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ORIGINAL RESEARCH & CONTRIBUTIONS

Adverse Reactions Associated with Therapeutic Antibiotic Use after Penicillin Skin Testing

Eric Macy, MD, MS
Ngoc J Ho, PhD

Abstract

Background: There is little prospective data on the antibiotics prescribed and the adverse reactions associated with their use after penicillin skin testing.

Objective: Provide data on antibiotic use and new antibiotic "allergy" incidence after penicillin skin testing.

Methods: All patients who had penicillin skin testing at our Medical Center between 1-1-2000 and 12-31-2004 were followed through 12-31-2009. All therapeutic antibiotic use and all new "allergies" listed in their electronic medical records were reviewed.

Results: There were 1684 study subjects of whom 1191 (70.7%) were female. There were 118 (7.0%) positive to at least one penicillin skin test reagent and 3 (0.2%) were positive only to amoxicillin. The mean follow-up period was 4.5 ± 2.9 years. Subjects were exposed to a mean of 8.2 ± 10.5 therapeutic antibiotic courses during follow-up. The highest new antibiotic "allergy" incidence rates in skin test-negative subjects were noted for penicillins, 2.9%, and sulfonamides, 2.7%, p = 0.9097. Females had higher overall incidences of new antibiotic "allergy," independent of skin test result. Penicillin skin test-negative females treated with penicillin had a nonsignificantly higher new penicillin "allergy" incidence, 3.3% per course versus 1.9% for males, p = 0.0644. Cephalosporins had new antibiotic "allergy" incidence rates not significantly different from tetracyclines, quinolones, macrolides, clindamycin, metronidazole, nitrofurantoin, and other antibiotics.

Conclusions: Females had higher new antibiotic "allergy" incidence rates. New "allergy" to cephalosporins occurred no more frequently than with non-beta-lactam-antibiotics, independent of skin test result. Sulfonamide antibiotics were associated with the higher rates of new antibiotic "allergy" than cephalosporins.

Introduction

Recent reviews on adverse drug reactions note that only a small minority of the adverse reactions associated with antibiotic use are either IgE or T-cell mediated.[1,2] The vast majority of antibiotic-associated adverse drug reactions, and, thus, drug "allergy" reports in the medical record, do not have an immunologic cause and their recurrence is not reliably predicted by immediate type hypersensitivity skin tests or oral challenges. Clinically, it is important to know both the incidence and expected severity of new adverse reactions associated with therapeutic antibiotic use in patients with a history of penicillin "allergy." It is important to have data on reactions associated with the use of both penicillins and nonpenicillin antibiotics, after both positive and negative penicillin skin testing, to make rational prescribing decisions.

Decay of true IgE-mediated allergy over time does completely explain why historically less than 20%, and recently for our group less than 5%, of penicillin skin tests are positive.[3] There may be less IgE sensitization to penicillin because of less parenteral penicillin use. Testing individuals who are not Allergy Department patients may also identify more individuals with non-IgE-mediated reactions. Resensitization, documented by a history of penicillin "allergy," an initial negative penicillin skin test, a reaction associated with a therapeutic penicillin use or challenge, and then a positive penicillin skin test, has been shown to be a rare event by our group and other investigators.[4-7]

Previously we reported on therapeutic antibiotic-associated adverse reactions after penicillin skin testing in a relatively small, 249 patient, case-control study.[8] We noted adverse reaction rates of 3.2% to 5.4% per antibiotic course, comparing penicillin, cephalosporin, and other non-beta-lactam antibiotic use during three years of mean follow-up. Penicillin skin testing was only able to predict penicillin-associated adverse drug

Eric Macy, MD, MS, is an Allergy Specialist and Researcher in the Department of Allergy at the San Diego Medical Center. He is a Partner Physician with the Southern California Permanente Medical Group, and an Assistant Clinical Professor of Medicine at the University of California, San Diego. E-mail: eric.m.macy@kp.org.
Ngoc J Ho, PhD, is a Researcher in the Department of Research and Evaluation, in Pasadena, CA. E-mail: ngoc.j.ho@kp.org.

reactions in penicillin skin test-positive individuals. Excluding accidental penicillin exposure in penicillin skin test-positive individuals, non-beta-lactams were associated with adverse drug reactions more often than penicillins or cephalosporins, independent of the penicillin skin test result. Cephalosporins were used as or more safely than non-beta-lactams in both penicillin skin test-positive and negative individuals. However, not all of these reports resulted in a new antibiotic "allergy" being entered in the medical record, as there was no uniform place that the drug "allergy" history was kept in the paper medical record at that time.

