Drug Induced Hemolytic Anemia From Ceftazidime/Avibactam, A New Old Antimicrobial: A Case Report

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Abstract

Background: Hemolytic anemia is a serious, immunologically mediated adverse event which may be precipitated by exposure to certain medications including antibiotics. This condition although rare, is life threatening and requires a high index of clinical suspicion, appropriate laboratory testing and immediate cessation of the offending agent. Diagnosis depends on a decrease in hemoglobin along with an elevated lactate dehydrogenase (LDH), decreased haptoglobin and a positive direct Coombs test. Many medications have been known to cause false positive Coombs test without clinical evidence of hemolytic anemia. Ceftazidime/avibactam (C/A) is a newly approved antimicrobial with a unique β-lactamase inhibitor approved in 2015.
Methods: We report the first case of documented hemolytic anemia resulting from exposure to C/A.
Results: A 67 year old lady was admitted to University Medical Center of Southern Nevada from a skilled nursing facility for management of a left upper quadrant abdominal wall abscess at the site of a prior chest tube. After undergoing surgical debridement, cultures revealed a carbapenemase producing *K. pneumoniae.* She was initiated on C/A, becoming tachycardic and hypotensive within 72 hours. She was noted to have an acute drop in hemoglobin from 9.4g/dL to 6.8g/dL, along with an undetectable haptoglobin; elevated LDH and retic count. A direct Coombs test was positive. Review of medications pointed to C/A as the possible offending agent. She was treated with blood transfusions and C/A was discontinued. Within 3 days, the patient demonstrated improvement of her clinical symptoms.
Conclusion: In phase III trials, 1.9% of patients on C/A had a documented positive conversion of a previously negative direct Coombs test; however none of the patients developed clinical evidence of hemolytic anemia. Ceftazidime, the base compound of this combination, has been available for use in the US since 1985 with 7 documented cases of acute hemolytic anemia. Based on these case reports it is reasonable to assume that the combination of ceftazidime and avibactam could also result in this life threatening adverse effect. As such, if a patient develops symptoms of hemolytic anemia, C/A should be included in the list of causative agents and discontinued pending further workup and patient stabilization.

Background

- Drug induced immune hemolytic anemia is extremely rare
  - Estimated at 1 in 1 million patients
- Multiple drug classes implicated with antimicrobials being most common at 42%,
  - Prior to 2007: 70% of cases involve cephalosporins
  - Since 2007: piperacillin most common (~44%)
- Cephalosporins have been shown to interfere with the direct Coombs test making diagnosis of hemolytic anemia more difficult

Case Summary

67yo female transferred from a long term acute care hospital (LTAC) for a potential chest tube since the CT scan suggested worsening pleural effusions.

PMH:
- Coronary artery disease
- Hypertension
- Diabetes mellitus type 2
- DVT
- *C. difficile* infection
- Myocardial Infarction (2015)
- Systolic Heart failure
- Hypothyroidism
- HIT
- Asthma

Allergies: codeine, tetracycline, tramadol, heparin

Home medications (incomplete list)
- Levothyroxine
- Warfarin
- NPH insulin
- Hydrochlorothiazide
- Furosemide
- Prednisone
- Atorvastatin

PSH: Coronary artery bypass graft (2015)
AICD placement (2015)
Mitral valve replacement (2015)
Thrombectomy
Thoracostomy tube

A/P: Bilateral pleural effusions - tubes removed; monitor to determine if need to replace
Acute kidney injury (resolving) – Renal consult
Left lower chest/upper quadrant wound – ID consult

Timeline

Day 1: Empirical antibiotics started; chest tubes removed and monitor
- Metronidazole 500mg PO TID
- Ceftriaxone 1g q24h

Day 4: Culture results show multi-drug resistant *K. pneumoniae*
Call ID Consult for evaluation; changed antibiotics
- Ceftolozane/tazobactam 1.5g q8h

Day 5: Hodge test positive; change antibiotics for possible KPC producing *K. pneumoniae*; CT: no abscess so plan 10d course
- Ceftazidime/avibactam 2.5g q8h

