Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Soliris® (eculizumab)

- **Prime Therapeutics will review Prior Authorization requests**
  Prior Authorization Form:
  https://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Soliris.pdf

  Link to Drug List (Formulary):
  https://www.bcbsks.com/drugs/ shtml

Professional
Original Effective Date: November 1, 2018
Revision Date(s): November 1, 2018
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Institutional
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The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Soliris (eculizumab) Medical Drug Criteria is to ensure appropriate selection of patients for treatment according to product labeling, and/or clinical practice guidelines, and/or clinical studies, and according to dosing recommended in product labeling.

Target Agent

- **Soliris®** (eculizumab)

FDA Approved Indications and Dosage[1]

Agent(s)	Indication(s)	Dosing
Soliris® (eculizumab)	Indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis	For patients ≥18 years of age: • Administer by IV infusion 600 mg weekly for the first 4 weeks, followed by • 900 mg for the fifth dose 1 week later, then • 900 mg every 2 weeks thereafter
	Indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS)* to inhibit complement-mediated thrombotic microangiopathy	For patients ≥18 years of age: • Administer by IV infusion 900 mg weekly for the first 4 weeks, followed by • 1200 mg for the fifth dose 1 week later, then • 1200 mg every 2 weeks thereafter For patients <18 years of age: administer Soliris based upon body weight- see prescribing information for dosing specifics
	Indicated for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive	• Administer by IV infusion 900 mg weekly for the first 4 weeks, followed by • 1200 mg for the fifth dose 1 week later, then • 1200 mg every 2 weeks thereafter

POLICY

Initial Evaluation

Soliris (eculizumab) will be approved when ALL of the following are met:

1. ONE of the following:
    a. The patient is an adult (≥18 years of age) with a diagnosis of generalized Myasthenia Gravis (gMG) AND ALL of the following:
        i. The patient has a positive serological test for anti-AChR antibodies
        AND
        ii. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IV
        AND
        iii. The patient has a MG-Activities of Daily Living total score of greater than or equal to 6
        AND

iv. ONE of the following:
    1. The prescriber has assessed the patient's current medications and discontinued any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides, etc)
    OR
    2. The prescriber has provided clinical rationale indicating that discontinuation of the offending agent is not clinically appropriate

AND

v. ONE of the following:
    1. The patient has tried and had an inadequate response to pyridostigmine
    OR
    2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to pyridostigmine

AND

vi. The patient has tried and had an inadequate response to treatment over at least 1 year with ONE of the following:
    1. At least 2 or more immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) either in combination or as monotherapy
    OR
    2. At least 1 immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) AND ONE of the following:
        a. The patient required chronic intravenous immunoglobulin (IVIG) (i.e., at least every 3 months over 12 months without symptom control)
        OR
        b. The patient required chronic plasmapheresis/plasma exchange (i.e., at least every 3 months over 12 months without symptom control)
    OR
    3. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL immunosuppressive therapies and plasmapheresis/plasma exchange

OR

b. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as confirmed by
flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI)-linked proteins (prescriber must provide supportive documentation)
OR
c. The patient has a diagnosis of atypical Hemolytic Uremic Syndrome (aHUS) AND BOTH of the following:
    i. The patient has demonstrated complement dysregulation by at least ONE of the following:
        1. Genetic mutation (e.g., *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5*)
        OR
        2. Antibodies to complement factors
        OR
        3. A differential diagnosis of complement-mediated HUS has been demonstrated [i.e. screening for Shiga toxin-producing E. coli (STEC) for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13) <10% activity for thrombotic thrombocytopenic purpura (TTP), screening for defective cobalamin metabolism]
    AND
    ii. The patient is negative for Shiga toxin-producing *E. coli* (STEC)

AND

2. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis
AND
3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND
4. The requested dose is within FDA approved labeling for the requested indication

Length of Approval: Generalized Myasthenia Gravis: 3 months
Paroxysmal Nocturnal Hemoglobinuria: 6 months
Atypical Hemolytic Uremic Syndrome: 6 months

Renewal Evaluation

Soliris (eculizumab) will be approved when ALL of the following are met:

1. The patient was previously approved for the requested agent through the Prime Therapeutics Medical Drug Review process
   AND
2. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
3. The prescriber has submitted documentation that the patient has had clinical benefit with the requested agent as shown by ONE of the following:
   a. Paroxysmal Nocturnal Hemoglobinuria (PNH) – e.g., decreased requirement for RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH)
      OR
   b. Atypical Hemolytic Uremic Syndrome (aHUS) – e.g., improved platelet count, reduction of lactate dehydrogenase (LDH), stabilization/improvement of renal function
      OR
   c. Generalized Myasthenia Gravis (gMG) – e.g., improved MG-ADL total score, improved quantitative myasthenia gravis total score
   AND
4. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
5. The requested dose is within FDA approved labeling for the requested indication

