Understanding and managing HELLP syndrome: The integral role of aggressive glucocorticoids for mother and child

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Aggressive glucocorticoids/corticosteroids
Obstetric

Antepartum or postpartum HELLP syndrome constitutes an obstetric emergency that requires expert knowledge and management skills. The insidious and variable nature of disease presentation and progression challenges the clinician and complicates consensus on universally accepted diagnostic and classification criteria. A critical review of published research about this variant form of severe preeclampsia, focused primarily on what is known about the pathogenesis of this disorder as it relates to patient experience with corticosteroids for its management, leads to the conclusion that there is maternal-fetal benefit realized when potent glucocorticoids are aggressively used for its treatment. Although acknowledging the need for definitive multicenter trials to better define the limits of benefit and the presence of any maternal or fetal risk, and given an understanding of the nature of the disorder with its potential to cause considerable maternal morbidity and mortality, we recommend for the present that aggressively used potent glucocorticoids constitute the cornerstone of management for patients considered to have HELLP syndrome.

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Recognition that a particularly potent form of preeclampsia-eclampsia exists has been evident since case reports first appeared in the late nineteenth and early twentieth century. Between 1950 and 1980, several case series were published that related patients and poor obstetric outcomes to clinical and laboratory findings that are consistent with what we recognize today as HELLP syndrome. Credit for formally consolidating the concept and creating the acronym of HELLP (H = hemolysis, EL = elevated liver enzymes and LP = low platelets) goes to Louis Weinstein who in 1982 reported a group of 29 pregnant patients he considered to have a distinct subset of severe preeclampsia/eclampsia. All patients expressed findings suggestive of microangiopathic hemolytic anemia with moderate-to-severe thrombocytopenia, misshapened erythrocytes on peripheral smear, and abnormal liver function tests usually in conjunction with epigastric pain, nausea, and vomiting. Severe hypertension and proteinuria were frequently coexistent as well.

Since 1982 there has been an outpouring of obstetric literature seeking to better define the pathogenesis, natural history, clinical spectrum, classification and management strategies for patients considered to have HELLP syndrome. Because the incidence of this disorder is low
(1-6 per 1000)\(^{19,20}\), most clinical research endeavors have been small, single institution case series or randomized trials. Until definitive large multicenter trials are undertaken, clinicians must rely on less robust information to guide patient care. Despite several recent comprehensive reviews on the subject of HELLP syndrome,\(^{21-24}\) none to date have examined the available data and patient experience primarily from the perspective of corticosteroid impact on disease expression and progression. The current review is constructed from this perspective, synthesizing and summarizing the pertinent English literature on HELLP syndrome to understand how corticosteroids appear to play an integral role in its management.

Pathogenesis and natural history

HELLP syndrome usually develops suddenly during pregnancy (27-37 weeks’ gestation) or in the immediate puerperium.\(^{25-28}\) As a form of severe preeclampsia, it likely has its origins in aberrant placental development, function, and ischemia-producing oxidative stress, which triggers the release of factor(s) that systematically injure the endothelium via activation of platelets, vasoconstrictors, and loss of normal pregnancy vascular relaxation.\(^{29-36}\) Although variable, HELLP syndrome onset and progression usually is rapid (35%-50% decrease in platelets per 24 hours; mean daily reduction of 40,000/µL platelets) as lactic acid dehydrogenase (LDH) and aminotransaminases (aspartate [AST] and alanine [ALT]) rise until 24 to 48 hours postpartum when laboratory values begin to recover.\(^{37-42}\) Absent corticosteroids, most patients (85%-90%) achieve platelets 100,000/µL or greater within 6 to 8 days of delivery or within 72 hours of platelet nadir, and total LDH/transaminases trend toward normal within 96 hours postpartum.\(^{37,41-43}\) Onset of disease occurs postpartum in approximately 15% to 25% of cases.\(^{25-28}\)

Although most patients with HELLP syndrome eventually exhibit hypertension and proteinuria, these 2 major signs of severe preeclampsia bear no consistent relationship with laboratory parameters of the underlying vasculopathy.\(^{26-28,38}\) A variety of symptoms can be elicited that are ambiguous, subtle, and focused primarily on the gastrointestinal-hepatic systems.\(^{28}\) The central place that the liver occupies in the disorder of HELLP syndrome is an important clue to pathogenesis. Severe epigastric/right upper quadrant pain often heralds underlying rapidly progressive disease.\(^{44}\) The extent of periportal hepatocyte dysfunction or cell death in a given patient probably correlates with the severity of maternal illness. Recall that CD95 (APO-1, Fas)-mediated apoptosis of hepatocytes is a major pathogenic mechanism for liver disease in general.\(^{45}\) The Fas-Fas ligand system is a well-studied cell death system that can mediate apoptosis. As a member of the tumor necrosis factor receptor superfamily, Fas is a 36 to 45 kDa type I surface protein containing a single transmembrane region.\(^{46}\) It induces apoptosis by binding to Fas-ligand, a 40 kDa type II transmembrane protein of the tumor necrosis factor receptor family.\(^{47}\) In the context of pregnancy and patients with HELLP syndrome, apoptosis in liver tissue and cytotoxic activity for primary human hepatocytes has been reported in serum from patients with HELLP syndrome (CD95 ligand produced by placenta) that increases over time and in proportion to disease severity.\(^{48}\) In addition, caspases 3, 8, and 9 are all required to effect apoptotic cell death, and active forms of all 3 are detected in liver extracts of HELLP patients. Blocking of CD95 signaling reduces the hepatocytotoxic activity of HELLP serum. Thus, systemic CD95L is a placenta-derived humoral factor that is involved in the pathogenesis of HELLP syndrome. CD95L-rich membrane fragments or soluble CD95L are postulated by Strand et al\(^{45}\) to be shed into the maternal circulation as important progenitors in the pathogenesis of HELLP syndrome.

The previously described findings and the proposal that placenta-derived proteins damage hepatic cells are compatible with many other findings that cast HELLP syndrome as a placenta-instigated, liver-targeted acute inflammatory condition and disordered immunologic process.\(^{21}\) The similarity between HELLP syndrome and systemic inflammatory response syndrome (SIRS) has been emphasized by several researchers.\(^{48-50}\) The perturbations present in patients who have HELLP syndrome develop may be additive to, or altered by, the pathophysiology leading to preeclampsia in general. A listing of some of the supportive evidence for these concepts is contained in Table I. Decreases in haptoglobin are a sequel, not an instigator of the vascular hemolytic process.\(^{66}\) In patients with HELLP syndrome, the metalloprotease ADAMTS-13 is not severely deficient or undetectable as it is in many patients with thrombotic thrombocytopenic purpura (TTP),\(^{69,70}\) No genetic markers or evidence for association with thrombophilic or antiphospholipid disorders have been established.\(^{71-75}\)

Diagnosis

The diagnosis of HELLP syndrome is most assured in a pregnant patient with signs and symptoms of preeclampsia-eclampsia and a triad of laboratory abnormalities suggesting red cell trauma (H = hemolysis), hepatic damage and dysfunction (EL = elevated liver enzymes), and thrombocytopenia (LP = low platelets). The greater the extent of laboratory abnormalities, the greater is the physician’s confidence in the diagnosis.

