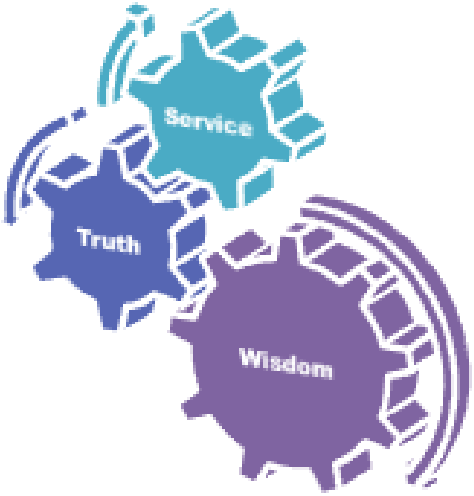
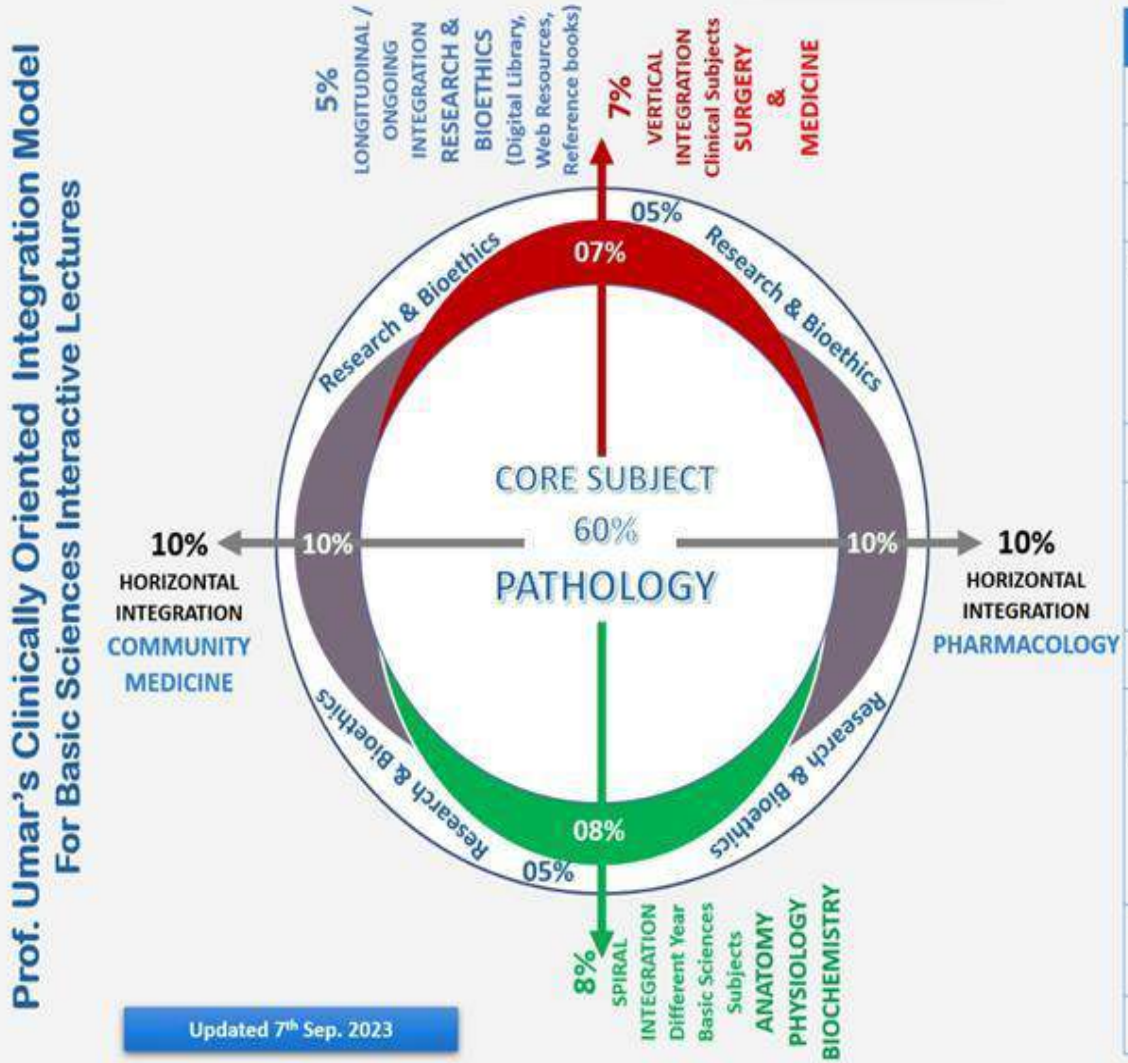

