Hematology Board Review: Blueprint Study Guide and Q&A is a concise, outline-based study guide covering all topics that appear on the Hematology Certification Exam. The book includes all topics listed in the American Board of Internal Medicine (ABIM) blueprint as essential material for the exam and highlights topic areas that are often found on the test.

For hematology and oncology fellows as well as practicing clinicians needing a refresher before taking MOC, this handy study guide which comes with a mobile-optimized App provides succinct overviews of all blood disorders, syndromes and diseases with practice questions on the go. Each disorder or disease-based chapter provides the same structure for ease of use beginning with the epidemiology, and followed by the etiology and risk factors, signs and symptoms, diagnostic criteria, indications for treatment, prognostic factors, treatment recommendations, and special considerations. The authors provide the most accurate and up-to-date information, including well-established treatment regimens for a variety of blood disorders, including iron disorders, bone marrow failure syndromes, platelet and megakaryocytic disorders, hemostasis, thrombosis, and hematologic malignancies. Later chapters review other major subspecialty areas found on the exam including transfusion medicine and hematopoietic cell transplantation. With 200 board-style questions and answers with detailed rationales, Hematology Board Review is the go-to, quick review for any trainee preparing for initial certification and for hematologists or oncologists preparing for recertification.

**Key Features:**
- Includes 200 board-style questions and answers with rationales
- Provides key point summaries of each topic area for quick study and easy recall
- Thorough coverage of hematologic malignancies, blood disorders, transfusion medicine, hematopoietic cell transplantation, and standard treatment regimens
- Tables providing key data and information related to staging, treatment options, and disease classifications
- Includes free access to mobile and online app—track and sync your progress on up to three devices!
Hematology Board Review
Hematology Board Review
Blueprint Study Guide and Q&A

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Preface

Preparation for board examinations can be a daunting and an overwhelming process for many of us. As trainees, we are often busy with research projects, manuscripts, and a large clinical volume, making it difficult to find time to study for board examinations. As practicing physicians, we find it hard to keep up on material needed for board recertification.

Questions on the board examinations are drawn from well-established, validated medical literature and widely accepted clinical guidelines. With this said, the University of Michigan Hematology and Oncology fellowship program and the University of Utah Hematology/Oncology fellowship program have designed this board review book to be an excellent resource for individuals who are preparing for their hematology boards as well as for hematologists or oncologists needing a refresher in practice or in preparation for maintenance of certification (MOC). This book is not intended to be an all-encompassing review. Rather, it is intended to help summarize the important facts that one might need to know for one’s examination, similar to taking notes of relevant information that one would like to memorize. We created each chapter to cover all topics listed by the American Board of Internal Medicine (ABIM) as material one should know for the Hematology Board Examination.

In this review, we provide the most accurate and up-to-date information, including well-established treatment regimens for a variety of blood disorders, iron disorders, bone marrow failure syndromes, platelet and megakaryocytic disorders, hemostasis, thrombosis, and hematologic malignancies as well as indications, risks, and complications for transfusion medicine and hematopoietic cell transplantation (HCT).

We hope that fellows, practicing hematologists, and practicing medical oncologists preparing for their certification or recertification will find the Hematology Board Review as a useful tool. Our goal is to help our readers summarize and solidify many important clinical facts and to help them build confidence in their exam preparation about their knowledge.

As the hematology/oncology fellowship program director at the University of Michigan (Ann Arbor, MI) and as the Chair of Internal Medicine at the University of Utah, we engaged our fellows and faculty to develop the Hematology Board Review. Each chapter is written by a fellow and edited by an expert faculty member or an ancillary staff clinician at the University of Michigan or University of Utah. The book is similarly formatted to the Oncology Boards Review, 2nd Edition with approximately five questions, answers, and rationales provided at the end of each chapter so that individuals preparing for the boards will be able to assess their readiness for all key topics that they will find on the actual exam.
Finally, we dedicate this book to Michelle Reinhold for her continued devotion and immeasurable service to the University of Michigan Hematology/Oncology Fellowship Program as program coordinator.

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Share
Hematology Board Review:
Blueprint Study Guide and Q&A
DEVELOPMENTAL HEMATOPOIESIS

1. Where and when does the earliest hematopoiesis occur in humans?
   - Earliest hematopoiesis occurs in the yolk sac starting with primitive erythropoiesis at around 3 to 5 weeks of gestation, followed soon in the aorta-gonad-mesonephros (AGM). Many cells from AGM also express cell surface markers that are in common with endothelial cells, suggesting that hematopoietic and endothelial cells share a common precursor, called “hemangioblast.”