Thrombocytopenia may be the first indicator of disease when the results of a complete blood count return to the physician. A platelet count less than 150,000/µL represents mild (100,000-150,000/µL), moderate (50,000-100,000/µL), or severe (<50,000/µL) thrombocytopenia...
in the nonpregnant as well as pregnant patient. Requiring a threshold of less than 100,000/\(\mu\)L to consider the diagnosis of thrombocytopenia is ill advised. Maternal morbidity doubles from 11% to more than 20% when patients with severe preeclampsia have mild thrombocytopenia develop in association with increasing LDH (\(\geq 600\) IU/L) and transaminases (AST and/or ALT \(\geq 40\) IU/L). Significant pathology such as hepatic hemorrhage and rupture can first appear in the patient with HELLP syndrome before the platelet count falls below 100,000/\(\mu\)L. Indeed, the onset of epigastric pain in patients who are eventually diagnosed with HELLP syndrome has occurred at a platelet count as high as 283,000/\(\mu\)L in our patient population (unpublished). Hepatic injury and dysfunction

In Weinstein’s initial 1982 report, thresholds of what constituted abnormal serum levels of aspartate transaminase (AST), alanine transferase (ALT) and bilirubin to merit a diagnosis of HELLP syndrome were not stated. In healthy pregnant patients in our hospital laboratory exhibited normal transaminase values less than 20 IU/L, with greater than 48 IU/L for AST 3 SD above the mean. A threshold for AST of 70 IU/L or greater to qualify for the diagnosis of HELLP syndrome when platelets are 100,000/\(\mu\)L or less has been consistently advocated by Martin et al and Sibai. Transaminase values between 40 and 70 IU/L reflect borderline hepatic dysfunction regardless of the platelet count (especially in the 100,000-150,000/\(\mu\)L range). Glutathione S-transferase alpha has been proposed as a better marker for acute liver injury than the aminotransferases, but there has been limited work on this possibility.

**Erythrocyte injury and death**

Evidence for hemolysis is the third laboratory criterion for HELLP syndrome. In addition to a progressive anemia, other laboratory evidence of hemolysis classically includes decreased serum levels of haptoglobin, increased serum total LDH 600 IU/L or greater, increased serum AST, increased serum indirect bilirubin, an abnormal peripheral smear showing variable amounts of disrupted or destroyed red blood cells (schistocytes, echinocytes, burr cells), and/or a declining hematocrit or hemoglobin. Depending on laboratory methodology, LDH thresholds for abnormal values begin between 200 and 600 IU/L.

**Classification**

Classification systems have been created to enable physicians to identify patients at risk for significant maternal morbidity, to guide therapeutic intervention and assess efficacy or outcome, and to provide a common platform for comparison of research results. The 2 most commonly used systems for diagnosis and classification were developed in the 1980s by investigators at the Universities of Tennessee and Mississippi (Table II).

The **Tennessee Classification** defines “true” or “complete” HELLP syndrome if all of the following criteria are met: (1) moderate to severe thrombocytopenia with platelets 100,000/\(\mu\)L or less; (2) hepatic dysfunction with AST 70 IU/L or greater; and (3) evidence of hemolysis with an abnormal peripheral smear in addition to either total serum LDH 600 IU/L or greater or bilirubin 1.2 mg/dL or greater. The patient who exhibits some but not all of these parameters is termed “partial” or “incomplete” HELLP syndrome: ELLP syndrome (missing

<table>
<thead>
<tr>
<th>Table I</th>
<th>Research findings contributory to an inflammatory pathogenesis for HELLP syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum concentrations of soluble Fas.</td>
<td>Elevated serum concentrations of soluble Fas.</td>
</tr>
<tr>
<td>Cytokine and neutrophil-mediated liver injury in necropsy liver specimens with strong staining for tumor necrosis factor-alpha and neutrophil elastase antibody.</td>
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</tr>
<tr>
<td>Leukocytosis proportionate to disease severity.</td>
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</tr>
<tr>
<td>Increased plasma concentrations of anaphylatoxins C3a and C5a.</td>
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</tr>
<tr>
<td>Decreased unstimulated neutrophil oxygen radical production possibly secondary to an exhausted cellular response.</td>
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</tr>
<tr>
<td>Abnormal circulating cytokine concentrations.</td>
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</tr>
<tr>
<td>Increased bioactive tumor necrosis factor alpha possibly secondary to immune injury of the vascular endothelium or muscle.</td>
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</tr>
<tr>
<td>Depression of both T- and B-cell potential and impaired monocyte handling of intracellular pathogens precedes clinical/laboratory disease by 1-2 wks.</td>
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</tr>
<tr>
<td>Decreased placental vascular endothelial growth factor (VEGF) expression in placentas from HELLP syndrome pregnancies analogous to decreased circulating levels of free VEGF and platelet-derived growth factor (PLGF) in preeclamptic patients without HELLP syndrome.</td>
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</tr>
<tr>
<td>Dysregulation of VEGF ligands and receptors with higher serum VEGF compared to healthy matched pregnant controls (but less elevated than patients with non-HELLP preeclampsia.</td>
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</tr>
<tr>
<td>Hypersensitivity to pressors using laser-doppler digital fluxometry microcirculation studies.</td>
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</tr>
<tr>
<td>Increased intracellular retention of cadherin-5.</td>
<td>Increased intracellular retention of cadherin-5.</td>
</tr>
<tr>
<td>Increased plasma and red cell thiobarbituric acid reactive substances (TBARS) and glutathione peroxidase activity.</td>
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</tr>
</tbody>
</table>
evidence for hemolysis), EL syndrome (severe preeclampsia with mildly elevated liver enzymes only), HEL (hemolysis and elevated liver enzymes absent thrombocytopenia), or LP syndrome (low platelets syndrome as severe preeclampsia with thrombocytopenia, gestational thrombocytopenia, or immune thrombocytopenic purpura).22 Maternal and perinatal outcomes are progressively worse for patients with preeclampsia, partial HELLP syndrome, and complete HELLP syndrome, respectively.79 Incomplete criteria initially can progress to complete expression of HELLP syndrome.

