

Hypothesis & Experience  
Case Report



# Cytokine release syndrome – a unique entity of Augmentin hypersensitivity reaction

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Conflict of Interest

The authors have no financial conflicts of interest.

## ABSTRACT

Cytokine release syndrome (CRS) is a type of hypersensitivity reaction which has been previously described with chemotherapy and monoclonal antibodies, but not with antibiotics. We present 2 pediatric cases of Amoxicillin/Clavulanic acid (Augmentin) anaphylaxis resembling CRS. Both our patients presented during the index reaction with symptoms suggestive of an acute systemic inflammatory response mimicking sepsis. Their symptomology was reproducible at drug provocation test as anaphylaxis, but with suboptimal response to intramuscular adrenaline. Their infective workups were unremarkable and illnesses followed a self-limiting course. All these point towards a severe hypersensitivity reaction resembling CRS.

**Keywords:** Drug hypersensitivity; Cytokine release syndrome; Amoxicillin-potassium clavulanate combination

## INTRODUCTION

Cytokine release syndrome (CRS) is a type of hypersensitivity reaction which has been previously described with chemotherapy and monoclonal antibodies, but not with antibiotics. We present 2 pediatric cases of Amoxicillin/Clavulanic acid (Augmentin) hypersensitivity reactions resembling CRS that were reproducible at drug provocation testing (DPT).

## CASE REPORT

The first case is a 16-year-old Malay male with a background of asthma and allergic rhinitis. He was prescribed Augmentin 625 mg twice a day for a forehead laceration. Forty-five minutes after the second dose, he developed generalized flushing, chest tightness, and drowsiness. There was no urticaria, angioedema, hoarseness of voice, wheezing, or vomiting. The mother administered metered-dose inhaler salbutamol and cetirizine prior to seeking medical attention. In the Children's Emergency, he was febrile (temperature 39.3°C) but hemodynamically stable, with a normal physical examination except for generalized flushing. He was admitted for monitoring. Investigations (Table 1) showed neutrophilia, raised

**Author Contributions**

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**Table 1.** Investigations during index reaction and DPT

Variable	Patient 1		Patient 2	
	Index reaction	DPT	Index reaction	DPT
WBC count ( $\times 10^9/L$ )	18.19	8.61	21.32	11.27
Neutrophil (%)	91.0	90.0	90.0	91.5
Eosinophil absolute ( $\times 10^9/L$ )	0.89	0.09	0.67	0.24
CRP (mg/L)	30.0	164.2	200.0	ND
Procalcitonin ( $\mu g/L$ )	ND	4.98	79.53	ND
Renal panel	Unremarkable	AKI (Cr, 119)	AKI (Cr, 83)	Unremarkable
Liver function test	Unremarkable	Unremarkable	Unremarkable	Unremarkable
Acute/baseline tryptase ( $\mu g/L$ )	ND	4.9/2.7	ND	2.4/3.2

DPT, drug provocation testing; WBC, White blood cell; CRP, C-reactive protein; ND, not done; AKI, acute kidney injury; Cr, creatinine.

inflammatory markers, and a positive dengue serology (immunoglobulin M) test. He was managed symptomatically and his fever resolved within 24 hours.

The second case is a 15-year-old Chinese female with a background of allergic rhinitis. She was prescribed Augmentin 625 mg twice a day for an infected right foot wart. Five hours after the first dose, she developed generalized flushing, swelling of extremities, dyspnoea, and abdominal pain with vomiting. There was no urticaria, hoarseness of voice, wheezing, or drowsiness. In the Children's Emergency, she was febrile (temperature 39.2°C) but hemodynamically stable, with a normal physical examination except for generalized flushing. She was treated as for anaphylaxis with intramuscular adrenaline, intravenous hydrocortisone, cetirizine, omeprazole, and paracetamol and admitted for observation. Her inflammatory markers were markedly raised (Table 1) and she was treated for presumed toxic shock syndrome with intravenous ceftriaxone and clindamycin.

As their symptoms developed soon after the Augmentin dose, a DPT was performed to rule out a drug hypersensitivity reaction. Skin testing was not performed as suspicion for drug hypersensitivity was low. Upon oral challenge with 1 g of Augmentin, both patients developed a drug reaction similar to their index reaction (Table 2). Both were treated with intramuscular adrenaline and cetirizine. Inpatient, they were febrile but hemodynamically stable, and fever resolved within 48 hours. Both were treated with intravenous hydration, and the former was also treated for presumed gastrointestinal sepsis with intravenous ceftriaxone and metronidazole. Acute tryptase was not elevated (Table 1). Both patients have been offered further evaluation with skin prick and intradermal testing to beta-lactam antibiotics to further elucidate and rule out type 1 IgE-mediated hypersensitivity; but unfortunately, both declined further investigations.