2. What are the embryonic hemoglobin types?
   - Hemoglobin Gower (Gower 1 and 2) and hemoglobin Portland (Portland I and II)

3. Where does hematopoiesis take place in the developing fetus?

<table>
<thead>
<tr>
<th>Hematopoietic Organ</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yolk sac</td>
<td>3 to 5 weeks of gestation until about 3 months</td>
</tr>
<tr>
<td>Aorta-gonad-mesonephros (AGM)</td>
<td>4 to 6 weeks of gestation</td>
</tr>
<tr>
<td>Liver and spleen</td>
<td>Starts at about 2 months until 6 months; embryonic hemoglobin switch to fetal hemoglobin</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Starts around 4 months and continues onward into postnatal life</td>
</tr>
</tbody>
</table>

4. Where does hematopoiesis take place after birth?
   - In children, it occurs mostly in the marrow of the long bones, such as femur and tibia, while in adults, the majority of hematopoiesis occurs in the vertebrae and pelvis. Sternum, cranium, ribs, femur, and tibia develop the rest.

5. How is fetal hemoglobin (HbF) different?
   - HbF is made of α2γ2 and has higher oxygen affinity than adult hemoglobin A (α2β2).

HEMATOPOIETIC STEM CELLS

1. What is the difference between hematopoietic stem cells (HSCs) and progenitor cells (HPCs)?
   - The difference between HSC and HPC is not very clear-cut. However, while HSCs are the pluripotent undifferentiated cells that can replenish the whole
blood system, HPCs are those that have somewhat started to differentiate and commit toward a specific lineage. Both HSCs and HPCs are morphologically indistinguishable. The ambiguous term hematopoietic stem/progenitor cells (HSPCs) is still widely used.

<table>
<thead>
<tr>
<th>Hematopoietic Stem Cell (HSC)</th>
<th>Progenitor Cell (HPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated and has ability to self-renew</td>
<td>Progressively lose self-renewal capacity as they become more differentiated</td>
</tr>
<tr>
<td>Pluripotent—can replenish the entire blood system</td>
<td>Oligopotent—can replenish the lineage specific cells</td>
</tr>
<tr>
<td>Usually in quiescent state (G0 phase)</td>
<td>More inclined to divide and proliferate</td>
</tr>
<tr>
<td>Can undergo unlimited cell divisions</td>
<td>Can undergo limited cell divisions</td>
</tr>
<tr>
<td>Usually resistant to cytokines</td>
<td>More responsive to cytokines</td>
</tr>
</tbody>
</table>

2. How do you identify a HSC?
- There is no unique immunophenotype marker for HSC, because progenitor cells and cells that have started to differentiate toward a specific lineage also express many of the cell surface markers that are found on HSCs. It is the absence of any lineage-specific marker that defines a bona fide HSC. Some predominant cell surface markers on HSC are:
  - CD34: mediates cell adhesion to marrow stroma
  - CD117, also called stem cell factor receptor (SCF receptor) or C-kit receptor: promotes stem cell survival and proliferation
  - CD133: develops and maintains cell membrane protrusions
  - CD110 also called c-MPL or thrombopoietin receptor: promotes stem cell growth

3. What are colony forming assays?
- Colony forming assays are in vitro techniques to test for hematopoietic stem cell and progenitor cell (HSPC) function. When HSPCs are cultured in a semisolid methylcellulose medium, they form discrete colonies of lineage-committed cells, all arising from a single progenitor cell. Depending on the committed lineage, they are called colony forming unit-erythroid (CFU-E), CFU-granulocytes/macrophage, (CFU-GM), burst forming unit-erythroid (BFU-E), and CFU-granulocytes/erythroid/macrophages/megakaryocytes (CFU-GEMM).

HEMATOPOIETIC MICROENVIRONMENT

1. What is the function of bone marrow stroma?
- Bone marrow stromal matrix includes fibroblasts, osteoclasts, osteoblasts, adipocytes, mesenchymal cells, endothelial cells, and macrophages. They provide an environment or a “niche,” conducive for hematopoietic stem cells to maintain, self-renew, grow, and differentiate, regulated by multiple signals mediated through various growth factors and cytokines produced by the stromal matrix.
2. How is hematopoiesis regulated?