The Mississippi-Triple Class System for HELLP syndrome divides patients into 3 classes or groups that are based primarily on the platelet portion of the laboratory diagnosis.21,28,38 Final class assignment or diagnosis is based on the lowest platelet count registered during the disease course. The span of thrombocytopenia between zero and 150,000 platelets is divided into 3 equal ranges consistent with mild, moderate, and severe thrombocytopenia. For a patient to merit a diagnosis of HELLP syndrome, class 1 requires severe thrombocytopenia (platelets ≤50,000/μL), evidence of hepatic dysfunction (AST or ALT ≥70 IU/L), and evidence suggestive of hemolysis (total serum LDH ≥600 IU/L); class 2 requires similar criteria except thrombocytopenia is moderate (>50,000 to ≤100,000/μL); and class 3 includes patients with mild thrombocytopenia (platelets >100,000 but ≤150,000/μL), mild hepatic dysfunction (AST and/or ALT ≥40 IU/L), and hemolysis (total serum LDH ≥600 IU/L). Peripheral smear findings and bilirubin abnormalities are not obtained.

Neither classification system is ideal; both have shortcomings. Because class 1 and 2 HELLP syndrome patients are combined in the Tennessee system, discrimination between groups and outcomes is difficult and benefit from corticosteroids (arrest of disease in class 2, prevention of progression from class 3 to 2 or even 1) cannot be demonstrated. On the other hand, the Mississippi classification system is very useful for directing individual patient therapy with aggressive corticosteroids and for comparing pregnancy outcomes. The Mississippi system, although including class 3 patients, does not include those with incomplete or partial forms of the disease, and excludes patients from analysis when causes of consumptive coagulopathy such as placental abruption are present. Two (Tennessee) or even 3 (Mississippi) groupings or classes insufficiently describe the multitude of clinical scenarios (antepartum vs postpartum, epigastric pain present or absent, degrees of laboratory value abnormality, different gestational age epochs) encountered by the clinician. The importance of a transitional group of patients is clearly demonstrated by instances of hepatic ruptures in patients with class 3 HELLP syndrome80 and other reports of increased eclampsia and higher perinatal morbidity/mortality in patients with incomplete/partial HELLP syndrome.21

### Table II

<table>
<thead>
<tr>
<th>HELLP class</th>
<th>Mississippi classification</th>
<th>Tennessee classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Platelet count ≤50,000/μL</td>
<td>Platelet count ≤100,000/μL</td>
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<tr>
<td></td>
<td>AST or ALT ≥70 IU/L</td>
<td>AST ≥70 IU/L</td>
</tr>
<tr>
<td></td>
<td>LDH ≥600 IU/L</td>
<td>LDH ≥600 IU/L</td>
</tr>
<tr>
<td>2</td>
<td>50,000/μL ≤ Platelet count ≤ 100,000/μL</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>AST or ALT ≥70 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH ≥600 IU/L</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>100,000/μL ≤ Platelet count ≤ 150,000/μL</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>AST or ALT ≥ 40 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH ≥ 600 IU/L</td>
<td></td>
</tr>
<tr>
<td>Partial HELLP/</td>
<td>N/A</td>
<td>(Severe preeclampsia + one of the following: ELLP, EL, LP)</td>
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<tr>
<td>incomplete HELLP</td>
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</tr>
</tbody>
</table>

ELLIP, Absence of hemolysis; EL, elevated liver functions; LP, low platelets.

### Imitators of HELLP Syndrome

Patients presumptively diagnosed with HELLP syndrome can have other disorders concurrent with HELLP syndrome or other disorders altogether. Lack of response to aggressive corticosteroid administration, especially with persistence of disease or first presentation of disease more than 7 days after delivery, should instigate testing to evaluate other diagnostic possibilities (Table III). In our experience, the most common HELLP imitators are patients with well-advanced acute fatty liver of pregnancy (AFLP), acute renal failure with acute tubular necrosis (usually not hemolytic uremic syndrome), “neglected” class 1 HELLP syndrome coming to medical attention too late for aggressive corticosteroids to prevent progression and multiorgan dysfunction, previously undiagnosed systemic lupus erythematosus/antiphospholipid syndrome, and either immune thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura (TTP).98 See the excellent reviews of potentially confusing conditions written by Goodlin16,99 and Sibai.100
Clinical presentation

Signs and symptoms with HELLP syndrome are variable but depend largely on the stage of the patient’s disease, whether class 1, class 2, or class 3. Right upper quadrant/epigastric pain is the most important symptom suggestive of underlying HELLP syndrome, found in 100% of Weinstein’s initial 1982 series of 29 advanced cases. Half of patients with class 1 HELLP syndrome, 33% with class 2, and 16% with class 3 compared with only 13% of severely preeclamptic patients without HELLP syndrome exhibit epigastric pain or right upper quadrant discomfort. Frequently epigastric pain occurs in association with nausea or vomiting. Overall, the incidence of epigastric pain/nausea/vomiting ranges between 30% and 90%. Any pregnant patient presenting in the second half of gestation with epigastric or right upper quadrant pain, particularly if associated with nausea and/or vomiting, has HELLP syndrome until proven otherwise. A pregnant patient with signs and symptoms of severe preeclampsia who suddenly has severe, writhing epigastric/upper abdominal pain develop likely has hepatic bleeding or rupture constituting an obstetric emergency.

Malaise or viral syndrome-like symptoms can occur with advanced HELLP syndrome. Headache occurs in a substantial number (33%-68%) of patients with any form of preeclampsia whether HELLP syndrome is present, with visual complaints in a lesser number.

Hypertension and proteinuria are not always present. Neither of these signs bears a consistent relationship in the individual patient with stage of disease, although on a population basis higher blood pressures and more proteinuria tend to occur more frequently as HELLP syndrome worsens from class 3 to 2 to 1 and eventually almost all patients are mildly hypertensive during the course of their disease and recovery. Significant dipstick proteinuria (3-4+) at presentation occurs in approximately half of patients with class 1 or 2 HELLP syndrome, but no proteinuria is detected in approximately 1:6 patients.

Although the presence and severity of symptomatology (epigastric pain, nausea, vomiting) and hypertension in general are related to maternal disease severity and the potential to develop severe morbidity, individual patient predictive value (with the probable exception of severe epigastric pain) is low. Significant maternal morbidity becomes more likely when 1 or more of the laboratory thresholds are exceeded as listed in Table IV. Very high LDH, AST, and/or uric acid have the highest predictive value and are risk-additive with worsening thrombocytopenia.

Maternal morbidity and mortality

The development of HELLP syndrome places the pregnant patient at significant risk for morbidity and mortality. Morbidity is categorized by major organ system(s) affected and is stratified by extent of disease using the Mississippi classification system. Constituents of these categories are listed in Table V and presented in decreasing order of frequency, emphasizing that there is enormous variability among patients.

