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 publications have been known to cause false positive Coombs test without clinical evidence of hemolytic anemia.

Ceftriaxone/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 also noted to have a CERD on C/A, became hypertensive 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 hemolytic anemia. Ceftriaxone, with a less intense combination, has been available for use in the US since 1985 with 7 documented cases of acute hemolytic anemia. Based on these cases reports it is reasonable to assume that the combination of ceftriaxone 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.

Day 1: Empirical antibiotics started; chest tubes removed and monitor • Metronidazole 500mg PO TID • Ceftazidime 2g q8h

Day 4: Culture results show multi-drug resistant K. pneumoniae • Call ID Consult for evaluation; changed antibiotics

Day 5: Hodge test positive; change antibiotics for possible KPC producing K. pneumoniae; CT no abscess so plan 10d course • Ceftazidime/avibactam 2g q8h

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

Day 8: Up grade 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 hemolysis vs. hemolysis; transfusing blood and reverse coagulant

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

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

Day 12: Haptoglobin/s-Staph/Fibrinogen/avibactam 1g q24h; Ceftazidime challenge was done of the C/A, caution is warranted

Day 14: Discharge to use any component of C/A in the future for our patient

Antibiotics changed after things improved and alternative treatment was utilized for her infection

Additional treatment was given due to persistent infection

Patient significantly improved when the C/A was discontinued and alternative treatment was utilized for her infection

Although no rechallenge was done of the C/A, caution is warranted to use any component of C/A in the future for our patient

References
1) Avtzon (package insert). Merck & Co., Inc. Whitehouse Station, NJ 08886. 2010
4) Santry AC, Bodey GP: Drugs that have shown to cause drug induced immune hemolytic anemia or pseudo drug induced immune hemolytic anemia: A useful compilation. Clin Infect Dis. 2010;50:301-307
5) Table 1: Summary of cases of drug induced immune hemolytic anemia based on an analysis of case reports. Br J Clin Pharmacol. 2008;65:649-653