Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Risk-stratified management to remove low-risk penicillin allergy labels in the patients with COVID-19 in the intensive care unit

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Clinical Implications

Patients with coronavirus disease 2019 commonly develop superimposed bacterial infections where beta-lactams are preferred treatment. Direct oral amoxicillin challenge appears to be safe and effective in delabeling low-risk penicillin allergy labels in critically ill patients acutely hospitalized with coronavirus disease 2019.

Through February 2022, more than 426 million cases of coronavirus disease 2019 (COVID-19) have been reported globally, resulting in more than 5.8 million deaths. Severe cases of COVID-19 may result in hypoxemic respiratory failure, acute respiratory distress syndrome, and septic shock.[1]

Because of the severity of illness and prolonged lengths of stay, bacterial superinfections, including bacteremia and pneumonia, are common in critically ill patients with COVID-19. First-line antimicrobial therapy for these infections is frequently impacted by an allergy label to penicillins and other beta-lactams.[2-4] Medical intensive care unit (MICU) patients have risk factors for multiple drug allergy labels, which further constrict antibiotic choices.[5,6]

Of the up to 15% of the US population that carries a penicillin allergy label (PAL), less than 5% have been verified by allergy testing.[7] We previously demonstrated that direct oral challenge with amoxicillin is safe and effective for removing the PAL in MICU patients with low-risk penicillin allergies (Figure 1).[8,9] Whether the practice is similarly safe in patients with COVID-19 is unknown. We prospectively assessed the safety and efficacy of direct oral amoxicillin challenge in MICU patients with COVID-19 who have low-risk PALs, as well as the proportion who used penicillins following delabeling.

Between April 2020 and February 2022, all patients in our MICU with a PAL and stabilized COVID-19 were identified through an ongoing pharmacist-driven program to tackle unnecessary penicillin allergies.[8,9] Patients who were hemodynamically stable, not receiving invasive or noninvasive mechanical ventilation, not pregnant, not a prisoner, and who could provide a history of their index reaction underwent a risk assessment, as shown in Figure 1. Patients with low-risk PAL were offered a direct challenge with 250 mg oral amoxicillin followed by a 1-hour observation. Chart review was performed on all eligible low-risk patients to determine antibiotic use during COVID-19 hospitalization and use of penicillin therapy after the direct amoxicillin challenge.

During the time frame of interest, 2670 COVID-positive patients were admitted to our MICU. Penicillin allergies were identified in 285 (10.6%) of these patients. Twenty-four patients admitted to the MICU had a low-risk PAL and recently stabilized COVID-19 (Table I). Median age was 62 years, 37.5% were female, and 70.8% were White patients. Hypertension (54.2%) and diabetes mellitus (41.7%) were the most common comorbidities. The most common admission diagnosis to the MICU was hypoxic respiratory failure (75%). Complications of COVID-19 included noninvasive supplemental oxygen (54.2%), mechanical ventilation (29.2%), sepsis/septic shock (62.5%), pulmonary embolism (12.5%), and cardiac arrest (12.5%). Despite temporary stabilization allowing for inclusion in our study, there were 5 deaths from COVID complications.

All low-risk PAL patients who met the inclusion criteria (off ventilatory support, off vasopressors, able to give necessary history[9]) were offered an oral amoxicillin challenge through written informed consent. Nineteen of 24 patients (79.2%) accepted the challenge. All 19 of these patients successfully passed the challenge and were subsequently delabeled of their PAL.

Before being offered penicillin allergy delabeling, 16 of 24 (66.7%) received at least 1 nonpenicillin antibiotic for treatment of a documented or presumed bacterial complication during their acute hospitalization for COVID. After delabeling, 6 of the 19 delabeled patients (31.5%) had an indication for antibiotics and were subsequently treated with a penicillin in the hospital; 5 patients received piperacillin-tazobactam, and 1 patient received amoxicillin-clavulanate. All 5 patients who opted not to have their allergy label challenged did have infections that complicated their COVID hospitalization. We noted that empiric coverage typically favored cefepime plus vancomycin in the absence of being able to use piperacillin-tazobactam. At a median of 10 days following hospital discharge, 2 of 19 (10.5%) patients had received additional penicillin antibiotics for a median of 10 days, without report of an allergic reaction. No adverse events secondary to penicillin administration were reported in any of the penicillin-delabeled patients. Encouragingly, no patients were found to be relabeled (incompletely delabeled) following the oral amoxicillin challenge or subsequent treatments.

