Clinical approach to anemia

Mehrdad payandeh ,MD

KUMS

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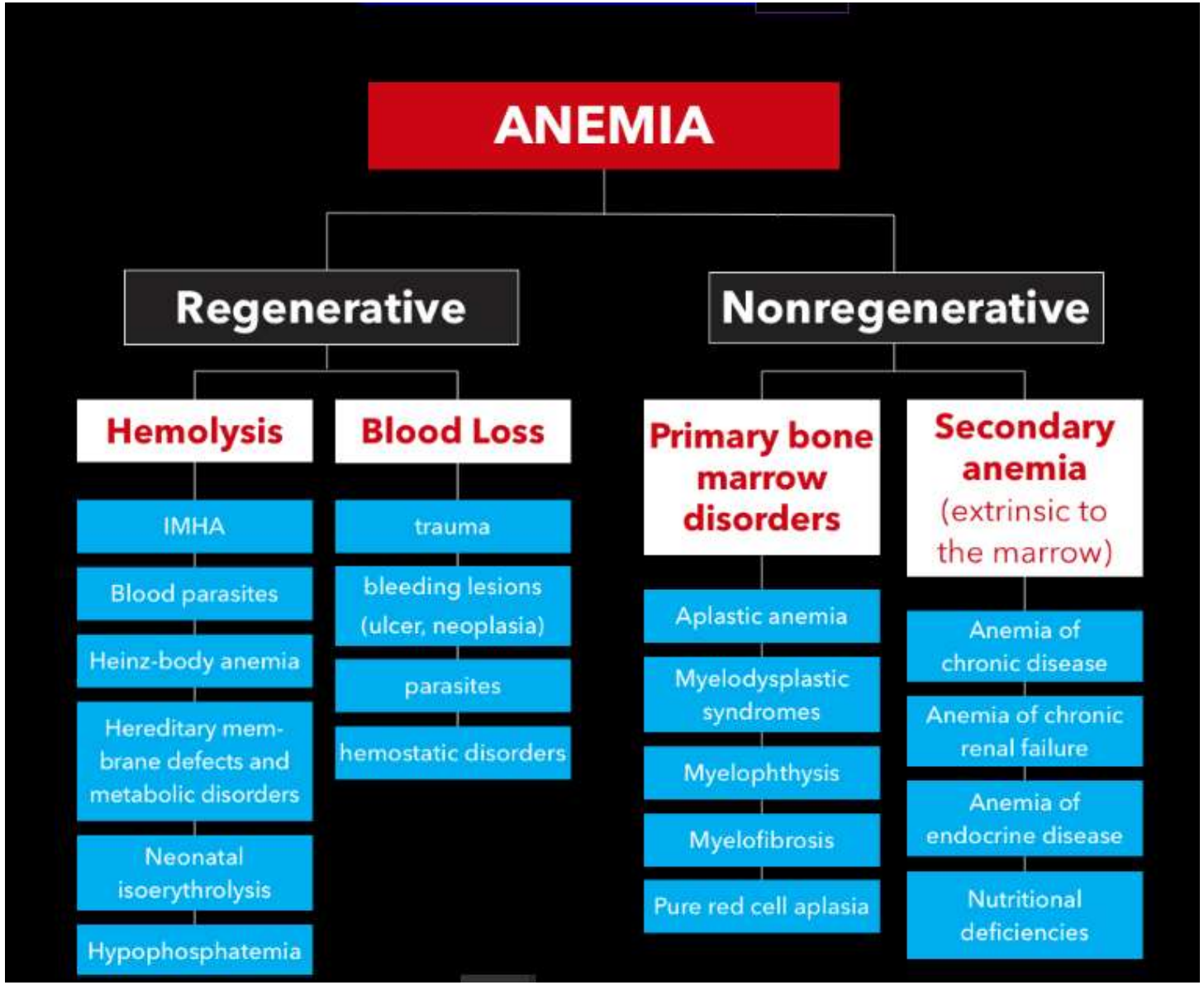
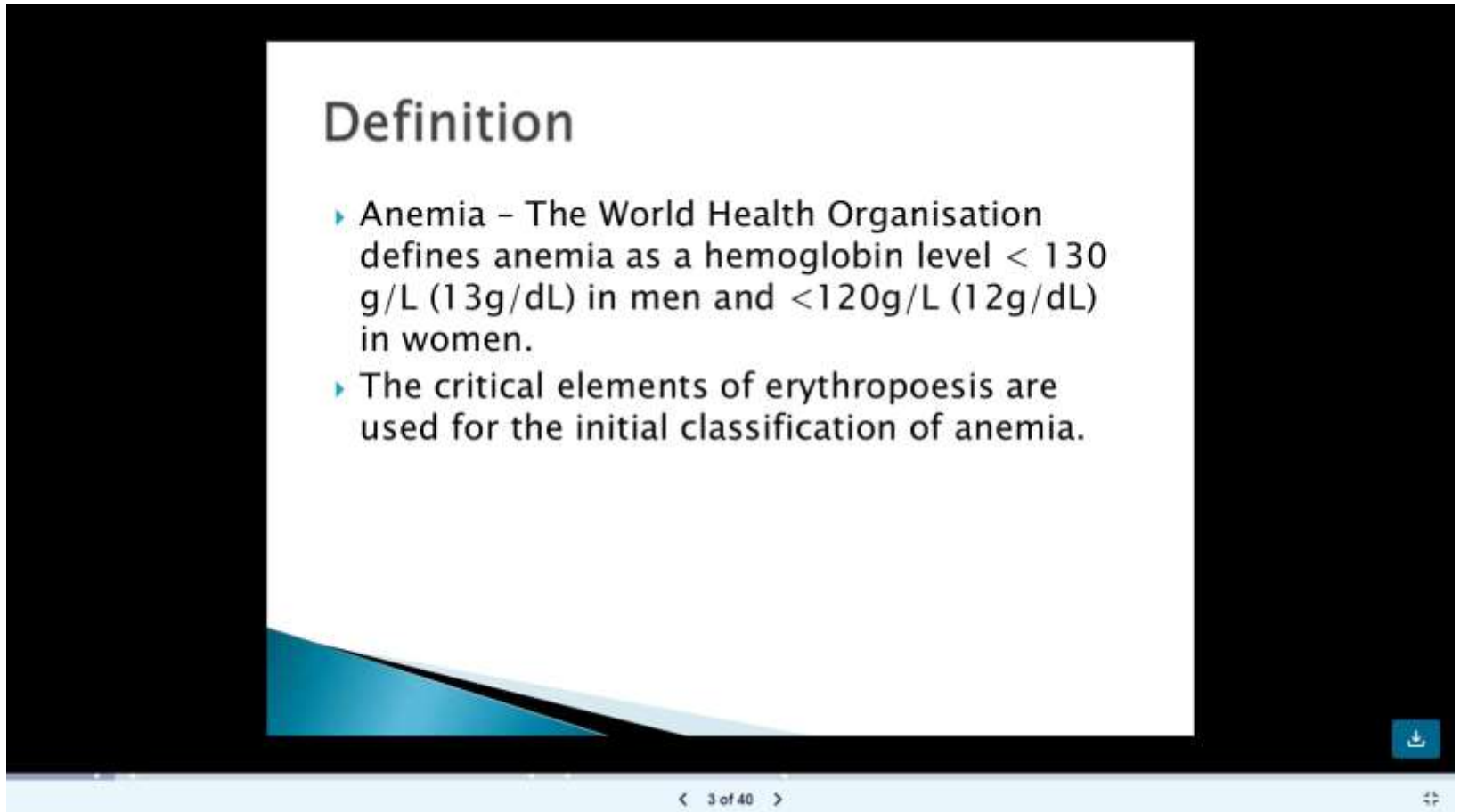

ANEMIA
Regenerative
Nonregenerative
Hemolysis
Blood Loss
Primary bone marrow disorders
Secondary anemia (extrinsic to the marrow)
IMHA
Blood parasites
Heinz-body anemia
Hereditary mem-brane defects and metabolic disorders
Neonatal isoerythrolysis
Hypophosphatemia
trauma
bleeding lesions (ulcer, neoplasia)
parasites
hemostatic disorders
Aplastic anemia
Myelodysplastic syndromes
Myelophthysis
Myelofibrosis
Pure red cell aplasia
Anemia of chronic disease
Anemia of chronic renal failure
Anemia of endocrine disease
Nutritional deficiencies


Definition
Anemia – The World Health Organisation defines anemia as a hemoglobin level < 130 g/L (13g/dL) in men and <120g/L (12g/dL) in women.
The critical elements of erythropoesis are used for the initial classification of anemia.
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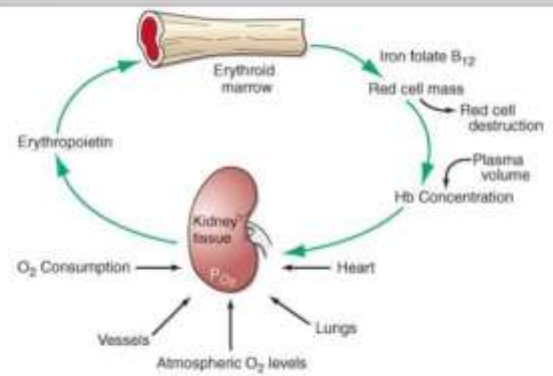
Physiological regulation of red cell production

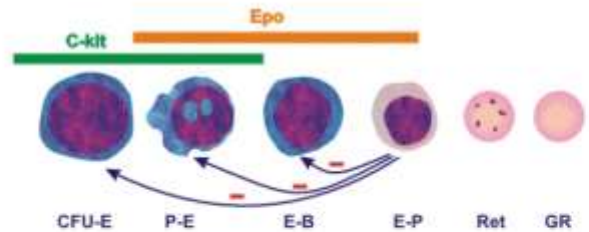
Figure 57-1



The physiologic regulation of red cell production by tissue oxygen tension. Hb, hemoglobin.

Elements of Erythropoiesis

- EPO production
- Iron availability
- Proliferative capacity of the bone marrow
- Effective maturation of red cell precursors



http://www.oncoprof.net/Generale2000/g09_Chimiotherapie/Complements/g09-gb_comp56.html