- Hematopoiesis is mainly regulated by a complex network of growth factors and transcription factor signaling pathways. Other cells, such as neurons from the sympathetic nervous system, also play a role in the regulation of hematopoietic stem cells (HSCs), mainly by diurnal modulation of HSC homeostasis.

3. What is HSC “homing”?

- HSC “homing” is the phenomenon by which a transplanted HSC migrates to take up its residence in the bone marrow (engraftment). Various receptors and chemokines play an important role in “homing.” One such chemokine is the stromal derived factor-1 (SDF-1) and its receptor CXCR4 is expressed on HSC. Plerixafor is a CXCR4 receptor antagonist that is clinically used in mobilizing and collecting stem cells prior to a stem cell transplant.

4. Which are the major growth factors involved in hematopoiesis?

- Examples of growth factors include various cytokines, erythropoietin, thrombopoietin, stem cell factor (SCF), granulocyte colony stimulating factor (G-CSF), and granulocyte/macrophage colony stimulating factor (GM-CSF).

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Source of Production</th>
<th>Target Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin (EPO)</td>
<td>Renal peritubular cells</td>
<td>Erythroid progenitors</td>
</tr>
<tr>
<td>Thrombopoietin (TPO)</td>
<td>Liver, kidney, marrow stromal cells</td>
<td>Stem cell, megakaryocyte progenitors</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Marrow stromal cells</td>
<td>Granulocytes</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Marrow stromal cells</td>
<td>Granulocytes, macrophages</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Marrow stromal cells</td>
<td>Monocyte progenitors</td>
</tr>
<tr>
<td>SCF (C-kit ligand)</td>
<td>Marrow stromal cells</td>
<td>Stem cells</td>
</tr>
<tr>
<td>Cytokines (interleukins), chemokines</td>
<td>Marrow stromal cells</td>
<td>Multipotent precursor cells of myeloid and lymphoid lineage</td>
</tr>
</tbody>
</table>

5. Give a few examples of the clinical use of growth factors.

- Recombinant erythropoietin (EPO), such as darbepoetin and epoetin, are used in anemia due to cancer chemotherapy, anemia of chronic kidney disease, and myelodysplastic syndromes (MDS).

- Granulocyte colony stimulating factor (G-CSF) and granulocyte/macrophage colony stimulating factor (GM-CSF) are used in chemotherapy-induced neutropenia.

- G-CSF and plerixafor (CXCR4 receptor inhibitor) are used in stem cell collection prior to stem cell transplant.

6. What are the major transcription factors (TFs) involved in hematopoiesis?

- Examples of TFs include Hox, GATA1, GATA2, RUNX1, MLL, CEBPa, PAX5, Ikaros, and PU.1, among many others. Mutations in the genes of these TFs can be pathogenic and lead to many hematological malignancies such as acute leukemia and lymphomas.

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7. What are the two main lineage progenitors arising from HSCs?
- Common myeloid progenitor (CMP) and common lymphoid progenitor (CLP)
- Myeloid progenitors are committed to myeloid lineage and give rise to all the myeloid lineage cells, including granulocytes (neutrophils, eosinophils, basophils), monocytes, erythrocytes, and megakaryocytes
- Lymphoid progenitors are committed to lymphoid lineage and give rise to all lymphoid cells, including B cells, T cells, and NK cells.

8. Where do myelopoiesis and lymphopoiesis occur?
- Myelopoiesis originates from the common myeloid progenitor and occurs in the bone marrow. Myelopoiesis includes erythropoiesis, granulopoiesis, and megakaryopoiesis.
- Early lymphopoiesis occurs in the bone marrow, but naïve lymphocytes migrate to the peripheral lymph nodes (B cells) or the thymus (T cells) for maturation and then become activated once they are “trained” and “learn” to recognize antigens. They then circulate between the lymphatic system and blood circulation, scanning for any foreign antigens. Plasma cell is a terminally differentiated B cell, which produces immunoglobulins. NK cells originate and mature in the bone marrow.

ASSESSMENT OF HEMATOPOIESIS

1. How is hematopoiesis assessed?
- By complete blood count (CBC)
- By bone marrow aspirate and biopsy

2. How do you assess for hematopoiesis on a bone marrow biopsy and aspirate?
- By assessing the bone marrow cellularity—which is the “nonfat” portion of the marrow—for erythropoiesis, granulopoiesis, and megakaryopoiesis (commonly called the “trilineage hematopoiesis”). Cellularity is age dependent and is commonly measured as 100 – age = cellularity.

