

Rapid Desensitization after a Type I Hypersensitivity Reaction to Ceftazidime/Avibactam

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Background: Frequent antibiotic use increases the risk of multidrug-resistant pathogen formation and hypersensitivity to antibiotics, including Type I hypersensitivity reactions.

Presentation: We present a case of the first successful induction of tolerance procedure for the antibiotic ceftazidime/avibactam. The patient developed immediate generalized urticaria and flushing on his first dose of ceftazidime/

avibactam. He was able to tolerate a 12-step desensitization procedure that resulted in the clearance of his infection.

Conclusions: Drug desensitization procedures are useful for patients with adverse drug reactions in which optimal alternatives are not available. This is the first case report demonstrating a successful rapid induction of tolerance for the antibiotic ceftazidime/avibactam.

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Cerebral palsy (CP) embodies a collection of disorders involving permanent but nonprogressive motor dysfunction secondary to one of a variety of abnormal disturbances that can occur in the developing fetal or infantile brain.¹ The motor impairment of CP classically leads to irregularities in muscle tone, posture, and/or movement, resulting in limitations of functional abilities that vary in severity.^{1,2} Patients with CP commonly experience dysphagia, gastroesophageal reflux disease, impaired airway clearance, chest wall and spine deformities, restrictive lung disease, and/or recurrent aspiration.¹ Consequently, pulmonary disease is the leading cause of morbidity and mortality in patients with severe CP, characterized by recurrent bacterial infections.^{3,4}

Frequent antibiotic use increases the risk of multidrug-resistant pathogen formation and hypersensitivity to antibiotics. Life-threatening allergic reactions in a patient population with impaired lung function significantly complicates patient management, often leading to suboptimal treatment with second-line agents.⁵ This case study describes a previously penicillin-tolerant patient with CP who developed a type I hypersensitivity reaction to ceftazidime/avibactam and was treated successfully with the antibiotic after rapid induction of temporary tolerance.

CASE PRESENTATION

A 34-year-old male with a complex medical history of severe spastic CP and atonic seizures was recently diagnosed with ade-

nocarcinoma of the colon and admitted for ileostomy and sigmoidectomy. The surgery was complicated by spillage of intestinal contents into the peritoneal cavity 3 days postoperation. The patient was urgently taken to the operating room for exploratory laparotomy, culminating in remaining colectomy, complete abdominal washout, and wound vacuum placement. He continued to deteriorate clinically over the next few weeks, beginning with the development of feculent peritonitis and septic shock. Respiratory distress ensued, and the patient required a tracheostomy with mechanical ventilation. A computed tomography of the chest was consistent with multifocal pneumonia, and a respiratory culture of bronchioalveolar lavage fluid cultivated *Klebsiella pneumoniae*, a carbapenem-resistant Enterobacteriaceae.

The infectious disease service was consulted and recommended ceftazidime/avibactam as the only acceptable antibiotic to treat this organism. The patient had no history of drug hypersensitivities. However, he developed diffuse, generalized urticaria and predominately right-sided flushing immediately following the onset of the antibiotic infusion. The urticaria was pruritic. The patient did not have angioedema, and he did not experience any adverse respiratory, cardiac, gastrointestinal, or neurologic symptoms. The infusion was ceased immediately, and the patient was treated with a combination of diphenhydramine 50 mg IV and ranitidine 50 mg IV. Resolution of his hypersensitivity symptoms occurred within an

TABLE Ceftazidime/Avibactam 12-Step Desensitization Protocol

Steps	Solutions	Rate, mL/h	Infusion Time, min	Volume Infused, mL	Dose Administered, mg	Cumulative Dose, mg
1	1 ^a	2	15	0.5	0.25	0.250
2	1	5	15	1.25	0.625	0.875
3	1	10	15	2.5	1.25	2.125
4	1	20	15	5	2.5	4.625
5	2 ^b	5	15	1.25	6.25	10.875
6	2	10	15	2.5	12.5	23.375
7	2	20	15	5	25	48.375
8	2	40	15	10	50	98.375
9	3 ^c	10	15	2.5	125	223.375
10	3	20	15	5	250	473.375
11	3	40	15	10	500	973.375
12 ^d	3	80	22	30	1500	2473.375

^aSolution 1, 0.0005 g/mL.

^bSolution 2, 0.005 g/mL.

^cSolution 3, 0.05 g/mL.

^dAfter this step, administer target dose of 2.5 g every 8 h.

hour of treatment, and vital signs remained stable with no resurgence of symptoms. At the time of his reaction, the patient also was taking pantoprazole, valproate, metoprolol, risperidone, and oxycodone as needed for pain. A tryptase level was not measured.