Hematologic-coagulation

The prevalence of disseminated intravascular coagulation (DIC) increased from 2 of 193 patients (0.5%) with severe preeclampsia to 35 of 201 (17.4%) with class 1 HELLP syndrome, the latter very similar to the 15% incidence of DIC and 9% incidence of placental abruption reported by Audibert et al for classes 1

<table>
<thead>
<tr>
<th>Table III</th>
<th>Confounders and concurrent conditions: differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLP81</td>
<td>Lupus flare: Exacerbation of systemic lupus erythematosus (SLE)82,83</td>
</tr>
<tr>
<td>TTP84</td>
<td>Hemolytic uremic syndrome (HUS)85</td>
</tr>
<tr>
<td>ITP</td>
<td>Thrombophilias</td>
</tr>
<tr>
<td>Antiphospholipid syndrome76,83,86-91</td>
<td>Homozygous factor V Leiden</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Severe folate deficiency26</td>
</tr>
<tr>
<td>Cholangitis/cholecystitis/pancreatitis/ruptured bile duct</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Dissecting aortic aneurysm</td>
</tr>
<tr>
<td>Systemic viral sepsis (herpes, cytomegalovirus)93</td>
<td>SIRS/sepsis</td>
</tr>
<tr>
<td>Hemorrhagic or hypotensive shock</td>
<td>Stroke in pregnancy or puerperium</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria94</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Advanced embryonal cell carcinoma of the liver95</td>
<td>Acute cocaine intoxication</td>
</tr>
<tr>
<td>Myasthenia gravis96</td>
<td>Pseudocholinesterase deficiency97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Admission risk factors for significant maternal morbidity/mortality HELLP syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs/symptoms</td>
<td>Laboratory values</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Platelets &lt;50,000/μL</td>
</tr>
<tr>
<td>Nausea</td>
<td>Total serum LDH &gt;1400 IU/L</td>
</tr>
<tr>
<td>Vomiting</td>
<td>AST &gt;150 IU/L</td>
</tr>
<tr>
<td>Severe systolic hypertension</td>
<td>ALT &gt;100 IU/L</td>
</tr>
<tr>
<td>Severe diastolic hypertension</td>
<td>Uric acid &gt;7.8 mg/dL</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>CPK &gt;200 IU/L</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Serum creatinine &gt;1.0</td>
</tr>
</tbody>
</table>

Adapted from Martin et al.102

918 Martin, Rose, and Briery
and 2 combined. Clinically significant bleeding requiring transfusion and wound hematoma formation follow a similar pattern of increasing incidence with worsening disease.\textsuperscript{21,25-28,79,104,108} Approximately 10\% of patients with class 1 or 2 HELLP syndrome exhibit microscopic or macroscopic hematuria.\textsuperscript{28}

### Cardiopulmonary

The odds of developing a cardiopulmonary problem, particularly pulmonary edema, is more than doubled (2.2\times) for patients with class 1 HELLP syndrome (22\%) compared with non-HELLP severe preeclampsia.\textsuperscript{28,109} The overall percentage of 14.5\% (74/501) in the Mississippi series is similar to the combined 8\% incidence of pulmonary edema and less than 1\% incidence of adult respiratory distress syndrome in the Tennessee series.\textsuperscript{79} Copious large volume ascites identifies a patient at high risk for cardiopulmonary complications.\textsuperscript{110}

### Central nervous system/visual

Patients with noneclamptic class 1 or 2 HELLP syndrome (11/501 or 2.2\%) are 3.5 times more likely to have significant central nervous system (CNS) morbidity compared with class 3 HELLP syndrome or non-HELLP severe preeclampsia.\textsuperscript{28} This includes stroke, mental status changes and/or coma.\textsuperscript{111-114} Visual complications including retinal detachment, vitreal hemorrhage, and cortical blindness are infrequent in proportion to disease severity (1.4\% in class 1 and 2).\textsuperscript{28} These are usually short lived with full recovery within 1 to 6 months, except when cerebral hemorrhage/stroke is the cause.\textsuperscript{115-126}

### Renal

Placental abruption and puerperal onset of HELLP syndrome place the patient at increased risk for renal insult. In general, renal system morbidity increases as disease status worsens.\textsuperscript{28} All 4 of the patients with acute tubular necrosis in the Mississippi series had class 1 HELLP syndrome develop; acute renal failure complicated 3\% of cases of class 1 or 2 HELLP syndrome in the Tennessee series.\textsuperscript{26,79} However, acute renal dysfunction and/or failure has been described as often as 54\% and 33\% in some international series\textsuperscript{19,127} and as the most common cause of maternal morbidity in a report from Mexico.\textsuperscript{128}

### Hepatic

Catastrophic liver complications are relatively infrequent. Liver hemorrhage/rupture affected only 1% of patients with class 1 or 2 HELLP syndrome in the Tennessee series\textsuperscript{26,79} and only 3 patients had significant hepatic complications develop (2 subcapsular hematomas in class 2 and 3 HELLP syndrome patients, 1 liver rupture in a class 1 HELLP syndrome patient) in the Mississippi series—importantly all were classified as class 3 HELLP syndrome when the complication was first detected.\textsuperscript{27} According to Wicke et al,\textsuperscript{129} at least 1 of 5 patients with eventual liver rupture caused by HELLP syndrome had early subcapsular liver hematoma formation compatible with the class 3 level of disease.

### Infection/sepsis

Patients with HELLP syndrome more often have infectious morbidity develop than those with non-HELLP severe preeclampsia (43\% vs 20\%).\textsuperscript{25,27} At least 3 important variables are involved: corticosteroids, transfusion, and delivery. Corticosteroid utilization appears to reduce infectious morbidity from 43\% to 18\% by reducing or eliminating the need for transfusion of blood products.\textsuperscript{27,28} Abdominal delivery doubles infectious morbidity from 19\% to 41\%.\textsuperscript{28}
Obstetric issues

Cesarean delivery has been performed more often for patients with class 1 HELLP syndrome (61%) than class 2 (57%), class 3 (53%), or non-HELLP severe preeclampsia (48%). Mode of delivery is strongly influenced by gestational age, maternal-fetal status, class of disease, and corticosteroid utilization. Overall abdominal delivery is associated with a doubling of maternal morbidity (cardiopulmonary, hematologic-coagulation, and infectious) compared with vaginal delivery. In addition, risk for placental abruption, placenta previa, eclampsia, and episiotomy breakdown is increased compared to non-HELLP pregnancies.

Parity-eclampsia

The incidence of complications in hypertensive pregnant women varies by parity but not by gravidity. When HELLP syndrome complicates eclampsia, parous patients have double the incidence of significant maternal morbidity compared with nulliparous patients (50% vs 25%).

