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Risk-stratified Management to Remove Low-Risk Penicillin Allergy Labels in the ICU

To the Editor:

Between 8% and 15% of the U.S. population carries a penicillin allergy label, yet <5% of these can be verified by allergy testing (1).

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A false label has a negative impact on care, including use of broader-spectrum and second-line antibiotics, increased healthcare utilization, surgical site infections, and treatment failure for common infections, delayed antimicrobial therapy, and longer lengths of stay (1, 2). β -Lactam allergy labels also affect antimicrobial stewardship and are associated with increased infections with *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* (3–6).

Penicillin allergies are commonly diagnosed in childhood and go unquestioned throughout life (7). However, these allergy diagnoses are largely inaccurate, explained instead by viral exanthems, drug–viral interactions, or nonallergic side effects. Even for penicillin allergies verified by skin testing, $\geq 10\%$ lose reactivity every year without evidence of resensitization (8, 9).

Patients admitted to a medical ICU (MICU) often have chronic illnesses or altered immunity, increasing their need for immediate antibiotic use. We sought to determine whether MICU patients with low-risk penicillin allergy history could be challenged directly with amoxicillin to have their allergy label safely removed during an acute inpatient stay. Some results of this study have been reported in abstract form (10).

Methods

Penicillin allergy risk stratification tool. We developed a history-based risk-stratification tool to identify patients with a penicillin allergy label at low risk of having a true allergy (2). During routine clinical encounters in our outpatient drug allergy clinic, patients provide a history of their index reaction to penicillin and are appropriately skin tested using a standardized panel of reagents. After a negative skin test, patients proceed to an observed oral challenge with amoxicillin 250 mg. When oral challenge is asymptomatic after a 1.5-hour observation period and a 24-hour follow-up nursing phone call to assess delayed skin test reactions and symptoms, a patient's penicillin allergy label is removed. Data from these visits were used to derive and validate our risk-stratification algorithm. This project was approved by the Vanderbilt institutional review board (#181180 and #181734).

Data from 318 consecutive patients seen from 2014 to 2018 were collected using standardized chart review and data collection and were categorized via historical assessment by a physician into one of three groups: 1) highest risk-delayed reactions (blistering, mucosal involvement, severe rash, and/or immune-mediated organ injury); 2) moderate to high risk, where patients reported symptoms consistent with standard anaphylaxis criteria; or 3) low risk, where patients reported symptoms that were inconsistent with either of the higher-risk criteria (Figure 1). The outcomes of allergy testing in the clinic were compared with history-based risk criteria to estimate the negative predictive value for a positive penicillin allergy skin test and oral challenge among low-risk patients.

Penicillin allergy delabeling study. All patients admitted to the MICU between March 31, 2019, and October 31, 2019, who were both hemodynamically stable and could provide a history of their index reaction were screened. Those whose reported index reaction was consistent with a low-risk penicillin allergy were offered direct challenge with 250 mg oral amoxicillin followed by 1-hour observation. Consent for the clinical procedure was obtained

Higher Risk History		Low Risk History
Highest Risk: Severe delayed symptoms at any point in the past:	Moderate to High Risk: Anaphylaxis, especially in the last 5 years:	
<ul style="list-style-type: none"> • Mouth or eye ulcerations • Skin or mucosal sloughing or blistering • Serum sickness • Immune-mediated kidney injury • Immune-mediated liver injury • Stevens-Johnson Syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Acute generalized exanthematous pustulosis (AGEP) • Febrile skin rash without a better explanation 	<p>After administration of the first dose of a new treatment course with a penicillin, patient developed any of the following severe symptoms within one hour, up to 6 hours.</p> <ul style="list-style-type: none"> • Disseminated Hives/Urticaria/Flushing/Pruritis • Angioedema/Swelling of Face/Throat • Shortness of Breath, Wheezing, Coughing • Shock • Weak Pulse • Loss of Consciousness/Confusion • Severe Gastrointestinal Symptoms (Diarrhea, Vomiting) 	<ul style="list-style-type: none"> • Urticaria only, >5 years have passed • Self-limited cutaneous rash at any point • Gastrointestinal symptoms only • Remote childhood reaction with limited details • Family history of penicillin allergy only • Avoidant from fear of allergy only • Known tolerance of a penicillin since the original reaction occurred • Other symptoms, non-allergy

Figure 1. Risk stratification of a historical penicillin reaction. In patients who were already admitted to the ICU, historical reactions consistent with a low-risk penicillin allergy were offered direct challenge with 250 mg oral amoxicillin followed by a 1-hour observation period.

using a structured conversation guide. Patients lacking evidence of reaction after observation had their allergy label removed from their record at the point of care and were provided with a letter and wallet card detailing the delabeling procedure's implications.

