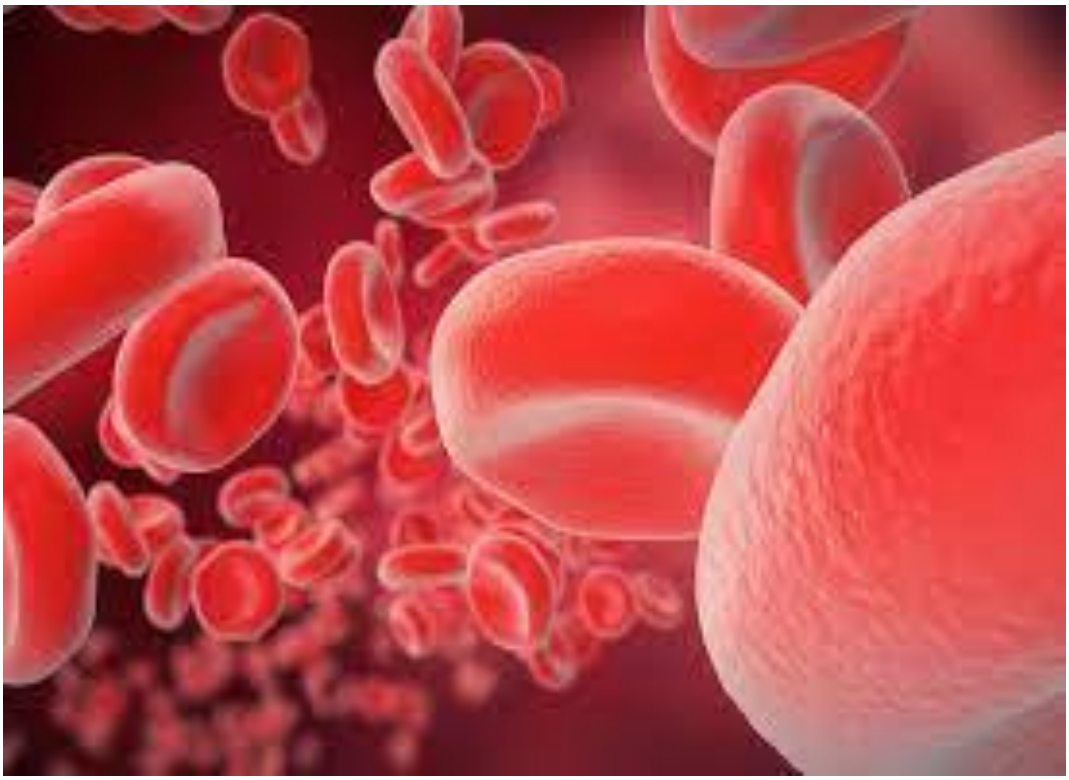

BLEEDING DISODERS

Educational-methodical manual

for students medical universities and teachers

OSH STATE UNIVERSITY

INTERNATIONAL MEDICAL FACULTY

Department of clinical disciplines 1

BLEEDING DISODERS

Educational-methodical manual

for students and teachers

Osh - 2022

Recommended by decision of the Academic Council International Medical Faculty

Osh State University

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Educational-methodical manual provides a summary of the etiology, pathogenesis, classification, diagnosis of Henoch-Schönlein purpura, immune thrombocytopenia, hemophilia, and disseminated intravascular coagulation (DIC). Modern approaches to the treatment of bleeding disoders are considered.

The educational-methodical manual is intended for students and teachers of medical universities for the study of the subject "Hematology".

Content

3.10. Pharmaceutical therapy. Mechanism of Action. Indication

3.11. Treatment: dosage of drugs, duration of treatment and adverse effects

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4. Hemophilia

Tables: Information block relating to: Immune thrombocytopenia.

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4.4. Classification

4.5. Symptoms and sings. Sites of bleeding in hemophilia. Approximate frequency of bleeding at different sites

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5. Disseminated intravascular coagulation (DIC)

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1. List of abbreviations

AZA: Azathioprine;
ACE: Angiotensin-converting enzyme;
ANCA: Anti-neutrophilic antibodies;
aPTT: Activated partial thromboplastin times;
AICC: Anti inhibitor coagulation complex;
APTT: Activated partial thromboplastin time;
CYC: Cyclophosphamide;
CNS: Central nervous system;
CMV: Cytomegalovirus;
CBC: Complete blood count;
DIC: Disseminated intravascular coagulation;
ERS: Eritrocyte sidamination rate;
FFP: Fresh frozen plasma;
GIT: Gastro intestinal tract;
Hb: Hemoglobin;
HLAs: Human leukocyte antigens;
HPAs: Human platelet antigens;
HSP: Henoch - Schonlein purpura;
HTN: Hypertension;

HIV: Human immunodeficiency virus;
IV: Intravenous;
ITP: Idiopathic thrombocytopenic purpura;
IgG: Immunoglobulin G;
IVIG: Intravenous Immunoglobulin G;
IVH: Intravascular hemolysis;
ITI: Immune tolerance indication;
IM: Intramuscular;
KFT: Kidney function test;
MP: Methylprednisolone;
MMF: Mycophenolate mofetil;
MRI: Magnetic resonance imaging;
NSAIDs: Nonsteroidal anti-inflammatory drugs;
PT: Prothrombin time;
PT: Platelet;
PC: Professional competencies;
RBC: Red blood cell;
TPO-RA: Thrombopoietin receptor agonists;
TPO: Trombopoietin;
vWF: von Willebrand factor;
WBC: White blood cell;
USG: Ultrasonography;

2. BLEEDING DISODERS

Bleeding disorders are characterized by defects in hemostasis that lead to an increased susceptibility to bleeding (also known as hemorrhagic diathesis). They are caused either by platelet disorders (primary hemostasis defect), coagulation defects (secondary hemostasis defect), or, in some cases, a combination of both.

VASCULAR DISODERS

Henoch-Schönlein purpura

2. 1. The objectives of the lesson:

- Diagnose Henoch-Schönlein purpura
- Prescribe appropriate treatment of Henoch-Schönlein purpura
- Recommend prevention of Henoch-Schönlein purpura

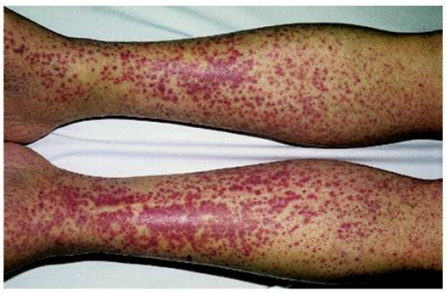
2.2. Professional competencies (PC) and Learning outcomes

Theme	Demonstrate professional competencies (PC)	Learning outcomes		
		Be able to:	Knows and understands:	Owns
Henoch-Schönlein purpura	1. Diagnose Henoch-Schönlein purpura 2. Prescribe appropriate treatment	1. Differentiate clinical syndromes. 2. Demonstrate skills in interpreting the results of laboratory, instrumental examination	(T 1) Definition, etiology and pathophysiology (T 2) Symptoms and sings (T 3) Diagnosis (T 4) Characteristic Laboratory Features and instrumental investigation of HSP (T 5) Complication of HSP (T 6): Differential diagnosis	1.Writing a case report 2. Make a plan of examination; 3. Justify the diagnosis of 4. Make a treatment plan of HSP
		2. Prescribe appropriate treatment	(T 7) Treatment of HSP	

Table 2.3. DEFINITION, ETIOLOGY AND PATHOGENESIS	
TERM	DEFINITION

Henoch-Schönlein purpura	Henoch-Schönlein purpura (HSP) is an acute immunoglobulin A (IgA)–mediated disorder characterized by a generalized vasculitis • involving the small vessels of the skin, • the gastrointestinal (GI) tract, • the kidneys, • the joints HSP is a systemic small vessel vasculitis characterized by the deposition of IgA complexes in tissues. *Usually seen in children* (Peak incidence in age of 4-7 years) May be seen in infants and adults
Etiology	No single etiologic agent has been identified; Environmental, genetic, and antigenic factors appear to contribute to the etiology of Henoch-Schönlein purpura. Many patients report a preceding infection. Upper respiratory tract infections are the most common; however, patients may also present with a previous gastrointestinal or pharyngeal infection. some associations (listed below): • Associated pathogens include (but are not limited to) group A Streptococcus, parvovirus B19, Bartonella henselae, Helicobacter pylori, Haemophilus parainfluenzae, coxsackievirus, adenovirus, hepatitis A and B viruses, Mycoplasma, Epstein-Barr virus, herpes simplex, Campylobacter, methicillin-resistant Staphylococcus aureus. • Vaccinations are rarely reported in association with HSP; however, there are some reports surrounding administration of MMR (measles, mumps, rubella), pneumococcal, meningococcal, influenza, and hepatitis B immunizations. • Environmental exposure: - Foods - Cold exposure – Drugs are most often associated with adults with HSP: acetaminophen, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (ARB), some antibiotics including clarithromycin quinolones, etanercept, codeine, nonsteroidal anti-inflammatory drugs

Pathophysiology	• Small vessel vasculitis6 (ANCA - Negative0) • Pathogenic mechanism of vasculitis is immune complex deposition • The most common class of Antibodies deposited in immune complexes is IgA • Autoimmune disorder in which IgA production is increased in response to trigger(s), IgA1 immune complexes then activate the complement pathway, leading to production of inflammatory cytokines and chemokines. • IgA-containing immune complex deposition results in small vessel inflammation which leads to fibrosis and necrosis within skin, intestinal mucosa, joints, and kidneys.

Table 2.4. SYMPTOMS AND SING	
Symptoms and sings	
1. Vasculitis of Skin (Cutaneous) Rash (most common presenting symptom):	– Palpable Purpura (most commonly distributed over the buttocks and lower extremities)
	– May start as urticaria, develops into nonblanching, palpable purpura, with or without petechiae, ecchymoses, and bullae
	– Palpable purpura distributed symmetrically over the lower limbs is typical, commonly extensor surfaces and buttocks. It may also involve arms.
	

2. Gastrointestinal (GI) vasculitis	• GIT involvement can occur in 50% to 70% of cases Gastrointestinal (approx. 60%) a) *Colicky Abdominal pain* (may precede rash); is the most characteristic manifestation. b) Vomiting, diarrhoea, periumbilical pain, upper gastrointestinal tract (GIT) haemorrhage, hematochezia/melena c) Intussusception in 4-5% patients;
3. Vasculitis of Joints (Arthralgias) , (about 75% of cases)	a) Arthralgia, reduced range of movement, periarticular oedema (synovial effusions typically absent); b) Knees and ankles most commonly affected, less commonly wrists, fingers and elbows. c) Mostly nonmigratory, transient, and nondeforming
4. Vasculitis of Kidney (about 20–55% of cases)	Of those with renal involvement: • 84% present within 4 weeks of disease onset; • 97% present within 6 months of disease onset. Renal involvement has a wide range of signs and symptoms: • Microscopic haematuria • Macroscopic haematuria • Proteinuria • Nephritic / Nephrotic syndrome • Hypertension • Renal impairment – Gross hematuria (higher in adults than children)
5. Other features:	a) Genital: Orchitis(5%):, cord haematoma, testicular pain, testicular necrosis, painful ecchymotic induration of the scrotum.– b) Central nervous system (CNS): • Seizures, encephalopathy, coma, Guillain-Barre, cortical blindness, intracerebral haemorrhages, stroke. c) Carditis; d) Parotitis; e) Pulmonary disease with haemorrhage;

Table 2.5. DIAGNOSIS
1.Palpable purpura/petechiae without thrombocytopenia and at least one of the following:

2	Diffuse abdominal pain
3	Biopsy with predominant IgA deposition
4	Arthralgia or arthritis
5	Renal involvement (hematuria or proteinuria)
6	Direct immunofluorescence showing IgA deposition (2)[A]

Table 2.6. CNARACTERISTIC LABORATORY FEATURES AND INSTRUMENTAL INVESTIGATION

	Laboratory and instrumental investigation:	Interpetetion of diagnostic Tests
• Diagnosis of HSP is mainly based on clinical signs and symptoms. • No single lab test confirms the diagnosis of HSP. • Labs directed toward excluding other illnesses and assessing degree of renal involvement		
	1. CBC, Platelet count	– Mild Leukocytosis and thrombocytosis may occur. Eosinophilia is common. – Hemoglobin is variable, depending on whether GI hemorrhage occurs.
		Erythrocyte sedimentation rate (ESR)/C-reactive protein: – Expect mild elevation
	2. Urinalysis:	– Gross or microscopic hematuria, proteinuria, and RBC casts indicate renal dysfunction.
	3. Prothrombin time/international normalized ratio and partial thromboplastin time:	– Normal in HSP. Abnormal coagulation studies may indicate an alternative cause of purpura.
4. Abdominal ultrasound:		– Sensitive for the detection of intramural bleeding in HSP and may also show thickened bowel wall, reduced peristalsis, intussusception.