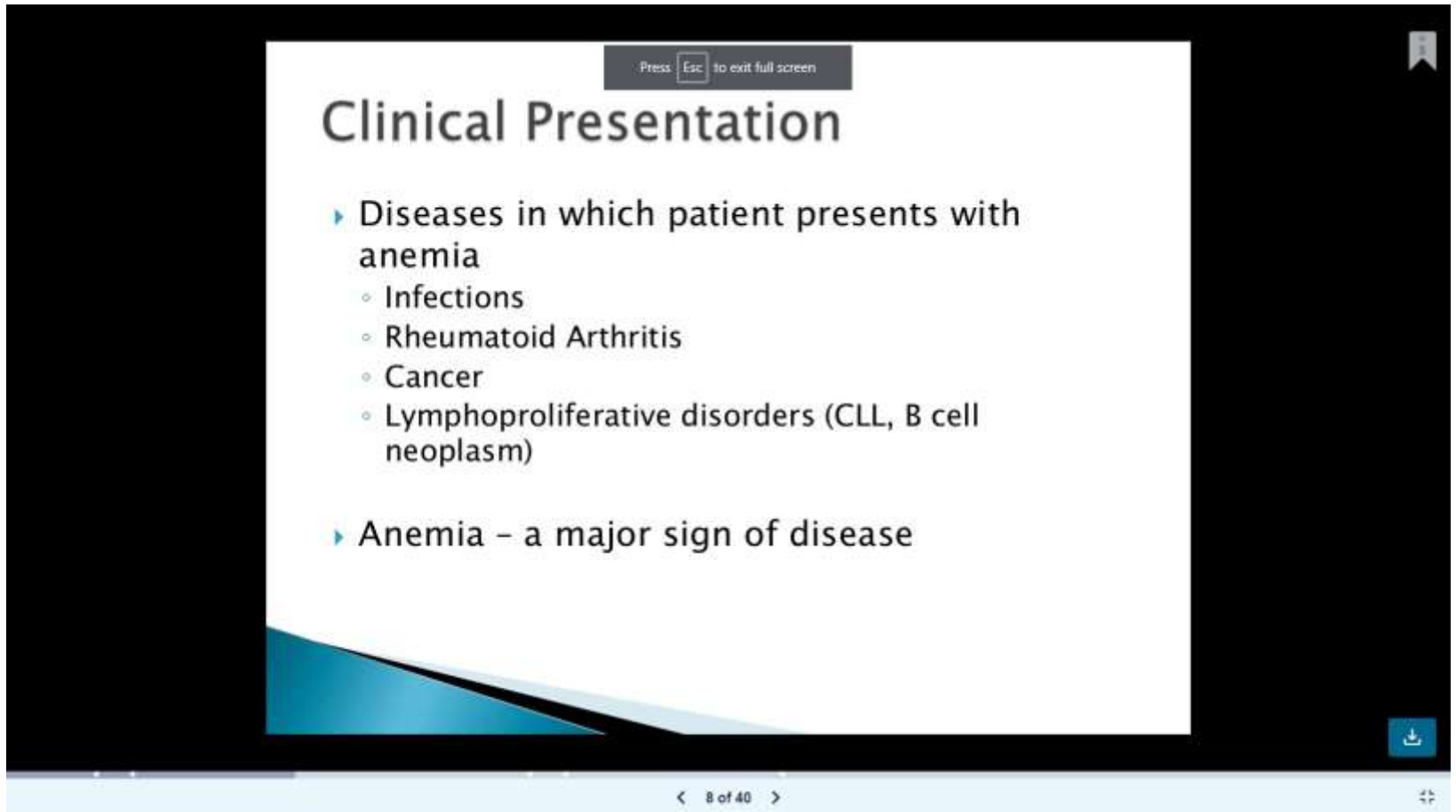
Clinical Presentation

- Often found during routine screening

- Acute blood loss – Hb/HCT does not reflect the volume of blood loss
  - Mild – No symptoms. Enhanced oxygen delivery by changes in pH and increased CO_2
  - 10–15% – hypotension and decreased organ perfusion
  - >30% – postural hypotension, tachycardia
  - >40% – hypovolemic shock: confusion, dyspnoea, diaphoresis

Clinical Presentation

- Acute hemolysis
  - Intravascular hemolysis: acute back pain, free hemoglobin in plasma and urine, renal failure
- Moderate anemia
  - Fatigue
  - Loss of stamina
  - Breathlessness
  - Tachycardia on physical exertion
  - Symptoms may not appear in young, healthy patients until hemoglobin is 7–8 g/dL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Clinical Presentation
Diseases in which patient presents with anemia
Infections
Rheumatoid Arthritis
Cancer
Lymphoproliferative disorders (CLL, B cell neoplasm)
Anemia – a major sign of disease
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History

- Evaluation by History:
  - Symptoms of known diseases causing anemia:
    - Gastric ulceration
    - Rheumatoid arthritis
    - Renal failure
  - Duration of symptoms:
    - Hemoglobinopathies in longer duration
  - Treatment history
    - Medications for pain, hematinics
  - Nutritional history

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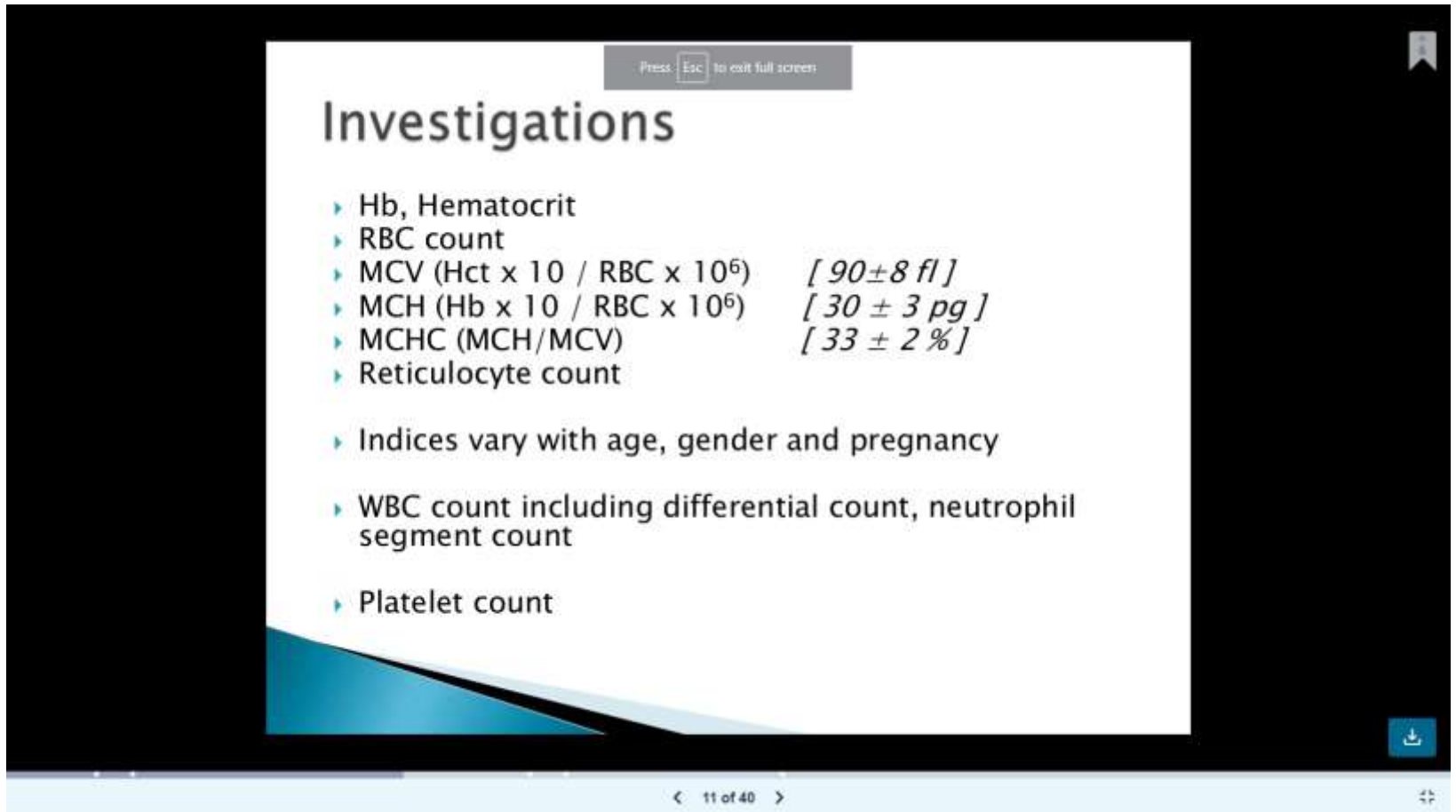
Examination

- Physical examination
  - Build, nourishment
  - Signs of disease
  - Vitals – fever, tachycardia, blood pressure
  - Pallor
  - Jaundice
  - Lymphadenopathy
  - Bone tenderness
  - Petechiae
  - CVS: Flow murmurs
  - RS: Dyspnoea
  - Abdomen: Splenomegaly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Investigations
Hb, Hematocrit
RBC count
MCV (Hct x 10 / RBC x 10⁶) [90±8 fl]
MCH (Hb x 10 / RBC x 10⁶) [30 ± 3 pg]
MCHC (MCH/MCV) [33 ± 2 %]
Reticulocyte count
Indices vary with age, gender and pregnancy
WBC count including differential count, neutrophil segment count
Platelet count
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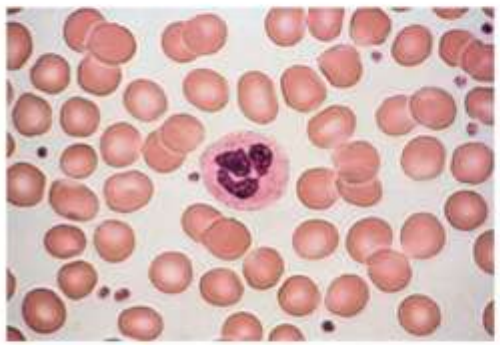
Peripheral smears

- Cell size
- Hb content
- Anisocytosis
- Poikilocytosis
- Polychromasia

- Gives clues to specific disorders



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Normal peripheral smear

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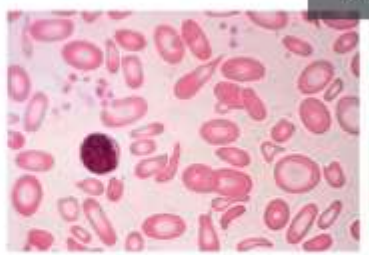
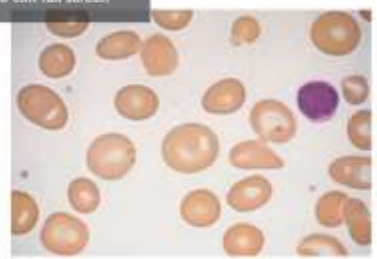


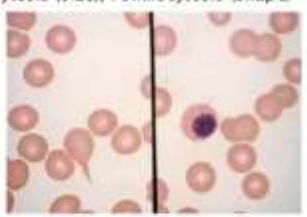
Severe Iron defeciency anemia

Anisocytosis (size), Poikilocytosis (shape)



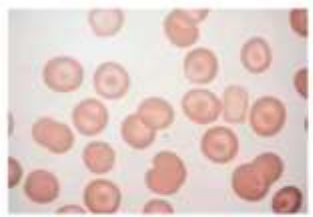
Macrocytosis

Macrocytes, Ovalocytes



Myelofibrosis

Tear drop shaped cells, nucleated cells



Thallassemia

Target cells

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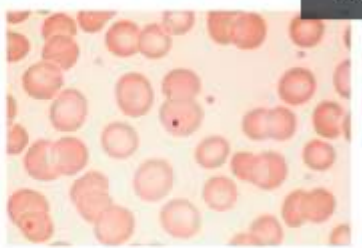
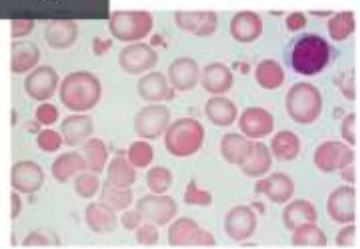
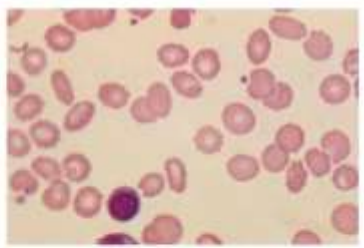