Other morbidity

Pancreatitis is uncommon in patients with preeclampsia or HELLP syndrome; the hemorrhagic form is uniquely associated with acute fatty liver of pregnancy. Diabetes insipidus, bone marrow necrosis with cerebral hemorrhage, and myocardial infarction are rare complications.

Mortality

Most deaths in patients with HELLP syndrome occur with class 1 disease (60%), and neurologic abnormality due mostly to cerebral hemorrhage/stroke is the most common system involved at autopsy (45%) (Figure 1). Delay in diagnosis appeared to be a factor in half of the deaths that could be adequately evaluated, and none of the 54 maternal deaths in the Isler et al series or in a subsequent case report occurred in association with the aggressive use of corticosteroids.

Perinatal morbidity and mortality

Perinatal morbidity and mortality are substantially higher in pregnancies with severe preeclampsia complicated by HELLP syndrome, primarily because of required preterm delivery. Fetal growth restriction and fetal distress after 32 weeks also may be more frequent. Although neonatal deaths and perinatal mortality rates tend to be progressively higher in parallel with increasingly severity of disease, outcomes are
primarily related to gestational age at delivery and not to disease status.\textsuperscript{28,141-146} Similarly, earlier prematurity is responsible for the higher perinatal mortality recorded in eclamptic pregnancies with HELLP syndrome compared with non-HELLP eclampsia.\textsuperscript{20,25,147} Neonatal survival was 100% in the Mississippi experience if newborn weight was 600 g or greater and following a full course and time interval (48 hours) of antenatal corticosteroids for fetal lung maturation.\textsuperscript{148}

Continuation of HELLP syndrome pregnancy beyond 26 weeks and the time necessary for steroid enhancement of fetal lung maturation increases the risk of stillbirth substantially.\textsuperscript{144,149} In the Mississippi series, stillbirth was almost tripled for class 1 or 2 compared with class 3 or non-HELLP severe preeclampsia,\textsuperscript{28} in part related to fetal growth restriction and placental abruption. Fetal growth restriction and abnormal Doppler velocimetry impact up to 39% and 48% of patients, respectively.\textsuperscript{22,136,150} Although neonatal thrombocytopenia occurs in a substantial percentage (up to 38%)\textsuperscript{130} of newborn infants, a higher incidence of intraventricular hemorrhage has not resulted.\textsuperscript{151,152} Long-term prognosis for the children of mothers with HELLP syndrome is comparable to controls matched for gestational age.\textsuperscript{152} Small-for-gestational-age neonates significantly increase weight and length over the first 4 years of life compared with matched controls.\textsuperscript{153} Newborn infants weighing less than 1250 g compared with birth weight-matched controls had significantly less cerebral palsy and mental disability at 3 years of life.\textsuperscript{146}

The integral role of corticosteroids

The probability that HELLP syndrome is a SIRS-like inflammatory form of severe preeclampsia\textsuperscript{50} leads to consideration of anti-inflammatory/immunosuppressive agents for treatment, specifically corticosteroids. The consistently favorable response of HELLP syndrome laboratory parameters to corticosteroids suggests the presence of an underlying corticosteroid-responsive step(s) in its pathogenesis and a therapeutic benefit to their use. Corticosteroids may act by one or more mechanisms to alter endothelial activity/interaction with circulating cells including erythrocytes and platelets, impact translation/transcription, interrupt hepatocyte damage by placenta-derived CD95-L and/or to disrupt signaling for inflammatory cytokine production by the endogenous immune system.\textsuperscript{154} A recent publication that thoroughly explores the pharmacology and physiology of corticosteroids relevant to pregnancy and HELLP syndrome is recommended to the interested reader for review.\textsuperscript{154}

The potential therapeutic value of corticosteroids for patients with HELLP syndrome was first recognized in the early 1990s by 2 groups of investigators, one in Denver\textsuperscript{155} and the other in Jackson, MS.\textsuperscript{156,157} The first 2 small randomized clinical trials (nonblinded, nonplacebo controlled) were undertaken in Jackson using intravenous (IV) high-dose dexamethasone versus no steroids during 1992 through 1993 in 65 patients with antepartum or postpartum HELLP syndrome.\textsuperscript{158,159} Stabilization and significant improvement in laboratory and clinical parameters associated with HELLP syndrome occurred in women who received antenatal and/or postpartum corticosteroids.\textsuperscript{158,159} Subsequent to the publication of these findings, retrospective scrutiny of selected data present in several published series of patients with severe preeclampsia from the 1970s and 1980s revealed findings consistent with this new observation that high-dose dexamethasone appeared to arrest the deterioration of laboratory parameters in patients fulfilling criteria for HELLP syndrome.\textsuperscript{16,139,160-162}

Four other small randomized, controlled trials have been undertaken comparing the use of high-dose dexamethasone or prednisolone (50 mg twice daily) with either no treatment, placebo, or with betamethasone. Two HELLP trials were undertaken antepartum\textsuperscript{63,163} and 2 evaluated postpartum corticosteroid treatment.\textsuperscript{164,165} Significantly improved biochemical parameters of HELLP syndrome and clinical parameters of mean arterial pressure and urinary output were consistently reported. In the most recently reported trial from The Netherlands,\textsuperscript{80} the prednisolone-treated group of 15 antepartum patients had a 50% reduction in HELLP syndrome exacerbations compared with 15 placebo-treated controls and a significantly shorter time to normalize postpartum platelets. All 3 major maternal complications occurred in the placebo group—formation of a liver hematoma in 2 patients and rupture of the liver in a third patient with maternal death. No significant neonatal differences between groups were noted in the immediate neonatal period or at infant follow-up.\textsuperscript{80}

On the basis of the findings from the first 2 prospective clinical trials and the preceding case series findings that led to the trials, interpreting them to collectively indicate a clear patient benefit to treatment, practice guidelines at University Hospital in Jackson were revised in mid-1993 to routinely initiate IV high dose (10 mg IV every 12 hours) dexamethasone antepartum or postpartum for (1) any patient with class 1 or 2 HELLP syndrome and (2) any patient with class 3 HELLP syndrome associated with epigastric pain, eclampsia, severe hypertension, and/or any evidence of major organ system morbidity. Patients with uncomplicated class 3 disease were monitored and subsequently treated if they met either of the 2 criteria.\textsuperscript{21,27,166,167} The dosage of drug used is approximately double that recommended for fetal lung maturation purposes and half the amount used for adults with newly diagnosed immune thrombocytopenic purpura.\textsuperscript{168,169} Postpartum and approximately 12 hours after the last antepartum
dose. IV dexamethasone is given twice more at 10 mg IV every 12 hours and usually tapered with 2 lesser doses of 5 mg IV every 12 hours for a full course. The regimen is lengthened or shortened to fit individual patient circumstances.167