**Table 2.** Symptoms during index reaction and DPT

	Patient 1	Patient 2
<b>Index reaction</b>		
Onset	45 Minutes after second dose	5 Hours after first dose
Symptoms	Fever, generalized flushing, chest tightness, and drowsiness	Fever, generalized flushing, swelling of extremities, dyspnoea, abdominal pain, and vomiting
<b>DPT</b>		
Onset	2.5 Hours after dose	4 Hours after dose
Symptoms	Fever with rigors, generalized flushing, chest tightness, drowsiness, and vomiting	Fever with rigors, generalized flushing, swelling of face and extremities, dyspnoea, abdominal pain, and vomiting

DPT, drug provocation testing.

## DISCUSSION

CRS has garnered a lot of attention during the coronavirus disease 2019 pandemic as it was found to be the major cause of morbidity and mortality in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. CRS is a systemic inflammatory response triggered by the release of proinflammatory cytokines caused by a myriad of factors, including infections and drugs [2]. It was first described in 1990 by Chatenoud et al. [3], following the introduction of monoclonal antibody therapy (OKT3) as an immunosuppressive treatment for solid organ transplantation.

Commonly reported triggers of CRS are infections (SARS-CoV-2, influenza), drugs (chemotherapy, monoclonal antibody), haploidentical donor stem cell transplantation, and chimeric antigen receptor T-cell therapy [1, 2]. Currently, the pathophysiology of CRS is not well understood but is postulated to be due to the activation of T cells that induce the release of interferon gamma and tumour necrosis factor-alpha (TNF- $\alpha$ ). This leads to activation of macrophages, dendritic cells, and endothelial cells to release proinflammatory cytokines such as interleukin-6 (IL-6), TNF- $\alpha$ , and IL-1 $\beta$  (IL-1 $\beta$ ), resulting in a profound, systemic inflammatory response [2].

CRS can present with a spectrum of nonspecific symptoms ranging from mild, flu-like symptoms to severe, life-threatening manifestations, mimicking sepsis. Mild symptoms include fever, chills, rigors, malaise, flushing, rash, cough, headache, nausea, vomiting, and myalgia. In severe cases, cytokine storm reactions can occur, leading to hypotension, dyspnoea, hypoxemia, and cardiovascular collapse. Some may progress into acute respiratory distress syndrome, disseminated intravascular coagulopathy, or multiorgan failure [2, 4]. Laboratory abnormalities that are commonly seen in patients with CRS include cytopenia, high CRP, elevated creatinine and liver enzymes, or deranged coagulation profile [2]. IL-6 was shown to be a valuable biomarker in determining the severity of CRS [5].

Management of CRS is mainly supportive. In mild cases, treatment with antipyretics and intravenous fluids would suffice. However, in severe cytokine storm reactions, prompt and aggressive treatment with vasopressors, corticosteroids, oxygen, mechanical ventilation, and Tocilizumab (humanized anti-IL-6 receptor monoclonal antibody), may be required. Treatment with empirical antibiotics should be considered if an infection cannot be ruled out [2, 6, 7].

This is the first case report of Augmentin-induced CRS in pediatric patients. Both cases demonstrated a unique manifestation of hypersensitivity reaction to Augmentin which was not previously reported. Both our patients presented with nonspecific symptoms suggestive of acute sepsis during their initial index reactions which were subsequently reproducible at DPT. Their reactions at DPT were not typical of IgE-mediated anaphylaxis, where both experienced delayed flushing instead of immediate hives, fever with rigors and had suboptimal response to intramuscular adrenaline. Their inflammatory markers were markedly high but infective work up for bacterial infection was negative. They also had rapid resolution of symptoms within 24 to 48 hours, making infection less likely to be the etiology. In addition, their clinical presentation in the absence of a rash, was not consistent with other severe drug hypersensitivity reactions such as Stevens-Johnson Syndrome or drug-related eosinophilia with systemic symptoms. Thus, a plausible explanation for their severe hypersensitivity reaction could be CRS. Limitations of our case report include the absence of evaluation with skin tests and IL-6. Both patients declined skin testing and IL-6 levels

were not measured due to logistic and cost reasons. Given patient factors, we were unable to determine if CRS was induced by amoxicillin or clavulanate component in Augmentin.

The endophenotypic pattern of drug hypersensitivity reactions is constantly evolving and newer entities have been observed [4, 6]. These 2 cases illustrate the importance of recognizing different clinical presentations of drug hypersensitivity reactions, so that prompt and appropriate management can be instituted.

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