Length of Approval: 12 months

Agent	Contraindication(s)
Soliris (eculizumab)	▪ Patients with unresolved serious *Neisseria meningitidis* infection ▪ Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

MG Activities of Daily Living (MG-ADL)

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

RATIONALE

Soliris is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.[1]

Atypical Hemolytic Uremic Syndrome (aHUS)

Soliris inhibits terminal complement-mediated intravascular hemolysis in patients with atypical hemolytic uremic syndrome (aHUS).[1]

Hemolytic uremic syndrome (HUS) is often diagnosed when there is simultaneous occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury; however, there are some individuals that will not present with these three findings. The most common cause of HUS is due to Shiga toxin-producing *Escherichia* coli (STEC) and complement dysregulation accounts for most of the non-STEC cases of HUS. Currently HUS is divided into 2 categories: primary causes without coexisting disease (e.g., complement dysregulation/atypical HUS) and secondary causes (e.g., infection, drug toxicity, pregnancy).[10,12] Atypical hemolytic uremic syndrome is a genetic, chronic, and progressive inflammatory disease caused by defects in regulation of the complement system. Patients have a risk of systemic clinical complications of

complement-mediated thrombotic microangiopathy (TMA), including damage to multiple organ systems.[1,5]

Most often the diagnosis of complement-mediated HUS is based on the clinical presentation of the classical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, and also the demonstration of complement dysregulation (due to gene mutations of complement proteins, or antibodies to complement factors). The minimum set of genes that should be screened includes *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5,* and *DGKE* (effectiveness of Soliris for individuals that have a DGKE mutation have not been established presumably because the underlying defect does not involve complement proteins[12]). However, screening for mutations and antibodies to complement proteins is not widely available. A differential diagnosis of complement-mediated HUS includes HUS due to other causes and conditions that are present concomitantly with anemia, thrombocytopenia, and acute kidney injury [e.g., screening for Shiga toxin-producing *E. coli* (STEC) for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) <10% activity for thrombotic thrombocytopenic purpura (TTP), screening for defective cobalamin metabolism (a rare cause of HUS)].[10]

Despite standard treatment with plasma therapy (exchange or infusion), many patients with aHUS progress to end-stage renal failure.[6] Current evidence suggests that Soliris improves renal function and outcomes related to thrombotic microangiopathy and is considered a first line treatment for aHUS.[5]

Generalized Myasthenia Gravis (gMG)
The precise mechanism by which Soliris exerts its therapeutic effect in generalized myasthenia gravis (gMG) patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.[1]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles as a result of antibody-mediated, T-cell dependent immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. Typically, there is a fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles affected.[1-3]

There are four therapeutic modalities used to treat MG including symptomatic treatments, chronic immunomodulating treatments, rapid immunomodulating treatments, and surgical treatment. Initial therapy for most patients with MG is an oral acetylcholinesterase inhibitor and may be all that is ever needed for treatment of symptoms for some patients. Pyridostigmine bromide (Mestinon) is the main cholinesterase inhibitor currently in use. The second therapeutic modality is an immunomodulating agent which is usually required for patients who remain significantly symptomatic on an acetylcholinesterase inhibitor, or who become symptomatic again after a temporary response to an acetylcholinesterase inhibitor. Even when immunomodulating agents are used, it is common to continue use of the cholinesterase inhibitor, in order to reduce the dosage of the immunosuppressive agents and minimize adverse effects. Rapid immunomodulating treatments include plasmapheresis and intravenous immune globulin (IVIG) which work quickly (over days) but provide transient benefit (weeks). Rapid immunomodulating treatments are most often used in the following situations: as a bridge to slower acting

immunotherapies, periodically to maintain remission in patients that are not well controlled with chronic immunomodulating agents, myasthenic crisis, and preoperatively before thymectomy or other surgery.[13]

Certain medications have established pharmacologic adverse effects on neuromuscular transmission. Use of these medications in a patient with MG can further reduce the effectiveness of neuromuscular transmission and cause increased clinical weakness. Medications that can cause a significant increase in weakness in patients with MG include fluoroquinolones, ketolides (particularly telithromycin) and aminoglycoside antibiotics, beta blockers, procainamide, quinidine, quinine, and magnesium. A number of other medications may unmask or exacerbate MG, particularly the neuromuscular blocking agents used during anesthesia, which can lead to prolonged postoperative weakness and ventilator dependence. Cautious use of these medications is advised whenever there is a clear requirement for any of these medications.[13]

