Intravenous Gammaglobulin as Rescue Therapy in a Patient with Sickle Cell and Septic Shock

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ABSTRACT
Introduction: We present a case involving a patient with sickle cell and hyposplenism, in which refractory septic shock quickly responded after the infusion of intravenous gammaglobulin (IV-GG) given as an adjuvant-rescue therapy.

Case Description: A 30-year-old African-American female with history of Sickle Cell disease was admitted for acute chest syndrome, septic shock and respiratory failure. Despite aggressive therapy the patient remained on two vasopressors and with persistent bacteremia. Within one day of starting IV-GG, both vasopressors (norepinephrine and vasopressin) were able to be discontinued.

Discussion: Patients with hyposplenism have functional opsonization failure. Infusion of IV-GG has been shown to improve such function in patients with hyposplenism. We were able to document a temporal association between IV-GG rescue therapy and septic shock improvement.

Conclusion: The utilization of intravenous gammaglobulin should be considered in patients with sickle cell disease and hyposplenism as an adjuvant therapy for refractory septic shock.

INTRODUCTION
Sepsis is the most frequent diagnosis on admission to a medical ICU. Standardization of management and process of care have been accomplished by the surviving sepsis campaign (recently updated, 2013) and by initiatives that address the appropriateness and timing of other components of medical care (i.e. sedation, anemia, and glucose control).

Management of special pathophysiological conditions cannot be covered on clinical guidelines directed for the general population. Functional hyposplenism is one such condition. An intact spleen function is required for sufficient immunoglobulin production and for encapsulated organisms’ opsonization. Disorders of hemoglobin production can be associated with anatomical and functional hyposplenism; consequence of the natural history of lifelong auto-splenectomy.

We describe a case of a patient with sickle cell disease and spleen size half of normal (anatomic hyposplenism) in which septic shock refractory, after fluid resuscitation, to conventional medical care (adequate antibiotic coverage, vasopressors, and steroids) quickly responded after the infusion of IV gammaglobulin given as an adjuvant-rescue therapy.

CASE DESCRIPTION
A 30-year-old African-American female with history of homozygous Sickle Cell disease, protein S deficiency and a history of previous DVT and PE presented to the ER with fever, chills, confusion, right shoulder, chest and back pain for the last 24 hours. Vital signs on admission were blood pressure 77/40 mmHg, pulse 175 beats per minute, respiratory rate of 26 per minute, temperature of 105 °F; and an oxygen saturation of 95% on 4L nasal cannula. Physical examination of the chest revealed bilateral inspiratory crackles. The remainder of the examination was within normal limits. Her respiratory status deteriorated and the patient was intubated for respiratory failure and to support her work of breathing. Initial laboratory results are shown in the Table. Chest x-ray revealed bilateral alveolar infiltrates.

Exchange transfusion was performed for management of her acute chest syndrome precipitated by an infection. With a clinical diagnose of septic shock due to community-acquired pneumonia, early goal-directed therapy was started. Sedation and glucose control were prescribed following hospital protocols. She received fluid boluses and after 5L of normal saline vasopressor support was initiated with the intent to maintain a MAP of 65 mm Hg. The patient required three vasopressors for hemodynamic support (norepinephrine 70 mcg/kg/min; phenylephrine 150 mcg/kg/min; and vasopressin at a fixed dose of 0.04 unit/min). She was started on steroid (hydrocortisone 200 mg bolus followed by a drip of 240 mg over 24 hours), prompt empiric broad spectrum antibiotics (piperacillin/tazobactam, vancomycin, and ciprofloxacin), and was admitted to the medical intensive care unit where appropriate glucose control was achieved. Chest CT scan showed bilateral lower lobes air space disease and absence of PE. Next day blood culture came back positive for Klebsiella pneumoniae and antibiotics were tailored per the organism sensitivity.

Despite aggressive therapy on day four, the patient remained in refractory septic shock on two vasopressors (Figure), and with persistent bacteremia. Transthoracic
echocardiogram was negative for vegetations. CT scan of abdomen showed a small spleen (6 cm) but was negative for abscesses. Rescue treatment with gammaglobulin was discussed by the medical team. Intravenous gammaglobulin (IV-GG) was started (70 grams IV daily for three days). Within one day of starting IV-GG, both vasopressors (norepinephrine and vasopressin) were able to be discontinued. Over the next day systemic inflammatory response syndrome resolved and negative blood cultures were obtained.

On day 19 she had a new episode of sepsis, this time from a catheter-induced infection, and broad spectrum antibiotics were initiated. Blood culture was positive for methicillin-resistant staphylococcus epidermidis. She required vasopressor support with norepinephrine. Due to her previous clinical response to gammaglobulin, she received a new dose of adjuvant gammaglobulin. Within one day vasopressor support was discontinued and her blood culture came back negative. The patient was discharged from ICU after 35 days and later from the hospital alive.

**DISCUSSION**

We present a patient with sickle cell disease and anatomical hyposplenism (6 cm spleen; normal = 11 cm) who developed refractory septic shock due to bacteremia with an encapsulated organism. Persistent and poor clinical response in spite of adequate volume resuscitation and strict adherence to surviving sepsis campaign recommendations troubled the medical team caring for this patient.