Results

Validation of a penicillin allergy risk stratification tool. Of 318 drug allergy clinic patients, 195 (61%) were identified as low risk. The negative predictive value of low-risk categorization was 99% (95% confidence interval, 96–100%). Two low-risk patients had positive skin tests to penicillin G and ampicillin, respectively, and were not challenged. Of low-risk patients who agreed to undergo single-dose oral challenges, 184 of 184 (100%) were asymptomatic, demonstrating they no longer needed to be considered allergic to penicillin.

Penicillin allergy delabeling in the MICU. Over 7 months, there were 216 of 1,859 (11.6%) MICU patients admitted with a penicillin allergy label. Of these, 114 of 216 (53%) were eligible for evaluation during their stay, and all were evaluated. A total of 68 of 114 (60%) eligible patients had a low-risk history. A total of 54 of 68 (79%) low-risk patients agreed to observed amoxicillin oral challenge, of whom 54 of 54 (100%; 95% confidence interval, 93.4–100) had no immediate or delayed symptoms after direct challenge with amoxicillin 250 mg. These patients were counseled on the removal of their penicillin allergy and had their allergy removed from their chart (Table 1).

Several patients had an indication for and were subsequently treated with multiple doses of a penicillin (17 of 54; 31%) or

cephalosporin (24 of 54; 44%) during the same hospital stay or later health care encounters in our system, without report of allergic reaction. A total of 23 penicillin and 37 cephalosporin treatment courses in 30 delabeled patients were given after the removal of their penicillin allergy label. During the 7-month study period, only one patient, who experienced nausea and diarrhea associated with amoxicillin-clavulanic acid, was relabeled as penicillin allergic.

Discussion

Incorrect diagnoses of penicillin allergy are a problem that adversely affects patient care, public health, antimicrobial stewardship, and health care costs (1, 2). Although recent recommendations promote direct challenge for low-risk penicillin-allergic children, there has been limited evidence supporting direct oral challenge in adults, in whom the reported severity of the index reaction can vary (2). Tucker and colleagues demonstrated that in healthy Marine recruits, most patients reported a low-risk penicillin allergy, and therefore direct challenge only elicited symptoms in 5 of 328 (1.5%) patients (11). Our results demonstrate the safety of direct oral challenge among critically ill patients in a MICU with a low-risk penicillin allergy. When applying our results to the critical care setting, it is important to note that we only offered challenges to patients who were stabilized and able to participate. It is also important to note that our criteria for low risk includes some categories (urticaria >5 yr ago, cutaneous rash) that are deemed as moderate risk in recently proposed approaches (12).

Our study was conducted in a MICU, a highly controlled environment with staff experienced in managing

Table 1. Characteristics and Outcomes of Risk-stratified Amoxicillin Oral Challenges Leading to Allergy Label Removal in ICU Patients (N = 114)

Risk Group	Low Risk: Challenge Performed (n = 54)	Low Risk: Declined Challenge (n = 14)	Higher Risk (Both Groups) (n = 46)
Median age (IQR), yr	57 (46–66)	48 (41–59)	50 (41–65)
Sex, F	24 (44)	5 (36)	29 (63)
Race			
White	51 (94)	12 (86)	41 (89)
Black	3 (6)	2 (14)	4 (9)
Asian	0 (0)	0 (0)	1 (2)
Non-Hispanic ethnicity	54 (100)	14 (100)	44 (96)
Immediate challenge outcome			
Tolerated amoxicillin oral challenge, leading to allergy removal from the chart	54 (100)	N/A	N/A
Primary outcomes at 7 mo			
Subsequent use of a penicillin treatment course	17 (31)	2 (14)	2 (4); 1 direct treatment, 1 after a desensitization
More than one subsequent penicillin treatment	4 (7)	1 (7)	0 (0)
No. of penicillin labels reentered into the chart during subsequent care	1 (2)	N/A	N/A
Secondary outcomes at 7 mo			
Subsequent use of a cephalosporin treatment course	24 (44)	9 (64)	21 (46)
More than one subsequent cephalosporin treatment	9 (17)	2 (14)	8 (17)

Definition of abbreviations: IQR = interquartile range; N/A = not applicable. Data are presented as n (%) unless otherwise noted.

allergic reactions. Oral challenge was safely tolerated in our low-risk group (total $n = 238$), both retrospectively and prospectively. Extrapolation of our results in adults beyond the ICU environment remains unknown, but we anticipate that our approach could be safely implemented in a wide variety of settings.

