REVIEW ARTICLE

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Penicillin Allergy

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In 1928, Sir Alexander Fleming discovered that the active component of a penicillium fungus had the capacity to kill bacteria in a petri dish, and he named it penicillin. In 1945, Fleming, Florey, and Chain were jointly awarded the Nobel Prize in Physiology or Medicine "for the discovery of penicillin and its curative effect in various infectious diseases." Since the early 1950s, penicillin has saved millions of lives, including those of children, pregnant women, and patients with sepsis, meningitis, or endocarditis, among other life-threatening infections. Penicillin G remains the only recommended treatment for the prevention of mother-to-child transmission of syphilis.

The first case of anaphylaxis associated with penicillin was reported in 1945, and a report from the World Health Organization in 1968 stated that the rate of death from anaphylaxis was 0.002%.[1] No data suggest that the frequency of allergic reactions has increased in the past 60 years, and there is convincing evidence that penicillin sensitization is lost over time.[2] Anaphylaxis induced by exposure to penicillin has been observed with oral, subcutaneous, and intravenous administration.[3] On the basis of a nationwide survey in 1957, covering 827 hospitals in the United States, it was estimated that a total of 1000 penicillin-related deaths occurred during the first 10 years of penicillin use.[1,4] In addition, the increased use of penicillin since 1950 led to estimates that from 1965 to 1968 there had been 300 deaths annually from anaphylactic shock due to penicillin use in the United States, but these data were not verifiable.[1] A review of 151 deaths due to penicillin use published in the medical literature between 1951 to 1965 showed no sex predominance[1]; more than 50% of the persons were between 25 and 65 years of age, 44% had respiratory infections, 28% had preexisting allergies or asthma, and 69% had previous exposure to penicillin, of whom 36% had had previous reactions to the drug. The mean interval between the administration of penicillin and the onset of symptoms was less than 15 minutes in 85% of cases, and most patients died within 1 hour after administration.

Current Epidemiology and Geographic Relevance

Penicillin is the most common drug allergy identified in medical records, with a prevalence ranging from 6 to 25% across various regions and treatment populations.[5,6] Benign cutaneous reactions such as urticaria and delayed maculopapular exanthema are the most common type of reactions. The incidence of new reports of penicillin allergy in 2007 in the United States was 1.4% for females and 1.1% for males in a study that extracted data from the electronic health records of 411,534 patients who had received care from Kaiser Permanente.[7] A study in 1966 showed a 7.8% incidence of allergic reactions, with 22% of cases confirmed on the basis of positive penicillin skin tests[8]; however, longitudinal studies from a single center in the United States showed that the rate of positive penicillin skin tests

decreased from 15% in 1995 to 3% in 2007 and to 0.8% in 2013.[9,10]

Penicillins have been the most common cause of drug-induced fatal and nonfatal anaphylaxis in the United States[11,12] and the United Kingdom. The lowest rate of anaphylaxis is for oral penicillins, with a report from the United Kingdom of one case of fatal anaphylaxis from oral amoxicillin in 35 years and 100 million treatment courses.[13] Aminopenicillins are among the highest-risk drugs that cause benign delayed exanthems, which commonly occur in the context of acute Epstein–Barr virus infection.[14] Aminopenicillins are considered the most common cause of acute generalized exanthematous pustulosis (AGEP).[15] Penicillins have been associated with other severe cutaneous reactions, such as drug reaction with eosinophilia and systemic symptoms (DRESS) and the Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS–TEN).[16]

PENICILLIN AND BETA-LACTAMS

Unlike other beta-lactams, penicillins have a thiazolidine ring, and unlike cephalosporins and carbapenems, they do not have R2 or additional side-chain structures (Fig. 1A). The side chains of penicillins and first-generation cephalosporins are less complex than the side chains of later-generation cephalosporins, and although early studies indicated more than 5% cross-reactivity between penicillins and cephalosporins, contamination of the early cephalosporin preparations with penicillins was suspected.[17,18] Currently, no more than 2% of patients with positive reactions to multiple penicillin skin-test reagents have a reaction to cephalosporins,[19] with the exception of patients who are allergic to aminopenicillins but not to benzyl penicillin, penicillin VK, and other penicillins.[20] Such selective aminopenicillin allergy has been uncommonly reported in the United States[21] but appears to account for one third of cases of penicillin allergy in southern Europe, where 25 to 35% of patients who are selectively allergic to aminopenicillin have cross-reactivity with aminocephalosporins.[14,19,20] In 99% of patients with a history of penicillin allergy, a skin test and a challenge with carbapenems are associated with an acceptable side-effects profile.[22] There appears to be no immunologic or clinical cross-reactivity between penicillins and the monobactam aztreonam; however, in patients who are allergic to ceftazidime, there have been reports of aztreonam reactions, which are due to a shared R1 side chain.[22,23]

MECHANISMS OF PENICILLIN ALLERGY

Penicillins are small molecules that have been shown to covalently bind to proteins in plasma and create hapten–carrier complexes (Fig. 1B). The beta-lactam ring binds to lysine residues in serum proteins, and when binding to a polylysine matrix, it creates the major antigenic determinant, penicilloyl polylysine (Fig. 1B).[24] Haptenation from covalent binding to carboxyl and thiol groups leads to the creation of several minor determinants (Fig. 1B).[25] The hapten–prohapten model applies to immediate or antibody-mediated
penicillin hypersensitivity (Gell–Coombs type I, II, and III reactions (Fig. 2). In IgE-mediated reactions, dendritic cells bind and internalize the penicillin-bound proteins for presentation to naive CD4+ T cells (type 0 helper T cells). In the presence of interleukin-4, naive T cells develop into penicillin-specific type 2 helper T (Th2) cells, which then produce interleukin-4 and interleukin-13, inducing differentiation of B cells into plasma cells that secrete penicillin-specific IgE, which binds to Fc epsilon receptors on the surface of basophils and mast cells. On reexposure, polyvalent penicillin cross-linking of Fc epsilon receptors bound to IgE antibodies induces mast-cell degranulation and the release of soluble inflammatory mediators such as tryptase, histamine, prostaglandins, and leukotrienes, leading to the clinical manifestations of anaphylaxis.