5. Renal ultrasound:	– evaluates for hydronephrosis in cases of renal failure
6. IgA level:	– Often elevated, although nonspecific and nonsensitive

Table 2.7. COMPLICATIONS
1. Potential life-threatening complications include • intussusception, • bowel perforation, • bowel gangrene, and • massive hemorrhage. Intussusception is the most common life-threatening gastrointestinal complication, affecting 3% to 4% of patients with Henoch Schönlein purpura. 2. Nephrotic/nephritic syndrome and renal failure 3. HTN 4. Hemorrhagic cystitis 5. GI hemorrhage 6. Alveolar hemorrhage 7. CNS complications, including cerebral hemorrhage and seizure

Table 2.8. DIFFERENTIAL DIAGNOSIS 4.3.4.	
1	Sepsis;
2	Immune thrombocytopenia
3	Disseminated intravascular coagulation
4	Systemic vasculitides: • ANCA associated vasculitis; • Systemic lupus erythematosus; • Hypersensitivity vasculitis; • Polyarteritis nodosa.

<table>
<tr><td colspan="2">Table 2.9. Treatment of HSP</td></tr>
<tr><td colspan="2">GENERAL MEASURES</td></tr>
<tr><td colspan="2">1. Rest and elevation of affected areas may limit purpura.
2. Hydration and nutrition play a supportive role in treatment.</td></tr>
<tr><td colspan="2">MEDICATION
In the absence of renal dysfunction or complication, HSP is usually self-limited and best managed with supportive care.</td></tr>
<tr><td>1. Purpura + arthritis</td><td>• Supportive treatment, NSAIDs can be given with normal KFT
Acetaminophen
Ibuprofen
Ketoprofen
Naproxen

• NSAIDs effective for symptomatic joint pain. Caution is advised in cases of renal involvement and consider acetaminophen as an alternative.</td></tr>
<tr><td>2. GI
vasculitis/nephritis/orchitis/cerebral vasculitis/pulmonary hemorrhage
a. Mild-to-moderate cases
b. Severe cases (cerebral/pulmonary/GI)
c. Organ/life-threatening involvement</td><td>Steroids
Steroids may be helpful early in disease for patients with severe abdominal pain.
Oral
prednisone may decrease both duration of abdominal pain and severity of joint pain. This may have benefit in preventing GI bleeding and causes of surgical abdomen, including intussusception (3)[B].
– Steroids have benefit in treatment of severe and/or bullous purpura.
– Steroids given early in disease are effective for the acute treatment of crescentic nephritis
and may prevent chronic renal disease in such patients.
– Early steroids have no effect on prevention or development of renal involvement after 1</td></tr>
</table>

	year.
3.	• Plasma exchange* • Immunosuppressive therapy may be beneficial for patients with evidence of severe renal involvement. There have been many small case studies and case reports showing benefit in these patients. • High-dose IV pulse steroids, cyclophosphamide, rituximab, mycophenolate, and plasmapheresis, have all been described in small studies.

2.10. LIST OF PRACTICAL SKILLS

1. Make a plan of examination (demonstration of clinical skill) of patients with HSP
2. Writing a case report;
3. Interpret the results of laboratory and instrumental examination;
4. Justify the diagnosis of HSP
5. Make a treatment plan of HSP

2.11. QUESTIONS FOR SELF CONTROL

1. Definition, etiology and pathogenesis
2. Classification criteria for IgA vasculitis.
3. Symptoms and sings
4. Diagnosis
5. Laboratory an instrumental investigation of HSP
6. Treatment of HSP
7. Complications of HSP

2.12. TESTS FOR CHECKING THE FINAL LEVEL OF KNOWLEDGE

1. 2.5 years old female presents with palpable purpura over the buttocks, arthralgia, and abdominal pain with diarrhea with passage of blood per rectum. Patient also has presence of proteinuria. is the most probable diagnosis

A. Nephrotic syndrome
B. Nephritic syndrome
C. Talassemia
D. Henoch-Schonlein purpura

2. A 24 year old male presents with abdominal pain, rashes, arthralgia and palpable purpura. The most probable diagnosis is.

A. Henoch Schonlein Purpura (HSP)
B. Sweet syndrome
C. Meningococcemia
D. Hemochromatosis

3. One of the following is a characteristic of Henoch -Sehonlein Pиrpura:

A. Intracranial hemorrhage
B. Thrombocytopenia
C. Blood in stool
D. Susceptibility to infection

4. A 8 year old male had non blanching rashes over the shin and swelling of knee joint with haematuria +++ and protein +. Microscopic analysis of his renal biopsy specimen is most likely to show-

A. Tabular necrosis
B. Visceral podocyte fusion
C. Mesangial deposits of IgA
D. Basement membrane thickening

5. A 5-year-old child presents with non-blanching purpura over the buttocks and lower limbs along colicky abdominal pain. Further evaluation revealed deposition of IgA immune complexes. The most likely diagnosis is:

A. Henoch ShonJein Purpura

B. Kawasaki Disease

C. Wegner's Granulomatosis

D. Takayasu Disease

2.13. CASE STUDY

The girl, 17 years old, is hospitalized in clinic with complains of acute abdominal pain, vomiting, hemorrhagic rashes on skin, joint pain

On physical examination:

- Palpable purpura distributed symmetrically over the lower limbs, extensor surfaces and buttocks, her blood pressure is 110/70 mm Hg, her heart rate is 84 bpm ;

CBC:

erythrocyte-4,2x10 $^{12/l}$,
Hb-14g/l,
CI-0,9
LC-4,4x10 $^{9/l}$,
Platelets (PLT, thrombocytes)
300 x 109/L.
ESR-20mm/hr,
coagulation time is 2 minutes. Urinalysis: normal. Ultrasound of the kidney are normal

1. Formulates the preliminary diagnosis.
2. Explain the plan of investigation and interpretation of results.
3. Describe the complications associated with the disease process?
4. Describe plan of management on admission.

3.PLATELET DISODERS

IMMUNE THROMBOCYTOPENIA

3.1. The objectives of the lesson:

- To diagnose immune thrombocytopenia
- To prescribes appropriate treatment of immune thrombocytopenia, select the basic drug in the treatment of immune thrombocytopenia

3.2. Professional competencies (PC) and Learning outcomes

Theme 5-6	To demonstrate	Learning outcomes

	professional competencies (PC)	Be able to:	Knows and understands:	Owns
Immune thrombocytopenia	1. To diagnose immune thrombocytopenia 2. To prescribes appropriate treatment and defines individual management program for patient.	1. Differentiate clinical syndromes. 2. Describe the typical classic peripheral blood findings and the bone marrow findings of patients with immune thrombocytopenia	(T.3.3.1). Definition immune thrombocytopenia (T.3.3.2). Classification of immune thrombocytopenia (T.3.3.3). Etiology and pathogenesis (T.3.3.4). Symptoms and sings (T.3.3.5). Diagnostic criteria (T.3.3.6). Laboratory an instrumental investigation of immune thrombocytopenia (T.3.3.7). The clinical features of ITP in children and adults	1.Writing a case report 2. Make a plan of examination; 3. Justify the diagnosis of 4. Make a treatment plan of ITP
		2. To prescribes appropriate treatment and defines individual management program for patient.	(T.3.3.8). Treatment of immune thrombocytopenia: mechanism of action, indication (T.3.3.9). Treatment of immune thrombocytopenia: dosage of drugs, duration of treatment and adverse effects	

Table 3.3. DEFINITION	
TERM	DEFINITION
Immune thrombocytopenia	• Idiopathic or Primary Immune thrombocytopenia : Defined as isolated thrombocytopenia with – Platelet count < 100 x 10^9/L – No other cause of thrombocytopenia – No *clinically evident* secondary form of thrombocytopenia. ITP is a diagnosis of exclusion.
Pathogenesis	• Immune thrombocytopenia is an autoimmune condition. • Antiplatelet antibodies attach to platelets, most often directed against the platelet membrane glycoprotein anti-GpIIb/IIIa antibodies and lead to removal by splenic macrophages. No splenomegaly.

Table 3.4. CLASSIFICATION	
Acute form of immune thrombocytopenia - less than 6 months	Acute form of ITP: - Seen in children weeks after viral infection or immunization. - Self-limited disorder - resolves within weeks of presentation
Chronic - more than 6 months duration of thrombocytopenia	- Classically seen in child bearing age woman, adults • May be primary (idiopathic) or • secondary (strong association with lupus, Hepatitis B, C virus and others)

Primary (idiopathic)	Idiopathic
Secondary	• Immune thrombocytopenia is termed secondary if it is associated with an underlying disorder; • Thrombocytopenia from secondary causes can vary based on the presence of trigger factors, such as certain drugs, autoimmune diseases, viral infections, or vaccinations
International Working Group Descriptive Terminology for immune thrombocytopenia	
Newly diagnosed	Less than three months duration of thrombocytopenia
Persistent	Three to 12 months duration of thrombocytopenia
Chronic	More than 12 months duration of thrombocytopenia
Refractory	Persistence of severe ITP after splenectomy
Response	Platelet count $\geq 30 \times 10^9$/L and a greater than two fold increase in platelet count from baseline measured on two occasions (more than seven days apart)
Complete response	Platelet count $\geq 100 \times 10^9$/L measured on two occasions (more than seven days apart)

Table 3.5. ETIOLOGY and PATHOGENESIS	
Primary (idiopathic)	-IDIOPATHIC • Children: a history of a preceding viral infection or immunization • Primary autoimmune thrombocytopenia is a diagnosis of exclusion that constitutes about 80% of diagnosed patients
Secondary	• Immune thrombocytopenia is termed secondary if it is associated with an underlying disorder; • Thrombocytopenia from secondary causes can vary based on the presence of trigger factors, such as certain drugs, autoimmune diseases, viral infections, or vaccinations Autoimmune Disorders: • Systemic lupus erythematosus • Antiphospholipid syndrome Acquired bone marrow failure: • aplastic anemia, • myelodysplasia, • leukemia