We now present electronic medical record (EMR) data from a larger cohort with longer follow-up. We provide data on the incidence of new antibiotic "allergy" after all outpatient therapeutic antibiotic use in all the individuals who had penicillin skin testing at our medical center from January 1, 2000 through December 31, 2004. We stratify the results with respect to gender and penicillin skin test result. The data we present here gives a real world picture of the incidence and severity of new antibiotic "allergy" in patients with a history of penicillin "allergy."

Methods

This study was reviewed by the Southern California Kaiser Permanente (KP) institutional review board. Written informed consent was obtained from all study subjects prior to penicillin skin testing and medical record review. The majority of the subjects included in this article were also subjects in a previous publication.[3]

Data on demographics, total years of active Health Plan coverage after penicillin skin testing, diagnoses, drug "allergy" history, outpatient antibiotic courses used, and new drug "allergy" entries were extracted from the KP EMR, HealthConnect, and from other legacy electronic databases. Significant electronic data on drug "allergy" were maintained by KP pharmacies and were downloaded into HealthConnect before it became clinically active in 2006. The data were not available electronically to clinicians using primarily paper charts before 2006.

Drug "allergy" was defined as what was listed in the drug allergy field of the EMR. Oral and parenteral antibacterial antibiotic use was determined. Topical and ophthalmic antibiotics were excluded because the systemic exposure from these routes is typically low and often quite variable compared to oral or parenteral exposure. Antiviral, antiprotozoan, and antihelminth "antibiotics" were excluded. Inhaled antibiotics were considered as oral. If there was a break of fewer than three days in the use of any single antibiotic, it was considered a single course. Antibacteria antibiotics were divided into ten classes: penicillins, cephalosporins, tetracyclines, quinolones, macrolides, sulfonamides, clindamycin, metronidazole, nitrofurantoin, and others, for the purpose of determining antibiotic class allergy. The clindamycin class also included lincomycin. The other antibiotics category included amikacin, aztreonam, capreomycin, colistimethate, cycloserine, dapsone, ertapenem, ethambutol, ethionamide, fosfomycin, gentamicin, imipenen, isoniazid, linezolid, methenamine, neomycin, paromomycin, pyrazinamide, rifabutin, rifampin, tobramycin, and vancomycin. All other medications were divided into 13 classes: narcotics, nonsteroidal anti-inflammatory drugs, ACE inhibitors, other antihypertensives, anticholesterols, antiseizures, antidepressants, stimulants, contrast materials, local anesthetics, intact proteins, corticosteroids, and other medications. Thus, for the purposes of this analysis, the maximum number of drug class "allergies" one individual could have was 23. If more than one new

Table 1. Patient demographics

Attribute	Penicillin skin test-negative N = 1566 (93.0%)	Penicillin skin test-positive N = 118 (7.0%)	p value
Females (%)	1106 (70.6%)	85 (72.4%)	ns
Age in years (mean ± sd)	51 ± 22.7	43 ± 23.2	0.0003
Time since index reaction in years (mean ± sd)	23.7 ± 18.8 dna (152)	18.4 ± 16.9 dna (10)	0.0048
Length of follow-up in years (mean ± sd)	4.4 ± 2.8	5.2 ± 3.0	< 0.0001
Total antibiotic courses per year of follow-up (mean ± sd)	1.86 ± 2.41	1.64 ± 1.94	ns
Total antibiotic class allergies noted on 12-31-2009[a] (mean ± sd)	1.4 ± 0.7	1.2 ± 0.4	ns
Total nonantibiotic class allergies noted on 12-31-2009 (mean ± sd)	1.7 ± 1.1	1.7 ± 1.1	ns

[a] excluding initial penicillin "allergy"'
dna = data not available; ns = non-significant; sd = Standard Deviation

antibiotic "allergy" in a single class was reported after only one antibiotic use in that class in any one year, then only the first entry was noted. A common example would be a single oral use of amoxicillin resulting in an amoxicillin "allergy" report followed two weeks later by a penicillin class antibiotic "allergy" report.