بسم الله الرحمن الرحيم
وَأَمَّا مَا يَنفَعُ ٱلنَّاسَ فَيَمْكُثُ فِى ٱلْأَرْضِ
but as for that which benefits the people, it remains on the earth.
Quran 13:17 (Surah ar-Ra'd)

MOTTO AND VISION



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

HEMATOPOIETIC GROWTH FACTORS
LGIS

HEMATOLOGY AND IMMUNOLOGY MODULE
3rd YEAR MBBS 2024

Sources:

BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY
15TH EDITION

DR.MUHAMMAD ZAHEER SHEIKH

LEARNING OBJECTIVES

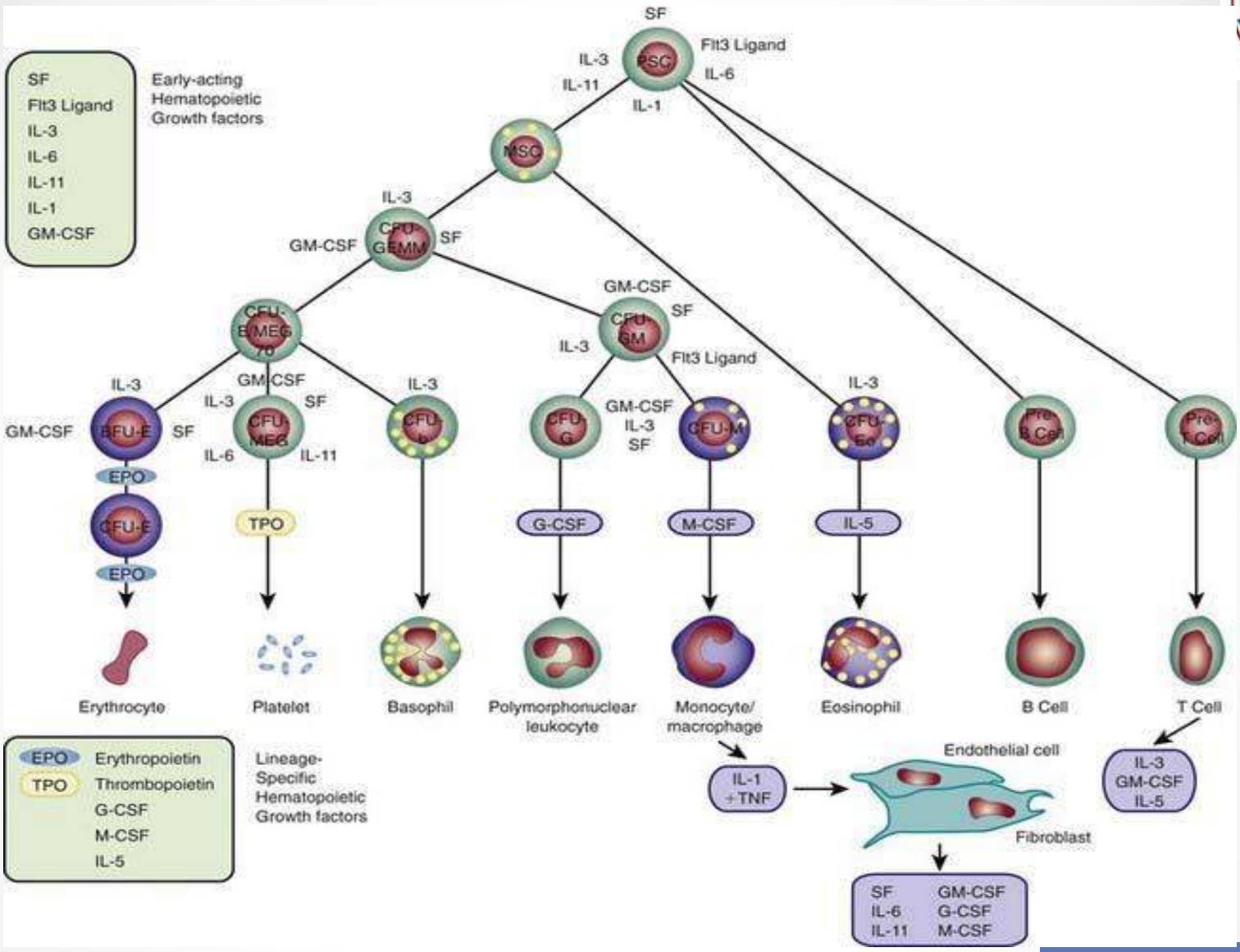
At the end of the lecture, students should be able to:

- Tabulate the Hematopoietic growth factor
- Describe the Mechanism of action, clinical uses and adverse effect of Epoietin.
- Describe the Mechanism of action, clinical uses and adverse effect of G-CSF Analogs.

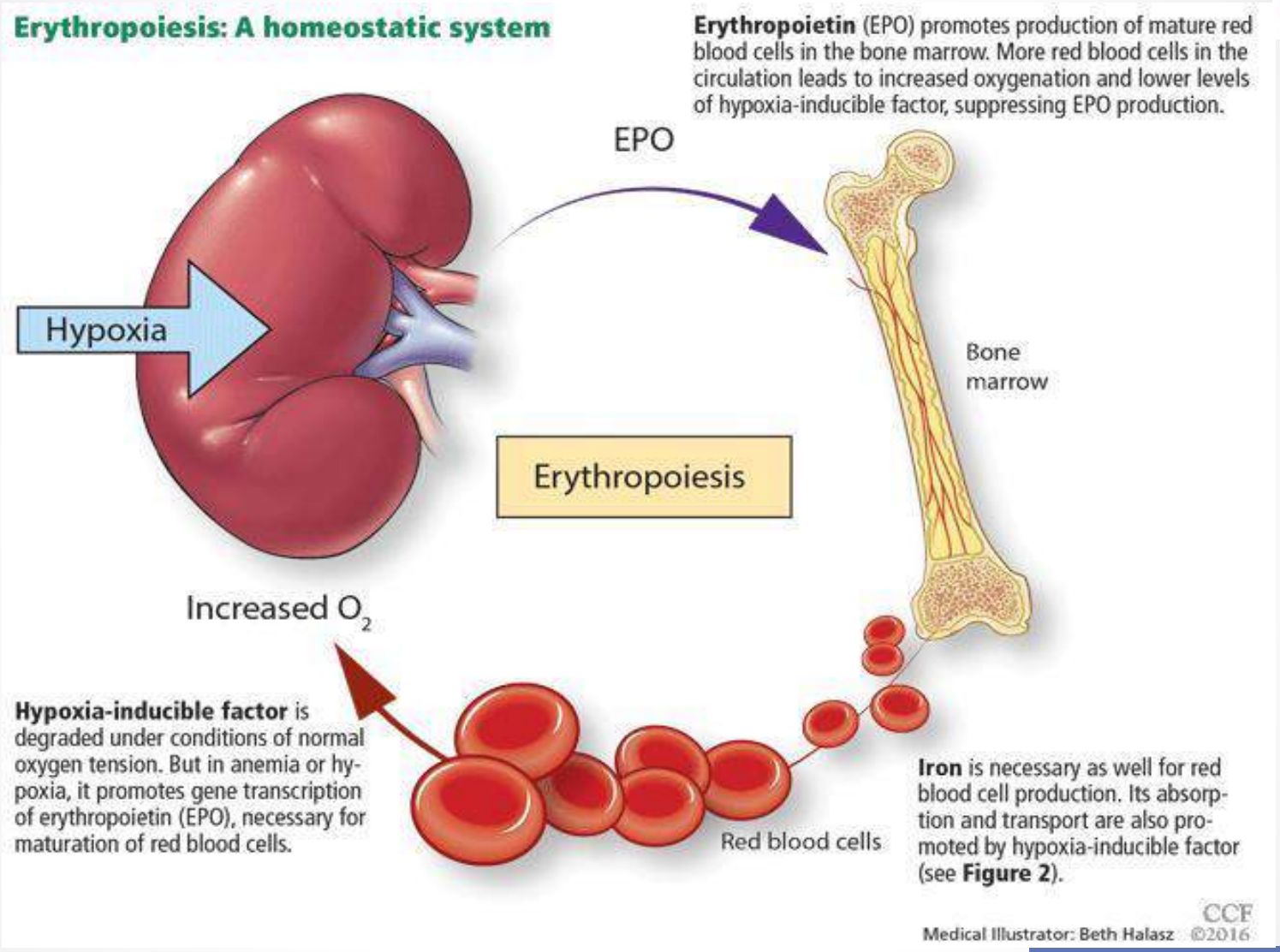
Haematopoietic Growth Factors Introduction

