Identification, Diagnosis, and Management of Acquired Hemophilia A (AHA)

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Background AHA Information

- AHA is an autoimmune bleeding disorder caused by development of inhibiting antibodies against coagulation factors, most commonly factor VIII
- Incidence increases with age, reaching ~1.5 per million people per year among older patients
- Possible etiologies: ~50% is idiopathic
  - Other etiologies include autoimmune disease, pregnancy, malignancy, and drugs

AHA: Underlying Conditions (≥3%)

European Acquired Haemophilia (EACH2) Registry (N=501)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (idiopathic)</td>
<td>51.9</td>
</tr>
<tr>
<td>Malignancy (solid tumors ~2X hematologic)</td>
<td>11.8</td>
</tr>
<tr>
<td>Autoimmune diseases (RA=34.5% of these)</td>
<td>11.6</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>8.4</td>
</tr>
<tr>
<td>Infection</td>
<td>3.8</td>
</tr>
<tr>
<td>Drugs (β-lactam antibiotics &gt; clopidogrel &gt; non-β-lactam antibiotics &gt; interferon &gt; NSAIDs &gt; others)</td>
<td>3.4</td>
</tr>
</tbody>
</table>

RA = rheumatoid arthritis; NSAID = nonsteroidal anti-inflammatory drug.
AHA: Principles of Treatment

- Clinicians not experienced in treating AHA should consult a hemophilia treatment center.
- Primary goals of treatment:
  - Restore hemostasis
  - Eradicate the inhibitor

AHA: Treatment Options

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic agents</td>
<td>pd-aPCC, rFVIIa, high-dose FVIII concentrate, DDAVP, antifibrinolytics</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>Prednisolone, cyclophosphamide, CsA, IVIg, vincristine, MMF, azathioprine</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Inhibitor-eradication procedures</td>
<td>Immunoadsorption, immune tolerance induction, plasmapheresis</td>
</tr>
</tbody>
</table>

pd-aPCC = plasma-derived activated prothrombin complex concentrates; rFVIIa = recombinant activated factor VII; DDAVP = desmopressin; CsA = cyclophosphamide; IVIg = intravenous immunoglobulin; MMF = mycophenolate mofetil.

Clinical Case 1

- 72-year-old woman presents with apparent diffuse subcutaneous bleeding
- No personal or family history of bleeding disorder
- No recent trauma or illness
- Not taking any drugs known to cause bleeding

Clinical Question

What is the most important differentiating clinical factor between AHA and CHA?
A. CHA is usually apparent at earlier ages than is AHA
B. CHA is usually a diagnosis of exclusion, whereas AHA is not
C. The first time patients and clinicians become aware of the presence of AHA, it may be because of a dangerous bleed
D. AHA is manifested more often in the skin and soft tissues, whereas bleeding in the joint is seen in CHA but not often in AHA
Clinical Question 1 Discussion

- “B” is not true: AHA is most often a diagnosis of exclusion, as bleeding is observed in a patient without a personal or family history of hemophilia, so this diagnosis may not be top of mind, and other possible reasons may be explored first.  
- Both “A” and “D” are true
  - Unlike CHA, AHA is primarily seen in older patients, except for a surge among immediately postpartum women in their 20s and 30s.  
  - Bleeding in the joints is rarely seen in AHA, whereas it is very common in CHA; conversely, in AHA bleeding is most often seen in skin and soft tissue.  
- Neither “A” nor “D,” however, is the most important differentiating factor  
- Index Bleeding Episodes: Causes and Sites

European Acquired Haemophilia (EACH2) Registry (N=501): 474 episodes (94.6%), 333 severe

<table>
<thead>
<tr>
<th>Precipitating event</th>
<th>% Total</th>
<th>% Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (spontaneous)</td>
<td>77.4</td>
<td>76.0</td>
</tr>
<tr>
<td>Trauma</td>
<td>8.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Surgery</td>
<td>8.2</td>
<td>9.1</td>
</tr>
<tr>
<td>Childbirth</td>
<td>3.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>% Total</th>
<th>% Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>53.2</td>
<td>46.2</td>
</tr>
<tr>
<td>Deep (musculoskeletal, retroperitoneal)</td>
<td>50.2</td>
<td>65.0</td>
</tr>
<tr>
<td>Mucosa</td>
<td>31.6</td>
<td>34.4</td>
</tr>
<tr>
<td>Joint</td>
<td>4.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>


- “C” is true; this is the most important differentiating factor between CHA and AHA  
  - Clinicians are not likely to be aware that patients have a coagulation defect until it is manifested in a major bleed, which can be a source of significant morbidity and mortality and may explain why patients with AHA have higher bleeding-related mortality rates than do those with CHA with inhibitors.  
  - The majority of patients with AHA present with a major bleeding event that will not respond to typical treatment strategies for hemorrhage.  
- Delayed or inaccurate diagnosis may impact treatment selection, initiation, and outcomes.

