

Clinical Communications

Teicoplanin hypersensitivity in perioperative anaphylaxis

O. Stephanie Kayode, BSc, MBChB, MRCP^a,
 Krzysztof Rutkowski, MD, MRCP^a,
 Rubaiyat Haque, MBBS, FRCP^a,
 Stephen J. Till, MBBS, MA, PhD, FRCP^{a,b}, and
 Leonard Q.C. Siew, MBChB, MSc, PhD, MRCP^{a,b}

Clinical Implications

- In approximately one-third of teicoplanin skin test—negative patients, teicoplanin hypersensitivity was confirmed on drug provocation test. Drug provocation test should be considered after negative skin test result. Reaction onset at 10 minutes or less and acute mast cell tryptase are useful predictors of teicoplanin hypersensitivity.

TO THE EDITOR:

Teicoplanin is a first-generation glycopeptide antibiotic with European Medicines Agency approval for use in Gram-positive bacterial infections. Indications include staphylococcus infective endocarditis, septicemia, osteomyelitis, multiresistant staphylococci, and *Clostridioides difficile* infection. Teicoplanin is often used as second-line therapeutic treatment in patients labeled penicillin allergic and in the United Kingdom first-line prophylactic treatment within the perioperative setting.¹

Unlike vancomycin, teicoplanin does not appear to cause direct histamine release.² Since 2015 there has also been a 3- to 4-fold increase in yearly suspected cases of teicoplanin-allergic reactions reported to the Medicines and Healthcare Products Regulation Agency, United Kingdom.³ Literature regarding teicoplanin hypersensitivity remains limited to a small number of case series.^{1,4} Although cross-reactivity has been observed between the first-generation glycopeptides teicoplanin and vancomycin,⁵ vancomycin-tolerant teicoplanin-allergic cases have also been reported.⁶

We sought to characterize the largest cohort of patients who have experienced perioperative teicoplanin anaphylaxis and hypersensitivity reactions. Ethical approval for this retrospective audit was not required in the United Kingdom. Data were extracted from review of electronic patient records including copies of anesthetic documentation. The severity of both the index and drug provocation test (DPT) reactions was graded using the Brown anaphylaxis grading scale.⁷ In assessing change in serum mast cell tryptase (MCT), an international consensus equation (ICE) of acute/peak MCT greater than $[1.2 \times \text{baseline MCT}] + 2 \mu\text{g/L}$ was used.⁸ Acute MCT results, where available, were compared against the threshold derived by the ICE.

Teicoplanin (Targocid, Sanofi, Surrey, UK) concentrations of 133 and 13 mg/mL were used for skin prick test (SPT) and intradermal test (IDT), respectively. Teicoplanin DPT was carried out as hospital day-cases on patients with negative skin test results (SPT and IDT) using a standardized graded protocol.

Increasing doses of teicoplanin (4, 46, 100, and 250 mg) were administered intravenously at 20-minute intervals with a final 1-hour observation period. A cumulative therapeutic dose of 400 mg was administered. Patients demonstrating positive SPT, IDT, or DPT results were suspected (positive SPT/IDT result) or confirmed (positive DPT result) to have a diagnosis of acute-onset teicoplanin hypersensitivity.

Statistical analyses were performed using IBM SPSS Statistics v25 (International Business Machines Corp, Armonk, NY).

There were 418 unique individuals evaluated for perioperative anaphylaxis and hypersensitivity reactions at the Department of Adult Allergy at Guy's and St Thomas' NHS Foundation Trust between 2013 and 2018. Of these, 49 (8%) were exposed to teicoplanin. Forty-one (6%) of the teicoplanin-exposed patients completed diagnostic workup for acute-onset teicoplanin hypersensitivity and are described in this report (Table 1). Of the 8 who were excluded, drug hypersensitivity was suspected to povidone-iodine on skin testing in 1 patient. The remaining 7 patients were excluded for not completing diagnostic workup. Acute-onset teicoplanin hypersensitivity was considered suspected (after positive SPT/IDT result) or confirmed (after positive DPT result) in 30 of 41 (73%) patients investigated. Of these 30 individuals, 3 were also suspected to be hypersensitive to gentamicin, chlorhexidine, and gelofusin on SPT or IDT. Eleven patients demonstrated negative teicoplanin SPT and IDT results and were considered as teicoplanin-tolerant after negative teicoplanin DPT result. In 3 of these 11 patients, acute hypersensitivity was suspected to chlorhexidine on IDT and gentamicin and diclofenac hypersensitivity presumed after negative challenges to all other drugs administered within the hour of reaction onset. The time interval between the index reaction and initial allergy review was 2 months or less in 29% ($n = 12$), 2 to 6 months in 56% ($n = 23$), and more than 6 months in 15% ($n = 6$) of cases. One-third (35% [6 of 17]) of patients with negative SPT and IDT results were positive for teicoplanin hypersensitivity on DPT (Table 1). The remaining 11 patients with negative SPT and IDT results were also negative on DPT.