3. Why does bone marrow cellularity decrease with aging?
- HSCs and the surrounding stroma undergo several changes with aging, including an increase in adipocytes, increased level of reactive oxygen species (ROS) production, altered HSC mobilization, and decrease in self-renewal capacity of the HSCs.

QUESTIONS

1. Which of the following statements about hematopoiesis is incorrect?
   A. Early hematopoiesis occurs in the yolk sac, starting with primitive granulopoiesis.
   B. Embryonic hemoglobin switching to fetal hemoglobin takes place during the liver hematopoiesis.
   C. Hematopoietic and endothelial cells arise from a common progenitor, the “hemangioblast.”
   D. The spleen is a site of extramedullary hematopoiesis in chronic myeloproliferative neoplasm (MPN) patients.
2. A 24-year-old male is referred for anemia by his primary care provider. His complete blood count (CBC) shows white blood cell (WBC) of 5.4 K/mcL, hemoglobin (Hb) of 12.5 g/dL, mean corpuscular volume (MCV) 89 FL, and platelet count of 299 K/mcL. Iron studies were normal. High-performance liquid chromatography (HPLC) shows HbA = 80%, HbA2 = 3%, and fetal hemoglobin (HbF) = 17%. Which of the following is correct?
A. Presence of HbF will shift the Hb-oxygen dissociation curve to the right.
B. The patient likely has hereditary persistence of fetal hemoglobin (HPFH) and his P50 is likely to be decreased.
C. Globin genotyping is likely to reveal an absence of beta-globin.
D. He is likely to have hepatosplenomegaly due to extramedullary hematopoiesis.

3. A 65-year-old man is admitted to the hospital due to a 2-week history of upper respiratory infection (URI)-like symptoms and complete blood count (CBC) at the emergency department (ED) showing white blood cell (WBC) 35 K/mcL, hemoglobin (Hb) 9.5 g/dL, and platelet count 35 K/mcL. Differential count shows 75% blasts and 20% neutrophils. A bone marrow biopsy and aspirate was done, and flow cytometry revealed an immunophenotype positive for CD13, CD33, CD34, CD117, and HLA-DR, but negative for CD15, CD64, and CD11b. Which of the following statements is incorrect?
A. This patient has acute myeloid leukemia, most likely arising from mutations in the hematopoietic stem cells (HSCs) and progenitor cells.
B. Progenitor cells progressively lose self-renewal capacity as they differentiate.
C. HSCs can be identified from the in vitro colony forming assays.
D. HSCs and progenitor cells are morphologically indistinguishable.

4. Which of the following statements is incorrect?
A. Erythropoietin is produced by the peritubular cells in the kidney.
B. Thrombopoietin is produced by the liver only in response to low platelet counts.
C. Mutations in granulocyte colony stimulating factor (G-CSF) receptor can be found in chronic neutrophilic leukemia.
D. Eltrombopag is a thrombopoietin (TPO) mimetic, which can be used for treating idiopathic thrombocytopenic purpura (ITP).
ANSWERS

1. A. Early hematopoiesis occurs in the yolk sac, starting with primitive granulopoiesis. Primitive hematopoiesis originates in the yolk sac, starting with erythropoiesis, to deliver oxygen to other parts of the developing embryo.

2. B. The patient likely has hereditary persistence of fetal hemoglobin (HPFH) and his P50 is likely to be decreased. HbF has higher Hb-oxygen affinity, which will shift the oxygen dissociation curve to the left. P50 is the partial pressure of oxygen when hemoglobin is 50% saturated, and with higher oxygen affinity, P50 will be decreased. An asymptomatic patient with mild anemia and a normal MCV with elevated HbF most likely has HPFH. Absence of beta-globin is seen in beta-thalassemia major, and HPLC would show complete absence of HbA. Hepatosplenomegaly associated with extramedullary hematopoiesis is typically found in thalassemia major and chronic myeloproliferative neoplasms.

3. C. HSCs can be identified from the in vitro colony forming assays. HSCs cannot be isolated or identified, as they are morphologically indistinguishable from progenitor cells and do not have any specific cell surface markers.

4. B. Thrombopoietin is produced by the liver only in response to low platelet counts. TPO is produced constitutively by the liver and is inactivated by binding to the TPO receptor (c-MPL) on circulating platelets. Therefore, it is the level of platelets that regulates availability of thrombopoietin to megakaryocytes.