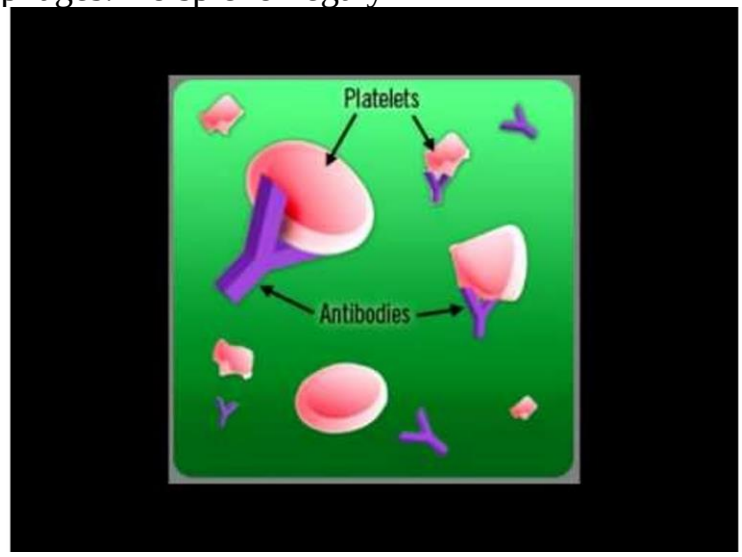
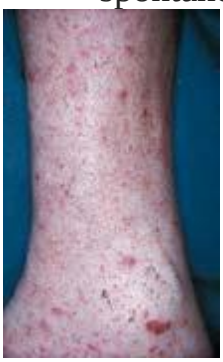
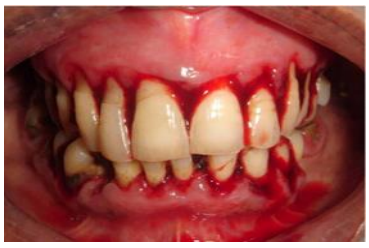
	Nutritional: • deficiency of vitamin B12, folate Infections: • Human immunodeficiency virus • Hepatitis B, C virus • Helicobacter pylori. The association of ITP with Helicobacter pylori infection is unclear Drugs: • Heparin • Penicillin • Nonsteroidal nti-inflammatory drugs Vaccinations: • Measles • Mumps • Rubella
Pathogenesis	• Immune thrombocytopenia is an autoimmune condition. • Antiplatelet antibodies attach to platelets, most often directed against the platelet membrane glycoprotein anti-GpIIb/IIIa antibodies and lead to removal by splenic macrophages. No splenomegaly • 

Table 3.6. SYMPTOMS AND SING	
The presentation depends on the degree of thrombocytopenia. No splenomegaly.	
1 The platelet count is below 20 × 10^9/L.	Spontaneous bleeding typically occurs only when the platelet count is below 20 × 10^9/L.
	• the spontaneous formation of bruises (purpura) and • spontaneous petechial haemorrhages, purpura (>3mm bleeding spots in skin), • spontaneous ecchymoses (>1cm), easy bruising).  Purpura/petechiae in thrombocytopenia
	spontaneous mucosal bleeding: •  • gum bleeding • epistaxis • menorrhagia • gastrointestinal bleeding
2. Severe thrombocytopenia (< 10 × 10^9/L)	may result in • wet purpura (blood blisters in the mouth) and
	• retinal hemorrhages may herald life-threatening bleeding,
	• fatal intracranial bleeding, but this is rare.
3. Platelet counts more than 50 × 10^9/L	Many cases with counts of platelet more than 50 × 10^9/L are discovered by chance Petechiae and purpura over trunk and limbs

Depending on the bleeding history, iron-deficiency anemia may be present.

#	Table 3.7. DIAGNOSTIC CRITERIA	
	Characteristic	Note
1	DIAGNOSIS The diagnosis of ITP is a process of exclusion. _ Thrombocytopenia on CBC ▪ Decreased platelet count is the main diagnostic finding. _ Absence of other factors to explain thrombocytopenia (diagnosis of exclusion)	1.Isolated thrombocytopenia without • anaemia, • leucopenia or • or blood film changes, 2. Without other abnormal findings, in particular • no pallor, • lymphadenopathy or • hepatosplenomegaly. 3.Confirmation rests on the adequate exclusion of other causes of thrombocytopenia, • to exclude are acute leukaemia, • other marrow infiltrative conditions and • aplastic anaemia.
2	Platelet abnormalities - microhemorrhage: mucous membrane bleeding, epistaxis, gingival, vaginal bleeding, petechiae, purpura	

Table 3.8. CNARACTERISTIC LABORATORY FEATURES AND INSTRUMENTAL INVESTIGATION		
	Laboratory an instrumental investigation:	Interpetetion of diagnostic Tests

1. CBC, Platelet count monitoring	• Isolated thrombocytopenia (decreased platelet count), with an otherwise • normal peripheral blood cells and smear, • normal WBC count
4. Bleeding time (BT)	• Prolonged bleeding time Bleeding time - prick patient and see how long it takes to stop bleeding - normal is 2-7 minute
5. Bone marrow should be examined in patients with • unexplained cytopenias in two or more lineages, • in patients older than 40 years with isolated thrombocytopenia, or • in those who do not respond to primary immune thrombocytopenia -specific therapy. • A bone marrow biopsy is not necessary in all cases to make an immune thrombocytopenia diagnosis in younger patients.	Bone marrow examination of immune thrombocytopenia shows: • normal or • increased megakaryocytes on bone marrow biopsy. - In patients older than 60 years- To look for an accompanying B-cell malignancy -Bone marrow examination may be helpful in confirming chronic immune thrombocytopenia
4. PT, prothrombin time;	Normal
5. PTT, partial thromboplastin time.	Normal
6.Fibrinogen	Normal
7. Fibrinogen Degradation product	Normal
8. Ultrasound	No splenomegaly (Normal-sized spleen)
9. Liver function tests	Normal
10.Hepatitis serology. Hepatitis (HCV, HBV) virus testing	Negative

11. Human immunodeficiency virus (HIV) testing for adults	Negative
12. Laboratory testing for antibodies (serologic testing) is usually not helpful due to the low sensitivity and specificity of the current tests.	

Table 3.9. The clinical features of immune thrombocytopenia in children and adults

#	In childhood	In adults
1. Onset of a diseases	**Children: Acute,** self-limited reaction to viral infection or immunization; treat only if severe. • ITP usually has an abrupt onset, often starting 1-2 weeks after a viral infection or • up to six weeks after vaccinations (generally the measles, mumps and rubella - MMR vaccination) • with recovery being spontaneous I around 70-80% of the cases within a few weeks regardless of therapy.	**Adults: Chronic,** autoimmune condition; • The disease has an insidious onset, • with no preceding illness and • frequently it has a chronic course.
2.Symptoms	Major bleeding risk is low in pediatric patients	In adults, additional modifiers such as existing comorbidities, age, activities and medications may affect the risk of significant bleeding

Table 3.10. PHARMACEUTICAL THERAPYOF IMMUNE THROMBOCYTOPENIA

Treatm e nt :	Characteristic	Mechanism of action	Indication

mechanism of action, indication			
Pharmaceutical therapy	ADULT TREATMENT PRINCIPLES • A platelet count of <20,000 is an indication of treatment. • 20,000- 50,000 patients are monitored. (Do not require treatment, except at times of increased bleeding risk, such as surgery and biopsy). • >50,000 treatment is not necessary.	The treatment of immune thrombocytopenia uses drugs that • decrease reticuloendothelial uptake of the antibody-bound platelet, • decrease antibody production, and/or increase platelet production	Individuals with platelet counts less than 20,000–30,000/mcL or those with significant bleeding should be treated;
1.First-line therapy for patients with spontaneous bleeding:	1.High doses of glucocorticoids, either prednisolone (1 mg/kg daily) or dexamethasone (40 mg daily for 4 days)	Corticosteroids act by reducing antibody production and preventing platelet destruction by macrophages (by reticulo-endothelial cells).	For patients with spontaneous bleeding - High-dose dexamethasone may be considered in specific situations when a higher early response rate is warranted.
	2.Administration of Intravenous Immunoglobulin G(IVIG) and	-To recover platelet count quickly -can raise the platelet count by blocking antibody receptors on reticulo-endothelial cells/	IVIG is recommended for patients with critical bleeding (In emergent situations)

	-is combined with glucocorticoid therapy	IVIG is derived from human plasma and is thought to saturate Fc receptors in the reticuloendothelial system, leading to decreased destruction of platelets that have bound autoantibodies.	and for those unresponsive to corticosteroidsıo First-line if corticosteroids are contraindicated or produce suboptimal response
	3.Anti-D immune globulin Anti-Rho (anti-D) -Prepared from the plasma of immunized Rh-negative human donors, it can be used an alternative to conventional IVIG for patients who have an Rh-positive blood type.	By acting against the D antigen, this treatment blocks the macrophage system, neutralizing binding of autoantibodies to platelets The mechanism of action of anti-D is not fully understood.	In emergent situations. Severe bleeding (GI/CNS), count <10,000
	4.Platelet transfusion - in addition to the other therapies.		Rarely. Emergency care, potentially life-threatening bleeding
2. Second-line therapies: for patients with persistent and	Characteristic	Mechanism of action	Indication
	1. Rarely, splenectomy is required It has also been established that second- and third-line treatments may be used in combination with	This quickly eliminates the main source of platelet destruction in your body and improves your platelet count,	Current guidelines suggest splenectomy may be considered for patients with immune thrombocytopenia

chronic immune thrombocytopenia.	steroids or other immunosuppressive agents. Combination therapies may be useful in patients who are refractory to monotherapies	though it doesn't work for everyone.	who have, at minimum, failed corticosteroid therapy. -Consider after multiple treatment failures -Splenectomy in refractory cases. -Accessory spleen(s) are a very rare cause of relapse.
	2.Immunosuppression. Immunosuppressants such as- rituximab, ciclosporin, mycophenolate and tacrolimus may also produce remissions.	Rituximab (Rituxan, Genentech), an anti-CD20-directed cytolytic monoclonal antibody, works by inhibiting B cells from producing autoantibodies as well as reverting T-cell abnormalities in patients who respond to treatment	For patients with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The role of rituximab for emergent treatment or in an acute setting is limited.
Second- or third-line therapies:	-The thrombopoietin receptor agonists (TPO-RA) eltrombopag and romiplostim. Romiplostim and eltrombopag are synthetic thrombopoietin for immune thrombocytopenia..	TPO-RAs work by activating TPO receptors on megakaryocytes and inducing platelet production via the JAK2 and STAT5 kinase pathways. that stimulate platelet production in the bone marrow.	-For patients with chronic immune thrombocytopenia . who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy -particularly in those who have a contraindication to splenectomy. -Romiplostim can be used

			effectively to manage chronic immune thrombocytopenia . regardless of whether patients have undergone splenectomy. -Eltrombopag is FDA approved for use in children over 1 year of age.