The following International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to determine possible significant life-threatening antibiotic-associated adverse reactions: 695.1 (Stevens Johnson syndrome), 695.10 (toxic epidermal necrolysis), 695.13 (Stevens Johnson syndrome), 695.14 (Stevens Johnson Syndrome and toxic epidermal necrolysis overlap including erythema multiforme), 695.15 (toxic epidermal necrolysis), and 995.0 (anaphylaxis). If one of these diagnoses was made within ±30 days of a new antibiotic "allergy" entry, it was considered related.

All statistical analyses were performed using SAS Enterprise Guide version 4.1 software (Carey, North Carolina). Descriptive statistics were summarized using frequency and percentage. Hypothesis testing for continuous variables was by means of student t-test. Chi-square was used for categorical variables. Alpha level of 0.05 was used for statistical significance.

Results

Patient demographics are reported in Table 1. These patients have all been previously reported on in part.[8] The mean follow-up was 4.5 ± 2.9 years for the entire cohort. The mean follow-up times were longer for the penicillin skin test-positive cohort because of the falling rate of positive penicillin skin tests that we have previously documented.[8,9] There were 787 (46.7%) study subjects who were still Health Plan members on December 31, 2009.

There were 1423 (84.5%) individuals exposed to at least one therapeutic antibiotic course. Study subjects were exposed to an average of 8.2 ± 10.5 courses of antibiotics during the follow-up period. Per year of follow-up, females, 1.85 ± 2.1, were exposed to as many antibiotic courses as males, 1.79 ± 2.9. There were 754 (44.8%) individuals exposed to a total of 2456 courses of penicillin-class antibiotics. Amoxicillin alone accounted for 1648 (67.1%) and amoxicillin/clavulanate accounted for 435 (17.7%) of the penicillins used. There were 873 (51.8%) individuals exposed to at least one course of a cephalosporin class antibiotic. There were 469 (27.9%) individuals exposed to at least one course of a sulfonamide antibiotic. There were 770 (45.7%) individuals exposed to at least one course of a quinolone antibiotic. There were 646 (38.3%) individuals exposed to at least one course of a tetracycline antibiotic. There were 480 (28.5%) individuals exposed to at least one course of a macrolide antibiotic.

Therapeutic antibiotic use and any associated new entry in the drug "allergy" field of the EMR during follow-up after penicillin skin testing are reported in Table 2. Females overall had higher new antibiotic "allergy" incidence rates, 1.9% per course versus 1.1% for males (p = 0.002). The highest overall new antibiotic "allergy" incidence rates in penicillin skin test-negative subjects were noted for penicillins, 2.9%, and sulfonamides, 2.7%, (p = 0.9097). In both sexes and in both skin test-positive and negative cohorts, cephalosporins had new "allergy" rates not significantly different from tetracyclines, quinolones, macrolides, clindamycin, metronidazole, nitrofurantoin, and other antibiotics. There was no significant difference in the overall new antibiotic "allergy" rate between the genders in the penicillin skin test-positive cohort, 1.2% for females versus 1.7% for males, (p = 0.5113).

Among the 70 penicillin skin test-negative patients noting a new penicillin "allergy," 37 reacted during the first reuse, 16 during the second reuse, and 17 during the third or greater reuse. The mean time to the new penicillin "allergy" report was 2.9 ± 2.3 years. Among the new penicillin "allergies" 52 were associated with amoxicillin, 8 with amoxicillin/clavulanate use, 6 with penicillin, and 2 each with ampicillin and dicloxicillin. There was 1 penicillin skin test-positive female, age 74 years when she was intradermal skin test-positive to penilloate only in 2000. She received oral amoxicillin in 2005 and intravenous ampicillin in 2007, with no desensitization prior to either episode and no reactions noted.

The oral challenge also helps the patient, and the referring physician, understand that the penicillin skin testing only predicts rapid onset IgE-mediated reactions.

There were a total of 54 penicillin skin test-positive individuals exposed to a total of 169 courses of cephalosporins with only 1 (0.6%, 95% confidence interval (CI) = -0.56, 1.75) new cephalosporin "allergy" noted. This reaction occurred 4 years after penicillin skin testing during the first course of intravenous cefazolin that individual was exposed to, 1.5 years after tolerating oral cephalexin. There were a total of 819 penicillin skin test-negative individuals exposed to 2485 courses of cephalosporins with 29 (1.2%, 95% CI = 0.78, 1.64) new cephalosporin "allergies" reported, 9 with the first course, 9 with the second course, and 11 with the third or greater course. One individual had a reaction associated with the tenth course used.