Delayed reactions (Fig. 2) are often associated with models that involve noncovalent binding, such as the pharmacologic interaction model or alteration of the specificity of the HLA peptide presentation (altered peptide repertoire model).[26,27] Common phenotypes of penicillin allergy include reactions within 1 to 6 hours after exposure (e.g., urticaria and anaphylaxis) and reactions occurring more than 6 hours after administration of a single dose or after multiple doses (e.g., maculopapular exanthems). Delayed T-cell–mediated reactions with systemic involvement include severe cutaneous reactions (SJS–TEN, DRESS, and AGEP) (Fig. 2).

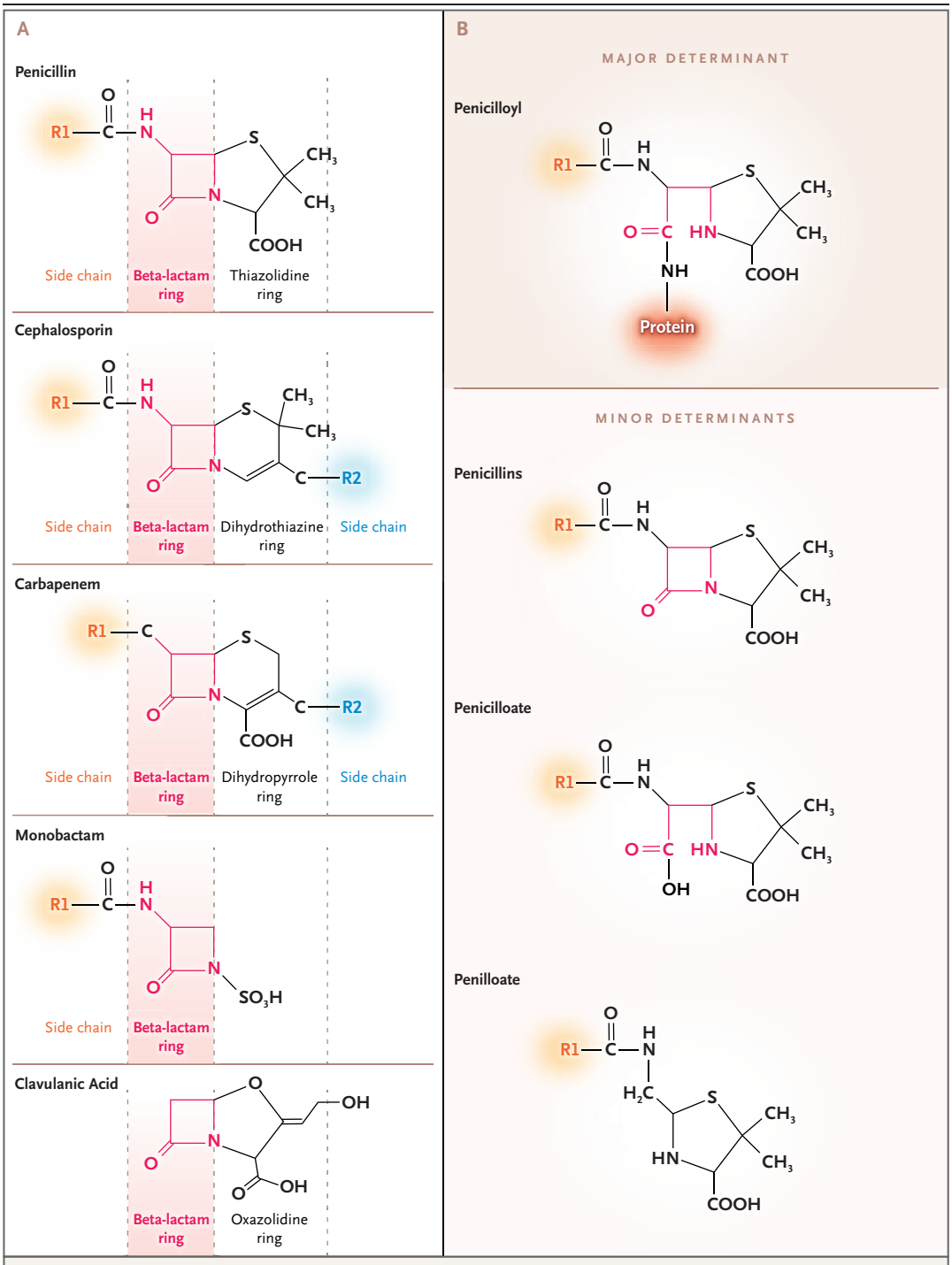

Figure 1. Penicillin and Beta-Lactam Structure and Major and Minor Penicillin Determinants.

Panel A shows that penicillin and beta-lactams share the beta-lactam ring (pink shading) but differ with respect to the adjacent ring and the R-group side chains R1 (position C7 of the beta-lactam ring) and R2 (position C3 of the beta-lactam ring). Penicillin-class beta-lactams have only an R1 group. The R1 side chain that is shared between some penicillins and cephalosporins, as well as among cephalosporins, has been shown to be a major driver of cross-reactivity. Clavulanic acid, a beta-lactam that is also a beta-lactamase inhibitor, is formulated with amoxicillin in most countries to increase its spectrum of activity. Clavulanic acid has been associated with selective IgE-mediated reactions. Panel B shows that penicillin drugs spontaneously break down to form the major allergenic determinant (penicilloyl) and several minor allergenic epitopes, the most important of which are the parent penicillin, penicilloate, and penilloate.