Table 3.11. TREATMENT: DOSAGE OF DRUGS, DURATION OF TREATMENT AND ADVERSE EFFECTS

Treatment	Medications to treat ITP	Dosage and administration	Adverse Effects
1. First-line therapy:	1.High doses of glucocorticoids: Prednisone Effective-70–80%	Prednisone 1.0–2.0 mg/kg daily for 3–4 weeks • Duration of treatment for 3- 4 weeks followed by a gradual taper Or	osteoporosis, diabetes, hypertension, weight gain
	1.2.Dexamethasone Effective-Up to 90%	Dexamethasone 40 mg daily Duration of treatment- for 4 days every 2 to 4 weeks for 1 to 4 cycles with no taper	Same as prednisone, but less frequent

	2.Administration of intravenous immunoglobulin (IVIG) Effective- Up to 85% However, response may be transient, lasting no longer than three to four weeks —prompting additional therapy once platelet counts fall below 30×10^9/L.	Intravenous Immune Globulin IVIG 1 g/kg daily for 1–2 days Duration of treatment- for 1–2 days An increase in platelet count is typically expected within 24 to 48 hours in up to 85% of patients. Not intended for long-term therapy because of limited duration of response and long-term toxicity	Infusion-related reactions, and infrequently include aseptic meningitis and renal failure.
	3.Anti-D immune globulin (in patients who have an Rh-positive blood type) Anti-Rho (anti-D). Effective- Up to 70–80% In comparison with IVIG, the advantages of anti-D immune globulin include lower cost and shorter time of administration (minutes versus hours).	Anti-D Immune Globulin 50–75 mcg/kg Only in D-positive patients; monitor patients for 8 hours after administration. Monitoring patients for 8 h after infusion is now advised, because of the rare complication of severe intravascular hemolysis Duration of treatment- not intended for long-term therapy because of limited duration of response and long-term toxicity	Fatal intravascular hemolysis (IVH) - (signs and symptoms of intravascular hemolysis, including fever, chills, vomiting. back pain, discolored urine, and anemia) and multiorgan dysfunction.
#	Medications to treat immune thrombocytopenia.	Dose. Duration of treatment	Adverse Effects
2 Second-line	1.Splenectomy Complete remission in about 70%-80% of patients and -		Postoperative bleeding complications, increased risk of infections,

therapies:	improvement in a further 20–25% in favourable cases		thrombotic events
	2.Immunosuppression. immunosuppressants such as- rituximab, Effective- 60%	Rituximab (Rituxan, Genentech), 375 mg/m^2 IV over 4 hours Duration of treatment- once weekly for 4 consecutive weeks Second-line therapy option To reduce the incidence of infusion-related reactions, rituximab is typically administered over an extended infusion of four hours	Infusion reactions, chills, vomiting, fever, and serum sickness neutropenia, infections, In patients being treated for more than 12 months, use has been associated with infections, malignancies,pneumonitis.
	Immunosuppressants such ciclosporin, mycophenolate and tacrolimus may also produce remissions.		
Second- or third-line therapies:	3.The thrombopoietin receptor agonists (TPO-RA) eltrombopag and romiplostim. (synthetic thrombopoietin for ITP). The TPO-RAs induce response in around 75% of cases, usually within 10–14 days.	Eltrombopag (Promacta, Novartis) 50–75 mg orally daily Second- or third-line option if treatment failure occurs Romiplostim (Nplate, Amgen) 1 mcg/kg subcutaneous once weekly	Hepatotoxicity, thrombotic events Due to eltrombopag's known effect on liver function, hematology and liver enzymes should also be monitored throughout therapy.

3.12. LIST OF PRACTICAL SKILLS

1. Examination (demonstration of clinical skill) of patients with immune thrombocytopenia.
2. Interpret the results of clinical, laboratory and instrumental examination;
3. Justify the diagnosis of immune thrombocytopenia.
4. Make a treatment plan of immune thrombocytopenia.

3.13. QUESTIONS FOR SELF CONTROL.

1. Definition, predisposing factors and pathogenesis
2. Classification of immune thrombocytopenia.
3. Symptoms and sings
4. Diagnostic criteria
5. Laboratory an instrumental investigation of immune thrombocytopenia. Analysis of blood and bone marrow expressions.
6. Treatment of immune thrombocytopenia.: mechanism of action, indication
7. Treatment of autoimmune thrombocytopenic purpura: dosage of drugs, duration of treatment and adverse effects

3.14. TESTS FOR CHECKING THE FINAL LEVEL OF KNOWLEDGE

1. Cause of ITP is -

a) Vasculitis

b) Antibody to vascular epithelium

c) Antibody to platelets

d) Antibody to clotting factors

2. A 37-year-old woman sees her physician because of gum bleeding, menorrhagia. Physical examination reveals petechiae, bruises on her legs. CBC: RBC 2.5 x 10^{12}/L, Hemoglobin 67 g/L, MCV 64 fl, CI – 0,7, Pl 41 x 10^9/L, platelets 30x10 ^{9}/l, WBC 7.9 x 10^9/L, Segmented Neutrophils 60%, Band Neutrophils 4%, Monocytes 5 %, Eosinophils 3 %, Lymphocytes 29 %, ESR 7 mm/h, lactate dehydrogenase (LDH), indirect bilirubin levels, blood urea nitrogen (BUN) and creatinine measurements are normal. Bleeding time 13 min. What is the most probably diagnosis?

A. Immune thrombocytopenia.
B. Henoch–Schonlein purpura
C. Haemolytic anemia
D. Macrocytic hyperchromic anemia

3. The following laboratory determinants is abnormally prolonged in immune thrombocytopenia. -

a) APTT b) Prothrombin time

c) Bleeding time d) Clotting time

4. Patients with immune thrombocytopenia.have

A. Normal-to-increased number of megakaryocytes
B. Elevated blasts
C. Elevated lymphocytes
D. Elevated plasmocytes

3.15. CASE STUDY

A 24-year-old woman presents to the emergency room on a Saturday afternoon with complaints of bleeding from her nose, gum bleeding since the previous night.

She also noticed small, reddish spots on her lower extremities when she got out of the bed in the morning. She denies fever, chills, nausea, vomiting, abdominal pain, or joint pain. The patient reports she had developed an upper respiratory infection 2 weeks prior to the emergency room visit, but the infection has now resolved. Her menses have been normal, and her last menstrual period was approximately 2 weeks ago. She denies excessive bleeding in the past, even after delivering her baby. Prior to this episode, she never had epistaxis, easy bruisability, or bleeding into her joints. There is no family history of abnormal bleeding. The patient does not take any medications.

On examination she is alert, oriented, and somewhat anxious. Her blood pressure is 100/70 mm Hg, her heart rate is 89 bpm, and she is afebrile. No pallor or jaundice is noted. There is bright red oozing from the nose and the gingiva. Skin examination reveals multiple 1-mm flat reddish spots on her lower extremities.

The rest of the examination is normal. There is no lymphadenopathy or hepatosplenomegaly.

Her complete blood cell count (CBC) is normal except for a platelet count of 17,0 x 10^{9}/L. Prothrombin time (PT) and partial thromboplastin time (PTT) are normal.

1. Formulate preliminary diagnosis and prescribe plan of investigations.
2. Formulates the clinical diagnosis, based on the diagnostic criteria of the disease.

3. Recommend immune thrombocytopenia. treatment, dosage and administration, duration of their usage, indication, mechanism of action, possible side effects.

COAGULATION DISODERS

4. HEMOPHILIA

4.1. The objectives of the lesson:

- To diagnose hemophilia
- Distinguish between signs and symptoms of primary hemostasis defects and plasma coagulation defects.
- To prescribes appropriate treatment of hemophilia and prevention.

4.2. Professional competencies (PC) and Learning outcomes of hemophilia

Theme	To demonstrate professional competencies (PC)	Learning outcomes		
		Be able to:	Knows and understands:	Owns
Hemophilia	1. To diagnose hemophilia	1. Differentiate clinical syndromes of hemophilia. 2. Describe the typical classic laboratory findings of patients with hemophilia	(T 1) Definition of hemophilia. (T 2) Classification, genetics of hemophilia. (T 3) Symptoms and sings (T 4) Diagnostic criteria (T 5) Investigation of hemophilia. Coagulation profile.	1.Writing a case report 2. Make a plan of examination; 3. Justify the clinical diagnosis of hemophilia 4. Make a treatment plan of hemophilia

			Radiological investigation.	
	2. To prescribes appropriate treatment	• Demand therapy Replacement therapy. • Prophylactic therapy. Prevention of hemophilia.	(T 6) Treatment and prevention of hemophilia. Emergency care at hemophilia bleeding.	

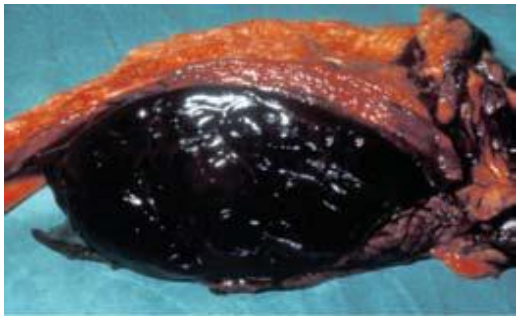
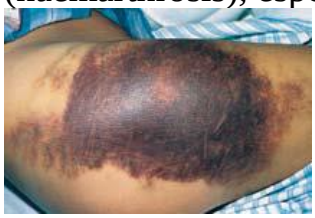
TERM	Table 4.3. DEFINITION, ETIOLOGY AND PATHOGENESIS
DEFINITION	Deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B) coagulation proteins leading to bleeding tendencies in affected individuals. <u>Hemophilia is an X-Linked Recessive Disorder and Hemophilia A represents 80–85% of the total hemophilia population; hemophilia B comprises the remaining 15–20%.</u>
Etiology and pathophysiology	Hemophilia is haemorrhagic disease due to mutations in the Factor 8 (F8) gene or Factor 9 (F9) gene • Hemophilia A (factor VIII deficiency): ~ 80% of cases. Hemophilia A ("Classic Hemophilia") Is caused by mutations in the F8 gene, which encodes for factor VIII • Hemophilia B (factor IX deficiency): ~ 20% of cases. Hemophilia B ("Christmas disease")

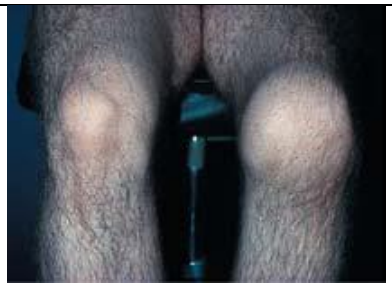
	Is caused by mutations in the F9 gene, which encodes for factor IX. • Hemophilia C (factor XI deficiency): very rare (increased frequency in Ashkenazi Jews); caused by an autosomal recessive defect. ➢ History For patients in whom hemophilia is suspected, inquire about the following: • History of hemorrhage disproportionate to trauma • History of spontaneous hemorrhage • Bleeding disorders in the family
Genetics	Congenital • The majority of cases Hemophilia are due to inherited genetic mutations in factor VIII or factor IX coagulation proteins. X-linked • The factor VIII gene is located on the X chromosome. • Haemophilia is associated with a range of mutations in the factor VIII gene. • As the factor VIII gene is on the X chromosome, haemophilia A is a sex-linked disorder. Typically and usually only Male subjects are clinically affected (Since the disease is X linked recessive). • Thus all daughters of a patient with haemophilia are obligate asymptomatic carriers and they, in turn, have a 1 in 4 chance of each pregnancy resulting in the birth of an affected male baby, a normal male baby, a carrier female or a normal female. Antenatal diagnosis by chorionic villous sampling is possible in families with a known mutation.

Table 4.4. CLASSIFICATION	
Intrinsic pathway coagulation defect (↑PTT).	❖ Hemophilia A: deficiency of factor VIII; X-linked recessive condition ❖ Hemophilia B: deficiency of factor IX; X-linked recessive. ❖ Hemophilia C: deficiency of factor XI; autosomal recessive.