Table 2. Antibiotic use and new antibiotic "allergy" reported in penicillin skin test

Antibiotic class	Patients exposed (%)	Total courses (mean, range)	New drug allergy reports (% per course)	95% CI
Negative females (N = 1106)				
Penicillins	528 (47.7%)	1704 (1,25)	56 (3.3%)	(2.45, 4.15)
Cephalosporins	578 (52.2%)	1741 (1,35)	25 (1.4%)	(0.93, 2.07)
Sulfonamides	308 (27.8%)	645 (1,15)	17 (2.6%)	(1.37, 3.83)
Quinolones	525 (47.4%)	1713 (1,26)	20 (1.2%)	(0.68, 1.72)
Macrolides	305 (27.5%)	596 (1,14)	11 (1.8%)	(0.73, 2.87)
Tetracyclines	420 (37.8%)	1072 (1,26)	16 (1.5%)	(0.77, 2.23)
Clindamycin	280 (25.3%)	639 (1,29)	11 (1.7%)	(0.7, 2.7)
Metronidazole	221 (19.9%)	368 (1,11)	4 (1.1%)	(0.03, 2.17)
Nitrofurantoin	326 (29.4%)	749 (1,22)	11 (1.5%)	(0.63, 2.37)
Others	37 (3.3%)	56 (1,6)	1 (1.8%)	(-1.68, 5.28)
Negative males (N = 460)				
Penicillins	225 (48.8%)	750 (1,26)	14 (1.9%)	(0.92, 2.88)
Cephalosporins	241 (52.3%)	744 (1,24)	4 (0.5%)	(-0.01, 1.01)
Sulfonamides	124 (26.9%)	360 (1,69)	10 (2.8%)	(1.1, 4.5)
Quinolones	193 (41.9%)	610 (1,51)	5 (0.8%)	(0.09, 1.51)
Macrolides	122 (26.5%)	264 (1,53)	0 (0%)	-----
Tetracyclines	171 (37.1%)	428 (1,21)	1 (0.2%)	(-0.22, 0.62)
Clindamycin	92 (20.0%)	171 (1,8)	1 (0.6%)	(-0.56, 1.76)
Metronidazole	63 (13.7%)	93 (1,7)	0 (0%)	-----
Nitrofurantoin	25 (5.4%)	41 (1,7)	0 (0%)	-----
Others	18 (3.9%)	72 (1,35)	2 (2.8%)	(-1.01, 6.61)
Positive females (N = 85)				
Penicillins	1 (1.2%)	2 (2)	0 (0%)	-----
Cephalosporins	37 (43.5%)	132 (1,16)	0 (0%)	-----
Sulfonamides	30 (35.3%)	65 (1,6)	4 (6.2%)	(0.34, 12.06)
Quinolones	39 (45.9%)	181 (1,21)	0 (0%)	-----
Macrolides	35 (41.2%)	71 (1,7)	3 (4.2%)	(-0.47, 8.87)
Tetracyclines	42 (49.4%)	160 (1,30)	1 (0.6%)	(-0.6, 1.8)
Clindamycin	25 (29.4%)	68 (1,8)	1 (1.5%)	(-1.39, 4.39)
Metronidazole	16 (18.8%)	20 (1,3)	0 (0%)	-----
Nitrofurantoin	21 (24.7%)	70 (1,13)	0 (0%)	-----
Others	2 (2.4%)	7 (1,4)	0 (0%)	-----
Positive males (N = 33)				
Penicillins	none	none	none	-----
Cephalosporins	17 (53.1%)	37 (1,6)	1 (2.7%)	(-2.52, 7.92)
Sulfonamides	13 (21.9%)	16 (1,7)	0 (0%)	-----
Quinolones	13 (40.6%)	43 (1,11)	1 (2.3%)	(-2.18, 6.78)
Macrolides	18 (56.3%)	52 (1,10)	1 (1.9%)	(-1.81, 5.61)
Tetracyclines	12 (37.5%)	53 (1,16)	0 (0%)	-----
Clindamycin	10 (31.3%)	18 (1,3)	1 (5.6%)	(-5.02, 16.22)
Metronidazole	6 (18.8%)	12 (1,3)	0 (0%)	-----
Nitrofurantoin	1 (3.1%)	1 (1)	0 (0%)	-----
Others	1 (3.1%)	1 (1)	0 (0%)	-----

CI = confidence interval

There were no episodes of life-threatening antibiotic-associated adverse drug reactions such as toxic epidermal necrolysis, Stevens Johnson syndrome, toxic epidermal necrolysis/Stevens Johnson syndrome overlap, or anaphylaxis in the entire cohort during the follow-up period.