- The haematopoietic growth factors are glycoprotein hormones that regulate the proliferation and differentiation of haematopoietic progenitor cells in the bone marrow.

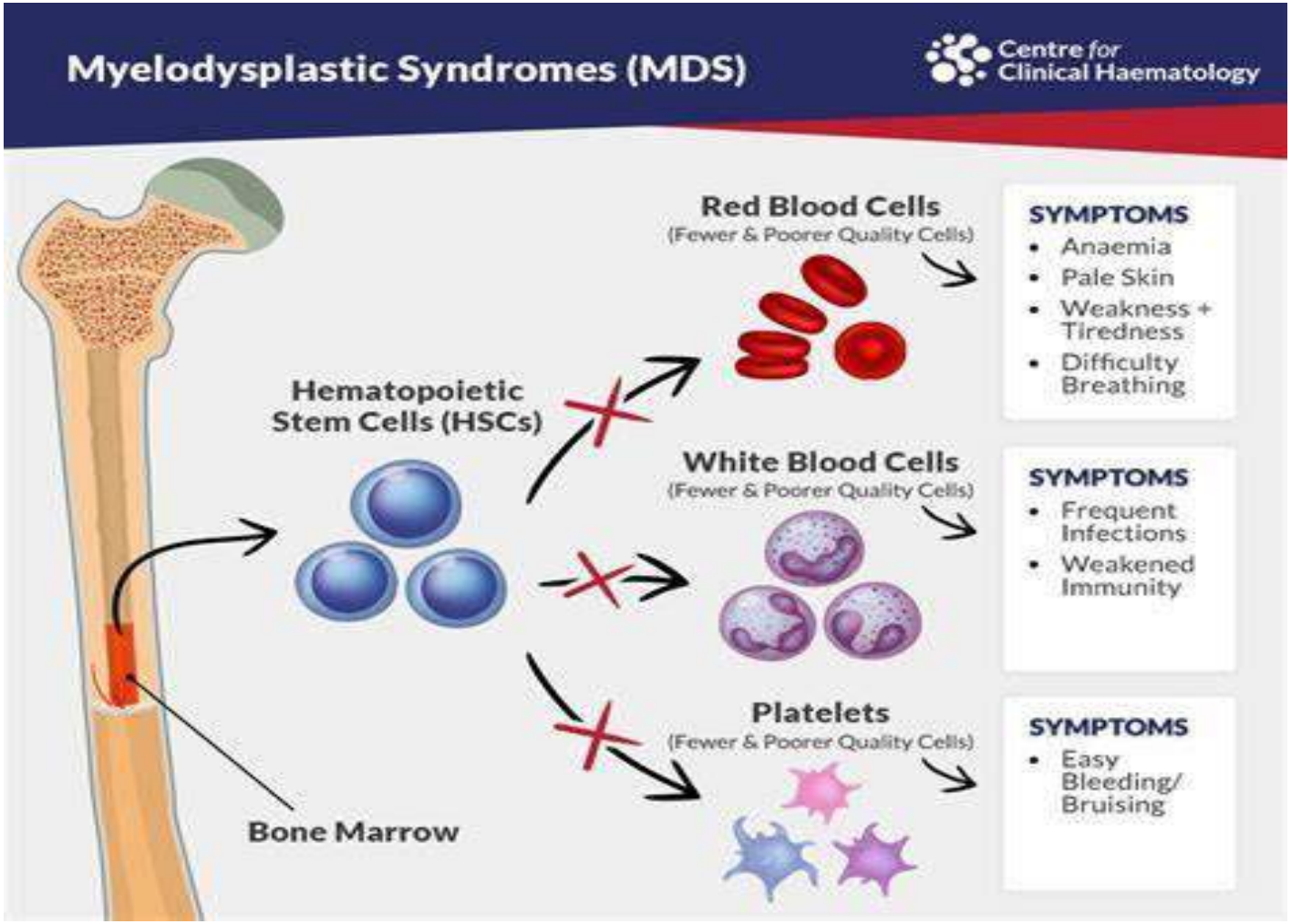
Core Subject



Spiral Integration



Horizontal Integration



Spiral Integration

Haematopoietic Growth Factors

- **Haematopoietic Growth Factors:**
- **Erythropoietin Receptor Agonist/ erythropoisis stimulating agents**

Epoetin alpha

Epoetin beta

Darbepoetin alpha

Methoxy polyethylene glycol-epoetin beta

Core Subject

- **Granulocyte colony stimulating factor**

Filgrastim

Pegfilgrastim

- **Granulocyte macrophage colony stimulating factor**

Sargramostim

- **Thrombopoitin receptor agonist**

Romiplostim

Eltrombopag

- **Recombinant interleukin 1**

oprelvekin

Summary

- Erythropoietin (epoetin alpha and epoetin beta)
- Myeloid growth factors
    - Purified from cultured human cell lines
        - G-CSF
        - GM-CSF
    - Recombinant human
        - G-CSF (rHuG-CSF; filgrastim) bacterial expression
        - Pegfilgrastim
        - GM-CSF (rHuGM-CSF; sargramostim) yeast expression
- Megakaryocyte growth factors