Routine high-dose IV dexamethasone according to the Mississippi regimen is now in its twelfth year of practice utilization in Jackson; historical control groups from the era before 1992 when corticosteroid trials began are the only potential comparison groups of patients. Compared with 246 patients with class 1 or 2 HELLP syndrome treated between 1985 and 1991 when only 16% received a complete or incomplete course of corticosteroids to enhance fetal lung maturation, significantly reduced composite maternal disease was observed in 228 patients managed between 1994 and 2000 with 90% aggressive corticosteroid utilization. There were significantly improved laboratory parameters, less progression to class 1 HELLP syndrome, less frequent need for antihypertensive therapy, less requirement for transfusion, lower incidence of major maternal morbidity, and shortened postpartum recovery.170 Overall maternal morbidity rates of 64% for class 1 HELLP syndrome, 54% for class 2, and 40% for class 3 improved to 49%, 22%, and 21%, respectively, with an aggressive corticosteroid regimen compared with an 11% baseline for non-HELLP severe preeclampsia.25,27,28 Compara-

ble qualitative and quantitative benefits occurred in similarly treated patients with postpartum HELLP syndrome—a more rapid normalization of platelet counts and LDH values and a clinically significant reduction of indicated transfusion, need for intubation or intensive respiratory therapy, invasive hemodynamic monitoring, infectious- or bleeding-related morbidity, and length of postpartum hospital course.171

At least 7 other groups have also retrospectively reviewed case series and found that corticosteroids improve laboratory indices and positively impact HELLP syndrome severity and pathogenesis.172-178 Tompkins and Thiagarajah,173 for instance, interpret their data to show best benefit using 2 doses of intramuscular (IM) betamethasone (12 mg each) given 12 hours apart rather than the National Institutes of Health (NIH)179 recommended interval of 24 hours. The findings of O’Brien et al175 point toward accelerated (shorter interval) standard dose fetal lung maturation steroids (either 12 mg betamethasone IM every 12 hours × 2 or dexamethasone IV 6 mg every 6 hours), or a higher than Mississippi regimen of IV dexamethasone (10 mg every 6 hours × 2, then 6 mg every 6 hours × 2-4 doses) given to patients with antepartum HELLP syndrome to improve platelet counts, reduce liver enzyme abnormalities, and prolong latency to delivery in a dose-dependent manner.

In addition to these 13 publications, several other observations are offered that favor the routine inclusion of aggressive corticosteroids for patients with HELLP syndrome:

- Liver hemorrhage or rupture is rarely encountered in the undelivered pregnant patient with preeclampsia/eclampsia who is receiving corticosteroids for fetal lung maturation or aggressive corticosteroids for treatment of HELLP syndrome.21,28
- Liver complications may be particularly susceptible to interdiction with early aggressive corticosteroids, especially in the symptomatic class 3 HELLP syndrome patient with other underlying pathology.56 Pauzner et al36 noted recently that antiphospholipid syndrome was present in all 4 patients with hepatic infarction and HELLP syndrome (described as incomplete in 3 of 4 cases), and their literature survey noted that anticardiolipin antibodies and/or lupus anticoagulant were positive in 15 or 16 patients with hepatic complications for whom laboratory data were available. A similar series and a case report were published recently from France.90,91
- Because renal and/or hepatic dysfunction with HELLP syndrome exhibit can be exhibited very early in disease development before class 1 or 2 criteria are met, it is possible that routine initiation of aggressive corticosteroids in class 3 and “partial” HELLP patients might prevent disease progression and significant maternal hepatorenal morbidity.
- When aggressive corticosteroids are not used, significant maternal morbidity180 or mortality can occur that might otherwise have been avoided. For instance, HELLP syndrome developing in association with severe systolic hypertension above 160 mm Hg may enhance the potential of cerebral blood vessels to bleed when corticosteroids are absent from management. Among a highly selected group of 28 women with preeclampsia-induced severe systolic hypertension who had cerebral hemorrhage and stroke, 18 (64%) had evidence for concurrent class 1, 2, or 3 HELLP syndrome before the cerebral catastrophe and no patient had been a recent corticosteroid recipient.181 None of 54 patients dying with HELLP syndrome in the Isler series received corticosteroids, many of whom had CNS pathology.138 Corticosteroids use was not described in 104 patients from France with a 79% complication rate in the class 1 HELLP category.106 or in recent series from Germany, China, and Turkey with high rates of maternal morbidity,130,182,183 and they were usually absent from the management of patients with significant maternal morbidity reported before 1990.6,17
- Aggressive corticosteroids can effect an increase in platelet count sufficiently to undertake regional anesthesia (from 0% to 42%) and to enable cervical ripening, induction of labor and vaginal delivery.184,185 Up to 75% of patients with HELLP
syndrome can become candidates for regional anesthesia after high-dose corticosteroid administration if a platelet threshold of 75,000/µL is deemed adequate, and a higher rate of vaginal delivery can be accomplished than would otherwise be possible especially in relatively preterm gestations. In the absence of corticosteroid use, the cesarean rate is high and vaginal delivery is a rare event.

- A recent prospective randomized clinical trial undertaken in the authors’ hospital found no clear treatment benefit with postpartum high-dose dexamethasone for puerperal patients with non-HELLP severe pre-eclampsia at diagnosis. The only 2 patients to subsequently have postpartum HELLP syndrome develop were in the placebo group, and both responded quickly to the emergent initiation of IV dexamethasone after study assignment as placebo was ascertained.

**Choice of corticosteroid**

Although approximately equivalent in potency, IV dexamethasone appears to be more effective than IM betamethasone, perhaps by delivering the drug directly into the vasculature of the affected organ systems. Preferences for other regimens by others were listed earlier. Sibai recommends an aggressive corticosteroid regimen similar in potency to the Mississippi protocol (dexamethasone 10 mg IV every 12 hours) for antepartum HELLP syndrome to improve maternal status, using 2 doses of either betamethasone 12 mg IM every 12 hours (instead of every 24 hours) or dexamethasone 12 mg IV (instead of 5 or 6 mg) every 12 hours with delivery to be accomplished within 24 hours after the last dose of corticosteroids. Determination of preferred drug, dosage, and regimen specific to clinical circumstances awaits large multicenter studies.

