HEMOLYTIC UREMIC SYNDROME

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Disclosures

- None

Hemolytic uremic syndrome

- 1955 – Gasser et al. described in 5 patients:
  - “Bilateral necrosis of the renal cortex in acute acquired hemolytic anemia”
  - Specific findings noted
    - Microangiopathic hemolytic anemia (MAHA)
    - Thrombocytopenia
    - Acute renal failure

What is MAHA?

- MAHA
  - “subgroup of hemolytic anemia causes by factors in the small blood vessels”

What do you see?

- Schistocytes
- Helmet Cells

MAHA
Causes of MAHA

- DIC
- DIC
- Malignancy
- OB complications
- Trauma
- Sepsis
- TTP
- HUS

Pathophysiology of HUS

E. Coli’s association with HUS

- 1983-1985 – initial identification that E Coli 0157.H7 associated with HUS
  - Smith HR – Phage determined production of vero cytotoxin strains of Escherichia coli serogroup O157 (Lancet 1984)

E. Coli’s association with HUS

- 1983-1984 – initial identification that E Coli 0157.H7 associated with HUS
  - Karmali MA – Sporatic cases of HUS associated with faecal cytotoxin and cytotoxin-producing Escherichia coli in stools (Lancet 1983)

E. Coli’s association with HUS

- 1983-1985 – initial identification that E Coli 0157.H7 associated with HUS
  - Hemolytic-uremic syndrome associated with Escherichia coli 0157.H7 enteric infections (MMWR 1985)
What else causes HUS?

- E coli seemed to only account for 80+% of cases. What was leading to the other cases?

Pneumococcus and HUS

- 1989: Possibility of pneumococcal disease with HUS
  - HUS and Thomsen Friedenrich antigen (McGraw ME Pediatric Nephrology 1989)

What else causes HUS?

- Now at 90+% of cases – what makes up the remainder?

Pneumococcus and HUS

- HUS reported with streptococcus pneumoniae meningitis (Martinot A 1989 Eur J Pediatrics)
  - "recommend that HUS must be considered in cases of renal failure and/or anemia associated with pneumococcal meningitis"


- "The incidence of recurrence of HUS in renal allografts appears to vary by center...It is possible that the high rate of HUS recurrence at this institution reflects a transplant population skewed towards patients with a form of HUS that is more likely to recur in the allograft"


- 18 of 24 patients had atypical HUS
  - 3 with classical HUS
  - 3 indeterminate
  - 18 of 24 patients had atypical HUS
  - 16 episodes of recurrence in 14 grafts
  - Timing ranged from within the first week to 10.5 years after transplant

- Atypical HUS

- Causes of HUS
  - Infection related
    - E Coli 0157:H7
    - Other forms of E Coli
  - Other infection
    - Pneumococcal
  - Complement factor abnormality
    - Factor H deficiency, Factor I deficiency
  - Miscellaneous
    - Malignancy, Drugs, etc.

- Pathophysiology of E Coli HUS
  - E Coli HUS
    - Shiga-toxin producing forms of E coli
    - Shiga-toxin leads to enterocolitis with associated bloody diarrhea
    - Injury to the endothelial cells
    - Fibrin formation

- Pathophysiology of Pneumococcal HUS
  - Pneumococcal HUS
    - Neuraminidase mediated
    - T-Antigen exposure
Atypical HUS

1981 – first case of HUS with factor H deficiency described
1998 – 3 families with HUS provided association with CFH

Complement abnormalities and aHUS

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Source</th>
<th>Location</th>
<th>% of aHUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor H</td>
<td>CFH</td>
<td>Liver</td>
<td>circulates</td>
<td>~15-30%</td>
</tr>
<tr>
<td>Factor I</td>
<td>CFI</td>
<td>Liver</td>
<td>circulates</td>
<td>~5-10%</td>
</tr>
<tr>
<td>Membrane</td>
<td>MCP</td>
<td>Widespread</td>
<td>Membrane bound</td>
<td>~10-15%</td>
</tr>
<tr>
<td>Complement</td>
<td>CFH</td>
<td>Liver, ?</td>
<td>circulates</td>
<td>~&lt;5%</td>
</tr>
<tr>
<td>Anti-FH-Ab</td>
<td>C3</td>
<td>Lymphocyte</td>
<td>circulates</td>
<td>~5-10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
<td></td>
<td>~10%</td>
</tr>
</tbody>
</table>

Evaluation of aHUS

- Key atypical features requires consideration for plasma exchange

- C3 level should be part of every HUS evaluation
Evaluation of aHUS

- Key atypical features requires consideration for plasma exchange
- C3 level should be part of every HUS evaluation
- Patients with aHUS should undergo genotyping for the most up-to-date list of complement-related disorders

Plasma therapy

- Fluid phase complement proteins reside in plasma and are subject to plasma therapy
- Plasma Infusion
  - Repletes but does not remove mutant protein
- Plasma Exchange
  - Removes mutant protein and repletes

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- Plasma Infusion
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  Many anecdotes with prolonged preservation of kidney function in patients with CFH mutation, though most eventually suffer ESRD:
  Benefit is not clear for MCP mutations – most episodes seem to recover with or without exchange
Eculizumab therapy

- 2013 – Eculizumab described in NEJM

Eculizumab therapy

- 2011 – approved by FDA
- 2013 – Eculizumab described in NEJM

“Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with aHUS”

Eculizumab mechanism of action

- Eculizumab
  - Terminal complement inhibitor
  - Monoclonal antibody
  - Blocks generation of proinflammatory C5a and C5b-9
Eculuzimab side effects

- Headaches
- Diarrhea
- Hypertension
- URI
- Abdominal pain
- Vomiting
- Nausea
- UTI
- Edema
- Fever

Eculuzimab side effects

- Imunosuppression!!!
- FDA: “Solaris (aka eculuimab) works by blocking part of your immune system. This can help your symptoms but it CAN also increase your chance for infection”

“Call your doctor or get emergency medical care right away if you have any of these signs:”

- Headache with nausea or vomiting
- Headache and a fever
- Headache with stiff neck or stiff back
- Fever of 103 F or higher
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eye sensitive to light

Eculuzimab therapy

- Every 2 weeks
- IV
- Duration: “life long”
What else causes HUS?

- 95+% of cases are E Coli, pneumococcal, or complement mediated