DIAGNOSIS OF IGE-MEDIATED PENICILLIN ALLERGY

After years of widespread use of penicillin antibiotics, penicillin reagents to identify the populations at risk for allergic reactions and anaphylaxis were identified.[28,29] This led to the initial use of the major determinant (penicilloyl polylysine), which is penicilloyl coupled to lysine for stabilization as a diagnostic agent; use of a minor-determinant mixture for this purpose began in the early 1960s (Fig. 1B).[25] A 1971 study of the prospective use of penicillin skin testing with penicilloyl polylysine and a minor-determinant mixture in nonconsecutive, hospitalized patients with a clinical indication for the therapeutic use of penicillin identified 54 patients with a history of penicillin hypersensitivity but nonreactive skin tests who were treated with penicillin; only 1 patient had a reaction (urticaria and arthralgias within 24 hours after therapy).[30] On the basis of this study and others, the positive predictive value for penicillin skin testing with these reagents was established at 50 to 75%, and the negative predictive value at more than 93%.[21,30]

PENICILLIN SKIN TESTING FOR IGE-MEDIATED REACTIONS

Drug challenges with penicillin are considered the reference standard for assessing tolerance of the drug. Challenges can be performed by administering increasing amounts of drug over time (e.g., one tenth of the dose followed after 30 minutes to 1 hour by the full dose) or administering a single full dose followed by at least 1 hour of observation. Most recent studies of penicillin skin testing have evaluated the negative predictive value after a penicillin challenge. The current negative predictive value with the use of a complete set of major and minor determinants is estimated at approximately 98%, with a 2 to 3% rate of false negative reactions after penicillin challenge and generally mild cutaneous reactions.[21]

In the United States, a complete panel of minor determinants that includes amoxicillin has never been commercially available; penicilloyl polylysine and benzyl penicillin are the most common reagents used to assess penicillin allergy. Of globally available reagents for skin testing, penicilloyl polylysine used as the major determinant and benzyl penicillin used as one minor determinant, followed by amoxicillin challenge, have been shown to have a negative predictive value of more than 95% in non–high-risk populations with a history of remote penicillin reactions.

In Europe and Australia, selective sensitization to aminopenicillins and occasionally clavulanic acid in patients with negative results of skin testing with penicilloyl polylysine and a minor-determinant mixture has been described more frequently, with all these reagents commercially available for testing.[31] Patients with side chain–specific reactions appear to be less common in the United States. However, a panel with minor determinants that included amoxicillin would yield more confidence for testing in high-risk patients (Fig. 1B), and a complete testing kit is currently being evaluated by the Food and Drug Administration.[21] In the absence of the global availability of these reagents, the use of an ingestion challenge with amoxicillin after negative penicillin skin testing with penicilloyl polylysine and benzyl penicillin is considered an acceptable method to examine the possibility of an IgE-mediated reaction to amoxicillin and other penicillins, although patients with serious or recent IgE-mediated reactions are excluded from testing.

DIRECT CHALLENGE WITHOUT SKIN TESTING FOR CHILDREN

Penicillin skin testing is safe and effective in the evaluation of children with a history of penicillin allergy.[32] A retrospective cohort study involving 369 children with negative penicillin skin tests who were challenged with penicillin showed that 14 patients (3.8%) had a mild reaction.[32] Given the current low prevalence of confirmed penicillin allergy, several studies have evaluated the safety and effectiveness of performing direct penicillin challenges without initial skin testing. The majority of these studies have involved children with a low rate of confirmed penicillin allergy, even when tested 2 months after a benign exanthem in reaction to amoxicillin.[18] In a prospective and retrospective observational study involving 818 young children with a history of low-risk reactions to amoxicillin (no children with a history of anaphylaxis were included), Mill et al. performed amoxicillin challenges with two graded doses administered 20 minutes apart. The authors reported that 2.1% of the children