Suspected/confirmed teicoplanin hypersensitivity was associated with a higher percentage of patients manifesting reactions within 10 minutes of teicoplanin administration ($P = .001$, Kruskal-Wallis), with 97% (29 of 30) of these patients receiving teicoplanin within this time frame (Figure 1).

A greater mean percentage change in MCT was observed in the suspected/confirmed teicoplanin-hypersensitive group compared with the teicoplanin-tolerant group (333% vs 70%; $P = .022$, Student t test) (Table 1). An acute MCT level either greater than $14 \mu\text{g/L}$ or above the threshold derived by the ICE was more frequently observed in patients evaluated as having suspected/confirmed teicoplanin hypersensitivity (87% vs 29%; $P = .014$) (Figure 1).

Of patients suspected/confirmed to have acute-onset teicoplanin hypersensitivity, 53% (16 of 30) had a documented penicillin allergy label at the time of teicoplanin administration (Table 1).

Patients evaluated as suspected/confirmed teicoplanin hypersensitivity were also less likely to receive the vasopressor metaraminol (20% vs 64%; $P = .019$) during the treatment of their index reaction (Figure 1). This may suggest that choice of drug

TABLE I. Cohort demographics, history, and investigation outcomes

Characteristic	Total (n = 41)	Confirmed/suspected hypersensitive (n = 30)	Tolerant (n = 11)
Age (y), mean $\pm$ SD	57 $\pm$ 16	55 $\pm$ 17	63 $\pm$ 8
Sex			
Male	14 (34)	11 (37)	3 (27)
Female	27 (66)	19 (63)	8 (73)
Atopic	9 (22)	7 (23)	2 (18)
History of chronic urticaria	3 (7)	2 (7)	1 (9)
History of previous anaphylaxis	2 (5)	1 (3)	1 (9)
Documented at time of induction			
No. of patients with documented penicillin allergy	18 (44)	16 (53)	2 (18)
No. of other antibiotic allergies listed, mean (range)	0.2 (0-1)	0.2 (0-1)	0.2 (0-1)
Documented prior teicoplanin or vancomycin exposure	8	7	1
Concomitant drugs administered within $\leq$ 1 h of reaction	39 (95)	28 (93)	11 (100)
Indication for teicoplanin			
Orthopedic surgery under spinal or GA	32 (78)	22 (73)	10 (91)
Breast surgery under GA	6 (15)	5 (17)	1 (9)
Cardiac surgery under GA	1 (2)	1 (3.3)	0 (0)
GI surgery under GA	1 (2)	1 (3.3)	0 (0)
Prostate surgery	1 (2)	1 (3.3)	0 (0)
Time from exposure to reaction			
10 min or under	34 (83)	29 (97)	5 (45)
10-30 min	4 (10)	1 (3)	3 (27)
30-60 min	3 (7)	0 (0)	3 (27)
Index IV teicoplanin administered			
Index dose known	32 (78)	23 (77)	9 (8)
Mean index dose given	447 mg	465 mg	400 mg
Index reaction			
Respiratory	20 (49)	15 (50)	5 (45)
Cutaneous	34 (83)	25 (83)	9 (81)
Cardiovascular	34 (83)	26 (87)	8 (73)
GI	0 (0)	0 (0)	0 (0)
Cardiorespiratory arrest	2 (5)	2 (7)	0 (0)
Index reaction severity			
Grade 1	5 (12)	2 (7)	3 (27)
Grade 2	3 (7)	2 (7)	1 (9)
Grade 3	33 (80)	26 (87)	7 (64)
MCT			
<1 h and baseline tryptase available		15 (50)	7 (64)
Mean tryptase rise		333.3%*	70.2%*
Treatment received during the index reaction			
Antihistamines		19 (63)	5 (45)
Corticosteroids		21 (70)	6 (55)
Adrenaline		22 (73)	4 (36)
Metaraminol		6 (20) [†]	7 (64) [†]
Investigation outcome			
SPT positive		5 (17)	0 (0)
SPT wheal diameter, mean (range, IQR)		4 (3-5, 1)	
IDT positive		19 (63)	0 (0)
IDT wheal diameter expansion, mean (range, IQR)		4 (2-9, 2)	
DPT positive		6 (20)	0 (0)
DPT threshold cumulative dose mean (range), mg		50 (4-400)	