Our results suggest that the safety of a direct oral challenge for low-risk PAL among critically ill patients with COVID-19 may be similar to that for other patients in our routine delabeling program.[9] The opportunity to challenge a low-risk penicillin allergy in a COVID-positive patient in the intensive care unit may also be rare overall. However, our observations may be of a higher value in hospitalized COVID-positive patients who are not critically ill, who could be approached similarly, because we did observe beneficial alterations in subsequent antimicrobial utilization. Unverified PALs can adversely impact patient care, public health, antimicrobial stewardship, and health care costs.[7] Bacterial superinfections occur commonly in critically ill patients with COVID-19, often resulting in the need for antibiotics including beta-lactams. For example, the incidence of ventilator-associated pneumonia has been shown to be higher in those with

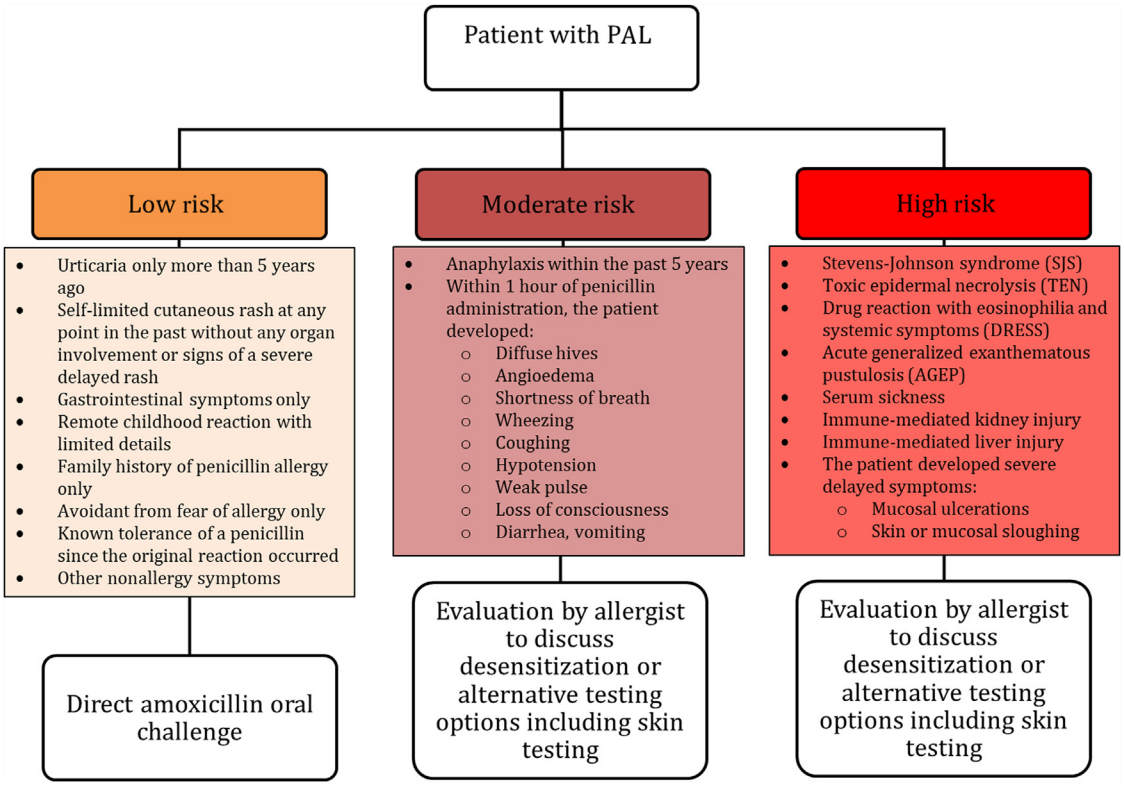

FIGURE 1. Risk stratification of a historical penicillin reaction. In patients who were already admitted to the ICU, historical reactions consistent with a low-risk penicillin allergy were offered direct challenge with 250 mg PO amoxicillin followed by a 1-hour observation period. *ICU*, Intensive care unit; *PO*, per os (by mouth).