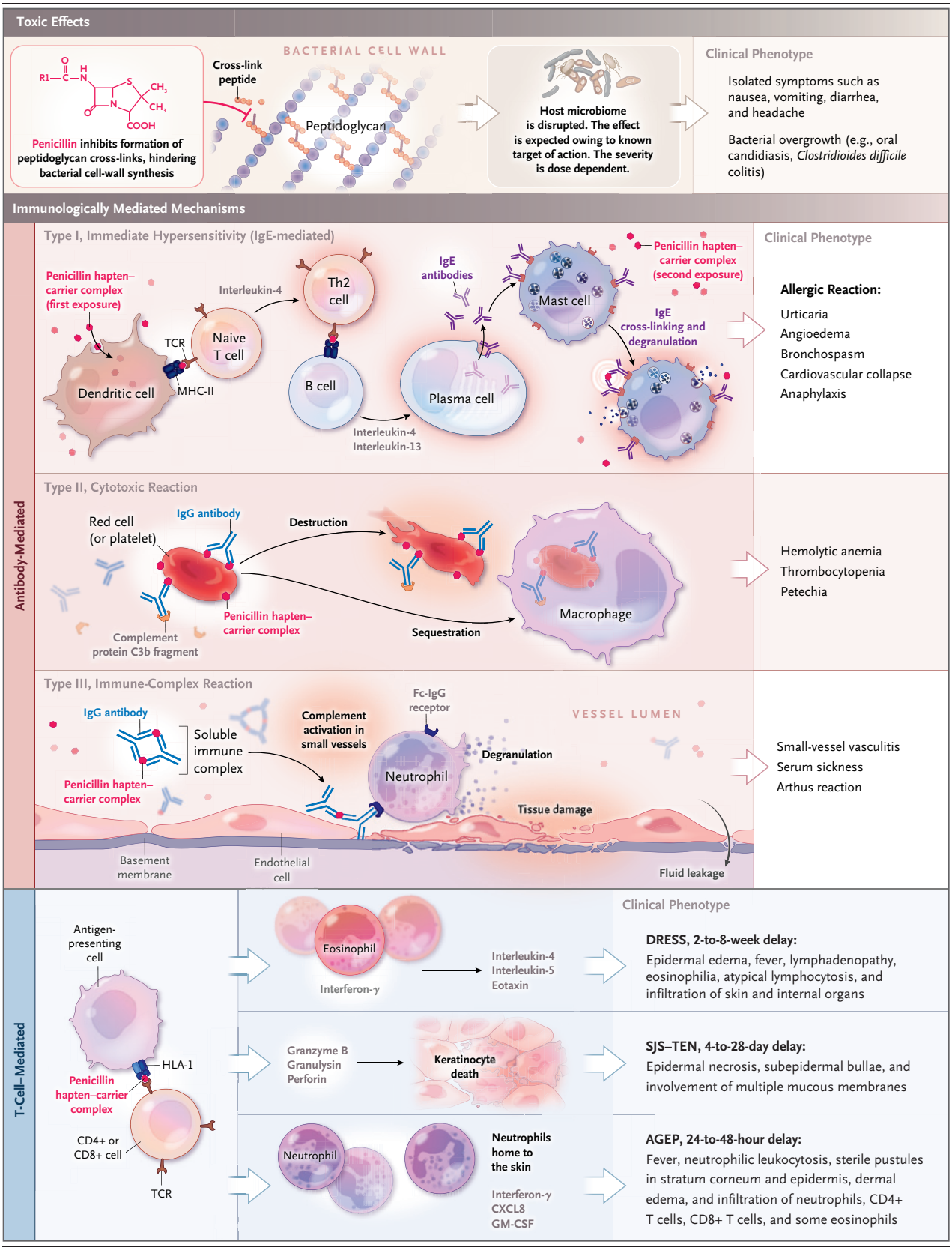

Figure 2 (facing page). Clinical Manifestations and Mechanisms of Adverse Reactions to Penicillins.

Penicillin inhibits bacterial cell-wall synthesis and specifically targets bacteria, since eukaryotic cells lack a cell wall. Penicillin affects the host microbiome and can lead to bacterial overgrowth such as *Clostridioides difficile* colitis and oral candidiasis (thrush). Clinically relevant immune-mediated reactions associated with penicillins are primarily either antibody-mediated or T-cell mediated. Penicillins are haptens that bind covalently to lysine within serum proteins and to cell-bound proteins. Antibody-mediated reactions to penicillin include immediate, IgE-mediated reactions (Gell–Coombs type I) that require prior exposure and sensitization. Penicillin-specific IgE bound to high-affinity IgE receptors on mast cells is cross-linked by penicillin, leading to mast-cell activation, release of mediators (tryptase and histamine), and clinical symptoms (hives, bronchospasm, hypotension, and anaphylaxis). In type II reactions, antibody or immune complexes target the cell-membrane structures of erythrocytes, leukocytes, or platelets, leading to cell destruction or sequestration, including hemolytic anemia and thrombocytopenia. In type III reactions, antibodies that are formed within 4 to 10 days react with the penicillin-protein carrier, forming soluble immune complexes. Complement activation and deposition in small vessels lead to recruitment of neutrophils by the Fc-IgG receptor, which releases proteolytic enzymes and leads to tissue damage and local vascular inflammation, such as small-vessel (hypersensitivity) vasculitis and serum sickness.

T-cell–mediated reactions occur more than 6 hours after penicillin administration or during the course of treatment after multiple exposures. An antigen-presenting cell processes drug-modified peptides and presents them in the antigen-binding groove of HLA for recognition by the T-cell receptor (TCR) on CD4+ or CD8+ T cells, leading to T-cell activation and release of cytokines and chemokines. Drug reaction with eosinophilia and systemic symptoms (DRESS) typically occurs 2 to 8 weeks after penicillin administration and is associated with fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, and infiltration of skin and internal organs (e.g., liver, kidneys, lungs, and heart) with CD4+ and CD8+ T cells and eosinophils. Single-organ involvement such as drug-induced liver injury and acute interstitial nephritis has been associated with penicillins. SJS–TEN (the Stevens–Johnson syndrome and toxic epidermal necrolysis) is a severe, painful blistering eruption occurring 4 to 28 days after drug administration; the disorder is CD8+ T-cell–dependent and HLA class I–restricted. Acute generalized exanthematous pustulosis (AGEP) most commonly occurs within 24 to 72 hours after exposure to aminopenicillins, with fever, neutrophilic leukocytosis, and sterile pustules in a flexural distribution. GM-CSF denotes granulocyte–macrophage colony-stimulating factor, MHC-II major histocompatibility complex class II, and Th2 cell type 2 helper T cell.

had immediate reactions, and 3.8% had nonimmediate mild reactions.[33] Ibáñez et al. performed a prospective multicenter study that included 732 children with a history of mild reactions to penicillins. Using a multistep challenge to the culprit penicillin, the authors found that 0.8% of the children had immediate reactions and 4.0% had delayed reactions, with one patient requiring epinephrine treatment.[34]

These and other studies suggest that a direct penicillin challenge without skin testing is probably appropriate for children with a history of a benign rash but without a history of anaphylaxis (Fig. 3). However, all studies to date that have examined direct penicillin challenges have been performed either by allergy specialists or in urgent care settings, and the safety of such challenges when they are performed in nonspecialty clinics and in adult populations is unknown.[14] Other indications for direct challenges include a recorded history of penicillin allergy involving symptoms that are not suggestive of allergy (e.g., nausea or headache), a family history of penicillin allergy, unknown reactions, and pruritus without rash. A direct penicillin challenge as a general approach is not recommended until larger studies can confirm its safety and effectiveness (Fig. 3).

TESTING FOR DELAYED PENICILLIN ALLERGY

Skin-testing procedures for delayed reactions to penicillins include patch, delayed prick, and intradermal testing (Fig. 3).[27] Penicillin and major and minor antigenic determinants penetrate the epidermis (patch testing and prick testing) or dermis (intradermal testing)[27] and interact covalently or noncovalently with proteins in the skin to form antigenic conjugates recognized by antigen-presenting cells that express major histocompatibility complex class I or II. These cells present the antigen–peptide complex to effector T cells, leading to proliferation of CD4+ T cells, CD8+ T cells, or both and resulting in local release of cytokines and an inflammatory response.[27] A prospective, 3-year, multicenter study that was performed to determine the sensitivity of patch testing in identifying the culprit for severe cutaneous drug reactions suggested that the sensitivity of delayed intradermal testing may exceed that of patch testing, particularly for maculopapular exanthems, DRESS, and AGEP.[35] Patch testing has poor sensitivity for SJS–TEN (<40%), and delayed intradermal testing is not