Classification according to plasma coagulation factors levels is as follows:		
	Levels of factor VIII	Cause of Hemorrhage
Mild hemophilia	❖ - FVIII level 6-40 % of normal (>5%) (>0.05 to < 0.40 IU/mL)	❖ Bleeding generally occurs in response to mild trauma
Moderate hemophilia	❖ - FVIII level 1-5% of normal (0.01-0.05 IU/mL)	❖ Mild-to-moderate trauma or surgery causes bleeding. ❖ Spontaneous bleeding, predominantly in the joints or muscles.
Severe hemophilia	❖ - FVIII level < 1% of normal (< 0.01 IU/mL)	❖ Life threatening Bleeding manifestations may be seen

Table 4.5. SYMPTOMS AND SING
Hemophilia A and B are indistinguishable clinically, as both demonstrate similar symptoms, similar inheritance patterns, and isolated prolongation of the PTT (PT and bleeding time are normal). Haemophilia A and B can be differentiated only by specific coagulation factor assays
• Symptoms and sings according to levels of coagulation factors Hemophilia is classified according to clinical severity as mild, moderate, or severe. • Spontaneous Haemarthrosis and spontaneous muscle haematomas are hallmark of moderate or severe congenital Factor VIII and IX deficiency(Hemophilia). • Spontaneous Mucosal Bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease (disorders of primary hemostasis or platelet plug disorders

1	Factor VIII levels <1% present with life-threatening bleeds • Intracranial hemorrhage: generally resulting from trauma; incidence of 1:10; fatal in 30% of cases. Bleeding in the CNS is the leading cause of hemorrhagic death in patients with hemophilia. • Babies with severe haemophilia have an increased risk of intracranial haemorrhage • Hematomas of bowel wall can cause obstruction or intussusception and pain mimicking appendicitis.  1. Massive retroperitoneal haemorrhage
2.	Serious bleeds • Newborn boys with severe hemophilia may present with prolonged bleeding at circumcision. • Approximately 30-50% of patients with severe hemophilia present with manifestations of neonatal bleeding (eg, after circumcision). Approximately 1-2% of neonates have intracranial hemorrhage. Other neonates may present with severe hematoma and prolonged bleeding from the cord or umbilical area. • • Spontaneous bleeding into skin, muscle (most commonly in the quadriceps, iliopsoas, and forearm) and joints (haemarthrosis), especially knees, elbows, ankles  2. Massive bruising • Acute pain, and swelling of joint. Recurrent bleeding into joints leads to synovial hypertrophy, destruction of the cartilage and chronic haemophilic arthropathy: ✓ Can result in fixed joints, muscle atrophy, and significantly impaired mobility, degenerative joint disease

	 3. Chronic haemophilic arthropathy with joint swelling and muscle wasting on left
	• Mucous membrane bleeding, such as in the genitourinary tract, leading to hematuria
3.	Individuals with moderate (factor activity 1–5%) and mild (factor activity 5–40%) haemophilia • present with the same pattern of bleeding but usually after trauma or surgery • Easy bruising may occur at the start of ambulation or primary dentition.
	• Other possible presenting symptoms include nose bleeds, GI bleeding, haematuria and prolonged bleeding with surgical procedures, trauma, and dental extraction, and may have spontaneous bleeding in soft tissues.

Physical Examination	
Systemic signs of hemorrhage include the following:	• Tachycardia • Tachypnea • Hypotension
Organ system–specific signs and symptoms of hemorrhage include the following:	• Musculoskeletal (joints) - Tenderness, pain with movement, decreased range of motion, effusion, and warmth • Central nervous system (CNS) - Abnormal neurologic exam findings, altered mental status, and meningismus • Gastrointestinal (GI) - Can be painless; hepatic/splenic tenderness, and peritoneal signs • Genitourinary - Bladder spasm/distension/pain and costovertebral angle pain

Sites of bleeding in hemophilia	
Serious	• Joints (hemarthrosis). Recurrent Spontaneous Hemarthrosis is commonly seen in patients with Hemophilia when factor VIII levels are less than 5 percent of normal (Moderate; Moderately severe form). • Muscles, especially deep compartments (iliopsoas, calf, forearm) • Mucous membranes of the mouth, nose, and genitourinary tract
Life- threatening	• Intracranial • Neck/throat • Gastrointestinal
Approximate frequency of bleeding at different sites	
Joints 70- 80%	• More common in hinged joints: ankles, knees, elbows • Less common in multi- axial joints: shoulders, wrists, hips
Muscles 10- 20%	
Other sites (major bleeds) 5-10%	
Central nervous system <5%	

Table 4.6. LABORATORY AND INSTRUMENTAL INVESTIGATION

Haemophilia A and B can be differentiated only by specific coagulation factor assays	
Laboratory an instrumental investigation:	Interpetetion of results
1. CBC with platelet count	• Hemoglobin/hematocrit: Normal (or low if associated bleeding) • Platelet count: Normal
2. PT	normal
3. vWF	normal
4. Diagnosis based on FVIII or IX activity	– Mild: ↓ 5 to 40 IU/dL – Moderate: ↓ 1 to 5 IU/dL – Severe: <1 IU/dL Normal factor levels: 50 to 150 IU/dL
5. Bleeding time	Normal
6. Prothrombin time (PT)	Normal
7. Activated partial thromboplastin times (aPTT)	• Prolonged. Hemophilia Presents with isolated prolongation of the a-PTT assay. • aPTT may be normal in patients with mild hemophilia. • Haemophilia A occurs due to deficiency or reduced activity of factor VIII (antihaemophilic factor). Factor VIIIis involved in the intrinsic pathway which is measured by a-PTT and not in extrinsic pathway which is measured as PT.
8. Genetic counseling, and participation in genotyping	

project for affected individuals and family.	
9. Inhibitors to factor VIII and IX Screen before invasive procedures and at regular intervals	Testing for inhibitors is indicated when bleeding is not controlled after infusion of adequate amounts of factor concentrate during a bleeding episode.
10. In patients with an established diagnosis of hemophilia, periodic laboratory evaluations include HBV, HCB, HIV infection.	Screening for transfusion-related or transmissible diseases such as hepatitis and HIV infection.
11. Radiological investigation	
• Head computed tomography	• Head computed tomography scans without contrast are used to assess for spontaneous or traumatic intracranial hemorrhage
• MRI joints/ abdomen	• MRI scans of the head and spinal column are used for further assessment of spontaneous or traumatic hemorrhage • MRI is also useful in the evaluation of the cartilage, synovium, and joint space
• USG joints for effusions	• Ultrasonography is useful in the evaluation of joints affected by acute or chronic effusions

• Radiographs of joints	• In these patients, radiographs may show synovial hypertrophy, hemosiderin deposition, fibrosis, and damage to cartilage that progresses with subchondral bone cyst formation. • Hemophilic arthropathy evolves through 5 stages, starting as an intra-articular and periarticular edema due to acute hemorrhage and progressing to advanced erosion of the cartilage with loss of the joint space, joint fusion, and fibrosis of the joint capsules.

Table 4.7. DIAGNOSTIC CRITERIA		
1.	Family history	History and initial presentation – 2/3 of presenting hemophilic patients have a positive family history.
2.	Clinical features	• Prolonged bleeding with circumcision, dental procedures, trauma or surgery • Excessive or easy bruising in early childhood • Spontaneous bleeding, especially in joints, muscle, or soft tissue
3.	Laboratory investigation	Diagnosis based on factor VIII or IX activity – Normal factor levels: 50 to 150 IU/dL – Mild: 5 to 40 IU/dL – Moderate: 1 to 5 IU/dL – Severe: <1 IU/dL
		A normal prothrombin time (PT) with prolonged activated partial thromboplastin times (APPT) is suggestive of haemophilia in a patient presenting with bleeding

Table 4.8. TREATMENT

MANAGEMENT –PRINICIPLES

- Patients can be treated with prophylaxis or with intermittent, on-demand therapy for bleeding events.
- Preventive therapy started early in childhood, as compared with on-demand treatment, can reduce total bleeds and bleeding into joints, resulting in decreased overall joint deterioration and improved quality of life. In most developed countries with access to recombinant product, prophylaxis is primary (ie, therapy is started in patients as young as 1 y and continues into adolescence). A cost-benefit analysis indicates that this approach reduces overall factor use and significantly reduces morbidity.
- Control bleeding episodes – replacement therapy. Treat early; acute bleeds should be treated as quickly as possible, preferable within 2 hours

- Avoid aspirin or other NSAIDs

- Patients should avoid high-impact contact sports

- Hepatitis A and B vaccinations are recommended.

For surgical prophylaxis

- If major surgery is undertaken, factor levels should be maintained at >50% for at least 2 to 3 weeks after the procedure:
- ✓ Fibrin glue products may be beneficial for oozing.
- ✓ Dental extractions: Antifibrinolytics (Amicar, tranexamic acid) may be used
- ✓ Minor procedures: may use desmopressin (DDAVP) in hemophilia A

- Antenatal diagnosis and counselling

- Immediate family members of affected patients should have factor VIII and IX levels checked prior to invasive procedures, childbirth, and if bleeding tendencies occur.

MEDICATION

First Line Principles of therapy	-Primary prophylaxis: administration of specific factor replacement therapy in the absence of bleeding to maintain adequate baseline plasma levels sufficient for hemostasis in all categories of severity (1)[A] • Lower frequency of acute bleeds and episodes of life-threatening hemorrhage compared to on-demand therapy • Standard of care for children with severe hemophilia A to prevent joint bleeds and joint degeneration
	– On-demand therapy (i.e. to treat a bleed): • treatment administered in response to occurrence of bleeding. Amount and duration of factor replacement depends on location and severity of bleeding: ■ Mild bleeds correct to a factor level of >30% major hemorrhages and large muscle bleeds require correction to levels between 50% and 100%. ■ Life-threatening bleeds require levels between 80% and 100%, sustained with bolus dosing or continuous infusion. Specific agents: Factor VIII concentrates on-demand Many recombinant FVIII concentrates are currently available. The advantage of such products is the elimination of viral contamination. Various purification techniques are used in plasma-based FVIII concentrates to reduce or eliminate the risk of viral transmission, including heat treatment, cryoprecipitation, and chemical precipitation. These techniques inactivate viruses such as hepatitis B virus, hepatitis C virus, and HIV. – Hemophilia A: Replacement with factor VIII concentrates is the treatment of choice: two sources for the factor available: o Purified plasma-derived factor VIII o Recombinant factor VIII ■ Dosing: 1 IU of factor VIII (the amount in 1 mL of plasma)/kg body weight administered will raise the plasma level of the recipient by 2%. ■ Most FVIII products have short half-lives, requiring frequent injections; novel recombinant factor VIII; rFVIIIFc, dosed prophylactically 1 to 2 times per week (4)[B]

	– Hemophilia B: Replacement with factor IX concentrates is the treatment of choice: o Plasma-derived factor IX and recombinant factor IX (preferred) are commercially available. o Dosing: 1 IU/kg body weight administered will raise plasma factor IX levels 1%.
	Hemophilia patients with inhibitors (neutralizing alloantibodies to factors VIII or IX) – Inhibitor formation should be *suspected when patients do not respond to factor replacement at therapeutic doses* – Low-titer (<5 BU/mL) patients: Replace with high doses of the deficient factor to overcome the circulating inhibitor concentration. – High-titer patients: Treat using products that bypass the factor neutralized by the alloantibody or emergently with high doses of the specific deficient factor: Two bypassing agents are available; both are efficacious at providing 80% of bleeding episodes: ■ Anti-inhibitor coagulation complex (AICC) ■ Recombinant activated factor VII (rFVIIa) • Immune tolerance induction (ITI): protocols to promote immune tolerance through repeated exposure to high-dose factor VIII therapy over 12 to 18 months, with or without immunosuppressive therapy (corticosteroids, cyclophosphamide, rituximab). Success rates are 60–80%.
Second Line	Cryoprecipitate and fresh frozen plasma (FFP) can be used in instances where the specific factor concentrate is unavailable for emergent hemostasis. • – FFP: contains all coagulation factors but generally difficult to attain high levels of factors VIII or IX. Starting dose: 15 to 20 mL/kg. Risk of HIV, HBV, HCV, CMV transmission – Cryoprecipitate: derived from precipitates of cooled FFP; contains significant levels of factor VIII (up to 100 IU/bag) but not factor IX: Dosing: 1 mL cryoprecipitate has ~3 to 5 IU factor VIII.
	Desmopressin (DDAVP): synthetic vasopressin;

	Desmopressin (DDAVP®) used in Mild Hemophilia A (Not Hemophilia B). (DDAVP) is a synthetic vasopresson anolog that causes a transient increase in FVIII and Willebfandfactor (VWF) but not F-IX through a mechanism involving release from endothelial stores; stimulates endogenous release of factor VIII (and vWF) from endothelial stores; – IV or SC: 0.3 μg/kg infused 30 minutes prior to procedure; may repeat if needed – Intranasal (150 μg/spray): adult dose, 1 spray to each nostril (300 μg total). Alternate dose if <50 kg: 150 μg once. – Adverse effect: hyponatremic seizures, especially in children; restrict fluids and watch sodium levels and urine output.
	Anti-fibrinolytic agents (e.g. tranexamic acid): inhibit plasminogen activation, thereby stabilizing the clot – *Recommended for Bleeding in the in the gums*, epistaxis, and menorrhagia; *during oral surgery*, prophylactically (e.g., prior to tooth extractions) ○ Tranexamic acid (25 mg/kg PO q6–8h or 10 mg/kg IV q6–8h) ○ Aminocaproic acid (Amicar) is less frequently used.
Acute and chronic arthritic pain management	• Nonsteroidal anti-inflammatory drugs can be effective in managing acute and chronic arthritic pain but significant caution must be used in dose and frequency due to concerns for increased risk of bleeding. Although they pose a risk of gastrointestinal bleeding, their effects on platelet function are reversible. • Avoid aspirin because of its irreversible effect on platelet function. Other analgesics may include acetaminophen in combination with small amounts of codeine or synthetic codeine analogs.