Clinical Question 2

What is the most accurate laboratory evidence of AHA?
A. Prolonged prothrombin time (PT)
B. Isolated, prolonged activated partial thromboplastin time (aPTT) with normal PT and platelet count
C. Thrombocytopenia associated with normal PT and aPTT
D. Bleeding associated with normal PT and aPTT
Clinical Question 2 Discussion

- A prolonged PT indicates other conditions, such as liver disease, vitamin K deficiency, or disseminated intravascular coagulation
- Thrombocytopenia with normal PT and aPTT is also not indicative of AHA; the platelet count is typically normal in AHA
- Nor is bleeding with normal PT and aPTT a sign of AHA; in fact, a small proportion of patients with AHA may present without an active bleed
- “B” is correct; in AHA, the PT and platelet counts are normal
- The prolonged aPTT is often the only laboratory sign of AHA, so even a minimally prolonged aPTT should be investigated, especially if the patient is bleeding
- The presence of an inhibitor rather than factor deficiency is confirmed by a mixing test
  - Mixing patient plasma with normal plasma will not correct the prolonged aPTT in the presence of an inhibitor
  - Lupus anticoagulants can mimic AHA and should be ruled out

Diagnostic Algorithm for AHA

Clinical Question 3

In the presence of a diagnosis of AHA, what should be the initial therapeutic intervention for a bleeding patient?
A. DDAVP
B. High-dose FVIII
C. rFVIIa
D. All of the above are equally effective
Clinical Question 3 Discussion

- This question addresses the first of the 2 primary goals of treatment: Restore hemostasis
- There is no high-level evidence supporting selection of any one treatment²
- That said, bypassing agents are the preferred first-line therapy for bleeding in patients with AHA²
- Both DDAVP and high-dose FVIII may effect hemostasis in patients with minor bleeding and low inhibitor titers, but their use should not delay administration of a bypassing agent²
- Use of bypassing agents is associated with a small risk of thrombotic events, but this is far outweighed by the risk of life-threatening bleeding if they are not used⁵
- No studies have directly compared rFVIIa and pd-aPCC, and they apparently have equivalent efficacy in AHA⁶
  - Choice should be individualized for patients based on other factors, eg, dosing schedule, comorbidities, and cost¹,⁶
  - If one is ineffective for a specific patient, the other can be tried⁶

EACH2: Hemostatic Therapy Use

![EACH2: Hemostatic Therapy Use](image_url)


Clinical Question 4

What is the mainstay of longer-term treatment for AHA?
A. Plasmapheresis
B. IVig
C. Prednison + rituximab
D. Prednisolone ± cyclophosphamide
Clinical Question 4 Discussion

- This question addresses the second of the 2 primary treatment goals: Eradicate the inhibitor
  - In recently published guidelines, a consensus panel stated that patients with AHA should be started on therapy to eradicate the inhibitor immediately following diagnosis²
- Extracorporeal procedures such as plasmapheresis, although they work quickly, have only a temporary effect¹
- A Canadian panel of hematology experts found no evidence of clinical benefit of using IVIg in AHA and recommended against its routine use⁷
- Rituximab, either alone or added to a steroid, is considered third-line therapy if the steroid alone or with a cytotoxic is not effective; CsA is also considered third-line therapy²
- Steroid (e.g., prednisolone), alone or in combination with a cytotoxic (e.g., cyclophosphamide), is the mainstay of therapy to eradicate inhibitors in AHA²
- Cytotoxics should be used with caution, especially in older patients, to avoid infection-related problems⁶

EACH2: Inhibitor Eradication


Clinical Pearl

“Acquired hemophilia is a lot less common than congenital hemophilia, so clinicians may think they’ll never encounter it, but it is important to know that it is possible, because, although it is rare, acquired hemophilia can pose a significant life-threatening dilemma – it is a low-frequency, high-burden disease.”
References


