Approach to Anemia

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• Definition of anemia
• Signs and symptoms related to anemia
• Classification of anemia
• Diagnostic approach
Anemia

• Anemia is the most common problem in consultative hematology
• Anemia is not a diagnosis itself
• Work-up for the cause of anemia can lead to a diagnosis of the underlying disease
Definition of Anemia

- A reduction in absolute number of circulating red blood cells as represented by RBC count, hemoglobin concentration, and hematocrit
- WHO criteria for anemia

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>&lt;13</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>&lt;39</td>
<td>&lt;36</td>
</tr>
<tr>
<td>RBC x10^{12}</td>
<td>&lt;4.5</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

World Health Organization; 1968.
Signs and Symptoms Related to Anemia

Depend on the degree of anemia and rate at which it has evolved

- Decreased oxygen delivery to tissues
  - Exertional dyspnea, dyspnea at rest, fatigue, lethargy, confusion and life-threatening complications such as congestive failure, angina, arrhythmia, and/or myocardial infarction.

- Hypovolemia (acute bleeding)
  - Postural dizziness, lethargy, syncope, hypotension, shock, and death.
# Causes of Anemia: Kinetic Approach

<table>
<thead>
<tr>
<th>Decreased RBC production (Hyporegenerative anemia)</th>
<th>Increased RBC destruction</th>
<th>Blood loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional deficiency: iron, B12, folate</td>
<td>Hemolysis</td>
<td>Obvious bleeding</td>
</tr>
<tr>
<td>Bone marrow disorders: aplastic anemia, PRCA, MDS, tumor infiltration)</td>
<td><strong>Inherited</strong>&lt;br&gt;- Membrane defects: HS, HE, SEO&lt;br&gt;- Enzymopathy: G-6-PD deficiency, pyruvate kinase deficiency&lt;br&gt;- Thalassemias</td>
<td>Occult bleeding</td>
</tr>
<tr>
<td>Bone marrow suppression: drugs, chemotherapy, radiation, alcohol, toxin)</td>
<td><strong>Acquired</strong>&lt;br&gt;- Immune: AIHA, alloimmune hemolysis&lt;br&gt;- Non-immune: PNH, drugs, chemical, infection, MAHA, mechanical hemolysis</td>
<td>Induced bleeding</td>
</tr>
<tr>
<td>Low levels of hormones: EPO (CKD), thyroid hormone (hypothyroidism), and androgens (hypogonadism)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia of chronic disease/inflammation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Causes of anemia: Morphologic Approach

<table>
<thead>
<tr>
<th>Microcytic anemia (MCV&lt; 80 fL)</th>
<th>Normocytic anemia (MCV 80-100 fL)</th>
<th>Macrocytic anemia (MCV &gt; 100 fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>Acute blood loss</td>
<td>Megaloblastic anemia (vitamin B12 deficiency, folate deficiency, drugs)</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>Hemolytic anemia: HS. G-6PD deficiency, PNH</td>
<td>Non-megaloblastic anemia (alcohol, liver disease, hypothyroidism)</td>
</tr>
<tr>
<td>Anemia of chronic disease/inflammation</td>
<td>-Anemia of chronic disease/inflammation -Anemia of CKD</td>
<td>Other bone marrow disorders: MDS</td>
</tr>
<tr>
<td>Sideroblastic anemia (congenital, lead poisoning, alcohol, drugs)</td>
<td>Hypersplenism</td>
<td>Reticulocytosis (eg. hemolytic anemia)</td>
</tr>
<tr>
<td>Copper deficiency, zinc poisoning</td>
<td>Bone marrow suppression/invasion: AA, PRCA, acute leukemia, MDS, myelophthisis</td>
<td></td>
</tr>
</tbody>
</table>

Approach to Anemia: Onset Approach

**Acute ( < 2 weeks)**
- Acute bleeding
- Acute hemolysis
  - Hereditary: G-6PD def.
    - Hb H dz.
    - HS
  - Acquired: Infection
    - AIHA
    - TTP/HUS
- Physical agents

**Subacute to chronic**
- Hyporegenerative anemia
  - ACD
  - IDA
  - Bone marrow failure
  - Marrow infiltration: acute leukemia, etc.
- Hemolytic anemia
  - Thalassemia disease, membrane defect
  - PNH
Diagnostic Approach

• History taking and physical examination
• Laboratory investigation
History Taking: Initial Evaluation