**Potential maternal-fetal risks**

Potential maternal risks include rebound thrombocytopenia, adrenal suppression, infection, and the masking of potential complications or other disease processes. The available data are insufficient to estimate if there are any adverse short- or long-term neonatal-infant effects from brief aggressive corticosteroids for HELLP syndrome. Neither dexamethasone or betamethasone is preferable from the fetal perspective in regard to short-term outcomes. The use of aggressive corticosteroids for antepartum HELLP syndrome is recommended exclusively as a short-term intervention; continuation of pregnancy after more than 48 hours of aggressive corticosteroid administration for very preterm HELLP syndrome pregnancy can lead to significant maternal and fetal morbidity and mortality. Evidence is meager (few case reports) regarding corticosteroid prolongation for many days to weeks of a preivable HELLP syndrome pregnancy to viability, and long-term potentially adverse implications to the newborn infant remain a question. Lower birth weight, lower head circumference, neonatal adrenal suppression, and increased infection are theoretical risks to a newborn infant exposed to even a very short course of high-dose corticosteroids, but evidence for this is lacking. Potent glucocorticoids used for pregnancies with HELLP syndrome may actually impart a fetal advantage because placental vascular resistance by Doppler assessment appears to be reduced briefly in singleton and multiple gestations after maternal betamethasone administration. In pregnant ewes receiving extended dexamethasone prenatally (20 days with 20 µg/kg maternal body weight), no evidence of altered renal function or predisposition to adult hypertension compared with controls was found.

**Summary**

Despite current limitations in sample size and study structure, a consistent positive picture of patient benefit emerges from a review of the present literature that we suspect will be shown definitively once large multicenter clinical trials are undertaken. This is consistent with our considerable bedside experience gained over many years and in a multitude of patient circumstances and situations that a routine practice of initiating aggressive corticosteroids early in HELLP syndrome pregnancies will prevent them from progressing along a continuum of worsening morbidity, a critically important concept for clinicians to embrace to reduce maternal mortality rates in patients with this disease. In view of the absence of a demonstrated downside to this approach either for the mother or the fetus, given the body of affirmative available literature, we believe it most beneficial to patients now to be managed according to the recommendations that follow.

**Fundamentals of practice—The application of aggressive corticosteroids**

The fundamental management concepts for treatment of patients with HELLP syndrome using aggressive corticosteroids is presented in core concepts (Table VI) and as an algorithm (Figures 2 and 3). Further considerations are discussed in paragraphs to follow.

In any patient suspected of having HELLP syndrome, basic laboratory evaluation includes a complete blood count with platelets, serum AST, and total serum LDH. Extended assessment can include serum creatinine, glucose, bilirubin, coagulation studies, and a peripheral smear. Elevation of direct bilirubin and prolongation of coagulation studies out of proportion to mild thrombocytopenia occurs early in patients with AFLP but is unusual with HELLP syndrome unless the disease is very advanced (class 1).
An aggressive corticosteroid regimen is initiated as soon as the diagnosis of class 1 or 2 HELLP syndrome is made or if the patient has complicated class 3 HELLP syndrome. Continuation during cervical ripening and induction of labor can be used to facilitate attempted vaginal delivery or to improve the mother’s hematologic status before abdominal delivery. If the fetus is preterm and preivable such that cesarean delivery is not a fetal consideration, presence or absence of fetal heart tones is assessed intermittently to determine whether a neonatal team should be summoned at delivery to assess the reasonableness of resuscitation efforts. Rarely a pregnancy with borderline viability has been prolonged with aggressive corticosteroids but this is not usually recommended. It is particularly discouraged in a patient with a fetal abnormality or major maternal morbidity such as renal failure. HELLP syndrome detected before fetal viability may identify a pregnancy complicated by partial mole/triploidy, trisomy 13, antiphospholipid syndrome, autoantibodies to angiotensin AT(1)-receptor, or severe preterm preeclampsia with “mirror” syndrome.

Maternal-fetal status, gestational age, presence of labor, cervical Bishop score, prior maternal obstetric history, and response to aggressive corticosteroids all impact management of the patient with a preterm viable fetus and HELLP syndrome. Immediate cesarean delivery is not generally indicated or recommended; vaginal or cesarean delivery after 24 to 48 hours of corticosteroids are better options to achieve maximal maternal and fetal benefit. Vaginal delivery rates of 32% for gestations less than 30 weeks, 61% at 30 to 31 weeks, and 62% at 32 to 33 weeks (overall induction success 145/247 or 59%, 37% <28 weeks) can be achieved. Nevertheless, because vaginal delivery rates with HELLP syndrome are below 50% for gestations less than 30 weeks, Sibai advocates elective cesarean delivery for all women diagnosed with HELLP syndrome at a gestation age less than 30 weeks when spontaneous labor is not present and the Bishop score is less than 5. A patient with a low Bishop score in association with fetal growth restriction and/or oligohydramnios may not be a good candidate for trial of labor. Otherwise, vaginal delivery is attempted in patients in active labor less than 30 weeks with ruptured membranes or with a Bishop score 5 or more in the absence of obstetric contraindications. Once the 30-week gestational age threshold is reached, an attempt at vaginal delivery is usually recommended while aggressive corticosteroids are initiated.

Epidural or spinal anesthesia is the preferred anesthetic for patients with preeclampsia. Approximately 50% of patients with HELLP syndrome can be candidates for regional anesthesia during a trial of labor using...
a threshold of 100,000/µL platelets. In these circumstances, the decision of abdominal versus vaginal delivery becomes more of an obstetric issue rather than a response to a rapidly worsening maternal-fetal condition. Furthermore, patients who receive regional anesthesia avoid the greater risks associated with general anesthesia. When motivated, providers can depend on corticosteroids to improve maternal platelet counts sufficiently to increase the epidural rate for patients with HELLP syndrome from 0% to 57%. When cesarean delivery without trial of labor is planned, waiting approximately 6 hours after beginning an aggressive corticosteroid regimen is recommended to stabilize the disease process, improve laboratory parameters, enable institution of regional anesthesia, and reduce the need for platelet or red cell transfusion. Given the absence of neurologic or hematologic complications with regional anesthesia in HELLP syndrome patients managed in Panama without corticosteroids or platelet count restrictions, the likelihood of bleeding complications with regional anesthesia is small.

Aggressive corticosteroid administration is associated with a significant decrease in the required use of blood products and consequently a secondary decrease in infectious morbidity. When emergent cesarean delivery must proceed without waiting for a steroid effect and/or in the rare patient with advanced disease and a platelet count less than 40,000/µL that is unresponsive to corticosteroid use, platelet transfusion of 6 to 10 units of platelets is recommended immediately prior to intubation.

Prevention of severe systolic hypertension (>160 mm Hg) is paramount; recommendations to maintain systolic pressures under 155 mm Hg and diastolic pressures under 105 mm Hg are reasonable goals. Labetalol, hydralazine, or nifedipine are the preferred agents for treatment of acute hypertension in this setting with infused dilute nitroglycerin held in reserve. There have been no randomized trials of cesarean operative technique for patients with HELLP syndrome. Delayed skin closure or type of skin incision do not appear to influence the frequency of wound complications. The treatment is tailored to the patient; corticosteroid dosage is reduced once an upward trend in platelets and

![Figure 2](image-url) HELLP management algorithm: aggressive corticosteroids.
a downward trend in total serum LDH is recorded, and discontinued with normalization of HELLP laboratory parameters and resolution of signs and symptoms of preeclampsia.