The allergy and immunology service was consulted for rapid desensitization to ceftazidime/avibactam as the culture and sensitivity test demonstrated the bacterium to be resistant to alternative antibiotics. Skin testing to ceftazidime/avibactam was deferred at the time due to the patient's critical illness. The patient was premedicated with diphenhydramine and ranitidine 50 mg IV. Rapid IV desensitization was performed using a standard 12-step protocol developed for chemotherapeutic agents but demonstrated as safe and effective when applied to antibiotics in patients with cystic fibrosis.⁵ The antibiotic was administered in sequential 15-minute intervals for a total of 12 progressively doubled doses with continuous monitoring for the appearance of allergic reactions (Table). The target dose of 2.5 g was successfully achieved, and the patient tolerated a complete 14-day treatment regimen with no fur-

ther adverse reactions to the medication. During the remainder of his hospital admission, the patient improved significantly without further complications.

DISCUSSION

This is the first reported case in the literature to describe a type I hypersensitivity reaction with rapid IV induction of tolerance to ceftazidime/avibactam. We describe his reaction as type I hypersensitivity because the patient developed immediate generalized urticaria and flushing. Use of a safe desensitization protocol, demonstrated in this case report, is paramount to optimal management of infections in patient populations with severely decreased lung function, such as CP.⁵⁻⁷ It provides a safe and effective technique to maintain patients on first line, preferred therapy, despite their increased risk of potentially life-threatening allergic reactions.

Interestingly, this patient previously tolerated penicillins and cephalosporins without adverse reactions, suggesting the possibility of a non-IgE-mediated vs an IgE-mediated mechanism to the hypersensitivity reaction. The patient also was receiving oxycodone at

the time of his reaction, and oxycodone can cause nonspecific mast cell degranulation. Additional information from skin testing to ceftazidime/avibactam could help determine whether the patient had an IgE-mediated hypersensitivity reaction. This information could help clarify the culprit agent and guide further avoidance recommendations.

Unfortunately, because the patient was critically ill, skin testing was not performed, and he underwent an urgent antibiotic desensitization with success. It was recommended that the patient follow up in the allergy and immunology clinic for further evaluation with skin testing to ceftazidime/avibactam as well as other β -lactams to determine his future risk of reaction. Unfortunately, he was lost to follow-up.

Frequent IV antibiotic use is a risk factor for the development of antibiotic allergies.^{8,9} This patient had received many prior courses of IV antibiotics, and this factor most likely contributed to his immediate hypersensitivity reaction to ceftazidime/avibactam. Fortunately, he tolerated a rapid induction of tolerance.

As life expectancies for patients with chronic medical conditions that involve recurrent infections increase, the associated emergence of multidrug-resistant pathogens and necessity for use of novel combination antibiotics should prompt further investigation of nonirritating doses of these drugs for skin testing in the case of drug hypersensitivities. This information would be essential for skin prick testing and determination of whether patients have a true IgE-mediated reaction to these antibiotics.

CONCLUSIONS

This is the first case report demonstrating a successful rapid induction of tolerance for the antibiotic ceftazidime/avibactam. Fortunately, the patient tolerated the desensitization procedure without further adverse

reactions, and he had a resolution of his infection.

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Ethics and consent

This article is a patient case report (not research) and is exempt from institutional review board approval. The exemption was provided by the Wilford Hall Institutional Review Board. The authors report that verbal consent was obtained from the patient.

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eAppendix Interview Guide

Interviewer name:

Interview date:

Initial interview date:

Start time:

End time:

Hello [Dr./Mr./Ms. interview participant name],

My name is [interviewer name]. I am with an evaluation team tasked with understanding how e-consults are used in [site].

These findings will be used to understand barriers and facilitators to e-consult utilization and expansion, and to develop 'best practices' recommendations and support tools to facilitate e-consult expansion. Your responses will be kept confidential and you and your facility will not be identified in any reports or publications. Nothing that you say will be reported back to your facility.

The call will take approximately 20 to 30 minutes.

Your participation in this interview is voluntary. You can stop the interview at any time, and let us know if you'd rather not answer a particular question.

Do you have any questions?

In order to make sure we capture all of the information you give us, we would like to record this call. The audio file for the recording will be uploaded to a restricted access file on the VA intranet immediately after we complete this interview. The audio file will be saved anonymously. We may transcribe the recording, and your name will be removed from any transcripts. Is this okay with you?

Grounded prompts: If responses are limited or require clarification, probes may be used to illicit more detailed responses. Probes should use words or phrases presented by the participant using one of the following formats:

1. What do you mean by _____?
2. Tell me more about _____.
3. Give me an example of _____.
4. Tell me about a time when _____.
5. Who _____?
6. When _____?