GA, General anesthetic; GI, gastrointestinal; IQR, interquartile range; IV, intravenous.

Values are n (%) unless otherwise indicated.

**P* = .022 (*t* test; 95% CI, 43-484).[†]*P* = .019 (Fisher exact test).

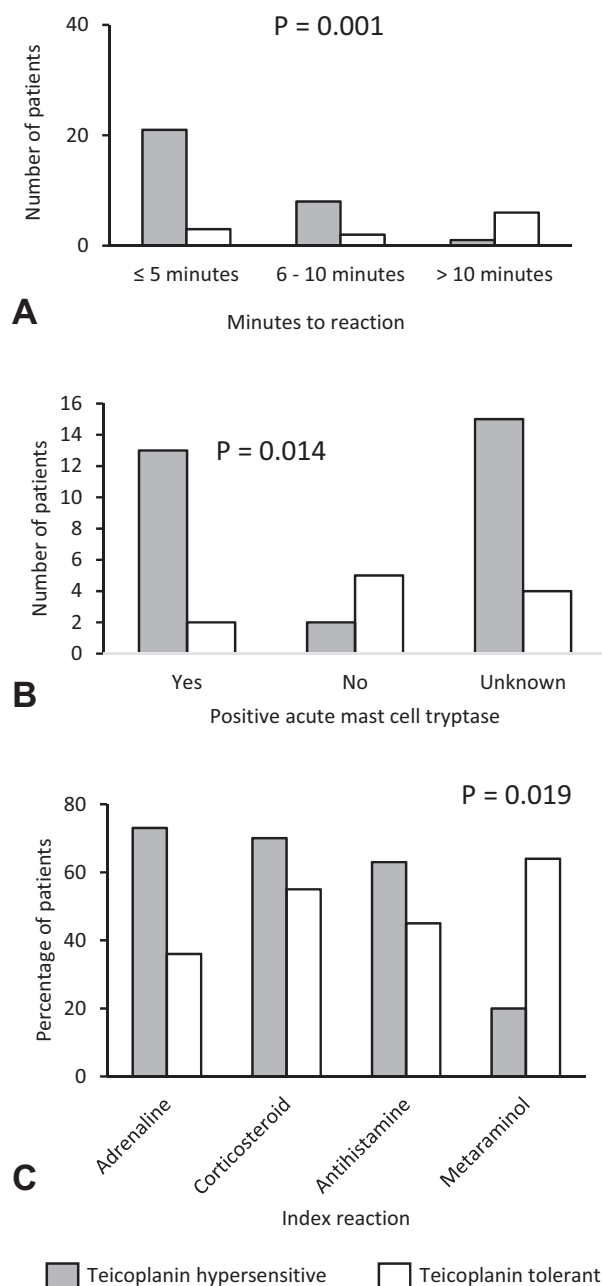


FIGURE 1. Comparison of suspected/confirmed teicoplanin-hypersensitive and teicoplanin-tolerant patients. **(A)** Timings from teicoplanin administration to reaction onset. Reaction onset of 10 minutes or less was significantly associated with teicoplanin hypersensitivity (Kruskal-Wallis). **(B)** Number of patients with positive and negative acute MCT results. Patients with suspected/confirmed teicoplanin hypersensitivity were more likely to have a positive acute MCT (as defined by either $>14 \mu\text{g/L}$ or above the threshold derived by the ICE equation). **(C)** Treatment administered during the index reaction. Metaraminol use was inversely associated with suspected/confirmed teicoplanin hypersensitivity (Fisher exact test).

treatment was influenced by the clinical picture; that is, metaraminol was preferred when hypotension alone was present.