Day 7: Clinical signs/symptoms on infection improving; AKI due to diuresis; renally adjust C/A

Day 8: Upgrade to ICU status for inotropic support; bleeding noted with increased SOB (no hemoptysis). Hemoglobin decreasing, INR elevated so coumadin held → 2 units PRBC

Day 9: Bleeding at multiple sites (gums, urine, stool)
Anemia due to blood loss vs. hemolysis; transfusing blood and reverse coumadin

Day 10: Dialysis due to pulmonary edema and AKI, wound still erythematous with purulence; decrease dose of C/A

Day 11: Intubated due to respiratory distress, altered censorium, minimally responsive; Bleeding noted; Direct Coombs negative

Day 12: Haptoglobin <8; order direct Coombs test stat; stop C/A

Day 13: Direct Coombs positive; likely hemolytic anemia potentially due to antibiotic – ceftazidime/avibactam. Antibiotics changed

Lab Results

Day of Admission	#4	#5	#6	#7	#8	#9			#10		#11			#12		#13	#14	#15	#16		#17	#18
WBC (K/mm^3)	15.5	14.2	ND	10.5	8.6	8.6			14.4		15.3			11.2		8.2	10.5	14.4	9.6		9.8	8.3
Hematocrit (%)	28.8	27.5	ND	25.9	22.3	21.0	31.8	29.4	30.8	27.3	24.4	23.1	22.1	19.6	25.9	23.4	28.6	30.1	23.5	25.6	31.5	33.5
Hemoglobin (g/dL)	9.4	8.8	ND	8.6	7.3	6.8	10.5	9.6	9.9	8.6	7.8	7.3	7.3	6.2	8.4	7.7	9.6	9.7	7.7	8.2	10.4	11.1
Platelets (K/mm^3)	237	237	ND	196	158	130			167		123			65		40	81	62	25	21	112	81
Scr (mg/dL)	0.9	1.0	1.3	1.6	2.1	2.3			1.8		1.3			1.2		1.8	1.6	2.0	1.8		2.2	2.7
INR	1.9	2.1	2.3	2.4	3.2	2.9			2.8		3.6	2.1		1.8		1.9	1.7	1.7	1.9	2.0	1.3	1.6
D-Dimer (mg/L FEU)									1.70										3.32			
Fibrinogen (mg/dL)									345					340					506			
Haptoglobin (mg/dL)											<8			23				31	24			
D. Coombs											Negative			Positive								
LDH (U/L)											219			235			243	264				

Cultures

Location	Organism	Sensitive	Intermediate / Resistant		Date final
Wound R Groin	*K. pneumoniae* *Hodge test +	Tigecycline Colistin	Amikacin (I)	Amp/Sulb	Day #4
			Cefazolin	Ceftriaxone	
Urine			Cefepime	Gentamicin	
			Ciprofloxacin	Ertapenem	
			Meropenem	Pip/Tazo	
			TMP/SMX	Tobramycin	
Wound	None	N/A	N/A		Day #14
Urine	50-100 cfu Yeast	N/A	N/A		Day #14
Blood x 2	None	N/A	N/A		Day #16

Summary

- Within a short period of C/A starting, demonstrated signs and symptoms of anemia, resulting in transfer to ICU, intubation, inotropic support and dialysis
- Hemolytic anemia suspected, and testing done to determine if potentially drug induced
- Patient significantly improved when the C/A was discontinued and alternative treatment was utilized for her infection
- Although no re-challenge was done of the C/A, caution is warranted to use any component of C/A in the future for our patient

Conclusion

- Few reports of ceftazidime causing hemolytic anemia published
- Avibactam restores activity of ceftazidime against KPC carbapenemase producing organisms
- As the incidence of KPC producing organisms increase, the use of ceftazidime/avibactam may continue to increase as well
- Patients treated with C/A develop signs or symptoms of hemolytic anemia, C/A should be ruled out as the cause

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