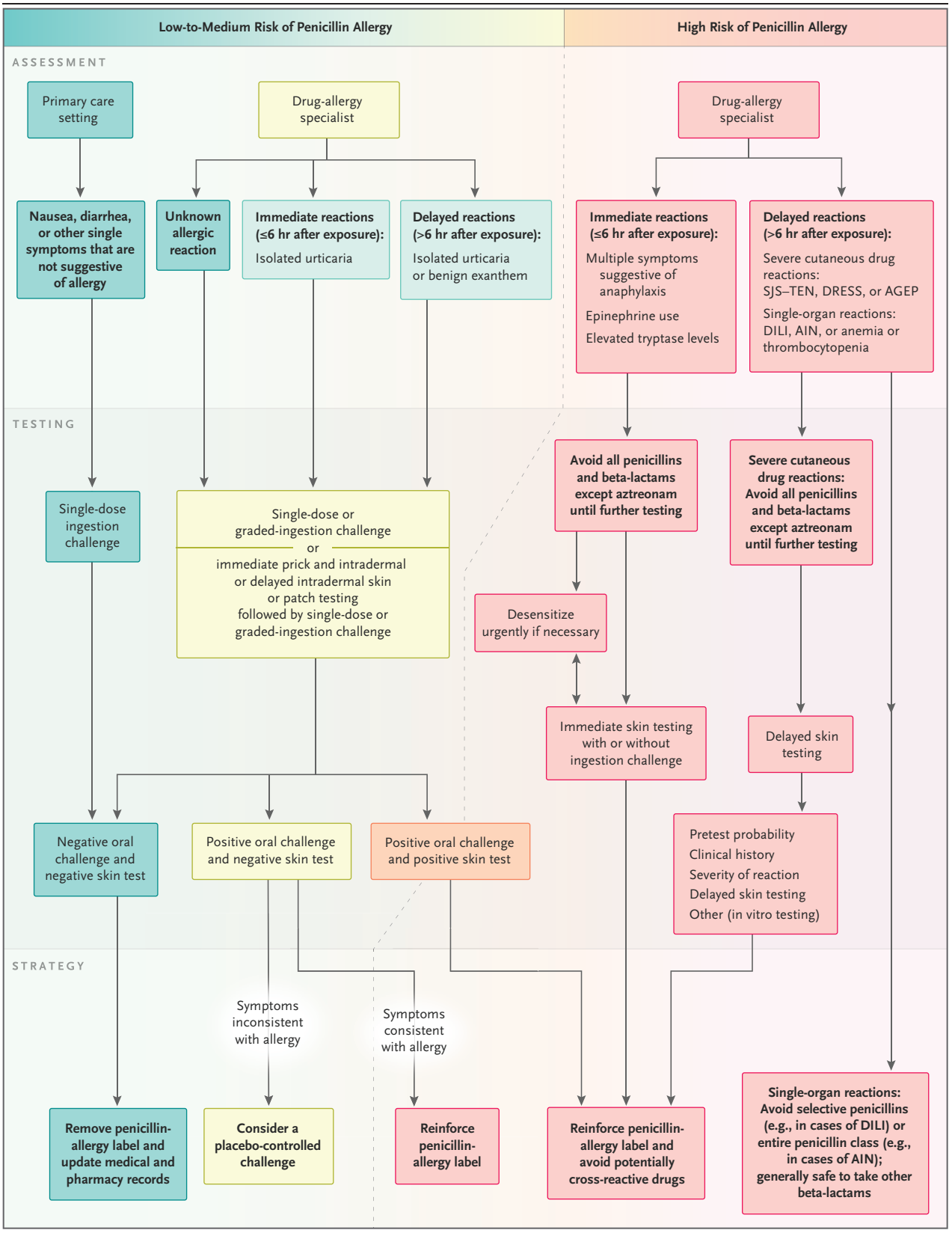

Figure 3 (facing page). Strategies for Penicillin-Allergy Delabeling and Drug Safety According to Risk.

Risk-based approaches can facilitate evaluation of patients who have a penicillin-allergy label. Approaches are shown for the lowest-risk patients (blue), medium-risk patients (yellow), and high-risk patients (red). The delabeling strategy is focused on low- and medium-risk patients; low-risk patients include those with a history of nausea, diarrhea, or headache in isolation and those with a remote or unknown history of penicillin allergy. Other low-to-medium-risk patients include those with a single symptom such as immediate or delayed urticaria or mild-to-moderate delayed exanthem. For patients with negative skin tests and a negative oral challenge, the penicillin-allergy label should be removed. Low-risk patients with negative skin tests and a positive oral challenge should be further risk-stratified on the basis of the oral-challenge reaction. The drug-safety strategy is for high-risk patients with immediate reactions, including those with multiple symptoms that suggest a severe IgE-mediated reaction or anaphylaxis, such as urticaria, angioedema, flushing, wheezing, and hypotension. Patients with a documented elevated tryptase level and those in whom epinephrine was administered are also considered to be at high risk. Care should be taken to label these patients as allergic to all beta-lactams other than aztreonam until further evaluation. If penicillin or another beta-lactam is the treatment of choice before a formal allergy assessment can be completed, desensitization should be performed. High-risk delayed reactions include severe cutaneous drug reactions (e.g., SJS–TEN, DRESS, and AGEP) and single-organ reactions, such as drug-induced liver injury (DILI), acute interstitial nephritis (AIN), and hematologic disorders (anemia or thrombocytopenia). In the case of severe cutaneous drug reactions, avoidance of all beta-lactams except aztreonam is recommended. In the case of single-organ disease, subspecialty assessment is recommended, since the reaction can be selective for a specific drug or class of drugs (e.g., DILI with flucloxacillin or interstitial nephritis with a semisynthetic penicillin).

recommended because of anecdotal reports of reproduction of initial reactions.