Core Subject

ERYTHROPOIETIN

Erythropoietin Mechanism

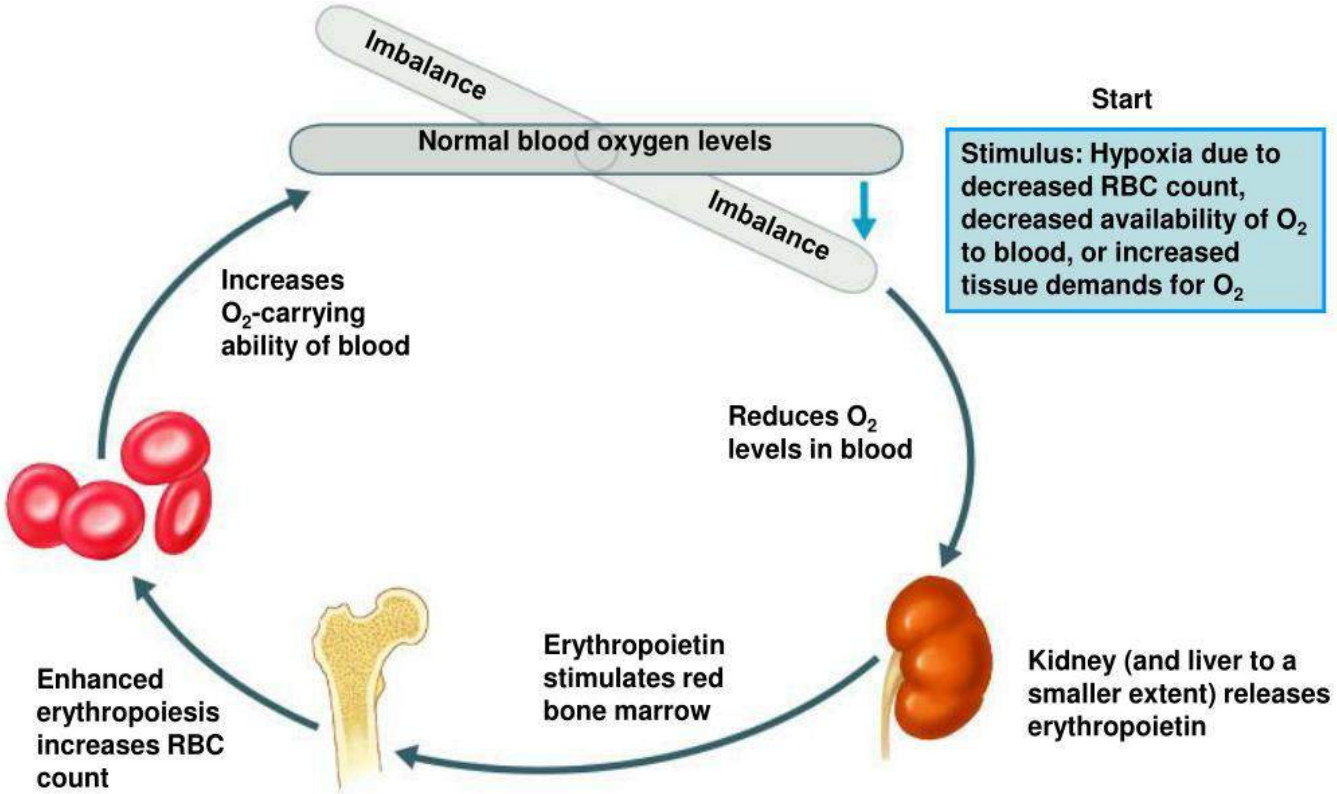


Figure 17.6

Core Subject

ERYTHROPOIETIN

- Inverse relationship exists between Hb level & serum erythropoietin level
- If Hb levels fall & anemia becomes more severe, serum erythropoietin level rises

Important exception to this inverse relationship: in anemia of chronic renal failure,

Core Subject

- **RECOMBINANT HUMAN ERYTHROPOIETIN**
- **Epoetin alfa:** half-life of 4–13 hrs, administered 03 times a week
- **Darbepoetin alfa:** modified form of erythropoietin, longer half-life than epoetin alfa, administered weekly
- **Epoetin beta:** long-lived recombinant product, administered as a single IV or S/C dose at 2-week or monthly intervals

Core Subject

CLINICAL INDICATIONS

Treatment of anemia in:

1. Patients with chronic renal failure
2. Primary bone marrow disorders and secondary anemias
   - ❑ Aplastic anemias and other bone marrow failure states ,myeoproliferative and myelodysplastic disorders ,multiple myeloma and other bone marrow malignancies
   - ❑ Anemia associated with chronic inflammations
   - ❑ HIV-infected patients treated with zidovudine
   - ❑ Cancer patients treated with myelosuppressive cancer chemotherapy
3. Preoperative increased blood production for patients undergoing elective, noncardiac, nonvascular surgery

Core Subject

ADVERSE EFFECTS

1. Hypertension
2. Thrombotic complications