Table 4.9. PREVENTION. COURSE AND PROGNOSIS	
Prevention	• Immunisation : not IM

	• Avoid IM injections- apply pressure 5 minutes • Avoid contact sports
Course and prognosis	Replacement therapy has its complications and includes: ✓ Development of F VIII antibodies ✓ Liver disease resulting from hepatitis B and C ✓ Infection with HIV

3.16. LIST OF PRACTICAL SKILLS

1. Examination (demonstration of clinical skill) of patients with hemophilia..

2.To predict the results of hemostatic screening tests (PT/INR, PTT, fibrinogen, factor VIII activity, platelet count, bleeding time) in a patient with hemophilia A.

3. Confirm the clinical diagnosis of hemophilia

4. Make a treatment plan of hemophilia

4.11. QUESTIONS FOR SELF-CONTROL

1.Definition, ethiology and pathogenesis of hemophilia

2.Classification of hemophilia

3.Distinguish between signs and symptoms of primary hemostasis defects and plasma coagulation defects.

4.Diagnostic criteria

5.Using inheritance patterns, clinical history and the results of laboratory tests, be able to distinguish hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency).

6.Treatment of hemophilia, prevention

4.12. TESTS FOR CHECKING THE FINAL LEVEL OF KNOWLEDGE

1. A 7-year-old boy is admitted with haemarthrosis of his left knee. These episodes have been recurrent since his early years. His Activated partial thromboplastin time is significantly prolonged but bleeding time is normal

a. Hemophilia A
b. Aplastic anemia
c. Idiopatic Trombocytopenia
d. chronic leukaemia

2. The boy, 4 years old, is hospitalized in clinic with nasal bleeding, which had appeared in 1 hour after trauma. From anamhesis: often hemarthroses, from 1 year of life. In the general blood analysis: er. 3.1x1012/l, Hb 89 г/л, thrombocytes 165x10 ^{9}/l, duration of the bleeding is 2 minutes, coagulation time is 15 minutes. What disease is possible in this child?

(A) Werlgof's disease
(B) Hemophilia
(C) Hemorrhagic vasculitis
(D) Willebrand's disease
(E) DIC-syndrome

3.A 5yo boy has cough and swelling at the knee after falling on the ground with bruises on the buttocks which are non-blanching. Prothrombin time (PT) =14 (Reference range of PT 9–12 secs), Activated partial thromboplastin time (APTT) =72, (Reference range of 26–36 secs), Hgb=10, WBC=9, Plt=220 (Reference range of Platelet count 150–400 × 109 /.) Choose the most likely diagnosis?

a. Hemophilia
b. Polycythemia vera
c. Aplastic anemia
d. Trombocytopenia

4. A 4yo boy presents with recurrent episodes of self limiting spontaneous bleeding. Coagulation test: PT normal, bleeding time normal, APTT prolonged, Factor VIII decreased. His father and uncle suffer from a similar illness. What is the most likelydiagnosis?

a. Hemophilia A
b. HemophiliaB
c. Aplastic anemia
d. Idiopatic Trombocytopenia

4.13. Case study

A 17 years old boy who was diagnosed with Haemophilia A since sixteen years of age. He presented to the clinic with left elbow swelling for one day after hitting it against the wall while playing. The swelling increased in size and became more painful. The left elbow had decreased in range of motion as the day progressed. He was unable to fully extend his arm. His father then brought him to the clinic the next morning.

His father and uncle suffer from a similar illness.

On examination of his upper and lower limbs, there were no bruises noted on the skin. There was a joint deformity with valgus deformity noted on his right elbow however range of motion of the right elbow was normal. On the examination of the left elbow, there was a swelling. On palpation, the joint was warm and tender to touch. There is presence of moderate effusion in the left elbow joint. There was restricted joint movement.. Examination of other systems was normal.

1. How would you confirm the diagnosis?
2. Plan of investigations.
3. Describe the complications associated with the disease process?
4. Describe plan of management on admission.

5. Disseminated intravascular coagulation (DIC)

5.1. The objectives of the lesson:

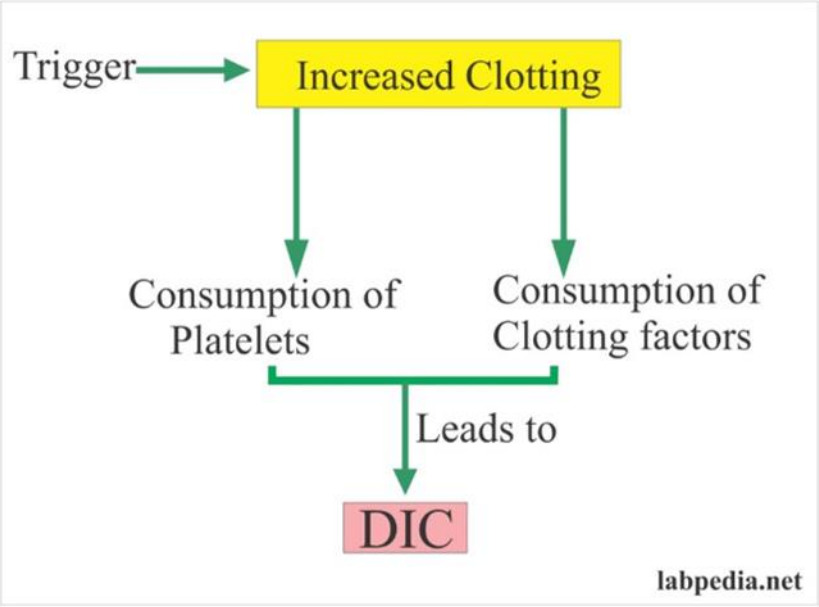
- Explain the etiopathogenesis of DIC.
- Differentiate clinical syndromes, laboratory criteria
- Prescribe appropriate treatment. Recognize and deal with situations requiring emergency medical care.

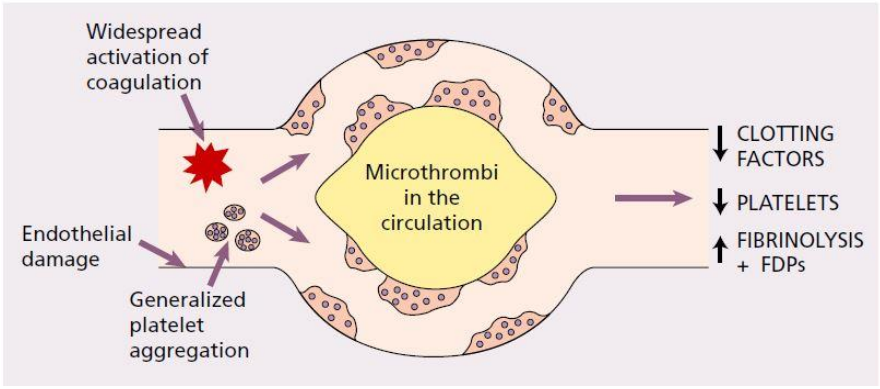
5.2. Professional competencies (PC) and Learning outcomes of disseminated intravascular coagulation (DIC)

Theme	To demonstrate professional competencies (PC)	Learning outcomes		
		Be able to:	Knows and understands:	Owns
Disseminated intravascular	1. To diagnose disseminated intravascular	1. Differentiate clinical syndromes of disseminated intravascular coagulation (DIC).	(T 1) Definition of disseminated intravascular coagulation (DIC). (T 2) Classification, genetics of disseminated	1.Writing a case report 2. Make a plan of examination;

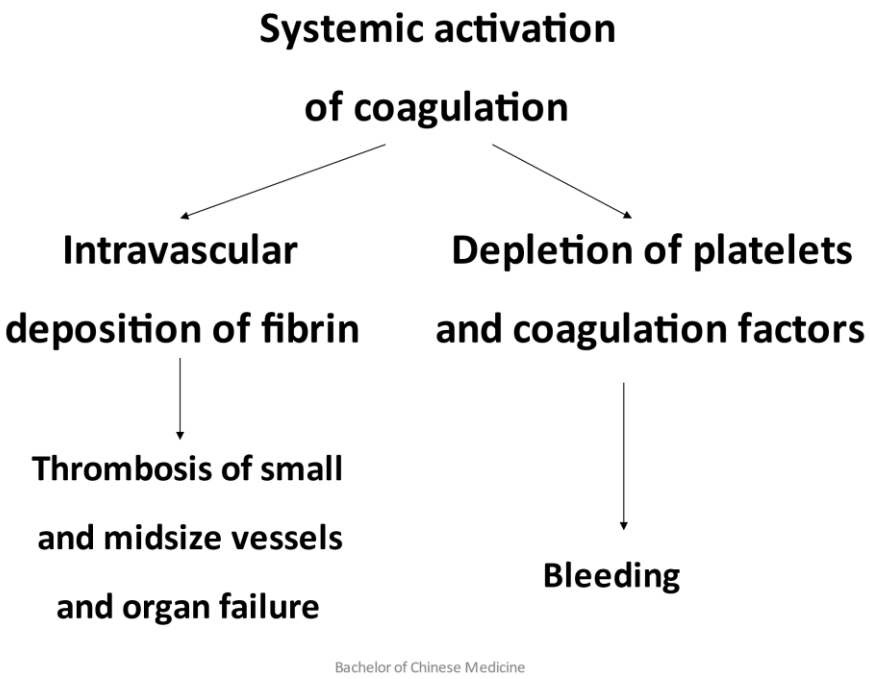
coagulation (DIC)	coagulation (DIC)	2. To identify in adult patients the main pathological symptoms and syndromes of DIC	intravascular coagulation (DIC) (T 3) Symptoms and sings (T 4) Investigation of disseminated intravascular coagulation (DIC). Coagulation profile. (T 5)	3. Justify the clinical diagnosis of DIC hemophilia
	2. To prescribes appropriate treatment	• Recommend treatment •	(T 6) Treatment of disseminated intravascular coagulation (DIC).	4. Make a treatment plan of DIC

TERM	Table 5.3. DEFINITION, ETIOLOGY AND PATHOGENESIS
Disseminated intravascular coagulation	Definition: a syndrome characterized by thrombosis, hemorrhage, and organ dysfunction caused by systemic activation of the clotting cascade, which leads to platelet consumption and exhaustion of clotting factors
	Underlying conditions

Etiology and pathophysiology	• Infection/sepsis • Trauma, bum, surgery • Obstetric, e.g. amniotic fluid embolism, placental abruption, pre-eclampsia • Severe liver failure • Malignancy, e.g. solid tumours and leukaemias • Tissue destruction, e.g. pancreatitis, burns • Vascular abnormalities, e.g. vascular aneurysms, liver haemangiomas • Toxic/immunological, e.g. Hemolytic transfusion reaction, snake bites
	• Disseminated intravascular coagulation (DIC) may complicate a range of illnesses. • It is characterised by systemic activation of the pathways involved in coagulation and its regulation. • Activation of coagulation cascade leads to microthrombi and consumption of platelets and coagulation factors (especially II, V, VIII, and fibrinogen); characterized by both thrombosis (may result in tissue ischemia and infarction) and hemorrhage; results from the release of tissue thromboplastin or activation of the intrinsic pathway. • There is consumption of platelets, coagulation factors (notably factors V and VIII) and fibrinogen. The lysis of fibrin clot results in production of fibrin degradation products (FDPs), including D-dimers. 