Discussion

Penicillin skin testing, followed by an oral challenge if negative, is now considered to be the gold standard test to reliably determine the presence of clinically significant IgE-mediated penicillin allergy and most clinically significant, thus reproducible, T-cell-mediated reactions.[9,10] Oral challenges were not routinely done in all penicillin skin test-negative individuals when the current study subjects were evaluated for penicillin allergy prior to 2005. Since 2009, oral challenges are routinely done in all penicillin skin test-negative individuals at our medical center.[9] We administer oral challenges in response to the relatively high rate of new "allergy" associated with the initial penicillin-class antibiotic reuse in penicillin skin test-negative individuals, particularly females, as we document in this report. Because the challenge is part of the testing protocol, the primary care, or other treating physician does not have to deal with these reactions. The oral challenge also helps the patient, and the referring physician understand that the penicillin skin testing only predicts rapid onset IgE-mediated reactions.

If a therapeutic use is functionally the same as a post-skin-test oral challenge, it may have been possible to identify some of the 37 individuals who had reactions with their first post-skin-test therapeutic penicillin use at the time of the testing. However, there may be higher rates of new "allergy" noted with therapeutic antibiotic use because of other factors, including concomitant viral infections.[11] Even though all of these patients were evaluated with a complete set of penicillin skin test reagents, the oral challenge should help identify patients at risk for clinically significant delayed onset T-cell-mediated reactions, and thus should reduce the rate of new penicillin "allergy" reports. We are in the process of collecting prospective data to determine this.

We noted 1684 individuals in this report, compared to 1638 in a previous publication, as having a penicillin skin test between January 1, 2000 and December 31, 2004.[8] This was because some of the individuals in the previous report had their initial penicillin skin test before January 1, 2000 and thus were not noted during the current study interval in the previous publication. Our current cohort used a mean of 1.82 antibiotic courses per year of follow-up compared to the 2.32 antibiotic courses per year of follow-up noted in our previous report.[7] This may reflect our Health Care Plan's efforts to reduce unnecessary antibiotic use.

Previously, in a large study that examined all of the antibiotic use and new antibiotic "allergy" in a population of 411,543 unselected Health Plan patients cared for in San Diego County in 2007, we have shown that females used more antibiotics than males.[12] Females had higher rates of antibiotic "allergy" prevalence for all classes of antibiotics. There was a steady increase in antibiotic "allergy" prevalence with aging for both sexes. Females had higher incidence rates of antibiotic "allergy" for all classes of antibiotics. The antibiotic "allergy" incidence rates in females were highest with sulfonamides, 3.4% per course, compared with 1.5% per course for penicillins, and 1 to 1.3% per course for all other classes of antibiotics. Antibiotic "allergy" incidence in males was also highest for sulfonamides, 2.2% per course, compared with 1.1% per course for penicillins, and 0.5 to 0.6% per course for all other classes of antibiotics. We did not see a statistically significant difference between new antibiotic "allergy" between the male and female penicillin skin test-positive cohorts in our current study because of the relatively small sample.

We did not note an increased rate of positive penicillin skin tests in females as reported by Park and coworkers.[13] This appears to be due to our using 5 mm or greater wheal, with flare greater than wheal, as the definition of a positive penicillin skin test result as opposed to the 3 mm or greater threshold used by the Park group at the Mayo Clinic.[9,13] Also, we saw a much lower overall rate of positive penicillin skin tests compared with the recent report by Lin and co-workers at the University of California Los Angeles.[14] They only tested hospitalized patients between 1995 and 2007. Though they used exactly the same penicillin skin test reagents as we used, they used a 4 mm wheal, instead of 5 mm, as the threshold for a positive test. They noted more individuals who were uniquely skin test-positive to amoxicillin, 5.8% versus 0.2%, ($p = 0.28$), but this difference was not significant. They did not provide a breakdown of positive skin tests by year of testing to see if they also had a falling rate of positive penicillin skin tests.