Script

1. Please tell me about your role with e-consults.

2. Please tell me about e-consults.
(PRISM: organizational perspective)

3. What, if any, are challenges to using e-consults at your site?
(PRISM: organizational perspective)
a. Do you have any suggestions for overcoming these barriers?

4. (If needed) What is a good e-consult?
a. Grounded probes-probe for specific examples

5. What, if anything, has made it easier to use e-consults at your site?
(PRISM: Organizational Perspective)

6. How have e-consults affected your workload?
(PRISM: organizational perspective)
a. How do e-consults fit into your practice?

7. How have e-consults affected communication between PCPs and specialists?

(PRISM: organizational perspective)

8. How do you think e-consults have affected the quality of care provided to patients?
(PRISM: Patient Perspective)
a. Can you give me an example?

9. What types of patients do you use e-consults for?
(PRISM: characteristics of organizational recipients)
a. Who were these people?
b. Can you give me an example?

10. What kind of communication or feedback do you receive from your division or facility leadership about your use of e-consults?
a. Can you tell me about how it was rolled out?
b. Are there expectations for e-consult use?

11. Is there anything else you would like us to know about the use of e-consults at your site?

12. Do you have any advice on e-consults for other sites and/or specialties?

a. Probe about templates

Thank you for that information about the e-consult program.

13. Do you have any questions for us?

Thank you for participating in this interview.

Specialist Interview Guide

Interviewer name:

Interview date:

Initial interview date:

Start time:

End time:

Hello [Dr./Mr./Ms. interview participant name],

My name is [interviewer name]. I am with an evaluation team tasked with understanding how e-consults are used in [site].

These findings will be used to understand barriers and facilitators to e-consult utilization and expansion, and to develop 'best practices' recommendations and support tools to facilitate e-consult expansion. Your responses will be kept confidential and you and your facility will not be identified in any reports or publications. Nothing that you say will be reported back to your facility. The call will take approximately 20 to 30 minutes.

Your participation in this interview is voluntary. You can stop the interview at any time, and let us know if you'd rather not answer a particular question.

Do you have any questions?

In order to make sure we capture all of the information you give us, we would like to record this call. The audio file for the recording will be uploaded to a restricted access file on the VA intranet immediately after we complete this interview. The audio file will be saved anonymously. We may transcribe the recording, and your name will be removed from any transcripts. Is this okay with you?

Grounded prompts: If responses are limited or require clarification, probes may be used to illicit more detailed responses. Probes should use words or phrases presented by the participant using one of the following formats:

1. What do you mean by _____?
2. Tell me more about _____.

3. Give me an example of _____.
4. Tell me about a time when _____.
5. Who _____?
6. When _____?

Script

14. Please tell me about your role with e-consults.
15. Please tell me about E-consults.
(PRISM: Organizational Perspective)
16. How did you end up being the one to respond to e-consults?
a. Were you selected by your Division or clinic? Did you volunteer?
17. What, if any, are challenges to answering e-consults that you receive?
(PRISM: Organizational Perspective)
a. Do you have any suggestions for overcoming these challenges?
18. What, if anything, has made it easier to answer E-consults that you receive?
(PRISM: Organizational Perspective)
a. Particular patients or questions that work well?
b. Do you have resources that assist you?
c. Did you receive training?
19. How have E-Consults affected your workload?
(PRISM: Organizational Perspective)
a. Do you have protected time for E-Consults
b. What's the demand at your site
c. What's the average time to complete an econsult
20. How do you think E-Consults have affected the quality of specialty care provided to patients?
(PRISM: Patient Perspective)
a. Are E-Consults more appropriate for certain types of patients?
21. Are E-Consults used to arrange procedures within your specialty?
(PRISM: Organizational Perspective)
a. Do E-Consults expedite scheduling of procedures?
- Thank you for that information. Now I would like to ask you a few questions about the sustainability of the E-Consult pro-

gram.

22. Are there people in your facility who have been especially instrumental in helping to sustain this initiative?
(PRISM: Characteristics of Organizational Recipients)
a. Who were these people?
b. What roles do these people play?
23. At your facility, how were leadership involved in rolling out E-Consults?
(PRISM: Characteristics of Organizational Recipients)
a. [if needed] Did leadership provide training for E-Consult use, or an expectation for E-Consult use?
24. At your facility, how does leadership support E-Consults?
a. What kind of communication or feedback do you receive from your division or facility leadership about your use of E-Consults?
b. Is there an expectation from your leadership that you complete a certain number of these, or respond in a certain amount of time?
25. Is there anything else you would like us to know about the use of E-Consults at your site?
26. Do you have any advice on E-Consults for other sites and/or specialties?
- Thank you. Those are all the questions I have:
27. Do you have any questions for us?
- Thank you for participating in this interview.