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Similar to aHUS, Soliris inhibits terminal complement-mediated intravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) patients.[1]

PNH is a rare acquired hematopoietic stem cell disorder characterized by complement mediated hemolysis resulting in anemia, hemoglobinuria, complications related to the presence of free hemoglobin (depletion of nitric oxide), and several other unusual groupings of clinical findings.[7,11] Although hemoglobinuria can occur at any time in PNH, paroxysms of hemolysis at night leading to hemoglobinuria (characterized by red/pink/black urine) give the disorder its name.[11] PNH is mainly a disease of adults with a median age of onset in the thirties.[11] Flow cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH in the appropriate clinical setting (e.g., Coombs-negative hemolytic anemia).[11] Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH.[11] Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., RBCs and WBCs) to establish the diagnosis of PNH.[11]

Patients with PNH have a median survival of ten years after diagnosis.[7] Approach to therapy depends on the severity of symptoms and the degree of hemolysis. The only established therapies for patients with classical PNH are allogenic hematopoietic cell transplantation and complement inhibition with Soliris.[14] Soliris improves symptoms of PNH by reducing hemolysis, stabilizing hemoglobin concentrations, and decreasing the need for RBC transfusions.[1] Patients reported less fatigue and improved health-related quality of life when treated with Soliris compared to treatment with placebo.[1]

Soliris Safety[1]
Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Soliris has a boxed warning for an increased risk of meningococcal infections. It is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection and patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection. All patients without

a history for meningococcal vaccination should receive the vaccine at least two weeks prior to receiving the first dose of Soliris.[1]

Soliris Efficacy
aHUS
The efficacy of Soliris for the treatment of patients with aHUS was evaluated in 3 clinical studies including 2 single-arm, open label prospective studies in adults and adolescents and one retrospective study in pediatric patients 2 months to 17 years of age with the disease. The first prospective study (n=17) included patients with progressing thrombotic microangiopathy despite plasma therapy, and the second study (n=20) included patients who were receiving chronic plasma exchange or infusion but generally did not have evidence of ongoing thrombotic microangiopathy. In all three trials the endpoints evaluated were platelet count change from baseline, hematologic normalization (maintenance of normal platelet counts and LDH levels for at least 4 weeks), complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of 4 weeks), TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion and new dialysis requirement), and daily TMA intervention rate (number of plasma exchange or plasma infusion interventions (PE/PI) and the number of new dialysis required per patient per day).[1,5]

Study 1, enrolled 17 patients with aHUS who were refractory to plasma therapy (PE/(PI). Patients were treated for a minimum of 26 weeks (mean was 38 weeks). Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from 109 ± 32 $x10^9$/L at baseline to 169 ± 72$x10^9$/L by one week with the effect maintained through 26 weeks. Hematologic normalization (platelet counts and serum LDH concentrations) and complete TMA response were maintained by all responders. Renal function improved as indicated by increases in the eGFR from baseline and requirements for dialysis were reduced. Responses to Soliris was similar in patients with or without complement gene mutations.

Study 2, enrolled 20 patients with aHUS who were sensitive to plasma therapy (PE/PI). Patients were treated for a minimum of 26 weeks (mean was 40 weeks). Soliris reduced signs of complement-mediated TMA in this study as well. Platelet counts were maintained at normal levels despite elimination of PE/PI. The mean platelet count was 228 ± 78$x10^9$/L at baseline and 233 ± 69$x10^9$/L at week 26. Hematologic normalization (platelet counts and serum LDH concentrations) and complete TMA response were maintained by all responders. Renal function was maintained during Soliris therapy.

Study 3 (retrospective study), included 19 pediatric patients (2 months of age to 17 years). The median duration of Soliris therapy was 16 to 38 weeks depending on the age of the patient. Efficacy results were consistent with the results of Study 1 and 2. Soliris reduced signs of complement-mediated TMA, as shown by an increase in mean platelet counts of 171 ± 83$x10^9$/L at baseline to 233 ± 109$x10^9$/L one week after therapy with the effect maintained through 26 weeks (mean platelet count 254 ± 79$x10^9$/L).[1,5]