- Acute vs subacute to chronic onset?
- Any bleeding?
- Evidence of hemolysis, urine color? If so, acute or chronic
- Is the patient iron deficient? If so, why?
- Has the patient systemic/chronic/inflammatory disease?
- Is the bone marrow affected (other cytopenia, myelophthysis)
- Is the patient taking medication, alcohol?
- Is the patient deficient in folate or vitamin B12? If so, why?
- Family history, and history of transfusion
Physical Examination

- Vital signs: tachycardia, hypotension, fever
- Pallor
- Jaundice
- Lymphadenopathy, hepatosplenomegaly, and bone tenderness
- Petechiae, ecchymoses, and other signs of bleeding disorder
- Signs of organ or multisystem involvement (e.g. heart failure, CNS)
- Signs of nutritional deficiency
Laboratory Investigation: Initial Tests

• Complete blood count
  --> Limitation:
    - Increased plasma volume: pregnancy, heart failure
    - Decreased plasma volume: dehydration, burn
  --> Discrepancy: Hb H disease, cold type AIHA

• Reticulocyte count

• Peripheral blood smear
Complete blood count

- Red cell parameters
- Absolute reticulocyte count
- WBC count and differential
- Platelet count

*Comparison to previous CBC*
Red cell parameters

• Direct measurement
  - Erythrocyte concentration (RBC) $\times 10^6$/L
  - Mean corpuscular volume (MCV) fL
  - Hemoglobin g/dL

• Indirect measurement
  - Hematocrit (Hct) = RBC x MCV/10 %
  - Mean corpuscular hemoglobin (MCH) = Hb x 10/RBC pg
  - Mean corpuscular hemoglobin conc. (MCHC)
    = Hb/Hct x 100 g/dL
  - Red cell distribution width (RDW) %

CBC: normal value

- MCV 80-100 fL
- MCH >27 pg
- MCHC 32-36 g/dL
- WBC 3.8-10.6 x10⁹/L men
  3.6-11.0 x10⁹/L woman
- Platelet 150-440 x10⁶/L
- RDW 11.5-14.5%

Reticulocyte count

- Non-nucleated RBC with polyribosome RNA as stained by supravital stain
- Polychromasia underestimate reticulocytes
- **Corrected reticulocyte %**
  \[ = \% \text{ reticulocyte} \times \text{patient's Hct} \]
  
  \[45\]

- **Absolute reticulocyte count**
  \[ = \% \text{ reticulocyte} \times \text{RBC} \]

  - 25,000-75,000/µL normal
  - > 100,000 regenerative anemia
  - < 50,000 hypoproliferative anemia
  - 50,000-100,000 combined etiologies

Reticulocyte index

- Reticulocyte index = %corrected RetiC/maturation time

<table>
<thead>
<tr>
<th>Maturation time (days)</th>
<th>Hct ≥ 40%</th>
<th>Hct 30-40%</th>
<th>Hct 20-30%</th>
<th>Hct &lt; 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>= 1</td>
<td>= 1.5</td>
<td>= 2</td>
<td>= 2.5</td>
</tr>
</tbody>
</table>

- The reticulocyte index (RI) for healthy individual
  - 1.0-2.0%
- RI < 1% with anemia
  - Decreased production of reticulocytes
- RI >2% with anemia
  - Loss of RBC e.g. destruction, bleeding

Peripheral blood smear

- **Microcytic hypochromic red cells**
  - Lymphocyte

- **Iron deficiency anaemia, thalassaemia, anaemia of chronic disease**
  - Megaloblastic anaemia
  - Sickle cell disorders
  - Hereditary spherocytosis, autoimmune haemolytic anaemia

- **Target cells**
  - Schistocytes
  - Burr cells
  - Tear drop red cells

- **Thalassaemia, HbC disease, sickle cell thalassaemia, obstructive jaundice**
  - Microangiopathic haemolytic anaemia
  - Uraemia
  - Myelophthisic anaemia, myelofibrosis

- **Polychromatric red cells**
  - Basophilic stippling
  - Howell-Jolly bodies
  - Bite cells

- **Haemolysis, blood loss**
  - Lead poisoning, thalassaemia, megaloblastic anaemia
  - Megaloblastic anaemia, thalassaemia, post-splenectomy
  - Glucose-6-phosphate dehydrogenase deficiency

- **Rouleaux formation**
  - Nucleated red cells
  - Autoagglutination
  - Normal red cells