Intravenous gammaglobulin (IV-GG) was used as a rescue therapy in our patient. We were able to document a temporal association between IV-GG rescue therapy and septic shock improvement demonstrated by a decrease requirement of vasopressor support (Figure).

The consistency of the observation during the two episodes of bacteremia also enhances the validity of our finding (Figure). Patients with hyposplenism have functional opsonization failure for encapsulated organisms. Infusion of IV-GG has been shown to improve such opsonization function in patients with hyposplenism. The events observed in our patient have biological plausibility and such experience supports our recommendation for the use of this rescue therapeutic intervention in patients with functional or anatomical hyposplenism (i.e. sickle cell disease) or overwhelming bacteremia.

Current sepsis management recommendations address general population needs. Special population like the one discussed in this report (functional hyposplenism) are not individualized in the surviving sepsis campaign management recommendations. Our observation is important for supporting this form of rescue therapy in patients with functional hyposplenism (i.e. sickle cell disease) as we were able to demonstrate: temporal relationship, consistencies of the results during two episodes of bacteremia, and biological plausibility (opsonization enhancement against encapsulated organisms).

There are several reports on the use of intravenous gammaglobulin. Results of these observations in sepsis do not have sufficient consistency to generate a general recommendation for the use of this therapy in the general population. We propose that narrowing the indication to patients with functional hyposplenism or overwhelming bacteremia will be necessary to achieve better outcomes with the intervention (IV-GG).

Even though ours is a single patient observation in a special population (sickle cell disease and hyposplenism) the strength of

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**TABLE. Sickle cell and septic shock laboratory data.**

<table>
<thead>
<tr>
<th></th>
<th>ADMIT</th>
<th>Day 4 — Day 6 IV-GG</th>
<th>Day 20 — Day 22 IV-GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell, (1000/mm3)</td>
<td>8.3</td>
<td>9.4 9.7</td>
<td>15.4 11.2</td>
</tr>
<tr>
<td>Bands, %</td>
<td>27</td>
<td>22 10</td>
<td>25 10</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>6.5</td>
<td>8.1 9.4</td>
<td>7.4 7.7</td>
</tr>
<tr>
<td>Platelets, (1000/mm3)</td>
<td>120</td>
<td>10 62</td>
<td>250 241</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>105</td>
<td>135 123</td>
<td>103 145</td>
</tr>
<tr>
<td>Lactate, mg/dL</td>
<td>4.3</td>
<td>2.6 1.4</td>
<td>2.3 1.7</td>
</tr>
<tr>
<td>SVO2, %</td>
<td>57</td>
<td>56 70</td>
<td>84 87</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>44</td>
<td>42 26</td>
<td>23 6.7</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>25</td>
<td>27 23</td>
<td>14 19</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.6</td>
<td>0.8 0.7</td>
<td>0.6 0.6</td>
</tr>
<tr>
<td>AST, u/l</td>
<td>550</td>
<td>393 287</td>
<td>34 35</td>
</tr>
<tr>
<td>ALT, u/l</td>
<td>181</td>
<td>155 172</td>
<td>42 50</td>
</tr>
<tr>
<td>ALKP, u/l</td>
<td>1026</td>
<td>269 189</td>
<td>100 119</td>
</tr>
<tr>
<td>Total bilirubin, (mg/dL)</td>
<td>5.1</td>
<td>2.3 2.1</td>
<td>0.7 1.3</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.2</td>
<td>2.1 2.5</td>
<td>2.0 2.2</td>
</tr>
<tr>
<td>PT, secs</td>
<td>24.2</td>
<td>30 22</td>
<td>16.9 18</td>
</tr>
<tr>
<td>INR</td>
<td>2.21</td>
<td>3 2</td>
<td>1.38 1.56</td>
</tr>
</tbody>
</table>

**Blood cultures**

<table>
<thead>
<tr>
<th></th>
<th>Klebsiella pneumoniae</th>
<th>Klebsiella pneumoniae</th>
<th>Staphylococcus epidermidis</th>
<th>Negative</th>
</tr>
</thead>
</table>

*IV-GG = Intravenous gammaglobulin*
our clinical observation is sufficient to propose the consideration of this rescue therapy in similar situations. Final recommendations regarding this therapy should wait for definitive randomized clinical trials. Meanwhile, evidence like this should not be ignored and be considered as supportive of this rescue therapy for the benefit of our patients.

**CONCLUSION**

In summary, we cared for a patient with sickle cell disease and anatomical-functional hyposplenism with refractory septic shock due to an encapsulated organism. In spite of a strict adherence to surviving sepsis campaign recommendations, our patient did not improve clinically. As a last resort the medical team decided to provide, in a rescue therapy fashion, intravenous gammaglobulin. Such intervention was associated with clinical improvement and survival of our patient.

The utilization of intravenous gammaglobulin should be considered in patients with sickle cell disease and functional hyposplenism as an adjuvant therapy for severe sepsis or refractory septic shock.

**References:**


Infection 1991; 19:216-227

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