PNH
One randomized, double-blind, placebo-controlled 26-week efficacy study (TRIUMPH) evaluated Soliris in the treatment of PNH (n=87). Patients with PNH who had received at least 4 red blood cell transfusions during the 12 months prior to study entry were randomized to receive Soliris or

placebo for 26 weeks. Patients were permitted to continue supportive therapies for PNH such as anticoagulants and systemic corticosteroids. Primary endpoints were stabilization of hemoglobin above the level required for transfusion and number of packed red blood cells transfused during the study period. Secondary efficacy measures included hemolysis, change in the level of fatigue as measured by FACIT-fatigue score, and proportion of patients with transfusion independence. Stabilization of hemoglobin levels occurred in 49% of Soliris treated patients compared to 0% in the placebo group ($p<0.001$). The median number of packed red blood cells infused was zero in the Soliris group compared to ten in the placebo group ($p<0.001$). Transfusion independence was achieved by 51% of patients treated with Soliris compared to zero for placebo ($p<0.001$). Fatigue scores were improved with Soliris (+6.4 points) versus placebo (-4 points) ($p<0.001$). Hemolysis was also reduced with Soliris therapy compared to placebo ($p<0.001$).[8]

Generalized Myasthenia Gravis

A 26-week, phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study (REGAIN) was conducted to determine the safety and efficacy of Soliris in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis. Eligible patients (N=125) were at least 18 years old; had a positive serological test for anti-acetylcholine receptor antibodies; had a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or more; had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II-IV disease; had vaccination against *Neisseria meningitides*; and had previously failed treatment with at least 2 immunosuppressive therapies or one immunosuppressive therapy and chronic intravenous immunoglobulin or plasmapheresis/plasma exchange (given at least four times per year, for 12 months without symptom control). The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score, as measured by the worst-rank ANCOVA. The primary analysis showed no significant difference between Soliris and placebo (least squares mean rank 56.6 [SEM 4.5] vs 68.3 [4.5]; rank-based treatment difference -11.7, 95% CI -24.3 to 0.96; p=0.0698). However, there was a statistically significant difference in the change in MG-ADL score from baseline to week 26 between Soliris and placebo in a pre-specified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariates, (least squares mean -4.2 (SEM 0.49) vs. -2.3 (0.48); least squares mean difference of change in score with Soliris relative to placebo -1.9, 95% CI -3.3 to -0.6; p=0.006).[1,4] The REGAIN trial discussion notes, "using the repeated-measures analyses, the benefit of Soliris compared with placebo occurred within the first 4 weeks of treatment, with most of the effect achieved by 12 weeks."[4]

MGFA Clinical Classification[9]

Class	Features
I	Any ocular muscle weakness; may have weakness of eye closure; All other muscles are normal
II	Mild weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class	Features
IV	Severe weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
V	Intubation with or without mechanical ventilation (exception: intubation for routine perioperative management). The use of a feeding tube without intubation places a patient in class IVb.

REVISIONS

11-01-2018	Policy published 10-01-2018. Policy effective 11-01-2018.
	Policy added to the bcbsks.com web site.

REFERENCES

1. Soliris prescribing information. Alexion. February 2018.
2. National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet. NIH Publication No. 17-768. July 2018.
3. UpToDate. Diagnosis of myasthenia gravis. Accessed July 2018. Literature review current through June 2018.
4. Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase randomized, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017 Oct 20. pii: S1474-4422(17)30369-1. [Epub ahead of print].
5. Legendre, C.M., et al. "Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome — NEJM." *New England Journal of Medicine*, Alexion Pharmaceuticals., 6 June 2013. 368 (23): 2169-81.
6. Fakhouri, F., et al. "Insights from the use in clinical practice of eculizumab in adult patients with atypical hemolytic uremic syndrome affecting the native kidneys: an analysis of 19 cases." *American Journal of Kidney Diseases*. 2014;63(1):40-48.
7. Parker, Charles, et al. "Diagnosis and Management of Paroxysmal Nocturnal Hemoglobinuria." *Blood*. 2005; 106(12):3699-3709.
8. Hillmen, P., et al. "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria." *New England Journal of Medicine.* 2006; 355(12):1233-1243.
9. Myasthenia Gravis Foundation of America. Myasthenia Gravis: A Manual for the Health Care Provider (PDF). 2010. Accessed 07/2018. http://webcache.googleusercontent.com/search?q=cache:5Sv5wCrblaIJ:www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx+&cd=1&hl=en&ct=clnk&gl=us. http://www.myasthenia.org/LinkClick.aspx?fileticket=TPIgma-npRI%3D&tabid=125
10. UpToDate. Atypical hemolytic uremic syndrome. Accessed July 2018. Literature review current through June 2018.
11. UpToDate. Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria. Accessed July 2018. Literature review current through June 2018.
12. National Organization for Rare Disorders. Atypical Hemolytic Uremic Syndrome. Accessed Nov 2017.
13. UpToDate. Treatment of Myasthenia Gravis. Accessed July 2018. Literature review current through June 2018.
14. UpToDate. Treatment and prognosis of paroxysmal nocturnal hemoglobinuria. Accessed July 2018. Literature review current through June 2018.