COVID-19 as compared with those without COVID-19 (25.5, 95% CI [23.7-27.45] vs 15.4, 95% CI [13.7-17.3] per 1000 ventilator days),[4] and the incidence of bloodstream infections has been shown to be as high as 10.3 per 1000 patients days at risk.[2]

Strengths of this study include the first known report of successfully delabeling low-risk PAL with a direct oral challenge in intensive care unit patients with COVID-19. The results suggest that the more common approaches of avoidance of penicillins (when rapid treatment is needed) and desensitization (for starting penicillin in patients with more concerning anaphylactic-like symptoms) are unnecessary for patients with low-risk PALs and COVID-19.

Limitations of this study include that data collection for subsequent use of beta-lactams and documentation of relabeling was only obtained from the local electronic medical record between April 2020 and February 2022. It is unknown whether further beta-lactams were administered outside of this time frame or outside of our institution. Our protocol did not include penicillin skin testing given the focus on low-risk patients. Skin testing is an additional step that can be used to help disprove penicillin allergies. However, we show that in low-risk patients, the added expense, time, and risk of false-positives is an unnecessary hurdle to scaling up penicillin allergy delabeling. Although 12 of the 19 patients who had an oral amoxicillin change were receiving dexamethasone, steroids would not prevent anaphylaxis. Steroids might prevent nonspecific delayed rashes after challenge. Finally, the small number of patients, 19, tested in this case series does not eliminate the possibility of a serious reaction. However, it does suggest that direct oral penicillin challenge of a low-risk PAL appears to be safe to attempt in COVID-19 patients who are both recently stabilized patients and also less critically ill.

In conclusion, direct oral penicillin challenges appear to be a safe and effective strategy to remove low-risk and unverified PAL from intensive care unit patients with COVID-19. Given the high rate of bacterial superinfections including bacteremia and pneumonia in COVID-19 patients, delabeling low-risk penicillin allergies to allow first-line beta-lactam treatment should be highlighted as a feasible and potentially important patient care strategy.

This project was approved by the Vanderbilt Institutional Review Board (nos. 181180 and 181734).

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TABLE I. Characteristics of low-risk PALs in COVID-positive ICU patients