In this patient cohort, 35% of teicoplanin skin test–negative patients were positive for acute-onset hypersensitivity on teicoplanin DPT. The performance of teicoplanin skin testing appears poorer than that of other antibiotics including beta-lactam skin testing, which has been demonstrated to have a negative predictive value of 98.9% in our department.⁹ We accept, among the 3 patients with positive skin test results to more than 1 suspected culprit drug, false-positive skin test results to either teicoplanin or the additional skin test–positive drug cannot be ruled out.

There is notable national variation in teicoplanin concentrations used from 20 to 125 mg/mL for SPT and 2 to 62.5 mg/mL for IDT.¹ Where guidelines do not offer recommended standardized skin test concentrations, departmental practice is to perform SPT and IDT with undiluted and 1:10 dilutions of the intravenous preparation, respectively. Further dilutions would be performed if there were concerns regarding irritant responses. We note that our SPT concentration is higher than that previously reported in the literature; however, our IDT concentrations are on the lower end of the range found in the literature. In view of this, we proceeded to IDT when SPT results were borderline positive, and none of the borderline positive SPT result patients had a negative IDT result. Furthermore, 11 teicoplanin-tolerant patients and 10 patients with a clinical history suggestive of delayed teicoplanin hypersensitivity reactions had unequivocal negative SPT and IDT responses on immediate (15–20 minute) readings. Work has not been conducted exploring the nonirritant concentration among controls.

In conclusion, both time to reaction onset (≤ 10 minutes) and acute MCT levels appear to be useful predictors of acute-onset teicoplanin hypersensitivity. Skin testing alone appears insufficient in ruling out teicoplanin hypersensitivity, and it is recommended to perform DPT in all skin test–negative patients. We did not experience reactions more severe than grade 1 among our DPT-positive patients.

^aDepartment of Allergy, Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

^bPeter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, United Kingdom

No funding was received for this work.

Conflicts of interest: All authors declare that they have no relevant conflicts of interest.

Received for publication September 24, 2019; revised February 1, 2020; accepted for publication February 7, 2020.

Available online ■■

Corresponding author: Leonard Q.C. Siew, MBChB, MSc, PhD, MRCP, Department of Adult Allergy, Guy's and St Thomas' NHS Foundation Trust, 2nd Floor Counting House, London SE1 9RT, UK. E-mail: Leonard.Siew@gstt.nhs.uk. 2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.02.015>

REFERENCES

1. Savic LC, Garcez T, Hopkins PM, Harper NJN, Savic S. Teicoplanin allergy—an emerging problem in the anaesthetic allergy clinic. *Br J Anaesth* 2015;115:595-600.
2. Svetitsky S, Leibovici L, Paul M. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. *Antimicrob Agents Chemother* 2009;53:4069-79.
3. Medicines and Healthcare products Regulatory Agency. Drug analysis print for teicoplanin. Available from: <https://info.mhra.gov.uk/drug-analysis-profiles/dap>.

- [html?drug=../UK_EXTERNAL/NONCOMBINED/UK_NON_000396732913.zip&agency=MHRA](#). Accessed January 12, 2020.
4. Azamgarhi T, Shah A, Warren S. Teicoplanin anaphylaxis associated with surgical prophylaxis. *Br J Clin Pharmacol* 2018;84:1038-44.
 5. Knudsen JD, Pedersen M. IgE-mediated reaction to vancomycin and teicoplanin after treatment with vancomycin. *Scand J Infect Dis* 1992;24:395-6.
 6. Macías E, Moreno E, Dávila I, Laffond E, Ruíz A, Batista JC, et al. Reaction to teicoplanin with tolerance to vancomycin. *J Investig Allergol Clin Immunol* 2008;18:71-2.
 7. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
 8. Baretto RL, Beck S, Heslegrave J, Melchior C, Mohamed O, Ekbote A, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. *Allergy* 2017; 72:2031-4.
 9. Siew LQC, Li PH, Watts TJ, Thomas I, Ue KL, Caballero MR, et al. Identifying low-risk beta-lactam allergy patients in a UK tertiary centre. *J Allergy Clin Immunol Pract* 2019;7:2173-81.