3. **Allergic reactions-----Pure red cell aplasia (PRCA)** accompanied by neutralizing antibodies directed against erythropoietin which inactivate endogenous hormone as well as recombinant dg
    - PRCA, seen in patients treated by epoetin alfa subcutaneously for a long period

Core Subject

Myeloid growth factors

Pharmacokinetics

- Route of administration:
  - Intravenous
  - Subcutaneous
- Plasma half life :
  - 2–7 hours after administration
  - Pegfilgrastim have half life of several days

Core Subject

Pharmacodynamics

- The myeloid growth factors stimulate proliferation and differentiation by interacting with specific receptors found on myeloid progenitor cells.
- These receptors are members of the JAK/STAT superfamily
- GM-CSF has broader biologic actions. It stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitor.

Core Subject

Clinical uses

- Cancer Chemotherapy-Induced Neutropenia
- neutropenia associated with
  - Congenital neutropenia
  - Cyclic neutropenia
  - Myelodysplasia
  - Aplastic anemia
  - Autologous stem cell transplantation for patients undergoing high-dose chemotherapy

Core Subject

Toxicity

- Bone pain
- Allergic reactions
- Splenic rupture is rare but serious
- GM-CSF can cause more severe side effects at higher doses
    - Fever
    - Malaise
    - Arthralgia
    - Myalgia
    - **Capillary leak syndrome** characterized by peripheral edema and pleural or pericardial effusions