- **Hypergammaglobulinaemia, multiple myeloma**
  - Haemolytic anaemia
  - Autoimmune haemolytic anaemia (cold antibody type)
Case 1
หญิง อายุ 30 ปี เหนื่อยง่าย 3 เดือน มีคนทักว่าซีด
PE: moderately pale, no jaundice, others: normal

<table>
<thead>
<tr>
<th>WBC</th>
<th>7.3 (3.6 - 10.4) *1000/ul</th>
<th>Hemoglobin</th>
<th>7.5 (13.1 - 16.9) g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>23.5 (39.4 - 50.8) %</td>
<td>Neutrophil</td>
<td>65 (35.6 - 70.5) %</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>30 (21.1 - 50.4) %</td>
<td>Monocyte</td>
<td>2 (2.3 - 11.1) %</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>2 (1 - 11.8) %</td>
<td>Basophil</td>
<td>1 (.8 - 1.6) %</td>
</tr>
<tr>
<td>MCV</td>
<td>57.8 (76.1 - 99.3) fl</td>
<td>MCH</td>
<td>18.5 (25.2 - 33.2) pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>32 (31.6 - 34.8) g/dl</td>
<td>RDW</td>
<td>23.1 (10.8 - 14) %</td>
</tr>
<tr>
<td>Platelet count</td>
<td>453 (156 - 393) *1000/ul</td>
<td>MPV</td>
<td>6.6 (6.5 - 9.5) fl</td>
</tr>
<tr>
<td>RBC</td>
<td>4.08 (4.36 - 5.9) *1000000/ul</td>
<td>Microcytosis</td>
<td>1 (-) -</td>
</tr>
</tbody>
</table>
Iron deficiency anemia (IDA)

• Iron is a key substrate for heme production

• Causes
  – Low intake :
  – Chronic blood loss***

• Symptoms and signs
  – Anemic symptoms, cold hand and feet, fatigue, dizziness, dyspnea, pica, spoon nail (koilonychia), murmur, pale glossitis, and heart failure
IDA: lab

- CBC
  - Hct ↓, Hb ↓
  - MCV ↓ (when Hb < 10 g/dL), MCH ↓, MCHC ↓
  - RDW ↑ (early sign)
- Reticulocyte count ↓
- Iron profile
  - Serum Iron ↓ (<60 µg/dL)
  - TIBC ↑ (> 400 µg/dL)
  - Ferritin ↓ *** (< 30 ng/mL)
- Bone marrow study (gold standard but more invasive): no iron stain

Transferrin saturation (Tsat) = SI/TIBC x 100
IDA : PBS

- Hypochromic microcytic RBC
- Poikilocytosis and anisocytosis
- Pencil cell
- Rare or no polychrome
**Case 2**

ชายอายุ 33 ปี ซึ่งเคยผ่าตัดลิ่มเลือดตอนเด็กปีละ 1-2 ครั้ง

PE: moderate pallor, mild jaundice, spleen 4 cm below LCM

<table>
<thead>
<tr>
<th>CBC(30101)(7.1.1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong></td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
</tr>
<tr>
<td><strong>Lymphocyte</strong></td>
</tr>
<tr>
<td><strong>Eosinophil</strong></td>
</tr>
<tr>
<td><strong>MCV</strong></td>
</tr>
<tr>
<td><strong>MCHC</strong></td>
</tr>
<tr>
<td><strong>MPV</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
</tr>
<tr>
<td><strong>Neutrophil</strong></td>
</tr>
<tr>
<td><strong>Monocyte</strong></td>
</tr>
<tr>
<td><strong>Basophil</strong></td>
</tr>
<tr>
<td><strong>MCH</strong></td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
</tr>
<tr>
<td><strong>RBC</strong></td>
</tr>
<tr>
<td><strong>RDW</strong></td>
</tr>
</tbody>
</table>
Case 2

- **Hb typing:** HbE 62.3%  
  HbF 30.3%

- **Diagnosis:**  
  β thalassemia/HbE disease
Thalassemia and hemoglobinopathies

Non-transfusion-dependent thalassemias

- Transfusions seldom required
- Occasional transfusions required
- Intermittent transfusions required
- Regular, lifelong transfusions required

α-thalassemia trait
β-thalassemia minor
HbC/β-thalassemia
Mild HbE/β-thalassemia
HbH disease
Deletional HbH
Moderate HbE/β-thalassemia
Non-deletional HbH
β-thalassemia major
Severe HbE/β-thalassemia

Thalassemia intermedia

Chipmunk (or Rodent face)

Facial bone abnormality:

- Bossing of skull
- Hypertrophy of the maxilla
- Exposing the upper teeth
- Depression of nasal bridge
- Periorbital puffiness
Case 3

ชายอายุ 20 ปี ไข้ 3 วัน เหนื่อยมากขึ้น

PE: moderately pale, mild jaundice, no organomegaly

CBC: Hb 7 g/dL, Hct 21%, MCV 92 fL, RDW 18%, WBC 15x10⁹/L, PMN 40%, L 50%, atypical lymph 3%, mono 7%, NRC 3/100 WBC, platelet 280x10⁹/L
- Hb contracted RBC
- polychromasia
- ghost cell
- Hb leakage cell
G-6PD deficiency

• X-linked recessive --> common in males
• Anemia after precipitating factors (infection, drugs)
  - Antimalarials (primaquine)
  - Sulfonamides (sulfamethoxazole, dapsone)
  - Antibiotics (cotrimoxazole, quinolones)
• Dark urine from hemoglobinuria
• Serious complications: renal insufficiency, hyperkalemia
Case 4
A 64-year-old man with underlying T2DM, HT, CKD (creatinine 2.0 mg/dL)

- Hb 9 g/dL, Hct 27.3%
- WBC 5.6 x10^9 /L, PMN 76%, L 20%, Mono 2%, Eo 2%, Baso 0%
- Platelet 230 x10^9 /L
- MCV 85 fL, MCH 26.6 pg, MCHC 33.4 g/dL, RDW 14.2%
Anemia of chronic disease; ACD (Anemia of inflammation; AI)

• Mild to moderate anemia (Hb 7-12 g/dL) associated with chronic infections, inflammation and malignancies.

• Inadequate erythrocyte production in the presence of low transferrin but preserved or even increased iron macrophage stores in marrow.

• Diagnosis by recognition of the underlying disease and exclusion of other associated cause of anemia.
Anemia of chronic disease; ACD (Anemia of inflammation; AI)

Serum levels that differentiate anemia of chronic disease from iron deficiency anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anemia of Chronic Disease</th>
<th>Iron-Deficiency Anemia</th>
<th>Both Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Reduced to normal</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal to increased</td>
<td>Reduced</td>
<td>Reduced to normal</td>
</tr>
<tr>
<td>Soluble transferrin receptor</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Ratio of soluble transferrin receptor to log ferritin</td>
<td>Low (&lt;1)</td>
<td>High (&gt;2)</td>
<td>High (&gt;2)</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Anemia of chronic kidney disease

- Normocytic, normochromic anemia
- Occurs as early as stage 3 CKD (eGFR < 60 ml/min/1.73m²), almost universal by stage 4
- **Primary cause:** insufficient production of EPO
- Associated with adverse consequences
  - Decreased tissue oxygen delivery and utilization
  - Increased cardiac output
  - Ventricular dilatation, ventricular hypertrophy
- **Clinical manifestations:** angina, heart failure, decreased cognition and mental acuity, impaired host defense against infection

Anemia of chronic kidney disease

Cause of anemia in CKD

- Relative deficiency of erythropoietin
- Diminished RBC survival
- Bleeding diathesis
- Iron deficiency
- Hyperparathyroidism/bone marrow fibrosis
- Chronic inflammation
- Folate or vitamin B12 deficiency
- Hemoglobinopathy
- Comorbid conditions: hypo/hyperthyroidism, pregnancy, HIV, autoimmune disease, immunosuppressive drugs

Case 5
หญิง อายุ 46 ปี เหนื่อยง่าย 2 สัปดาห์
CBC: Hb 6.2 g/dL, Hct 16%, WBC 19x10^9/L, PMN 76% band 5%, myelocyte 3%, L 16%, platelet 560x10^9/L, MCV 120 fL, RDW 22%
Numerous spherocytes
Increase polychrome
Adequate platelet
Causes of autoimmune hemolytic anemia

**Warm-autoantibody type:** autoantibody maximally active at body temperature (37°C), usually IgG
1. Primary of idiopathic warm AIHA
2. Secondary warm AIHA
   - Lymphoproliferative disorders (NHL, HL, CLL)
   - Connective tissue diseases, particularly SLE
   - Nonlymphoid neoplasms (e.g. ovarian tumors)
   - Chronic inflammatory disease (e.g. ulcerative colitis)
   - Drugs (e.g. α-methyldopa)