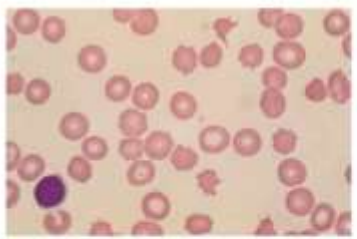
Howell–Jolly bodies



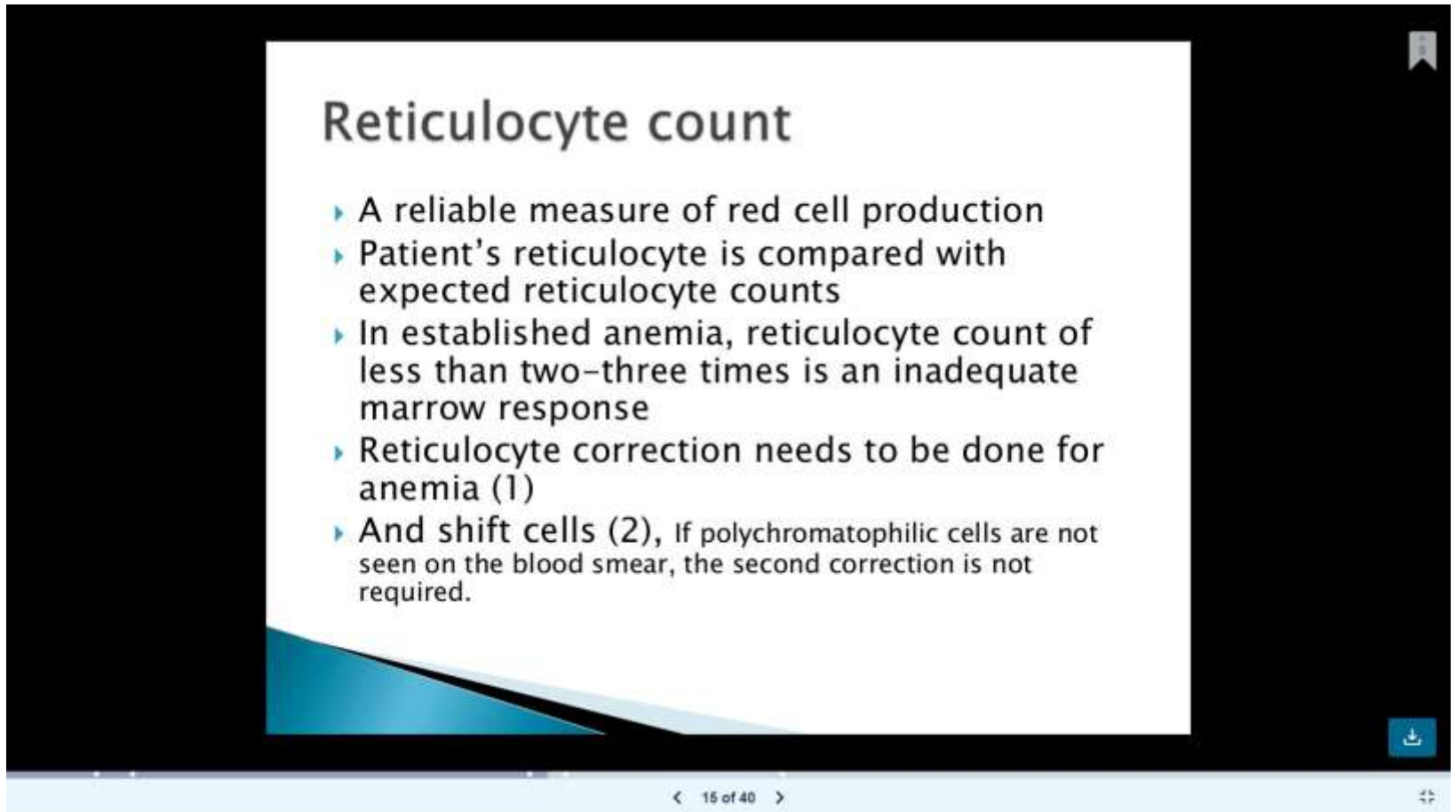
Red cell fragmentation



Uremia



Spur cells


Reticulocyte count
A reliable measure of red cell production
Patient's reticulocyte is compared with expected reticulocyte counts
In established anemia, reticulocyte count of less than two-three times is an inadequate marrow response
Reticulocyte correction needs to be done for anemia (1)
And shift cells (2), If polychromatophilic cells are not seen on the blood smear, the second correction is not required.
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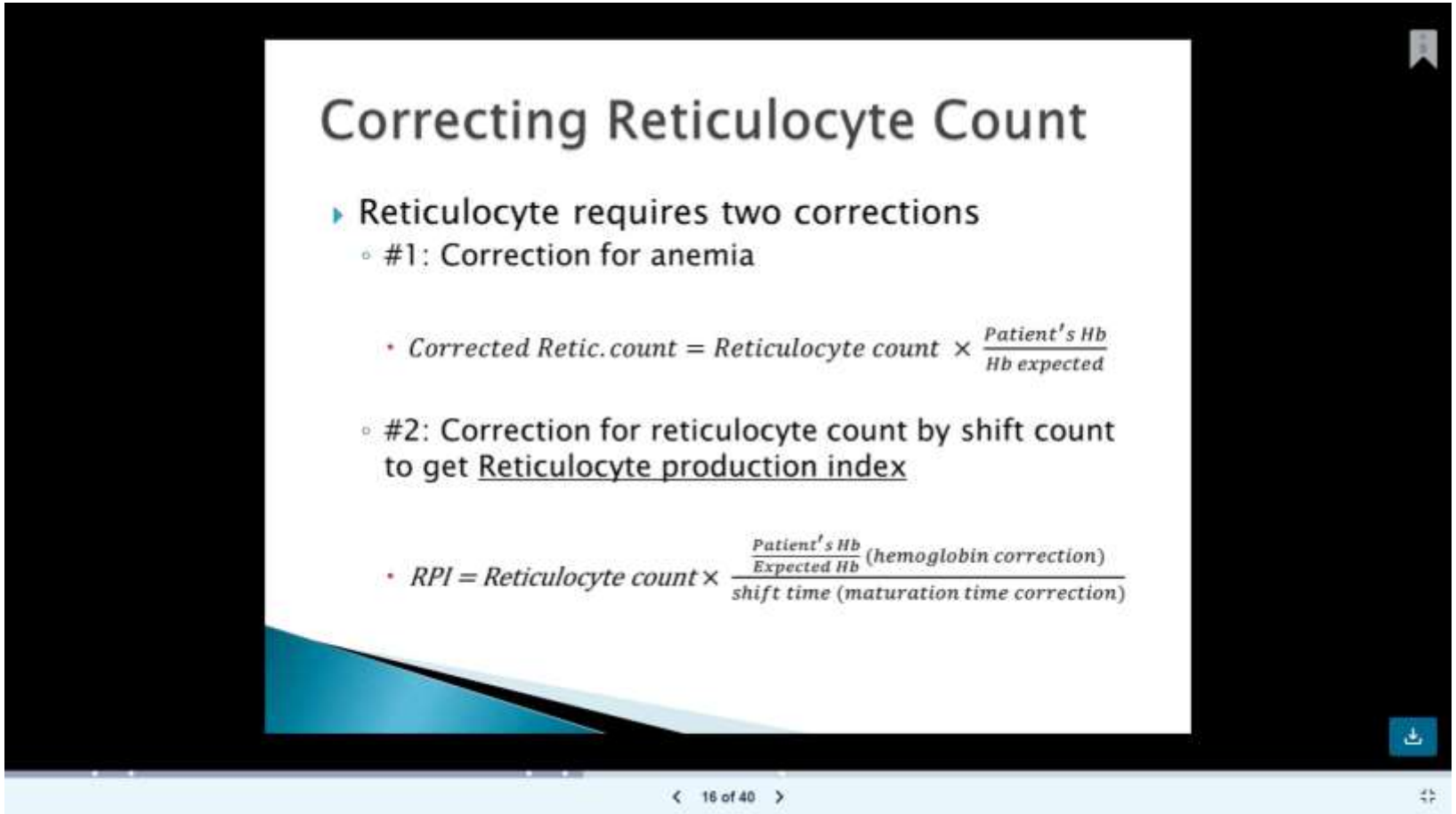
Correcting Reticulocyte Count
Reticulocyte requires two corrections
#1: Correction for anemia
$Corrected\ Retic.count = Reticulocyte\ count \times \frac{Patient's\ Hb}{Hb\ expected}$
#2: Correction for reticulocyte count by shift count to get Reticulocyte production index
$RPI = Reticulocyte\ count \times \frac{\frac{Patient's\ Hb}{Expected\ Hb}\ (hemoglobin\ correction)}{shift\ time\ (maturation\ time\ correction)}$
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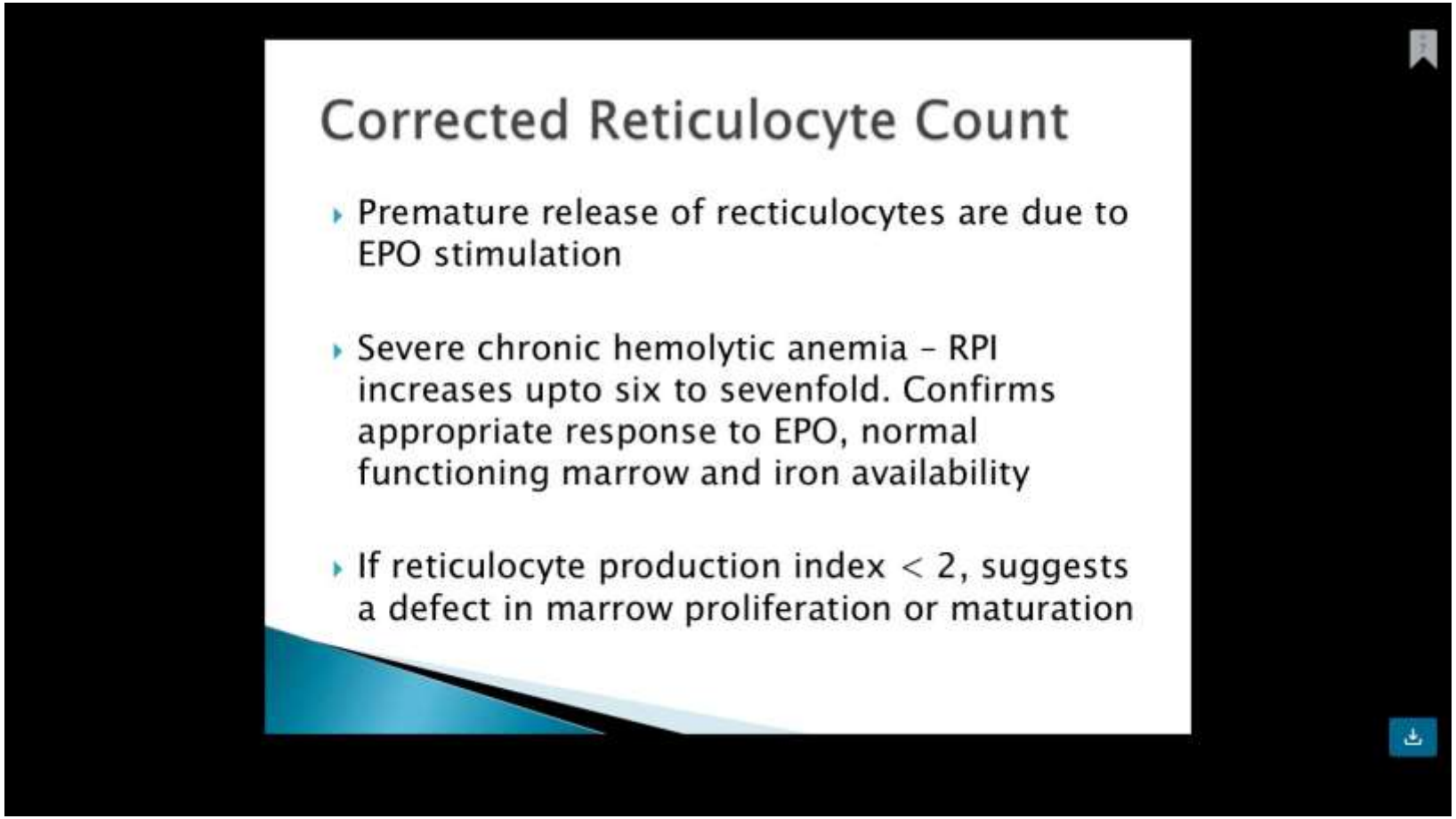
Corrected Reticulocyte Count
Premature release of recticulocytes are due to EPO stimulation
Severe chronic hemolytic anemia – RPI increases upto six to sevenfold. Confirms appropriate response to EPO, normal functioning marrow and iron availability
If reticulocyte production index < 2, suggests a defect in marrow proliferation or maturation

Iron Supply and Storage

- Serum Iron: 50–150 µg/dL
- TIBC: 300–360 µg/dL
- Serum ferritin (also an acute phase reactant)
  - 15–20 µg/dL – Lack of Iron stores
  - Women: ~30 µg/dL
  - Men: ~ 100 µg/dL
  - 200 µg/dL – adequate iron stores
- Serum Transferrin saturation: 25–50%