- 

- Formation of microthrombi that block blood vessels preventing blood and oxygen from suppling tissue and organs leading to tissue ischemia and possible multiorgan dysfunction syndrome (MODS);



- ❖ Nonsymptomatic type DIC: low-grade fibrinolysis and/or hypercoagulation
- ❖ Bleeding type DIC: hyperfibrinolysis due to excessive plasmin activity → increased fibrin degradation → thrombi becoming unstable and dissolving shortly after formation
- ❖ Massive bleeding type DIC: hypercoagulation and hyperfibrinolysis → consumption of platelets and all coagulation factors → bleeding diathesis

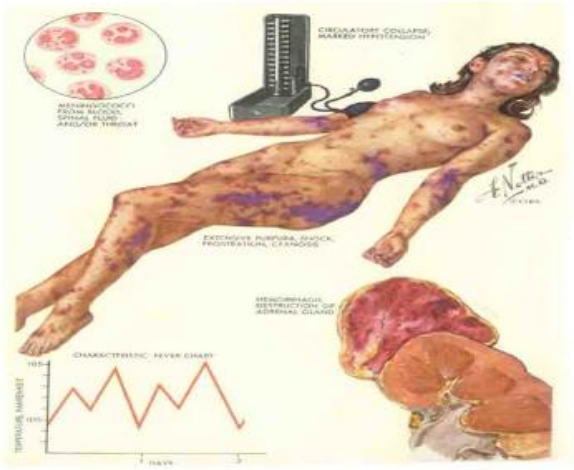
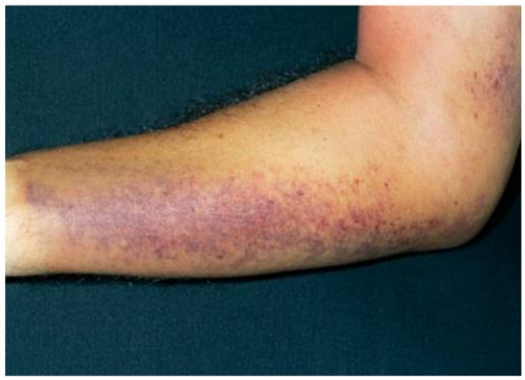
	❖ Organ failure type DIC: ↑ cytokines→ ↑ plasminogen activator inhibitor-I (PAI-I) and ↑ neutrophil extracellular traps (NETs) → hypercoagulation with suppressed fibrinolysis → platelet and fibrin-rich microthrombi → impaired perfusion and tissue necrosis

Table 5.4. CLASSIFICATION
According to disease onset

Latent DIC:	• no overt symptoms (little to no bleeding, increased risk of thrombotic events, laboratory abnormalities) –
Overt DIC:	• clear signs and symptoms (e.g., bleeding, thrombosis) that depend on the balance of the deranged processes
Acute DIC	• Excess thrombin generation leading to the formation of microthrombi and, eventually, microangiopathic hemolytic anemia (MAHA) • Rapid consumption of coagulation factors and platelets • Common causes include septic shock, acute pancreatitis, burns, snake bites, transplant rejection • Often starts as a hypercoagulable state (organ failure type DIC)
Chronic DIC	• Small thrombin generation over prolonged periods of time • Slower consumption of coagulation factors and platelets • Common causes include malignancies, aneurysms, retroperitoneal hematomas, intrauterine fetal death • Often manifests as nonsymptomatic type DIC Thrombosis is more common in symptomatic chronic DIC

CLASSIFICATION According to predominant clinical phenotype	
Thrombotic phenotype	• also called organ failure type, hypercoagulation type, suppressed-fibrinolytic-type, or hypofibrinolysis type DIC • most often observed in patients with infection, especially sepsis • characterized by strong coagulation activation and suppressed fibrinolysis with microvascular thrombosis and ischemic organ dysfunction/failure • thrombosis of larger vessels may also occur bleeding symptoms relatively mild
Fibrinolytic phenotype	• also called bleeding type, enhanced-fibrinolytic-type or hyperfibrinolysis type DIC • usually observed in patients with trauma, acute promyelocytic leukemia, aortic aneurysm, obstetric diseases, and prostate cancer • excessive fibrinolysis, with severe bleeding complications • organ failure (rare)
Subclinical DIC	• also called balanced-fibrinolytic-type DIC, non-symptomatic type of DIC or pre-DIC • characterized by presence of only laboratory features of DIC, with no evident of bleeding or thrombosis (usually seen in cancer-related DIC)

Table 5.5. CLINICAL FEATURES
The signs and symptoms depend on the underlying disease/ • **The clinical features of DIC may appear acutely (e.g., following trauma, sepsis) or subacutely (e.g., DIC following malignancy).** DIC leads to both bleeding and thrombosis; bleeding is far more common than thrombosis.

Bleeding:	• bleeding may occur at any site. Oozing of blood from surgical wounds or venipuncture sites • Petechiae, purpura, spontaneous bruising • Respiratory tract bleeding • Mucosal bleeding from the gums, mouth, nose • Possibly bleeding at sites of venipuncture/IV catheters • CNS bleeding, gastrointestinal bleeding, hematuria • Massive hemorrhage: collection of blood in body cavities (hemoperitoneum, hemothorax) • Low blood pressure  Disseminated intravascular coagulation, DIC 

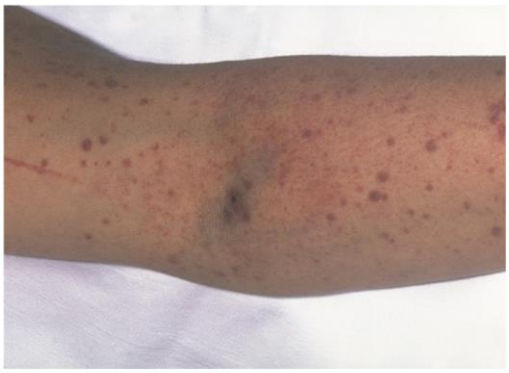
	The photograph shows purpura (bruises) and petechiae (dots) in the skin. Bleeding under the skin causes the purple, brown, and red colors of the purpura and petechiae 
Organ failure primarily due to hypercoagulation:	– Microangiopathic hemolytic anemia – Acute renal failure: oliguria – Hepatic dysfunction: jaundice – ARDS: dyspnea, rales – Pulmonary thromboembolism: dyspnea, chest pain, hemoptysis – Deep vein thrombosis: lower limb edema – Neurological dysfunction: altered mental status, stroke – Purpura fulminans: DIC with extensive skin necrosis – Waterhouse Friderichsen syndrome: adrenal infarcts → adrenal insufficiency – Signs of shock
Thrombosis:	Thrombosis: occurs due to vessel occlusion by fibrin and platelets. Skin, brain and kidneys are mostly affected, causing digital ischemia and 'gangrene, renal cortical necrosis, hemorrhagic adrenal infarction. • Microangiopathic hemolytic anemia. • Other manifestations: High incidence of cardio respiratory, renal failure & jaundice.
	• Subacute DIC is seen primarily in cancer patients and manifests as recurrent superficial and deep venous thrombosis (Trousseau's syndrome).

Table 5.6. LABORATORY STUDIES	
Laboratory **studies**:	Interpetetion of results
• Coagulation panel: Monitor frequently (e.g., every 6–8 hours or until stable or improving).	
12. CBC and blood smear	• Thrombocytopenia – ↓ Platelet count: due to consumption and/or bleeding – ↓ Hct: occurs with bleeding • Schistocytes: indicative of microangiopathic hemolytic anemia. Microangiopathic hemolytic anemia in 25% with fragmented RBCs on peripheral blood film.
13. Activated partial thromboplastin time (APTT) (Reference range 26–36 secs)	APTT – prolonged (clotting factors and platelets are consumed)
14. Prothrombin time (PT)	prolonged
15. Fibrinogen (Reference range 1.5–4.0 g/L)	Hypofibrinogenaemia • In addition, there is evidence of active coagulation with consumption of fibrinogen and generation of fibrin degradation products (D-dimers). – Note, however, that fibrinogen is an acute phase protein that may also be elevated in inflammatory disease – ↓ Fibrinogen: indicative of associated hyperfibrinolysis
– Fibrin degradation products (FDP), D-dimer test – Markers of fibrin breakdown:	– D-dimer levels or other FDPs typically are elevated
1. Antithrombin III level:	may be very low.

2. In subacute DIC	only thrombocytopenia and elevated D-dimer; fibrinogen and APTT may be normal.

- Other tests of organ function (e.g., renal function tests, liver chemistries): Order depending on clinical picture and underlying conditions.

- The diagnosis of DIC is not based on a single marker but on a combination of laboratory findings. Thrombocytopenia, elevated D-dimer, increased PT and aPTT, and low fibrinogen should immediately raise suspicion for DIC.

Table 5.7. **Differential diagnoses by underlying process**

- Decreased production of platelets and clotting factors
  - Severe hepatic dysfunction
  - Vitamin K deficiency
  - Bone marrow suppression
  - Hemophilia

- Increased destruction of platelets and clotting factors
  - Thrombotic thrombocytopenic purpura
  - Immune thrombocytopenic purpura
  - Heparin-induced thrombocytopenia
  - Acute hemolytic anemia
  - Hemolytic uremic syndrome

- Increased consumption of platelets and clotting factors
  - DVT/pulmonary embolism
  - Surgery
  - Infections

- Increased loss of platelets and clotting factors
  - Massive blood transfusion causing dilutional coagulopathy
  - Capillary leak syndrome
  -

The differential diagnoses listed here are not exhaustive.

Table showing different between acute and Chronic DIC:

Lab Tests	Acute DIC	Chronic DIC
PT	prolonged	normal
PTT	prolonged	normal
Fibrinogen	usually decreased	usually normal
D-dimer	positive	positive
FDP	positive >40 µg/mL	positive <40 µg/mL

Table 5.8. TREATMENT

Treatment
General principles

- First-line: treatment of the underlying disease
- Additional treatment depends on the subtype and is complicated. Involve specialists early.
  - Blood products as needed
  - Anticoagulation: if hypercoagulability is the leading problem (e.g., in organ failure type DIC)
  - Consider advanced treatment options (e.g., antithrombin) in consultation with a specialist.
- Supportive therapy
  - Avoid invasive procedures if possible
  - Vitamin K supplementation if deficiency is suspected
- Initiate clinical and serial laboratory monitoring to assess response to treatment.