In vitro tests for delayed reactions are only available in research or specialty centers, and their sensitivity and specificity vary according to the drug and the specific test. These tests are performed by exposing the patient's lymphocytes to the implicated drug. They include the lymphocyte transformation test, which measures the proliferation of the patient's T cells over a period of 5 to 7 days,[36] and the enzyme-linked immunosorbent spot (ELISPOT) test, which detects antigen-specific, cytokine-producing cells after 24 hours of incubation with polymorphonuclear blood cells. Both tests are performed in the presence of the implicated drugs.[36]

GENETIC RISK

The discovery of HLA associations with drug hypersensitivity syndromes has provided screening strategies to improve drug safety and has increased our understanding of the immunopathogenesis of delayed drug reactions.[26] There have been no significant genetic associations for immediate allergic reactions to penicillins, and candidate gene studies have shown the strongest association with genes involved in IgE synthesis, HLA class II antigen presentation, and cytokines such as interleukins 4, 10, and 18; however, none are currently in use for prevention or diagnosis.[37] Drug-induced liver injury related to flucloxacillin, a semisynthetic antistaphylococcal penicillin in use in the United Kingdom, Europe, and Australia, has been strongly associated with HLA-B*57:01 in a genomewide association study,[38] and drug-induced liver injury associated with amoxicillin–clavulanic acid has been associated in multiple studies with HLA-DRB1*15:01 and its haplotype, DQB1*06:02, and with HLA-A*02:01 in northern European populations.[26,39] Drug-induced liver injury is selective for these drugs on the basis of HLA restriction, and no cross-reactivity with other beta-lactams is apparent. Given the low positive predictive value of these HLA alleles for drug-induced liver injury (<1%), testing for them as a means to determine the possible presence of penicillin allergy is not currently used in routine clinical practice.

NATURAL HISTORY OF PENICILLIN ALLERGY

The natural history of IgE-mediated penicillin allergy has been the most extensively studied hypersensitivity reaction. In 1981, a retrospective study from the United States showed that the prevalence of positive penicillin skin tests was lower among patients who were tested 10 years or more after a documented reaction than among patients who were tested 7 to 12 months after a reaction (prevalence, 22% vs. 73%).[40] A prospective longitudinal study from Spain followed 31 patients with positive penicillin skin tests and showed that at 1 year, 81% of the patients had positive tests, and at 5 years, 12 of 18 patients (67%) continued to have positive skin tests, indicating a loss of penicillin-specific IgE over time.[41] A similar decline in the rate of posi-

tive skin tests over time has been shown for cephalosporins, although patients with positive skin tests for both penicillin and cephalosporins take longer to lose their sensitivity than patients sensitized only to cephalosporins.[42] Some children with a history of serum sickness–like reactions to amoxicillin have been shown to have no such reactions to amoxicillin when challenged, suggesting that the reaction is not durable; consideration should be given to future penicillin skin testing, an ingestion challenge, or both in this population.[43] The natural history of serious cutaneous reactions to penicillins is still unknown.

CLINICAL IMPLICATIONS OF A PENICILLIN-ALLERGY LABEL

Patients with penicillin allergy receive more vancomycin, fluoroquinolones, and clindamycin than patients without the allergy.[6] Penicillin is the drug of choice for syphilis[44] and other infections, and a label of penicillin allergy has associated implications, which have not always been fully appreciated (Fig. 4). Among patients with methicillin-susceptible *Staphylococcus aureus* bloodstream infections, the risk of death in 30 days is lower with beta-lactam therapy than with vancomycin,[45] and a higher rate of clinical failure with

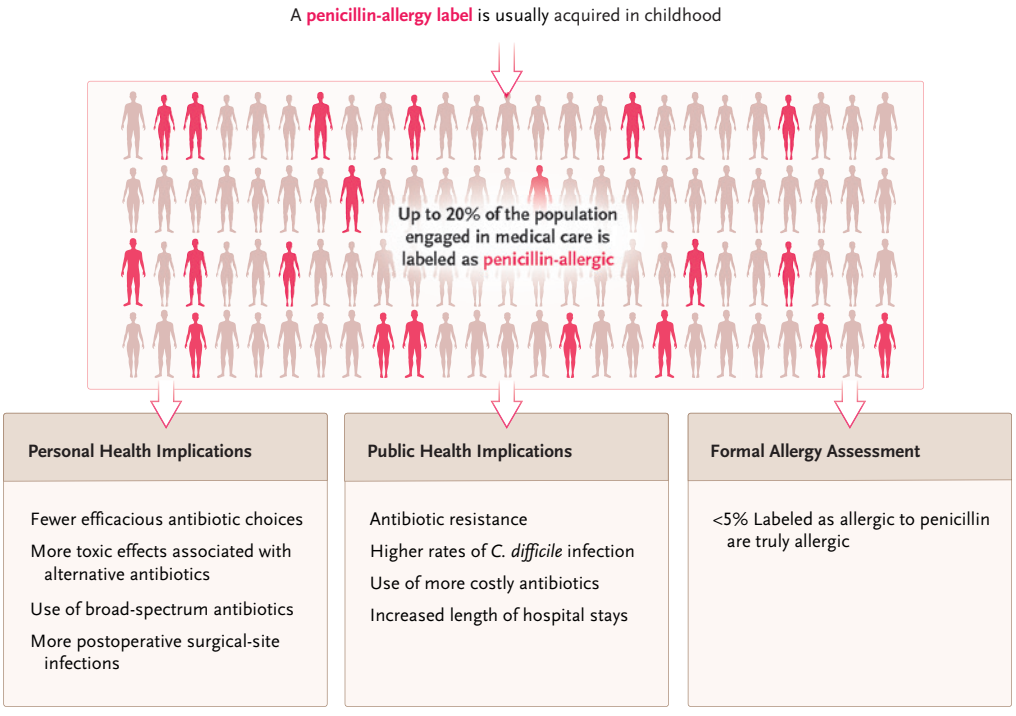

Figure 4. Health Implications and Burden of the Penicillin-Allergy Label.