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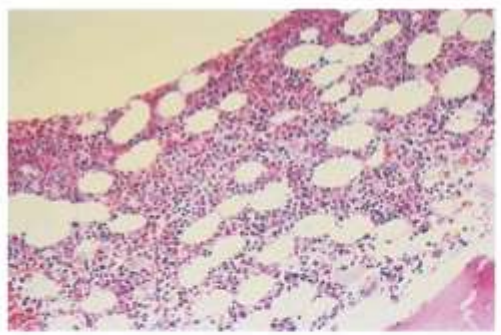
Bone Marrow Studies

- Marrow aspirate
  - M/E ratio
  - Cell morphology
  - Iron stain
- Marrow biopsy
  - Cellularity
  - Morphology



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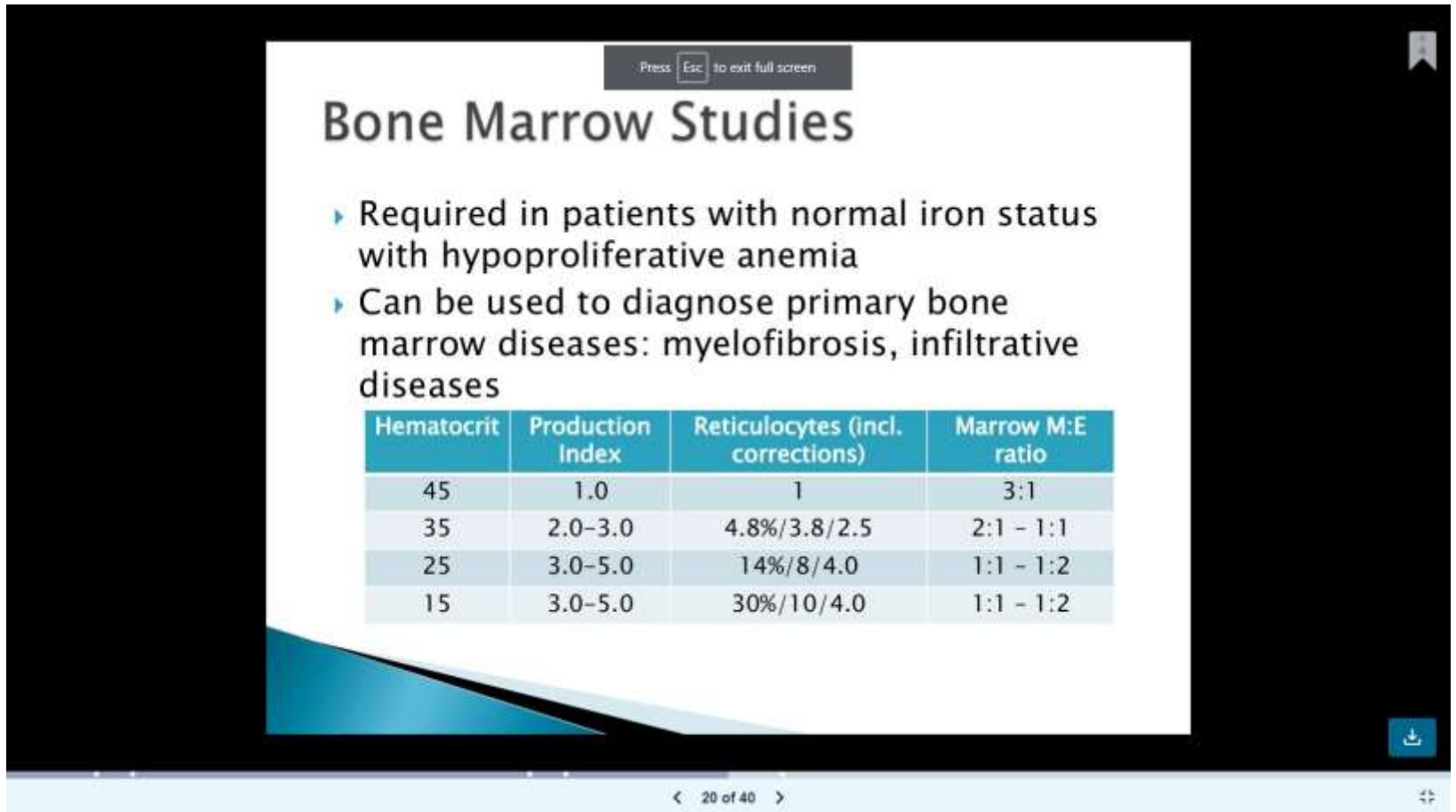
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Bone Marrow Studies
Required in patients with normal iron status with hypoproliferative anemia
Can be used to diagnose primary bone marrow diseases: myelofibrosis, infiltrative diseases
Hematocrit | Production Index | Reticulocytes (incl. corrections) | Marrow M:E ratio
45 | 1.0 | 1 | 3:1
35 | 2.0–3.0 | 4.8%/3.8/2.5 | 2:1 – 1:1
25 | 3.0–5.0 | 14%/8/4.0 | 1:1 – 1:2
15 | 3.0–5.0 | 30%/10/4.0 | 1:1 – 1:2
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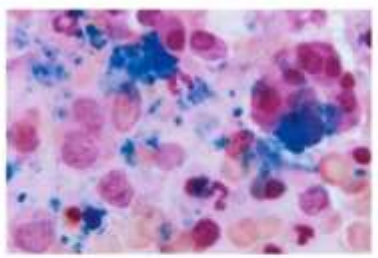
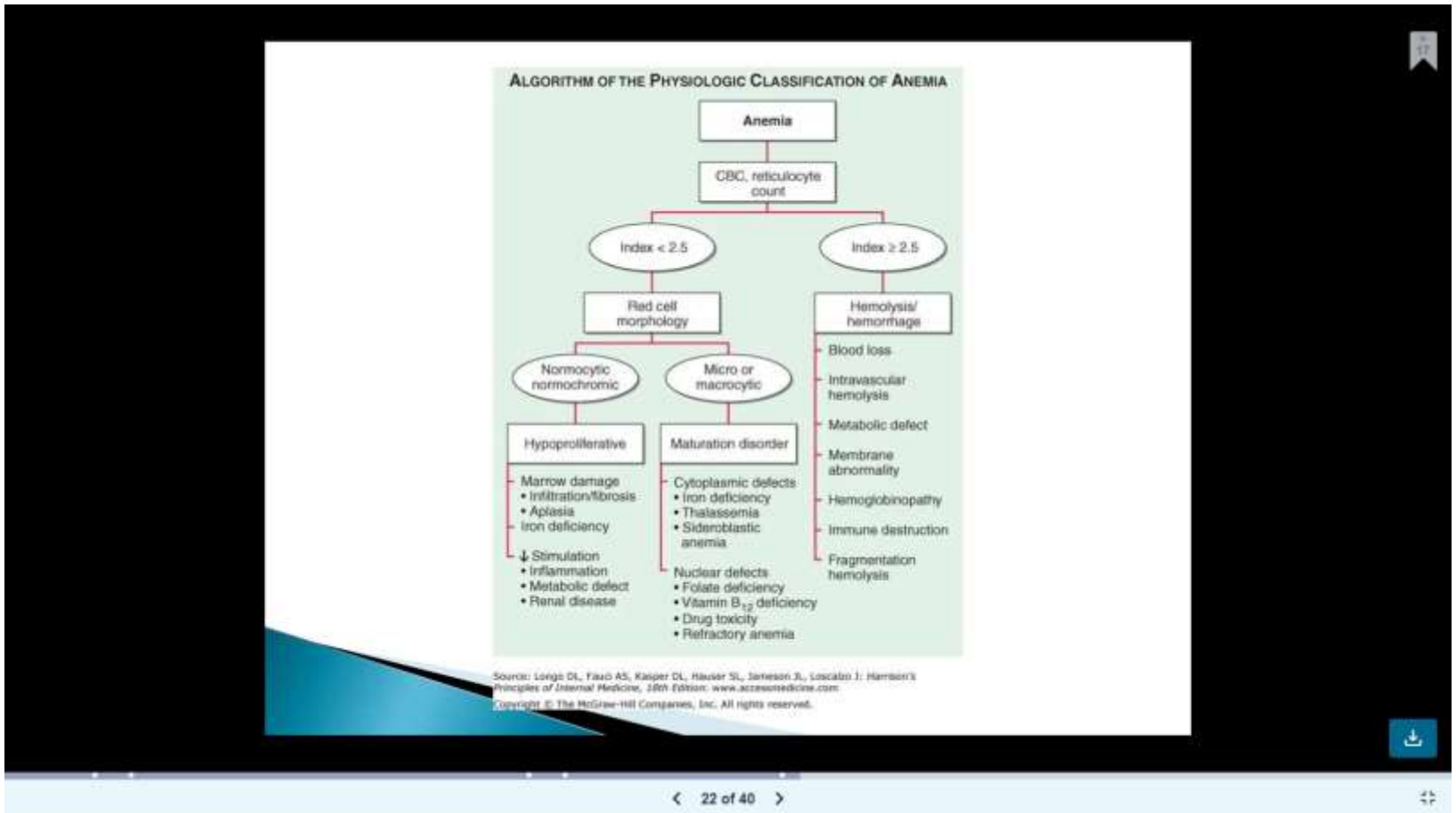
Bone Marrow Studies

- Can be stained to confirm iron status (ferritin / hemosiderin).
- Other laboratory tests maybe indicated depending on the type of anemia.



Normal Iron Stain

http://www.rightdiagnosis.com/phil/html/iron-deficiency-anemia/2657.html


ALGORITHM OF THE PHYSIOLOGIC CLASSIFICATION OF ANEMIA
Anemia
CBC, reticulocyte count
Index < 2.5
Index ≥ 2.5
Red cell morphology
Hemolysis/ hemorrhage
Normocytic normochromic
Micro or macrocytic
Blood loss
Intravascular hemolysis
Metabolic defect
Membrane abnormality
Hemoglobinopathy
Immune destruction
Fragmentation hemolysis
Hypoproliferative
Maturation disorder
Marrow damage
• Infiltration/fibrosis
• Aplasia
Iron deficiency
↓ Stimulation
• Inflammation
• Metabolic defect
• Renal disease
Cytoplasmic defects
• Iron deficiency
• Thalassemia
• Sideroblastic anemia
Nuclear defects
• Folate deficiency
• Vitamin B_{12} deficiency
• Drug toxicity
• Refractory anemia
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 18th Edition: www.accessmedicine.com
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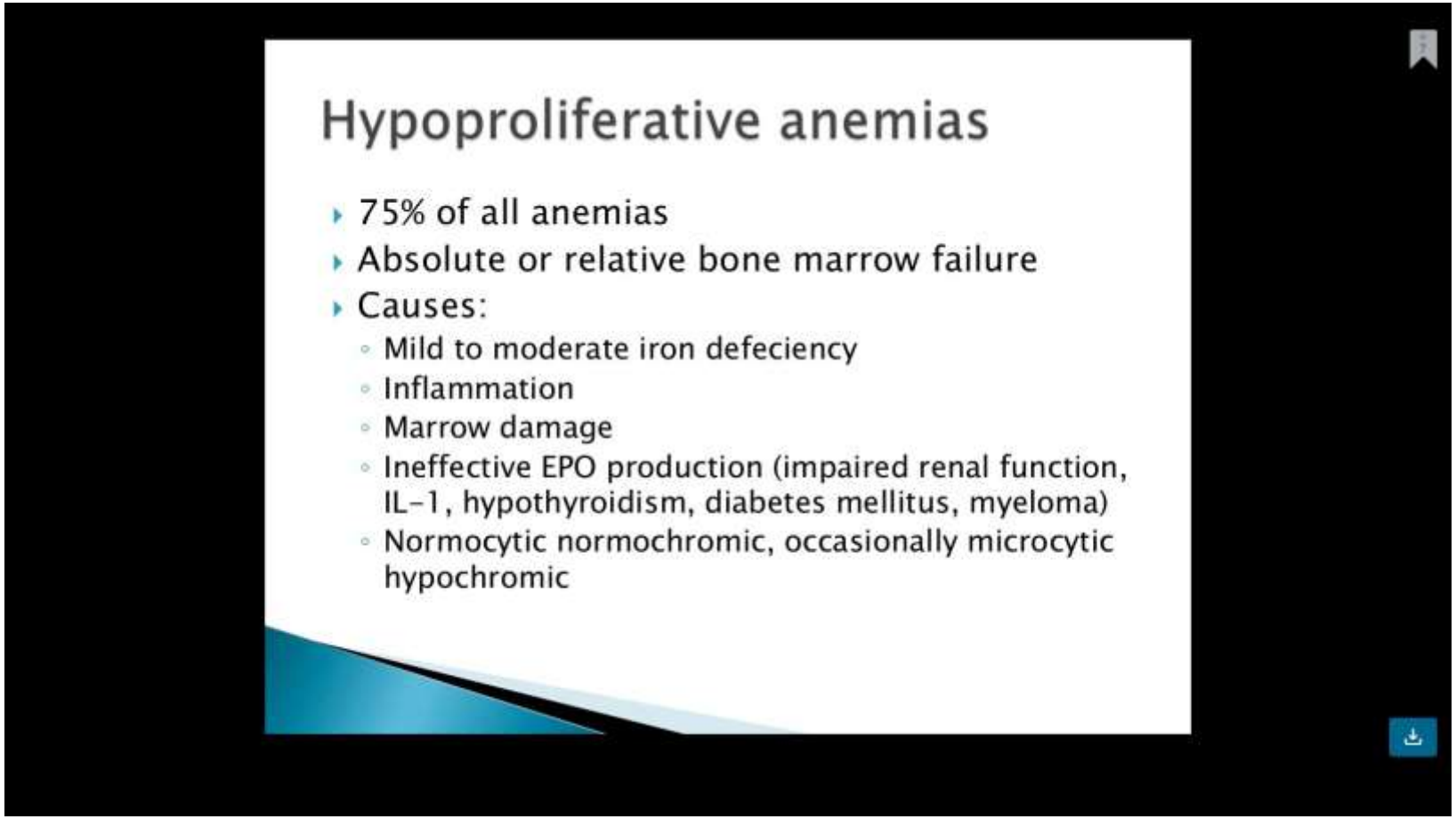
Hypoproliferative anemias
75% of all anemias
Absolute or relative bone marrow failure
Causes:
Mild to moderate iron defeciency
Inflammation
Marrow damage
Ineffective EPO production (impaired renal function, IL-1, hypothyroidism, diabetes mellitus, myeloma)
Normocytic normochromic, occasionally microcytic hypochromic