Core Subject

Megakaryocyte growth factors

Classification and Pharmacokinetics

- **Classification**
- Endogenous regulators of platelets
  - Thrombopoietin
  - IL-11
- Recombinant form of IL-11
  - Oprelvekin
- Peptibodies (agonists of Thrombopoietin receptors)
  - Romiplostin
  - Eltrombopag
- **Route of administration**
  - Subcutaneoous
  - Oral (Eltrombopag)
- **Plasma half life**
  - Oprelvekin (6-7 hours)
  - Romiplostin (3-4 days)

Core Subject

Pharmacodynamics

- Interleukin-11 acts through a specific cell surface cytokine receptor to stimulate the growth of multiple lymphoid and myeloid cells
- Romiplostim has high affinity for the human Mpl receptor. It causes a dose-dependent increase in platelet count

Core Subject

Clinical uses and toxicity

- **Clinical uses**
- secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy
- chronic idiopathic thrombocytopenia (ITP) who failed to respond adequately to previous treatment
- **Toxicity**
- fatigue,
- headache,
- dizziness,
- The cardiovascular effects include anemia (due to hemodilution), dyspnea (due to fluid accumulation in the lungs), and transient atrial arrhythmias
- Hypokalemia
- Increase in bone marrow reticulin

Core Subject

TABLE 33–4 Clinical uses of hematopoietic growth factors and agents that mimic their actions.

Hematopoietic Growth Factor	Clinical Condition Being Treated or Prevented	Recipients
Erythropoietin, darbepoetin alfa	Anemia	Patients with chronic renal failure
		HIV-infected patients treated with zidovudine
		Cancer patients treated with myelosuppressive cancer chemotherapy
		Patients scheduled to undergo elective, noncardiac, nonvascular surgery
Granulocyte colony-stimulating factor (G-CSF; filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim)	Neutropenia	Cancer patients treated with myelosuppressive cancer chemotherapy
		Patients with severe chronic neutropenia
		Patients recovering from bone marrow transplantation
	Stem cell or bone marrow transplantation	Patients with nonmyeloid malignancies or other conditions being treated with stem cell or bone marrow transplantation
	Mobilization of peripheral blood progenitor cells (PBPCs)	Donors of stem cells for allogeneic or autologous transplantation
Interleukin-11 (IL-11, oprelvekin)	Thrombocytopenia	Patients with nonmyeloid malignancies who receive myelosuppressive cancer chemotherapy
Romiplostim	Thrombocytopenia	Patients with idiopathic thrombocytopenic purpura

Vertical Integration

BIOETHICS

- **ERYTHROPOIETIN**
- Used illegally by athletes to increase their Hb levels (“blood doping”) & improve performance
- This misuse resulted in deaths of several athletes & strongly discouraged

Vertical Integration

Research

Griffiths EA, Alwan LM, Bachiashvili K, Brown A, Cool R, Curtin P, Geyer MB, Gojo I, Kallam A, Kidwai WZ, Kloth DD, Kraut EH, Lyman GH, Mukherjee S, Perez LE, Rosovsky RP, Roy V, Rugo HS, Vasu S, Wadleigh M, Westervelt P, Becker PS. **Considerations for Use of Hematopoietic Growth Factors in Patients With Cancer** Related to the COVID-19 Pandemic. J Natl Compr Canc Netw. 2020 Sep 1:1-4. doi: 10.6004/jnccn.2020.7610. Epub ahead of print. PMID: 32871558; PMCID: PMC9730290.

1. A 47-year-old woman exhibits severe neutropenia after a course of chemotherapy for breast cancer.Select the most appropriate drug therapy from the lettered choices.

   (A) cyanocobalamin
   (B) epoetin
   (C) ferrous gluconate
   (D) filgrastim
   (E) folic acid

End of Lecture Assessment

2. A 68-year-old man with diabetic nephropathy and endstage renal disease exhibits peripheral reticulocytopenia and anemia.Select the most appropriate drug therapy from the lettered choices.

(A) cyanocobalamin
(B) epoetin
(C) ferrous gluconate
(D) filgrastim
(E) folic acid

End of Lecture Assessment


جَزَاكَ اللَّهُ خَيْرًا