A label of penicillin allergy is commonly acquired in childhood, when allergic symptoms can be confused with symptoms of viral or bacterial illness. Up to 20% of persons in the general population (red figures) are labeled as allergic to penicillin by the time they reach adulthood. Each year, approximately 10% of persons with true IgE-mediated penicillin reactions (as evidenced by a history of an immediate reaction and a positive skin test), lose skin-test reactivity. After formal allergy assessment with skin testing and ingestion challenge, less than 5% of persons with a remote and low-risk history of penicillin allergy are found to be truly allergic. A penicillin-allergy label that is acquired in childhood is frequently not questioned and may lead to multiple non–beta-lactam exposures, adverse effects, and additional antibiotic-allergy labels. High rates of penicillin-allergy labeling also constitute a substantial public health threat and economic burden because the use of broad-spectrum antibiotics can lead to *C. difficile* infection, antibiotic resistance (e.g., methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci), and prolonged hospital stays.

non–beta-lactam antibiotics for bloodstream infections with gram-negative bacilli has been observed.[46] Decision-analysis models project that patients with methicillin-susceptible *S. aureus* bacteremia will have inferior outcomes if treated with vancomycin instead of having their penicillin allergy evaluated.[47] Case–control studies in the United States and United Kingdom that involved more than 50,000 patients labeled as allergic to penicillin showed increased rates of infection with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococcus, and *Clostridioides difficile* (formerly *Clostridium difficile*).[6,48] Prolonged hospitalizations and increased readmission rates have also been reported among patients with a penicillin-allergy label.[6,49] Surgical-site infections are reported to be 50% higher among patients with a penicillin-allergy label than among those without such a label.[50]

A label of penicillin allergy is also costly. Several studies from North America and Europe have documented higher costs of inpatient and outpatient care for patients with penicillin allergy,[51,52] and it is estimated that penicillin-allergy testing and delabeling lead to cost savings, with the largest study showing a reduction in total health care expenses of $1,915 (in U.S. dollars) per patient per year.[53-55]

PENICILLIN-ALLERGY ASSESSMENT IN ANTIBIOTIC STEWARDSHIP PROGRAMS

In contemporary clinical practice, more than 90% of patients labeled as allergic to penicillin can safely receive the drug. This observation, coupled with the estimate that, on average, 8 to 15% of unselected international patients are labeled as allergic to penicillin (Fig. 4),[56] indicates that many patients labeled as allergic to penicillin could safely receive it.

The high burden of penicillin-allergy labeling and the increasing evidence of associated adverse personal and public health consequences provide the rationale for a formalized, hospital-based process to prioritize assessment of penicillin allergy as part of an antibiotic stewardship program. Since the majority of adults with a penicillin-allergy label acquired it in childhood and since more than 90% of patients labeled as allergic to penicillin can have the label removed,[57] there is an opportunity to integrate risk-based and formalized testing strategies into antibiotic stewardship programs to target populations with the greatest need for antibiotics and at the highest risk for the development of antibiotic resistance and other conditions, such as *C. difficile* infection.[58] Retrospective and observational data suggest that direct oral-challenge procedures may be safe in the lowest-risk populations, including patients with a remote or unknown history of allergy or a mild cutaneous reaction.[33,59,60] Given the large number of labeled patients globally, an evidence base is needed to guide the safest, most effective approach to delabel patients with penicillin allergy in the context of these formalized programs.

BEST CLINICAL PRACTICES FOR REMOVING THE PENICILLIN-ALLERGY LABEL

Several methods have been used to remove penicillin-allergy labels in both inpatient and outpatient populations (Fig. 3). These include the use of allergy-trained clinical pharmacists to perform preemptive testing in patients with a history of penicillin allergy who are at high risk for antibiotic use,[61] the use of clinical decision-support tools and specific algorithms for penicillin testing,[54] and the use of penicillin skin-testing consultation through telemedicine (since there is a paucity of allergy specialists).[62,63] A systematic review of inpatient penicillin testing, including studies in intensive care units, confirmed the safety and effectiveness of this approach in removing the penicillin-allergy label, with 95% of patients having negative skin tests.[56] More recently, algorithms or pathways have been developed to guide nonallergist practitioners on the use of antibiotics in patients labeled as having penicillin allergy, with risk assessment based on the clinical history, the timing and phenotype of the reaction, and the associated coexisting conditions.[64]

Delabeling is accomplished with the use of oral or intravenous test doses and challenges for low-risk patients and with the use of skin testing for high-risk patients. A study of a decision-support pathway developed as part of a guideline for antibiotic prescription at several Partners HealthCare teaching hospitals in Boston showed

Table 1. Oral Penicillin Desensitization Protocol.*

Step	Penicillin Dilution†	Volume Administered	Penicillin Dose Administered‡		Cumulative Dose Administered‡	
	mg/ml	*ml*	*mg*	*units*	*mg*	*units*
1	0.5	0.1	0.05	80	0.05	80
2	0.5	0.2	0.1	160	0.15	240
3	0.5	0.4	0.2	320	0.35	560
4	0.5	0.8	0.4	640	0.75	1,200
5	0.5	1.6	0.8	1,280	1.55	2,480
6	0.5	3.2	1.6	2,560	3.15	5,040
7	0.5	6.4	3.2	5,120	6.35	10,160
8	5	1.2	6.0	9,600	12.35	19,760
9	5	2.4	12.0	19,200	24.35	38,960
10	5	4.8	24.0	38,400	48.35	77,360
11	50	1.0	50.0	80,000	98.35	157,360
12	50	2.0	100.0	160,000	198.35	317,360
13	50	4.0	200.0	320,000	398.35	637,360
14	50	8.0	400.0	640,000	798.35	1,277,360

* Adapted from Yates.[72] Desensitization is indicated for patients who are at high risk for penicillin allergy or who have penicillin allergy confirmed by skin testing or challenge and for whom penicillin is the first therapeutic choice. Penicillin desensitization can be performed through the oral, intravenous, intramuscular, and subcutaneous routes. For oral and other routes, doubling doses is recommended, with an interval of 15 to 30 minutes between doses (15 minutes between doses in this 14-step oral protocol). With the use of this protocol, mild breakthrough reactions, not precluding the completion of the desensitization, occur in up to 20% of patients. Anaphylaxis is rare (occurring in <1% of patients), and the target dose is achieved in more than 99% of patients, including those with initial anaphylactic reactions. The protocol can be used for all oral penicillins.

† A 1:100 dilution (steps 1–7) and a 1:10 dilution (steps 8–10) are made from the final concentration (steps 11–14) of 250 mg per 5 ml (50 mg per milliliter) of oral solution.