We did not note any significant difference in the rate of adverse reactions associated with future cephalosporin use in penicillin skin test-positive individuals compared with penicillin skin test-negative individuals, unlike a recent report by Park and coworkers.[15] They selected 85 penicillin skin test-positive cases exposed

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to 86 courses of cephalosporin, and 726 penicillin skin test-negative controls, exposed to 768 courses of cephalosporins. Cases were collected from 1991 to 2005. Controls were collected only from July 2002 to November 2003. Their report was significantly biased toward females among the cases: 78% of their cases were female compared with only 57% of their controls. We note that females are more likely to report a new "allergy" to all antibiotics, including cephalosporins. Our report is more robust because we tracked all individuals tested over the same interval, did not exclude children, and obtained data on the adverse reactions resulting in a new drug "allergy" entry being made in the EMR associated with all antibiotics used. There was no investigator bias using our method, because it merely reflects what patients, pharmacists, other clinicians, and treating physicians deem significant enough to report in the drug "allergy" section of the EMR, to avoid re-exposure in the future.

What is reported in the drug "allergy" fields in EMRs is becoming the gold standard to determine what patients, pharmacists, other clinicians, and treating physicians consider clinically significant enough to avoid re-exposure to, because prescribing, dispensing, and drug interaction warnings are directly linked to the "allergy" fields. There may be under or over reporting of adverse drug reactions, but if there is no "allergy" report, it cannot affect drug usage. Clinicians can override the stops in an EMR and prescribe medications to which patients carry an "allergy," but it requires extra work and, hopefully, extra consideration on the clinician's part. The drug "allergy" field is updated on virtually every health care interaction.

Also of interest is that drug interaction software packaged with our EMR has a warning not to give penicillins to individuals with a history of cephalosporin "allergy" and not to give cephalosporins to individuals with a history of penicillin "allergy." It has not been possible to specifically delete this warning to date. We have had to work around this through clinician education. Despite the drug interaction software, in our Health Plan in Southern California, during 2008, there were 20,398 (10.2%) of 199,178 penicillin "allergy" history positive individuals who received at least one cephalosporin compared with 156,170 (8.5%) out of 1,820,903 Health Plan patients with no drug allergies who received at least one cephalosporin.

Our work supports the conclusions of DePestel and coworkers in a review of cephalosporin use in patients with documented penicillin allergy noting very low, if any, clinically significant cross-reactivity between penicillins and cephalosporins.[16] We also provide data to support the conclusions of Apter and coworkers who noted higher rates of reactions associated with future sulfonamide antibiotic use compared with cephalosporin use in patients with a history of penicillin "allergy."[17]

In conclusion, there is a predictable rate of antibiotic-associated reactions and, thus, new antibiotic "allergy" reports with all therapeutic antibiotic use. Since higher levels of antibiotic use are associated with higher levels of antibiotic "allergy," antibiotic overuse, specifically for upper respiratory infections is an important factor.[18,19] Gender appears to be a more important factor in development of new antibiotic "allergy" than penicillin skin test results. In females, new antibiotic "allergies" occur at about twice the rate noted in males. New antibiotic "allergy" reports, with the exception of new penicillin "allergy" reports in females, are only slightly more frequent in penicillin skin test-negative individuals who do not receive an oral challenge, compared with random Health Plan patients.[12] Cephalosporins are safely used in patients with a history of penicillin "allergy," independent of the penicillin skin test result, with new "allergy" occurring no more frequently than with non-beta-lactam-antibiotics. Penicillins and sulfonamide antibiotics are associated with the highest, and essentially equivalent, rates of new antibiotic "allergy" in penicillin skin test-negative individuals who do not receive oral challenges at the time of testing. ❖

Disclosure Statement

This study was funded by the Kaiser Permanente Health Care Program. The author(s) have no conflicts of interest to disclose.

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Playing About

When I asked Sir Alexander Fleming about his views on research
his reply was that he was not doing research when
he discovered penicillin, he was just playing.

— The Art of Scientific Investigation, *Chapter XI, Sir WIB Beveridge, 1908-2006, Australian animal pathologist*