**Cold-antibody type:** autoantibody optimally active at temperature < 37°C, usually IgM
1. Idiopathic (primary) chronic cold agglutinin disease (CAD)
2. Secondary cold agglutinin hemolytic anemia
   - Postinfectious (e.g. mycoplasma pneumoniae or infectious mononucleosis)
   - Malignant B cell lymphoproliferative disorder
   - Paroxysmal cold hemoglobinuria (rare)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Special characteristic</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G6PD deficiency</strong></td>
<td>X-link recessive (male predominance), acute onset, precipitate(drugs, infection), dark urine, no hepatosplenomegaly PBS : NRC, polychromasia, Hb contracted red cell, Hb leakage cell, bite cell, ghost cell</td>
<td>G6PD enzyme assay</td>
</tr>
<tr>
<td><strong>Thalassemias</strong></td>
<td>Thalassemic face and hepatosplenomegaly may be seen. PBS : hypochromic, microcytic, target cell, polychromasia</td>
<td>-Hb typing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Inclusion body (HbH)</td>
</tr>
<tr>
<td><strong>Hereditary spherocytosis</strong></td>
<td>Autosomal dominant, pigmented gall stone, mild splenomegaly PBS : numerous spherocyte (normocytic anemia)</td>
<td>Incubated osmotic fragility</td>
</tr>
<tr>
<td><strong>AIHA</strong></td>
<td>Acute or subacute, mild splenomegaly PBS : autoagglutination (cold), microspherocyte, polychromasia</td>
<td>Direct Coomb’s test (DAT: direct antiglobulin test)</td>
</tr>
<tr>
<td>Disease</td>
<td>Special characteristic</td>
<td>Lab</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>PNH</td>
<td>Chronic/Intermittent intravascular hemolyisis, dark urine, thrombosis, jaundice, bone marrow failure</td>
<td>- Urine hemosiderin, - Flow cytometry for CD55, CD59</td>
</tr>
<tr>
<td></td>
<td>PBS : increase polychromasia, may be IDA coexisting, may be pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Chronic anemia, spoon nail (koilonychia), pica, history of chronic blood loss</td>
<td>- Serum ferritin - SI, TIBC, Tsat</td>
</tr>
<tr>
<td></td>
<td>PBS: hypochromic microcytic, anisocytosis, pencil cell, reactive thrombocytosis</td>
<td></td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Chronic anemia, glossitis (beefy tongue), neuropathy or psychotic problem (vit B12 def.)</td>
<td>- Serum cobalamin - Red cell/serum folate</td>
</tr>
<tr>
<td></td>
<td>PBS: macrocytic RBC, macroovalocyte, hypersegmented PMN, may be pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Bone marrow failure/infiltration</td>
<td>Anemia, fever, abnormal bleeding</td>
<td>Bone marrow study</td>
</tr>
</tbody>
</table>
Evaluation of anemia in the adult according to the mean corpuscular volume

Anemia detected on CBC

Evaluate MCV and look for other "flags" on CBC report for presence of abnormal RBCs, or examine peripheral smear

MCV low (≤80 fl)
- MCV low
- Minor population of microcytic RBCs present
  - Iron studies
    - Low Fe
    - High TIBC
    - Low ferritin
    - Anemia of chronic disease: infection, inflammation, or malignancy
  - Normal to high Fe
    - Normal or low TIBC
    - Normal or high ferritin
    - Iron overload present
      - Siderocytes on peripheral smear
      - Sideroblasts on bone marrow
    - Teardrop red cells
      - Target cells
      - Spleenomegaly
      - Positive family history
    - Sideroblastic anemia: determine cause
  - Alpha or beta thalassemia: perform hemoglobin electrophoresis

MCV normal (80 to 96 fl)
- MCV normal
- Minor population of macrocytic RBCs present
  - MCV increased (>100 fl)

MCV increased (>100 fl)
- MCV increased
- Dysplastic features present
- Cytophenias present
- Myelodysplastic disorder
- Serum B12 and folate levels
- Methylenonate (if needed)
- Homocysteine (if needed)
- Other causes:
  - Increased reticulocytes
  - Liver disease
  - Hypothyroidism
  - Drugs

Other causes:
- Low B12
- Elevated methylmalonate
- Elevated homocysteine
- B12 deficiency: determine cause
- Folate deficiency: determine cause

CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.
Conclusion

• Anemia is not a diagnosis itself
• Initial approach to the diagnosis
  - Perform complete history and physical examination
  - Review of the complete blood count with white blood cell differential, platelet count, reticulocyte count
  - Examination of the peripheral blood smear
• There may be more than one causes of anemia, including blood loss, effects of current medications, etc.