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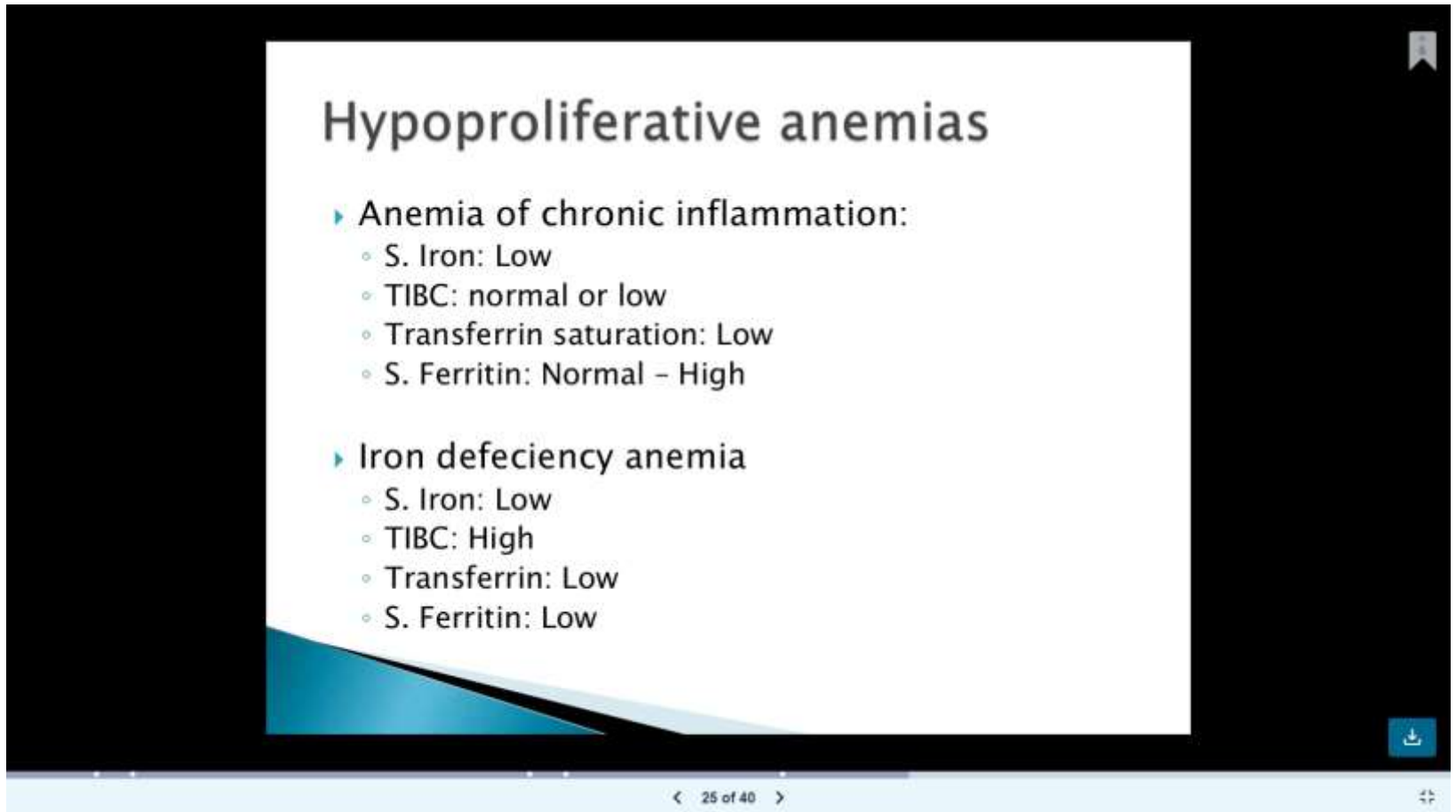
Hypoproliferative anemias

- Investigations:
  - S. Iron
  - TIBC
  - RFT
  - TFT
  - Bone Marrow biopsy/aspiration
  - Serum Ferritin
  - Iron stain of bone marrow


Hypoproliferative anemias
Anemia of chronic inflammation:
S. Iron: Low
TIBC: normal or low
Transferrin saturation: Low
S. Ferritin: Normal – High
Iron defeciency anemia
S. Iron: Low
TIBC: High
Transferrin: Low
S. Ferritin: Low
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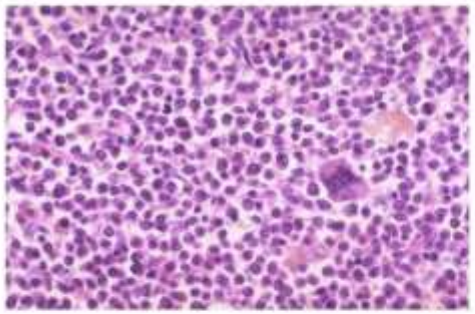
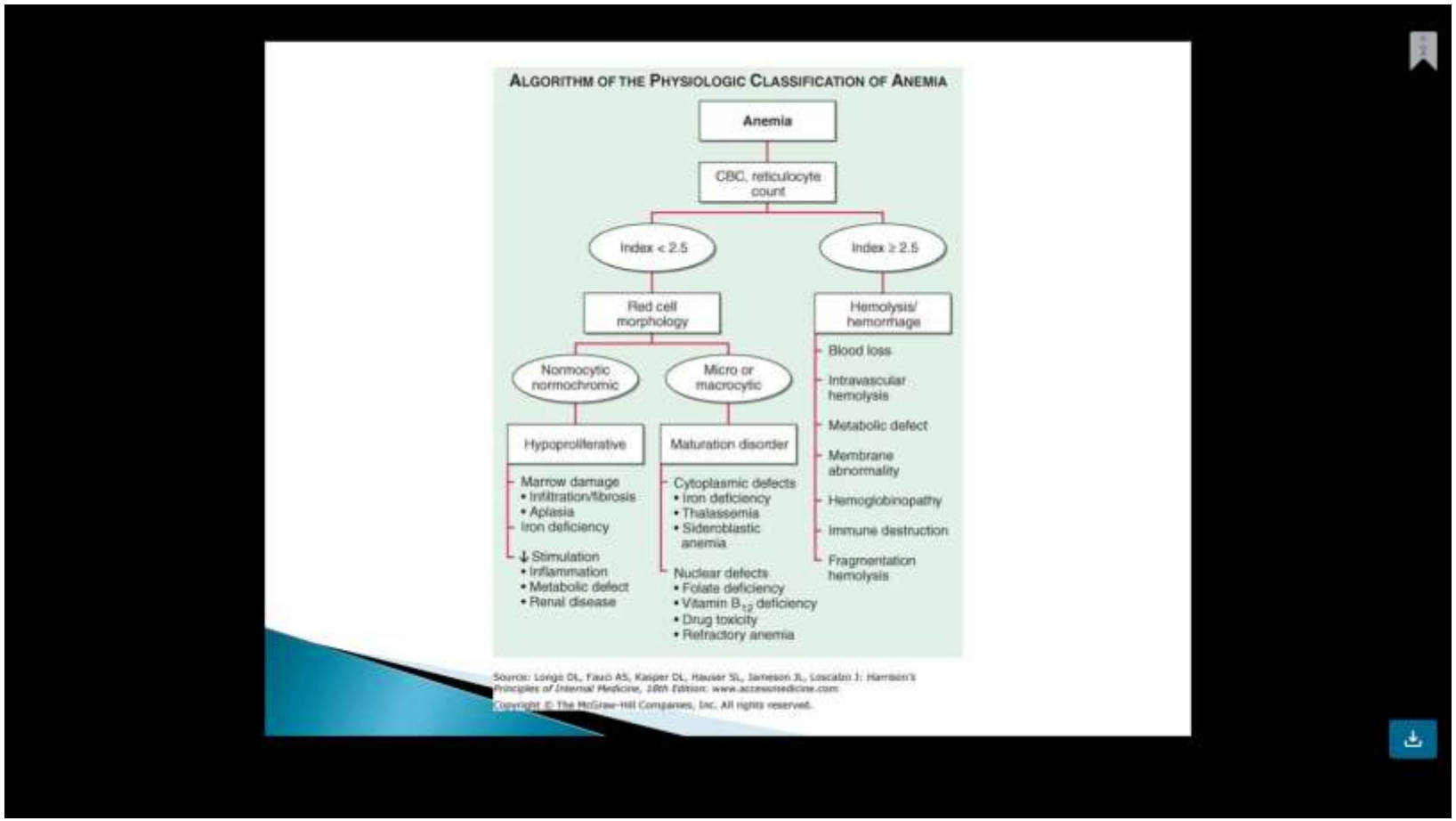
Hypoproliferative anemias

- Leukemia and lymphoma, marrow aplasia
  - Peripheral smear
  - Bone marrow biopsy