Patient characteristics, n (%) or median [IQR]	Total (n = 24)	Yes to challenge (n = 19)	No to challenge (n = 5)
Age (y)	61.5 [53.5- 67.75]	60 [49.5-68]	66 [62-69]
Female sex	9 (37.5)	6 (31.6)	3 (60)
Self-reported race			
Asian	1 (4.2)	1 (5.3)	0 (0)
Black	4 (16.7)	1 (5.3)	3 (60)
Other	2 (8.3)	2 (10.5)	0 (0)
White	17 (70.8)	15 (78.9)	2 (40)
Comorbidities			
Hypertension	14 (58.3)	10 (52.6)	4 (80)
Diabetes mellitus	10 (41.7)	7 (36.8)	3 (60)
Chronic lung disease	4 (16.7)	4 (21.1)	0 (0)
Heart disease/heart failure	6 (25)	5 (26.3)	1 (20)
Renal failure	5 (20.8)	3 (15.8)	2 (40)
Malignancy	2 (8.3)	1 (5.3)	1 (20)
How met low-risk PAL criteria			
Remote childhood reaction	9 (37.5)	8 (42.1)	1 (20)
Nausea, vomiting diarrhea only	2 (8.3)	2 (10.5)	0 (0)
Hives only, >5 y ago	4 (16.7)	3 (15.8)	1 (20)
Self-limited rash	4 (16.7)	3 (15.8)	1 (20)
Remote reaction with unknown details	4 (16.7)	3 (15.8)	1 (20)
Other symptoms not consistent with allergy	1 (4.2)	0 (0)	1 (20)
Admission diagnosis (n = 24)			
Hypoxic respiratory failure	18 (75.0)	15 (78.9)	3 (60)
Myocardial infarction	1 (4.2)	1 (5.3)	0 (0)
Thrombus	1 (4.2)	0 (0)	1 (20)
Other	4 (16.7)	3 (15.8)	1 (20)
COVID complications (n = 24)			
Noninvasive supplemental oxygenation	13 (54.2)	10 (52.6)	3 (60)
Mechanical ventilation	7 (29.2)	6 (31.6)	1 (20)
Sepsis/septic shock	16 (66.7)	11 (57.9)	5 (100)
Pulmonary embolus	3 (12.5)	3 (15.8)	0 (0)
Cardiac arrest	3 (12.5)	3 (15.8)	0 (0)
Death	5 (20.8)	4 (21.1)	1 (20)
Oral challenge outcome (n = 24)	**n (%)**		
Accepted challenge and delabeled	19 (79.2)	19 (100)	0 (0)
Declined challenge	5 (20.8)	0 (0)	5 (100)
Antibiotic use	**n (%)**		
No. of patients who used penicillin antibiotic after oral challenge offer during hospitalization for COVID	6 (25.0)	6 (31.6)	0 (0)
Piperacillin-tazobactam	5 (20.8)	5 (26.3)	0 (0)
Amoxicillin-clavulanate	1 (4.2)	1 (5.3)	0 (0)
No. of patients who used nonpenicillin antibiotic during hospitalization for COVID	16 (66.7)	11 (57.9)	5 (100)
Cefepime	12 (50)	7 (36.8)	5 (100)
Ceftriaxone	8 (33.3)	7 (36.8)	1 (20)
Cefazolin	1 (4.2)	0 (0)	1 (20)
Vancomycin	13 (54.2)	8 (42.1)	5 (100)
Azithromycin	5 (20.8)	4 (21.1)	1 (20)
Levofloxacin	2 (8.3)	2 (10.5)	0 (0)
Metronidazole	2 (8.3)	0 (0)	2 (40)
Doxycycline	1 (4.2)	0 (0)	1 (20)
No. of patients who used penicillin antibiotic after hospital discharge	3 (12.5)	2 (10.5)	1 (20)
Piperacillin-tazobactam	1 (4.2)	1 (5.3)	0 (0)
Amoxicillin-clavulanate	3 (12.5)	2 (10.5)	1 (20)

ICU, Intensive care unit.

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C.A.S. has received funding for this work from the Agency for Healthcare Research and Quality (grant no. 1K12HS026395-01) and the National Institutes of Health (NIH)/National Institute of General Medical Sciences (grant no. 5T32 GM007569-41), and has received project-related support specific to this research from both the VICTR Learning Healthcare System Platform under Clinical and Translational Science Awards (CTSA) award number UL1 TR002243 from the National Center for Advancing Translational Sciences (NCATS)/NIH and VICTR CTSA # VR52841. The contents presented here are solely the responsibility of the authors and do not necessarily represent official views of the NCATS or the NIH. E.J.Phillips reports grants from the NIH (grant nos. R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and additional funding from the National Health and Medical Research Council of Australia. C.J.L., T.W.R., and M.L.D. are supported in part by the NCATS/NIH (CTSA award no. UL1 TR002243).

Conflicts of interest: E. J. Phillips is codirector of IIID Pty Ltd, which holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity, and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 22, 2022; revised July 20, 2022; accepted for publication August 24, 2022.

Available online September 11, 2022.

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2213-2198

https://doi.org/10.1016/j.jaip.2022.08.043

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