Skin testing, as an additional step in disproving a penicillin allergy, may be unnecessary in low-risk patients, adding expense and time or being refused by the patient. Penicillin skin testing is also subject to false negatives in the critical care setting (13). Other studies have used full- or split-dose challenges, often not to the penicillin drug for which the patient was labeled allergic but to structurally unrelated drugs to which they were unlikely to react (e.g., ceftriaxone) (2). Direct oral challenge is safer than full- or split-dose intravenous challenge to the labeled drug in critically ill patients where patient tolerance is unknown. Direct oral challenge is also a procedure that delabels the patient's reported allergy, therefore creating a much larger number of therapeutic choices (2). The formalized ritual of an amoxicillin challenge providing a transition from "allergic" to "nonallergic" may be an important element of our intervention's success, requiring further study.

Moreover, our results suggest that desensitization, the current approach to initiate a penicillin treatment in someone who reports anaphylactic-like symptoms, is unnecessary for low-risk patients. Systematic application of risk-stratified penicillin allergy management could reduce the prevalence of adverse outcomes associated with penicillin allergy labels. ■

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BMP9/10 in Pulmonary Vascular Complications of Liver Disease

To the Editor:

Advanced liver disease can cause two distinct pulmonary vascular complications. Portopulmonary hypertension (POPH) is characterized by increased pulmonary vascular resistance and pulmonary artery pressure in the absence of other etiologies of pulmonary hypertension (PH). Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilatations and arteriovenous malformations (AVMs) and an increased alveolar–arterial oxygen gradient (A–a gradient). These diseases occur in approximately 6% and 20% to 30% of patients evaluated for liver transplantation, respectively (1, 2).

The biologic determinants of these vascular complications are poorly understood. BMP9 (bone morphogenetic protein 9) and BMP10 are produced in the liver (and for BMP10, right atrium) and circulate either as homodimers or heterodimers (3, 4). BMP9 and BMP10 are ligands for BMP receptor type II, activin A receptor like type 1, and endoglin receptor complex (5).

Receptor mutations cause hereditary hemorrhagic telangiectasia, a disease characterized by angiogenesis and pulmonary macrovascular and microvascular AVMs. The occurrence of pulmonary AVMs and cyanosis after the Glenn operation, where hepatic venous blood does not bathe the lungs normally, has been blamed on “hepatic factor,” hypothesized to be BMP9 (6). In addition, studies show that abnormal BMP9 signaling causes PH (7, 8). Circulating BMP9 levels are decreased in patients with POPH, and administration of BMP9 attenuates PH (9). We hypothesized that circulating BMP9 and BMP10 levels would be lower in patients with POPH and HPS when compared with control patients with advanced liver disease.

Methods

The PVCLD2 (Pulmonary Vascular Complications of Liver Disease 2) study was a multicenter, prospective cohort study of adult patients with portal hypertension undergoing evaluation for liver transplantation or with POPH (10, 11). Patients with active infection, recent gastrointestinal bleeding, or a history of prior liver or lung transplantation were excluded. The study sample was drawn from 454 patients at the University of Pennsylvania, Mayo Clinic, University of Texas–Houston, University of Texas–Southwestern, University of Colorado, Vanderbilt University, Tufts Medical Center, and Cleveland Clinic between 2013 and 2017. The institutional review boards approved this study, and patients gave informed consent.

Research assessments included a history and physical examination, anthropometrics, pulse oximetry, phlebotomy and clinical laboratory testing, 6-minute-walk testing, arterial blood gas sampling, spirometry, and contrast-enhanced transthoracic echocardiogram (TTE). Cases with POPH had mean pulmonary artery pressure > 25 mm Hg, pulmonary artery wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance > 240 dyn · s/cm⁵. Control subjects with liver disease had right ventricular systolic pressure < 40 mm Hg (if estimable) and absence of right ventricular dysfunction on TTE. We excluded patients with significant obstructive or restrictive ventilatory defects, HIV infection, or more than moderate aortic or mitral valvular disease or significant left ventricular systolic dysfunction.

HPS was defined by A–a gradient ≥ 15 mm Hg (or ≥ 20 mm Hg if age > 64 yr) and late passage of contrast on TTE. Control patients did not meet both the A–a gradient and late contrast criteria. We excluded patients with a significant obstructive or restrictive ventilatory defect or intracardiac shunting.

Plasma BMP9 and BMP10 concentrations were measured in duplicate with sandwich ELISA kits with plasma diluted in phosphate-buffered saline/1% bovine serum albumin/0.2% goat serum and 0.5% Triton X-100 (BMP9, diluted 1:4) or 0.1% Triton X-100 (BMP10, both neat and diluted 1:2) (DY3209 and DY2926, respectively; R&D Systems). Assays were performed with blinding to clinical information.

Rank sum tests, *t* tests, chi-square tests, and Fisher’s exact tests were used. Multivariate linear regression models regressed natural log-transformed BMP levels on case and control status after adjustment for age, sex, and Model for End-Stage Liver Disease–Na (MELD–Na). A *P* value < 0.05 was considered significant (STATA/MP 16.0).

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