Bone marrow biopsy in Acute Leukemia
http://wikidoc.org/index.php/Bone_marrow_examination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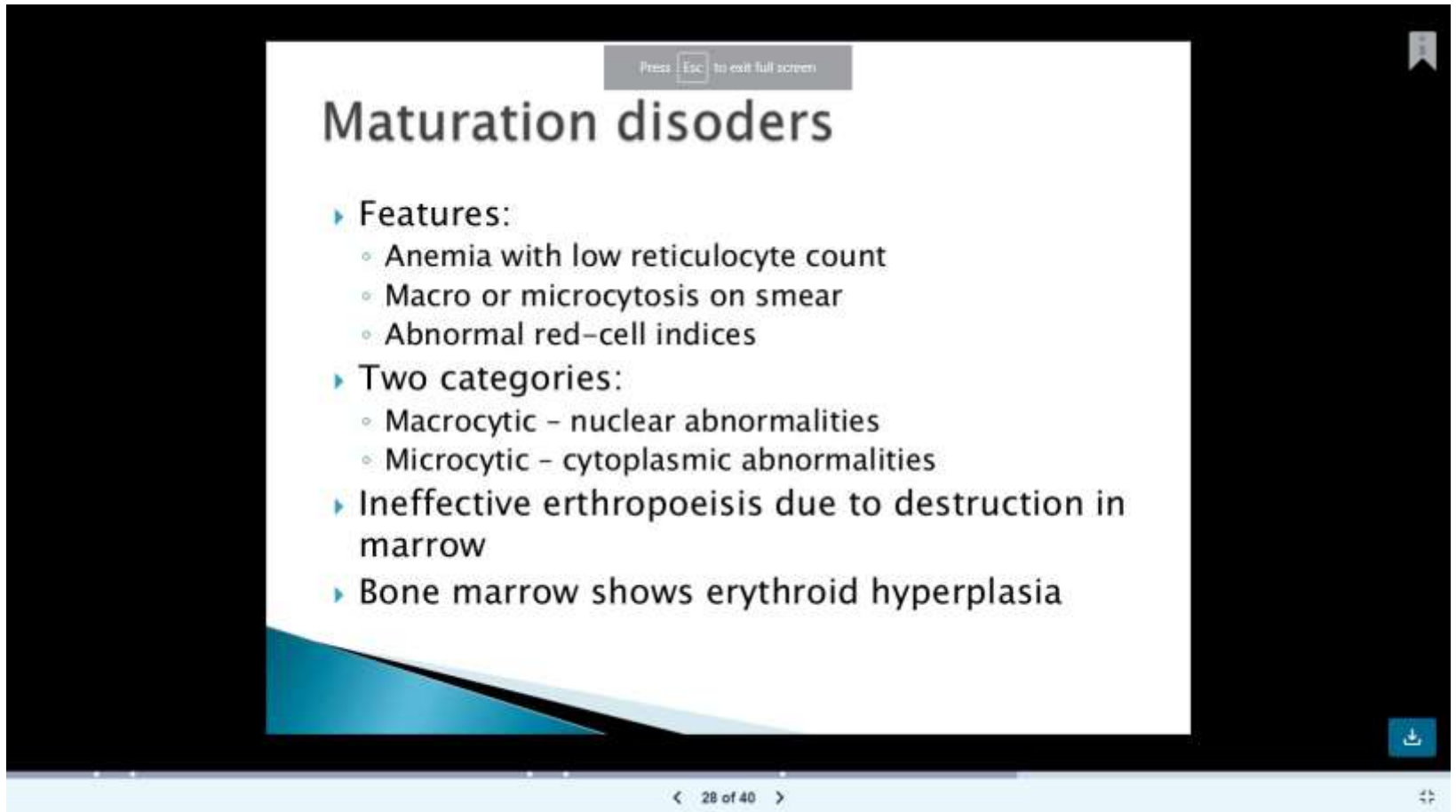
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Maturation disoders
Features:
Anemia with low reticulocyte count
Macro or microcytosis on smear
Abnormal red-cell indices
Two categories:
Macrocytic – nuclear abnormalities
Microcytic – cytoplasmic abnormalities
Ineffective erthropoeisis due to destruction in marrow
Bone marrow shows erythroid hyperplasia
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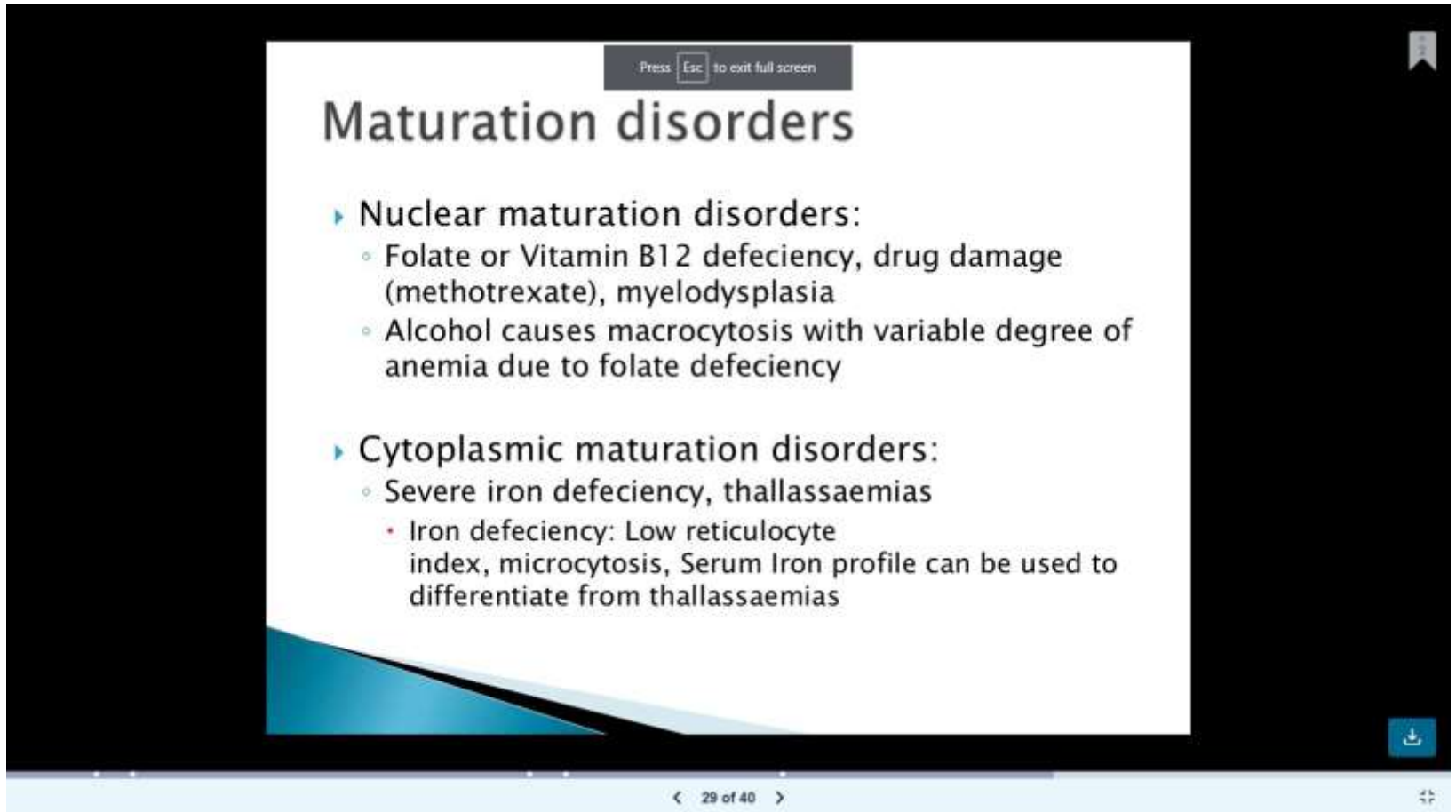
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Maturation disorders
Nuclear maturation disorders:
Folate or Vitamin B12 defeciency, drug damage (methotrexate), myelodysplasia
Alcohol causes macrocytosis with variable degree of anemia due to folate defeciency
Cytoplasmic maturation disorders:
Severe iron defeciency, thallassaemias
Iron defeciency: Low reticulocyte index, microcytosis, Serum Iron profile can be used to differentiate from thallassaemias
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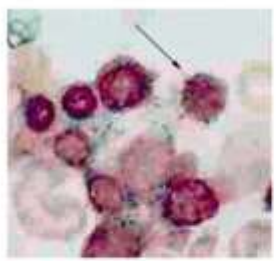
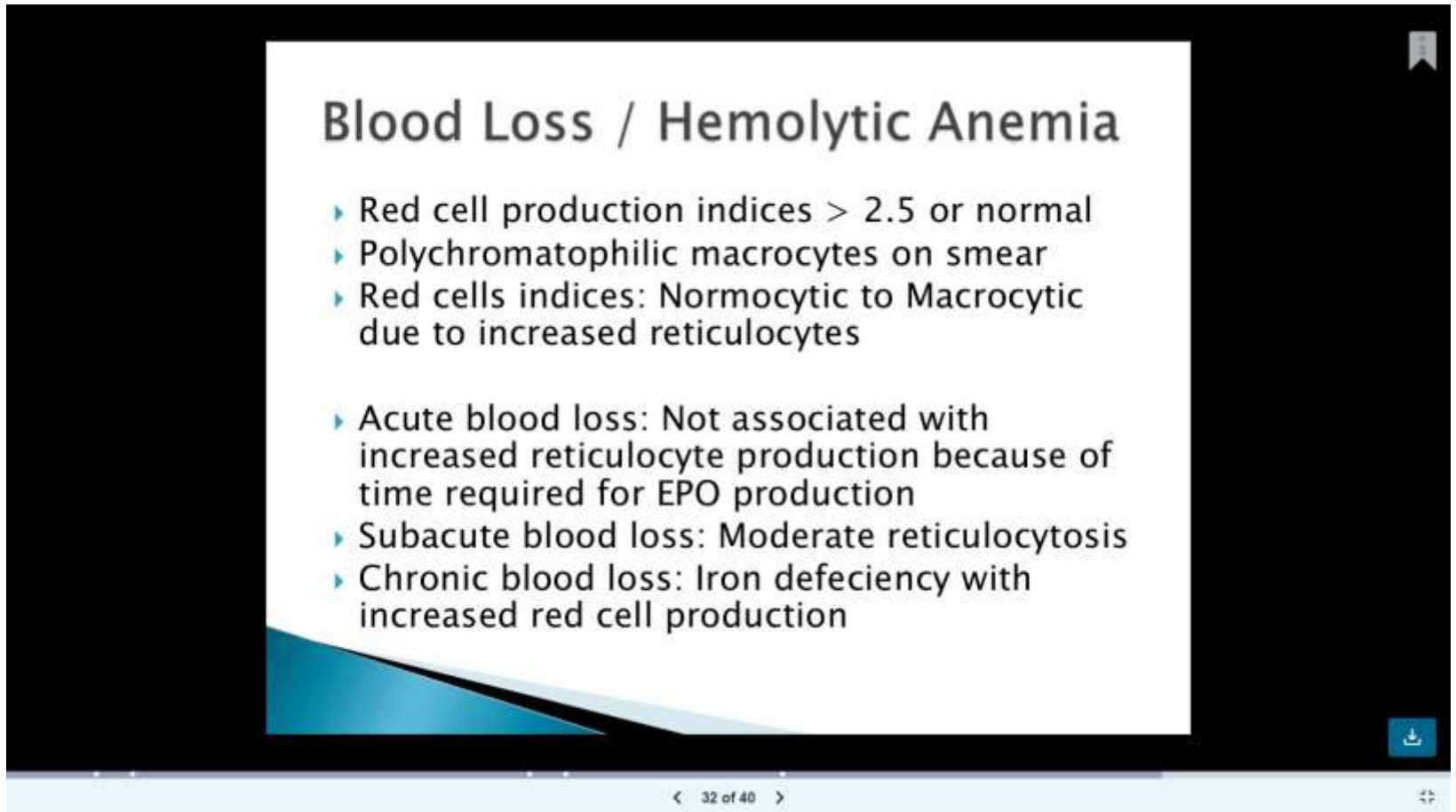
Maturation disorders

- Myelodysplasia:
  - Macro or microcytosis
  - Iron ring in mitochondria
  - Sideroblasts on marrow stain
  - Iron studies can help differentiate from other conditions