‡ Doses are provided in both milligrams and the equivalent units (1 unit of penicillin equals 0.0006 mg).

that house officers administered more cephalosporin test doses to patients labeled as having penicillin allergy after implementation of the guideline, with a resultant reduction in the use of vancomycin, aztreonam, and fluoroquinolones.[65] A follow-up study from the same investigators compared the use of penicillin skin testing and a computerized guideline with usual care and showed that both approaches led to higher rates of use of third- and fourth-generation cephalosporins, but only the skin-test group had a higher rate of penicillin use at discharge.[66] Such decision-support pathways improve antimicrobial stewardship[67] but do not lead to systematic removal of the penicillin-allergy label.

Evaluation of penicillin allergy in outpatient clinics and the use of alerts in electronic health records have facilitated the assessment of penicillin allergy preoperatively.[60,68,69] The use of an amoxicillin challenge without a penicillin skin test was associated with low morbidity in a cohort of marines who had a history of selective penicillin allergy[70] and in children with a history of low-risk symptoms of penicillin allergy.[71] However, larger studies are needed to assess safety in these and other populations.

PENICILLIN DESENSITIZATION

Patients with IgE-dependent penicillin allergy, including anaphylaxis, who require penicillin as first-line therapy are candidates for rapid desensitization (Fig. 3 and Tables 1 and 2). The first penicillin desensitization, attributed to O'Donovan during World War II, was performed by adding increasing amounts of oral penicillin to milk until the target dose was reached without side effects in a soldier who had had an anaphylactic reaction to intramuscular penicillin.[29] Since then, numerous patients have been successfully desen-

sitized with intramuscular, intravenous, and oral protocols.[73] The mechanisms of rapid desensitization have been studied in cellular and animal models,[74] which have led to the development of clinical protocols.[75] In 2009, Legere et al. successfully desensitized 15 patients who had cystic fibrosis and a forced expiratory volume in 1 second of less than 1 liter, including 1 patient who underwent desensitization during lung transplantation, using a standard 12-step, three-bag protocol, in which the concentration in each successive bag increased by a factor of 10 and doses doubled every 15 minutes until the target dose was reached in 6 hours.[76] This and similar protocols have been used for intravenous and oral penicillin desensitization (Tables 1 and 2) with 100% success, allowing administration of the target dose and maintenance of first-line therapy. Desensitization has temporary effects that last for at least two dosing intervals of the drug, after which desensitization needs to be repeated. Long-acting benzathine penicillin is associated with an acceptable adverse-events profile 1 to 3 weeks after penicillin desensitization.[73] Empirical desensitization in the absence of positive skin tests does not answer the question of whether a patient is truly allergic to penicillin, and follow-up for formal penicillin allergy testing is recommended after completion of the penicillin treatment course.

Table 2. Three-Bag, 12-Step Intravenous Penicillin Desensitization Protocol.*

Step	Bag	Rate	Time†	Volume Infused	Dose Administered	Cumulative Dose
		ml/hr	*min*	*ml*	*units*	
1	1	2.0	15	0.50	200.0	200.0
2	1	5.0	15	1.25	500.0	700.0
3	1	10.0	15	2.50	1,000.0	1,700.0
4	1	20.0	15	5.00	2,000.0	3,700.0
5	2	5.0	15	1.25	5,000.0	8,700.0
6	2	10.0	15	2.50	10,000.0	18,700.0
7	2	20.0	15	5.00	20,000.0	38,700.0
8	2	40.0	15	10.00	40,000.0	78,700.0
9	3	10.0	15	2.50	98,032.5	176,732.5
10	3	20.0	15	5.00	196,065.0	372,797.5
11	3	40.0	15	10.00	392,130.0	764,927.5
12	3	80.0	61.875	82.50	3,235,072.5	4,000,000.0

* Desensitization is indicated for patients who are at high risk for penicillin allergy or who have penicillin allergy confirmed by skin testing or challenge and for whom penicillin is the first therapeutic choice. Penicillin desensitization can be performed through the oral, intravenous, intramuscular, and subcutaneous routes. For intravenous desensitization, three bags with drug concentrations at dilutions of 1:100, 1:10, and 1:1 are administered in 12 steps. The volume of bag 1 is 100 ml, the concentration 400 U per milliliter, the total dose 40,000 ml, and the amount of the bag infused 9.25 ml. The volume of bag 2 is 100 ml, the concentration 4000 U per milliliter, the total dose 400,000 ml, and the amount of the bag infused 18.75 ml. The volume of bag 3 is 100 ml, the concentration 39,213 U per milliliter, the total dose 3,921,300 ml, and the amount of the bag infused 100.00 ml. Each bag is administered in 4 steps, and the dose in each step is essentially double the dose in the previous step. The rate of infusion is increased every 15 minutes and maintained in step 12 at 80 ml per hour to complete the infusion. The volume of penicillin in each bag matches the volume of undiluted drug for regular use. With the use of this protocol, mild breakthrough reactions, not precluding the completion of the desensitization, occur in up to 20% of patients. Anaphylaxis is rare (occurring in <1% of patients), and the target dose (in this example, 4 million units) is achieved in more than 99% of patients, including those with initial anaphylactic reactions.

† Total time is 226.875 minutes, or 3.78 hours.

CONCLUSIONS

The incidence of both IgE-mediated and non–IgE-mediated reactions has not increased worldwide in the past 50 years, and a penicillin-allergy label has serious consequences for both individual and public health (Fig. 4). Although a large number of patients are labeled as having penicillin allergy, more than 95% of them can safely receive penicillin when they are appropriately and safely evaluated. Penicillin allergy is lost over time, and using sensitive and specific tools to identify patients with true reactions should be a health priority implemented through delabeling algorithms and programs. Over time, it would be expected that delabeling patients who no longer have penicillin allergy will control the use of alternative and more expensive antibiotics and reduce the associated morbidity and mortality and the surge of organisms that are resistant to penicillin and beta-lactams. Protection of patients who are truly allergic to penicillin by means of accurate diagnosis, proper labeling, and if necessary, desensitization should be the next steps toward improved safety and quality of care in personalized medicine. Allergists should have a central role in facilitating outpatient and inpatient testing programs aimed at correctly identifying patients with penicillin allergy (Fig. 3). Through appropriate history taking and risk stratification to identify patients without IgE-mediated allergy, as well as low-risk patients, all health care providers can play a central role in alleviating the enormous individual and public health burden related to the penicillin-allergy label.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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