.

Rationale:

When individuals are correctly labeled as having an antibiotic-allergy, desensitization is possible if that antibiotic is the drug of choice for a future life-threatening infection. Skin testing all individuals with an unconfirmed penicillin allergy with a set of reagents as noted above will result in many more false positive test results than using appropriate risk-stratification and oral challenges those with a low-risk history and reserving skin testing for high-risk individuals. Only individuals with clinical symptoms compatible with an antibiotic-associated IgE-mediated reaction, and ideally confirmed by appropriate testing, should be labeled as having an allergy. Many individuals are incorrectly labeled with Stevens-Johnson syndrome when the diagnosis has not been confirmed by clinical findings and biopsy

References:

1. Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. *Curr Allergy Asthma Rep.* 2019;19:27.
2. Davis RL, Gallagher MA, Asgari MM, et al. Identification of Stevens-Johnson syndrome and toxic epidermal necrolysis in electronic health record databases. *Pharmacoepidemiol Drug Saf.* 2015;24:684-92.