Blood Loss / Hemolytic Anemia
Red cell production indices > 2.5 or normal
Polychromatophilic macrocytes on smear
Red cells indices: Normocytic to Macrocytic due to increased reticulocytes
Acute blood loss: Not associated with increased reticulocyte production because of time required for EPO production
Subacute blood loss: Moderate reticulocytosis
Chronic blood loss: Iron defeciency with increased red cell production
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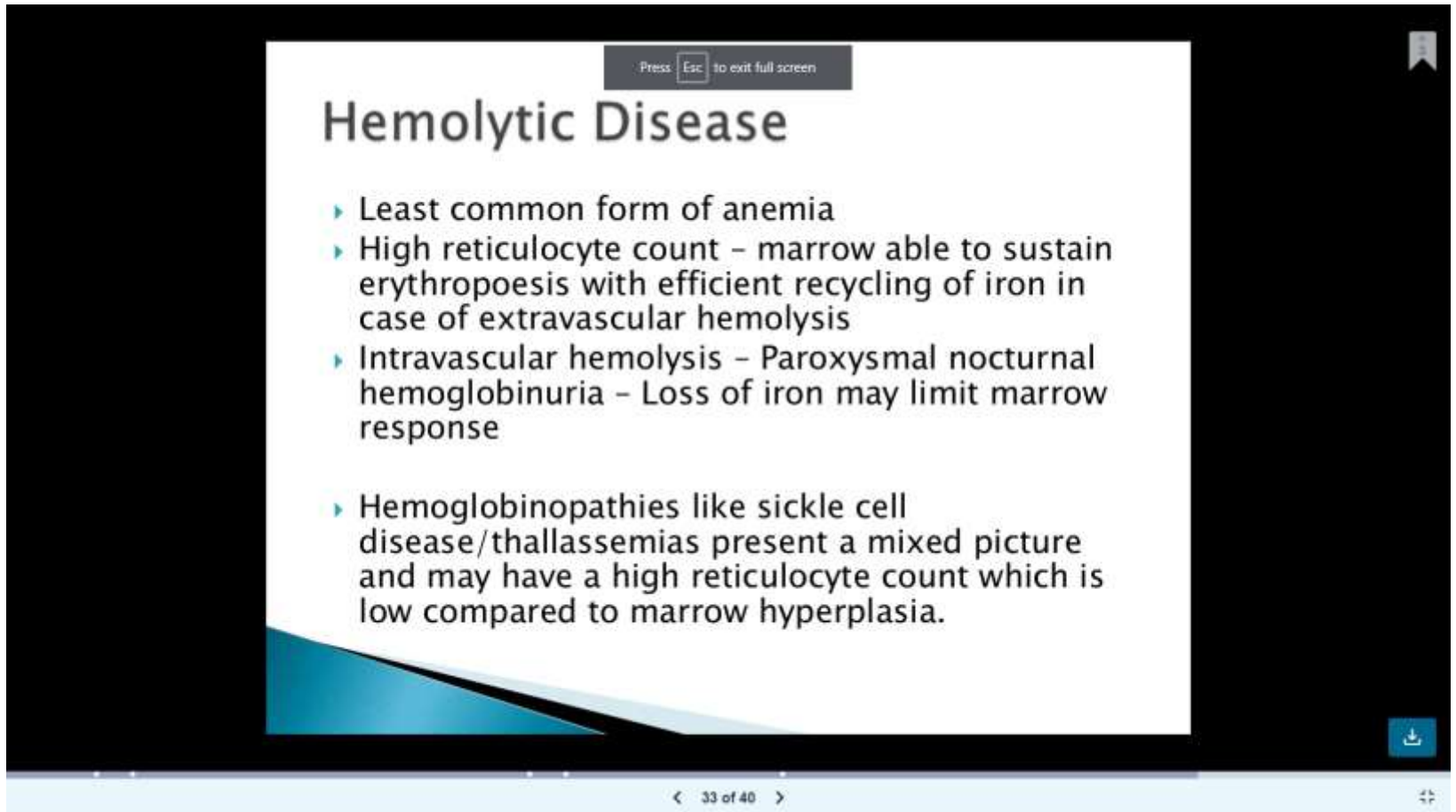
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Hemolytic Disease
Least common form of anemia
High reticulocyte count – marrow able to sustain erythropoesis with efficient recycling of iron in case of extravascular hemolysis
Intravascular hemolysis – Paroxysmal nocturnal hemoglobinuria – Loss of iron may limit marrow response
Hemoglobinopathies like sickle cell disease/thallassemias present a mixed picture and may have a high reticulocyte count which is low compared to marrow hyperplasia.
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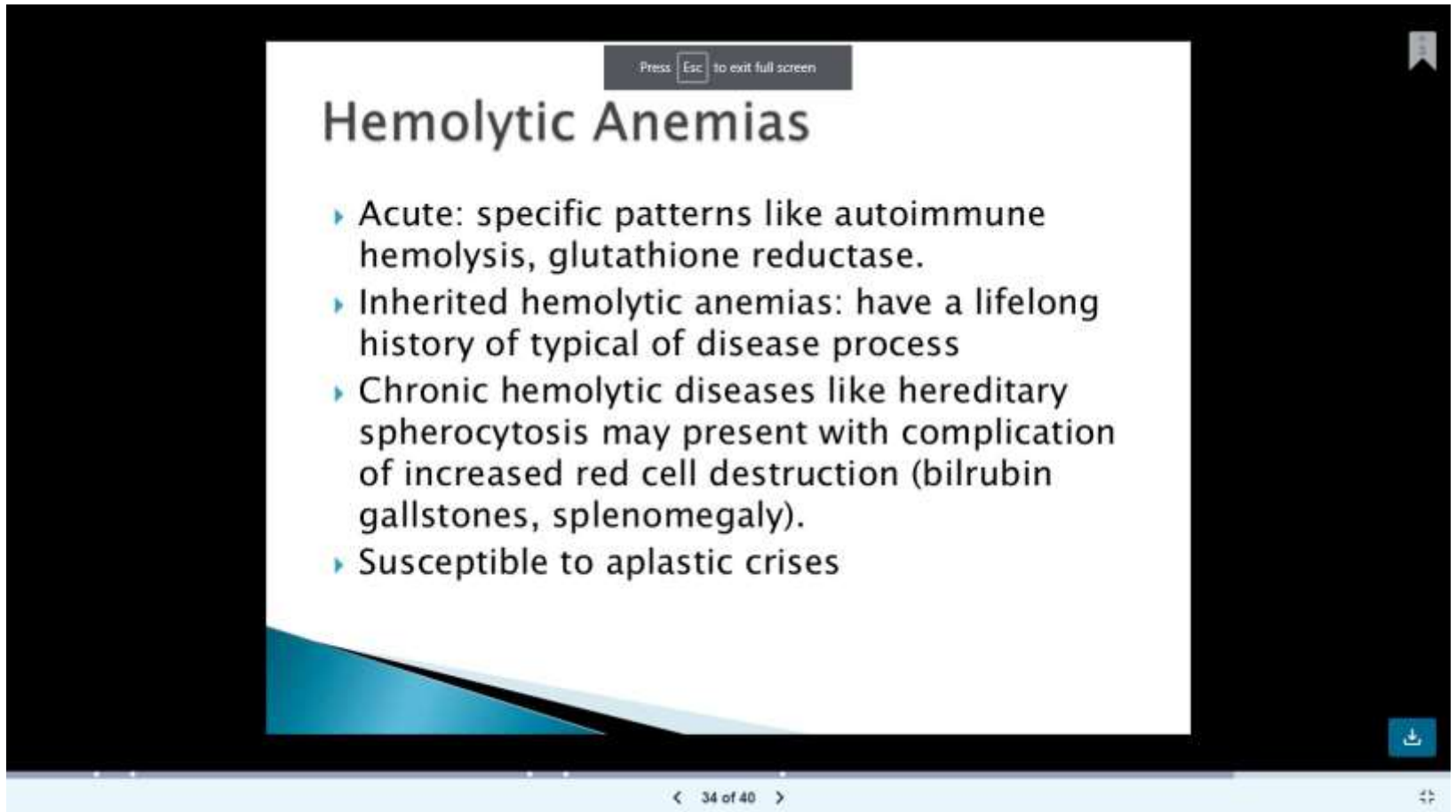
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Hemolytic Anemias
Acute: specific patterns like autoimmune hemolysis, glutathione reductase.
Inherited hemolytic anemias: have a lifelong history of typical of disease process
Chronic hemolytic diseases like hereditary spherocytosis may present with complication of increased red cell destruction (bilrubin gallstones, splenomegaly).
Susceptible to aplastic crises
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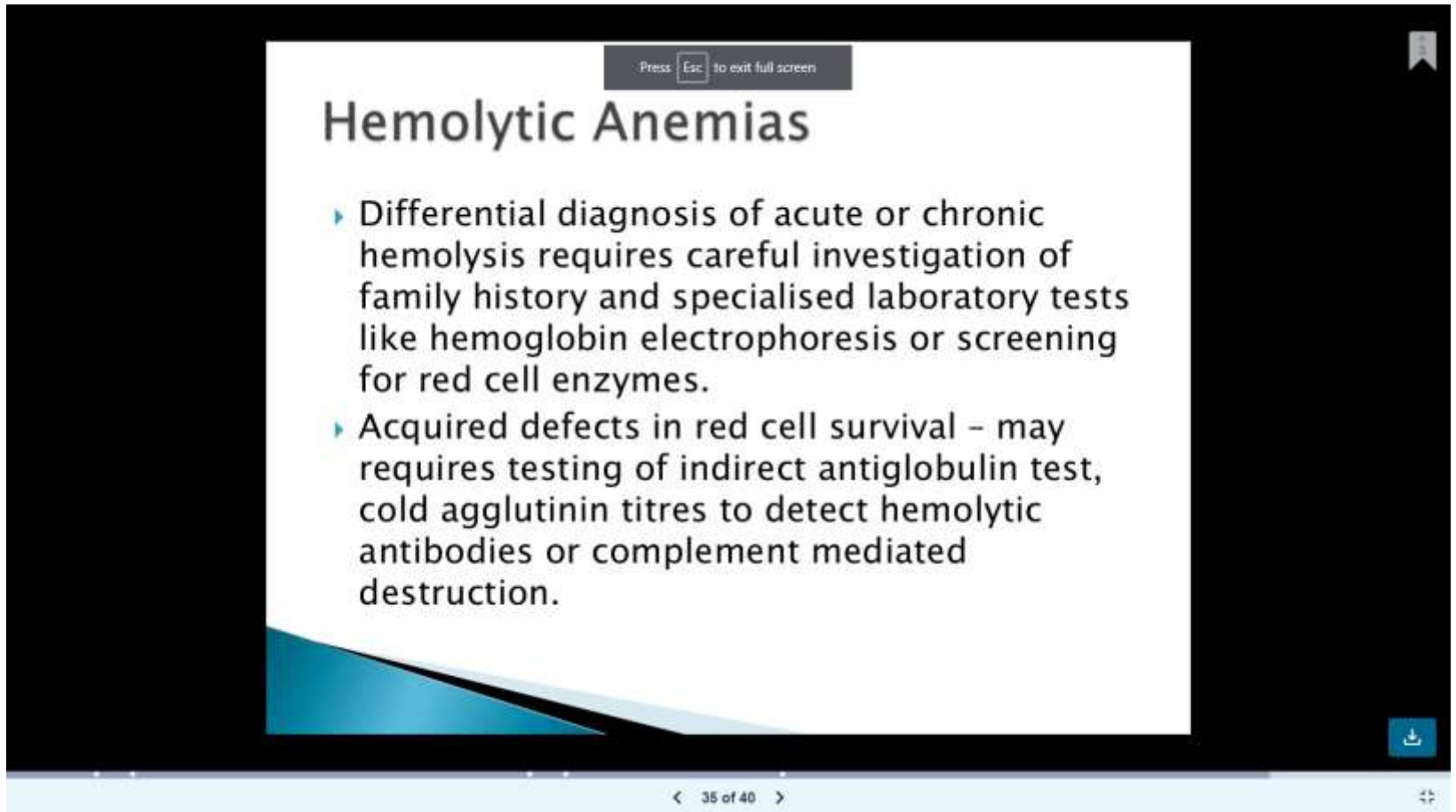