Significant renal injury is infrequently encountered in patients with HELLP syndrome unless placental abruption or a major hemorrhage also occurs. Most often renal dysfunction responds to measures short of dialysis or only a brief course of dialysis. Because a convincing renal benefit to aggressive corticosteroids has not been demonstrated, the basic patient management principles for patients with acute renal failure are used.

Almost all instances of spontaneous subcapsular hematomas or hepatic rupture in pregnancy occur in association with HELLP syndrome. As thrombocytopenia worsens into the lowest ranges (class 1), in conjunction with the onset of sudden epigastric pain, the likelihood of finding abnormal hepatic imaging with computed tomography or magnetic resonance imaging increases. For reasons given earlier, we speculate that it benefits patient care to immediately begin aggressive corticosteroids for any patient with suspected HELLP syndrome and having hepatic injury develop, regardless of disease class. Several excellent treatises have been published recently that review the management of HELLP-related hepatic complications such as hepatic rupture.

**Beyond corticosteroids**

Plasma exchange or plasma infusion have been used sparingly for recalcitrant and/or complicated HELLP syndrome that is unresponsive to standard therapy. Some of the postulated mechanism of actions include (1) clearance from the circulation of debris, toxins, antigen-antibody complexes, damaged red cell components or other substances that may be compromising normal coagulation and organ function; and (2) replacement of fluid, clotting factors, proteins, and other plasma components that are required to achieve homeostasis and healing. Prevention of intravascular fluid overload is enhanced versus straight transfusion, particularly in the patient with compromised renal function. Collaborative care with intensivists and hematologist/transfusion medicine subspecialists is imperative. Because patients in these circumstances are rare, unique, and difficult to accurately quantify, randomized
clinical trials are unlikely to be undertaken or even feasible. Thus, the role of plasma exchange in HELLP syndrome management remains controversial but less frequently a concern we speculate because of early diagnosis and aggressive corticosteroids.

There is little evidence suggesting efficacy to the use of heparin, activated factor VII, or haptoglobin for treatment of HELLP syndrome. Attempted prolongation of pregnancy with hydration and antihypertensives is not recommended because it is associated with increased maternal and perinatal morbidity related to placental abruption and hepatic rupture.

**Prognosis: Recovery**

Patients with HELLP syndrome usually recover completely, although relapses can occur in the absence of corticosteroid administration. After-effects of disease can persist for extended periods if hepatic or renal damage has occurred. Long-term follow-up of mothers and children from HELLP syndrome pregnancies are few in number. Renal function was not permanently impaired in 23 women with acute renal failure and HELLP syndrome who were monitored an average of 4.6 years; 8 patients had 11 subsequent pregnancies, 9 of which were term gestations. Similar normalization of renal function after a HELLP syndrome pregnancy was reported by Jacquemyn’s Belgian group, but higher systolic and diastolic blood pressures were observed at 5 years compared with controls. In Amsterdam, the incidence of subsequent hypertension requiring treatment was 3 times higher than controls. In the absence of acute renal failure, there was no detectable impairment of renal function at least 5 years after HELLP syndrome in 10 patients. Stroke in patients with HELLP syndrome left residual defects in 10 of 13 patients (77%) who survived the acute insult. No permanent adverse effects on liver function have been reported. Emotional trauma, both immediate and delayed, can be a significant patient issue.

**Patient counseling: Future pregnancy**

Women with a prior history of HELLP syndrome carry an increased risk of at least 20% (range 16%-52%) that some form of gestational hypertension will recur in a subsequent gestation. The rate of recurrent HELLP syndrome itself varies between 2% and 19% depending on the population studied, gestational age at onset, whether there is concurrent vascular disease of any type, and very likely the unique genetic profile of the individual patient, her partner, and her progeny.

In the Mississippi study with a 75% African-American profile, the recurrence risk was 42% to 43% for any type of preeclampsia-eclampsia, but this increased to 61% if the preceding affected pregnancy was very preterm (<32 weeks). To date, anything other than close monitoring of subsequent pregnancies for problems of prematurity and preeclampsia (preterm labor, bleeding, fetal growth restriction) has not been superceded by specific testing or augmented by effective preventative measures. Testing for LCHAD mutation (long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency) is rarely positive in patients with HELLP syndrome in contrast to the situation with AFLP and therefore not recommended.

**Challenges and conclusions**

An expanded, more inclusive disease classification system for HELLP syndrome is needed particularly if the potential for early aggressive corticosteroids to avert most significant maternal morbidity is to be studied adequately in appropriately structured, large multicenter clinical trials. Some form of a composite maternal morbidity index also is needed to better describe the spectrum of systemic morbidity potentially experienced by mothers with this condition. As expected with a disease process with variable rates of progression, different stages at initial presentation, alteration by various interventions, and characterization by inconsistent and variable laboratory methodologies, there has been a lack of consensus among researchers and confusion among clinicians. The issue of standardization of diagnosis and disease classification is an important goal, so that research findings are comparable and recommended clinical managements can become progressively more evidence based.

We believe that the scientific community is on the threshold of a much better understanding of the pathogenesis of HELLP syndrome specifically and preeclampsia-eclampsia in general. Knowledge of the findings related to the pathogenesis and pathophysiology of this disorder and the ameliorating effect of corticosteroids on the disease process is foundational to understanding the challenges of diagnosis, classification, and management. A patient can present initially anywhere along the spectrum of disease development, and disease expression is influenced by whether corticosteroids have been given for any reason. Thus, the accurate interpretation of any publication about HELLP syndrome requires a clear description of when in the development of HELLP syndrome laboratory or research testing was performed to study its pathogenesis or make its clinical diagnosis, including a statement of the presence or absence of corticosteroids during patient management ideally noting at what stage in disease these agents and dosages were given to the patient. Large-scale multicenter trials investigating various corticosteroid regimens for patients with this spectrum of HELLP syndrome conditions are desirable (including various types that cross or do not cross into the fetal circulation), with...
particular attention to define benefits and limitations according to the stage and circumstances in which therapy is initiated. Risk factors for severe renal and hepatic complications of HELLP syndrome require further investigation with regard to concurrent predisposing conditions such as antiphospholipid syndrome. Although short-term utilization of corticosteroids as currently used has not been shown to negatively impact the fetus or neonate, surveillance for possible adverse effects should continue. We believe that widespread dissemination of the information presented herein to practicing clinicians—better recognition through cognition and a management scheme focused on early aggressive corticosteroid administration—is needed now to minimize maternal-perinatal morbidity and mortality with this condition while more extensive study continues.

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