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Hemolytic Anemias
Differential diagnosis of acute or chronic hemolysis requires careful investigation of family history and specialised laboratory tests like hemoglobin electrophoresis or screening for red cell enzymes.
Acquired defects in red cell survival – may requires testing of indirect antiglobulin test, cold agglutinin titres to detect hemolytic antibodies or complement mediated destruction.
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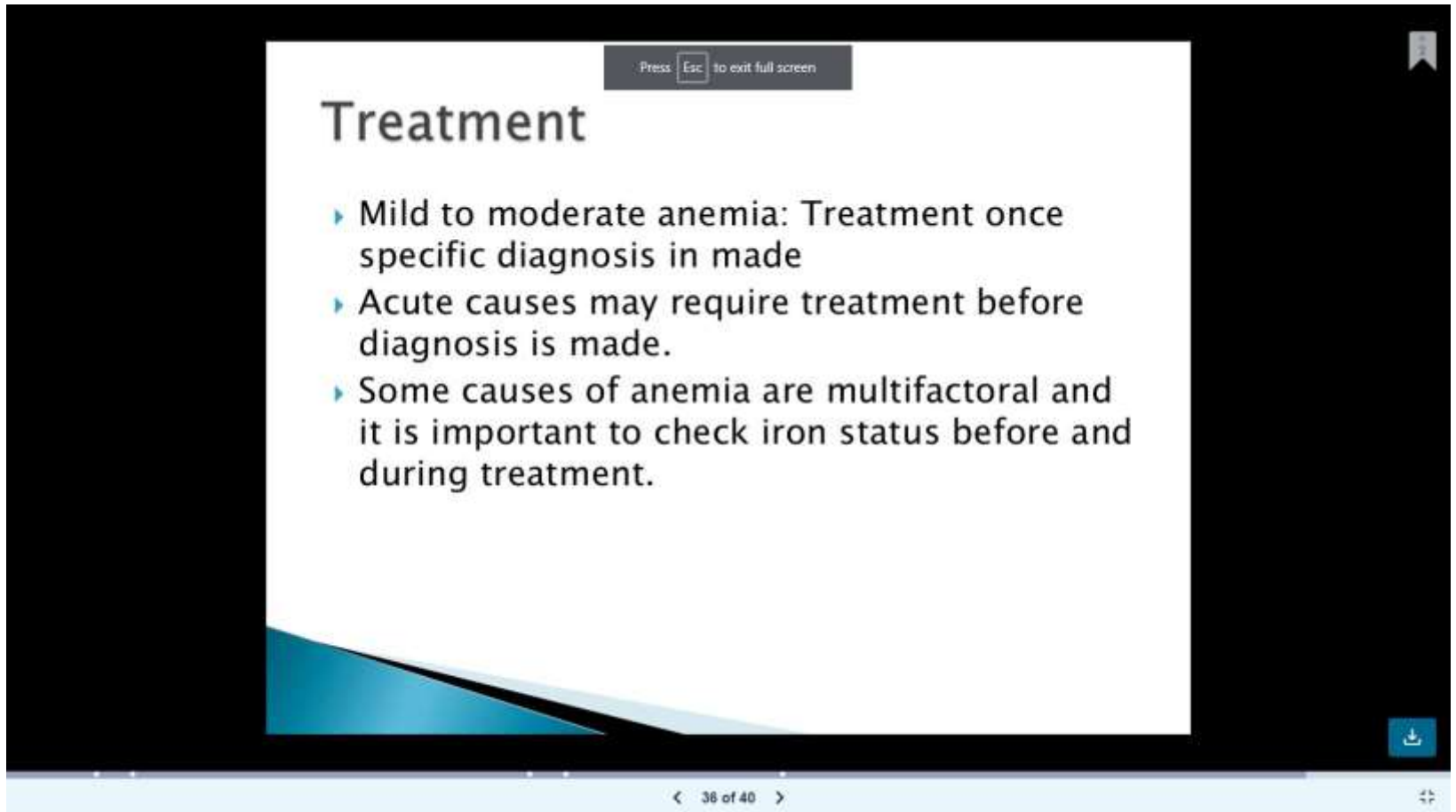
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Treatment
Mild to moderate anemia: Treatment once specific diagnosis in made
Acute causes may require treatment before diagnosis is made.
Some causes of anemia are multifactoral and it is important to check iron status before and during treatment.
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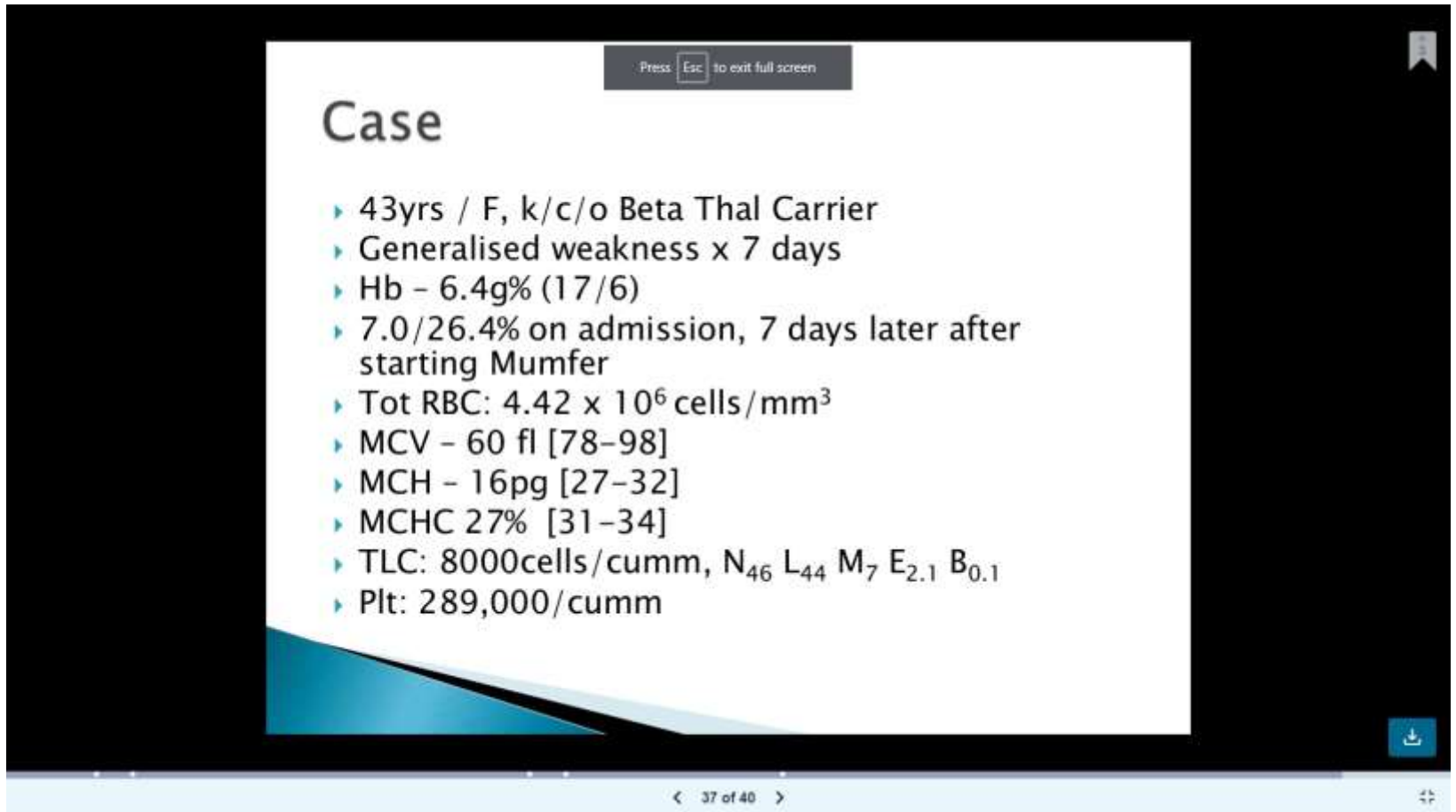
Press Esc to exit full screen
Case
43yrs / F, k/c/o Beta Thal Carrier
Generalised weakness x 7 days
Hb – 6.4g% (17/6)
7.0/26.4% on admission, 7 days later after starting Mumfer
Tot RBC: 4.42 x 10^6 cells/mm^3
MCV – 60 fl [78–98]
MCH – 16pg [27–32]
MCHC 27% [31–34]
TLC: 8000cells/cumm, N_{46} L_{44} M_7 $E_{2.1}$ $B_{0.1}$
Plt: 289,000/cumm
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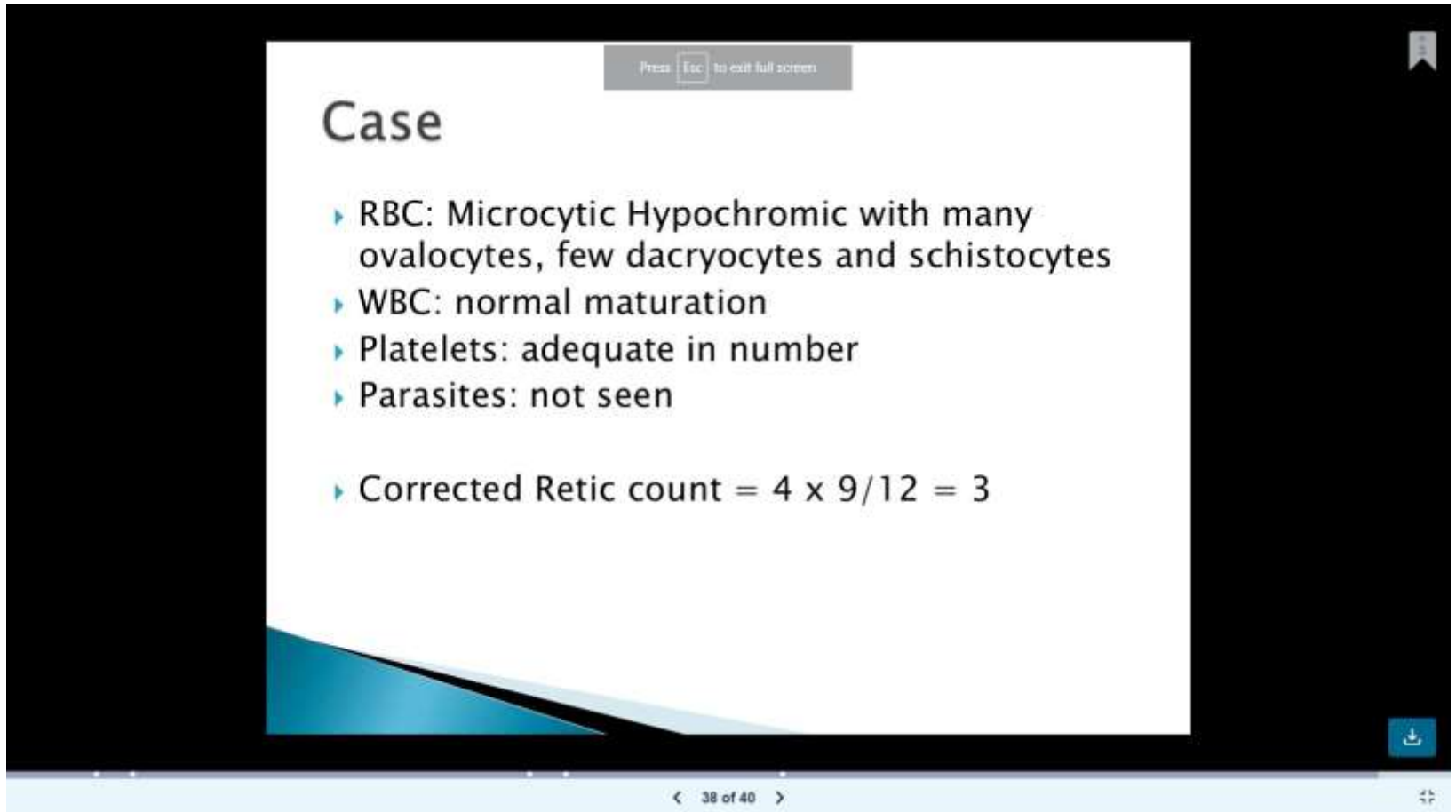
Press Esc to exit full screen
Case
RBC: Microcytic Hypochromic with many ovalocytes, few dacryocytes and schistocytes
WBC: normal maturation
Platelets: adequate in number
Parasites: not seen
Corrected Retic count = 4 x 9/12 = 3
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