MEDICATION

- Therapy is primarily aimed at the underlying cause.
- These patients will often require intensive care to deal with concomitant issues,

such as acidosis, dehydration, renal failure and hypoxia.	
Supportive treatments include replacing coagulation factors and fibrinogen with Blood component therapy, such as • fresh frozen plasma (PPF) infusion, • *cryoprecipitate* and •	• should be given if the patient is bleeding or • to cover interventions with a high bleeding risk, but should
• Platelets infusion if the platelet count is low	Indications – Active bleeding or high risk of bleeding (e.g, planned invasive procedure): platelet count < 50,000/mm3 – No bleeding: platelet count < 10,000–20,000/mm3 – Active bleeding or at high risk of bleeding: platelet count > 20–50,000/mm3.
• pRBCs:	indicated for patients with active bleeding or Hb ≤ 7 gr/dL (see “Packed red blood cells” for specific transfusion thresholds and goals and “Massive transfusion” in case of massive hemorrhage)
• Fresh frozen plasma (FFP) ;	Indications – PT or aPTT > 1.5 times the normal value if patient is bleeding or will undergo an invasive procedure – Consider if bleeding and fibrinogen < 150 mg/dL – As part of a massive transfusion protocol Goals – PT < 3 seconds prolonged – Fibrinogen > 100–150 mg/dL
• Cryoprecipitate	Indication: bleeding and fibrinogen levels < 150 mg/dL despite FFP or when FFP transfusion is not possible [16] Goal: fibrinogen level of > 100–150 mg/dL

	• Prothrombin complex concentrate – Individual decision in patients with active bleeding when FFP transfusion is not possible (e.g., due to volume overload) – Cautions ▪ May only partially correct coagulopathy ▪ Can tip the procoagulant-anticoagulant balance towards thrombosis. ▪ Monitoring of antithrombin activity and protein C levels is recommended.
• Prophylactic doses of heparin to prevent blood clotting,	• Should be given, unless there is a clear contraindication. • Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated. • The administration of heparin is not recommended in patients with massive bleeding type of DIC. • Heparin is recommended in patients with non-symptomatic type of DIC to prevent the onset of deep vein thrombosis
	Patients with DIC should not, in general, be treated with antifibrinolytic therapy, e.g. tranexamic acid

Table 5.9. COMPLICATION AND PROGNOSIS	
	• DIC can rapidly lead to organ failure and it is often fatal condition, especially when not identified and treated early.

	• Overall mortality from DIC is difficult to establish due to the severity and variety of the underlying conditions. • However, it has been estimated that mortality rates for sepsis and severe trauma double if DIC develops.

5.10. LIST OF PRACTICAL SKILLS

1. Examination (demonstration of clinical skill) of patients with DIC
2. To predict the results of hemostatic screening tests (PT/INR, PTT, fibrinogen, factor VIII activity, platelet count, bleeding time) in a patient with hemophilia A.
3. Confirm the clinical diagnosis of DIC
4. Make a treatment plan of DIC

5.11. QUESTIONS FOR SELF-CONTROL.

1.Explain the etiology, pathogenesis of DIC; syndrome of multiple organ failure;

1. Discuss the clinical picture and diagnosis of DIC .
2. Dynamics of the laboratory tests at different stages of development of DIC (hyperaggregation platelet hypercoagulability; thrombocytopenia and consumption coagulopathy, the deficit of physiological anticoagulants);
3. Recommend DIC treatment

5.12. TESTS FOR CHECKING THE FINAL LEVEL OF KNOWLEDGE

1. False statement regarding DIC is:

A. Thrombocytopenia
B. Decreased fibrinogen
C. Decreased PTT
D. Increased PT

2. The following is the finding seen in DIVC :

A. Increased fibrinogen , increased antithrombin III, increased thrombin-antithrombin III complexes
B. Increased FDP, decreased PT, increased antithrombin III

C. Increased FDP, prolonged PT, increased thrombin-antithrombin complexes
D. Increased FDP, prolonged PT, reduced Platlets

3.The most sensitive test for DIC is:
A. Serum fibrinogen levels
B. Serum levels of fibrin degradation products (FDP)
C. Prolonged PT and PTT
D. Thrombocytopenia

4.Which of the following features is NOT seen in DIC?
A. Thrombosis
B. Thrombocytopenia
C. Hyperfibrinogenemia
D. Consumption coagulopathy

5.Bleeding in DIC is most closely related to:
A. Raised fibrin degradation products level in blodd
B. Prolong prothrombin time
C. Low serum fibrinogen level
D. Raised thrombin time

6. A 23-year-old man is admitted to the hospital through the emergency department with probable appendicitis. He has been having right lower quadrant abdominal pain for several days, which has been becoming increasingly worse. His temperature 39.2 C (102.6 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 35/min. The abdomen is rigid with guarding. Multiple petechiae and purpura are present, and the patient is oozing blood from his oral mucosa. According to the patient's wife, he has not had bleeding problems in the past.

1.Given this patient's presentation, which of the following is the most likely cause of his petechiae, purpura, and mucosal blood oozing?

A. Disseminated intravascular coagulation
B. Hemophilia A
C. Idiopathic thrombocytopenic purpura
D. Von Willebrand disease
E. Wiskott-AIdrich syndrome

6.12. Answers for TESTS:

№	Answers for TESTS Schönlein-Henoch purpura

1	d)
2	a)
3	c)
4	c)
5	a)

№	Answer for tests immune thrombocytopenia :
1	c)
2	a)
3	c)
4	a)

№4.	Answer for tests Hemophilia
1	a)
2	b)
3	a)
4	a)

№	Answer for tests DIC
1	c)
2	d)
3	b)
4	c)
5	c)
6	a)

Table 6. 13. Answer for Case study

Answer for Case study: Schönlein-Henoch purpura Conduct diagnostics and treatment of Schönlein-Henoch purpura

Stage:	Be able to:	Knows and understands:	Owns
Stage I Orientations	1. Identify the known data (on the basis of the analysis conditions): 1) patient, 17 years old; • complains: complains of acute abdominal pain, vomiting, hemorrhagic rashes on lower extremities and buttocks, joint pain. medical history: • she had cold exposure, 2 weeks prior to the emergency room visit; 2) results of physical examination: • abdominal pain • palpable purpura distributed symmetrically over the lower extremities, extensor surfaces and buttocks	T. 1 T. 2 T. 3	1. Discuss about patient complaints, past medical history, family history, social history, and drugs and allergy history; 2. Examination (demonstration of clinical skill) of patients with HSP.
Stage II Formulate preliminary diagnosis	Preliminary diagnosis: Schönlein-Henoch purpura ?		

	Plan of investigations.	Interpetetion of diagnostic Tests	T. 4	1. Interpret the results of laboratory and instrumental examination;
	1. Diagnosis of HSP is mainly based on clinical signs and symptoms.			
	2. CBC	is normal		
	3. Coagulation time	are normal.		
	4. Ultrasound of the kidney	are normal		
Stage III Formulates the clinical diagnosis, based on the diagnostic criteria of the disease.	Clinical diagnosis: Schönlein-Henoch purpura based on 1. Patient complaints: • abdominal pain • palpable purpura distributed symmetrically over the lower extremities, extensor surfaces and buttocks • joint pain 2. Medical history: • she had cold exposure, 2 weeks prior to the emergency room visit; 3. Results of physical examination: • skin examination reveals palpable purpura distributed symmetrically over the lower extremities, extensor surfaces and buttocks; 4. The results of laboratory tests:			

	• CBC, coagulation time, ultrasound of the kidney are normal		
Describe the complications associated with the disease process	1. GI hemorrhage 2. Intestinal infarction, perforation, obstruction, stricture 3. Nephrotic/nephritic syndrome and renal failure	T. 5	
Stage IV	1. NSAIDs effective for symptomatic joint pain. 2. Oral steroids @1 mg/kg/day with gradual tapering 3. Plasma exchange	T. 6	1. Write prescriptions for Prednisone 2. Explain mechanism of action. 2. Explain side effect

Answer for Case study: Immune thrombocytopenia. Conduct diagnostics and treatment of Immune thrombocytopenia.			
Stage:	Be able to:	Knows and understands:	Owns

Stage I Orientations	1. Identify the known data (on the basis of the analysis conditions): 1) patient, 24 years old; complaints: • bleeding from her nose and mouth since the previous night; • small, reddish spots on her lower extremities medical history: • she had developed an upper respiratory infection, 2 weeks prior to the emergency room visit, but the infection has now resolved; • no family history of abnormal bleeding; • the patient does not take any medications; • She denies excessive bleeding in the past, even after delivering her baby. 2) results of physical examination: • she is alert, oriented, and somewhat anxious; • her blood pressure is 100/70 mm Hg, her heart rate is 89 bpm ; • she is afebrile ; • no pallor or jaundice is noted; • there is bright red oozing from the nose and the gingiva; • skin examination reveals multiple 1-mm flat reddish spots on her lower extremities; • there is no lymphadenopathy or hepatosplenomegaly. 3) The results of laboratory tests:	T. 1 T. 2 T. 3 T. 4 T. 5	1. Discuss about patient complaints, past medical history, family history, social history, and drugs and allergy history; 2. Examination (demonstration of clinical skill) of patients with ITP. 3. Interpret the results of laboratory and instrumental

<table>
<tr><td></td><td colspan="2">Complete blood cell count (CBC) is normal except for
a platelet count of 17,0 x 10 ^{9}/L.
Prothrombin time (PT) and
partial thromboplastin time (PTT) are normal.
4) the results of instrumental research methods: not perfomed</td><td></td><td>examination;</td></tr>
<tr><td>Stage II
Formulate preliminary diagnosis</td><td colspan="2">Preliminary diagnosis: Immune thrombocytopenia.?</td><td rowspan="6">T. 5</td><td rowspan="6"></td></tr>
<tr><td rowspan="5"></td><td>Plan of investigations.</td><td>Interpetetion of diagnostic Tests</td></tr>
<tr><td>1. Bleeding time (BT).</td><td>Increased bleeding time</td></tr>
<tr><td>2. HIV</td><td>Negative «-»</td></tr>
<tr><td>3. Hepatitis serology. Viral screening (HCV, HBV)</td><td>Negative «-»</td></tr>
<tr><td>4. Ultrasound</td><td>No hepatosplenomegaly. (Normal-sized spleen)</td></tr>
<tr><td>Stage III

Formulates the clinical diagnosis, based on the diagnostic criteria of the disease.</td><td colspan="2">Clinical diagnosis: Immune thrombocytopenia. based on
1. Patient complaints:
bleeding from her nose and mouth since the previous night;
small, reddish spots on her lower extremities
2.Medical history:
she had developed an upper respiratory infection, 2 weeks prior to the emergency room visit
3. Results of physical examination:</td><td></td><td></td></tr>
</table>

	• there is bright red oozing from the nose and the gingiva; • skin examination reveals multiple 1-mm flat reddish spots on her lower extremities; • there is no lymphadenopathy or hepatosplenomegaly. 4. The results of laboratory tests: • Isolated thrombocytopenia (decreased platelet count) • Increased bleeding time • Ultrasound: No hepatosplenomegaly.		
Stage IV Recommend immune thrombocytopenia. treatment, duration of their usage, possible side effects, indication, mechanism of action.	First-line therapy: • Prednisone 1.0–2.0 mg/kg daily • Duration of treatment for 3- 4 weeks followed by a gradual taper • Possible side effects: -osteoporosis, -diabetes, -hypertension, -weight gain • Indication: Individuals with platelet counts less than 20,000–30,000/mcL or those with significant bleeding should be treated; • Mechanism of action: Corticosteroids act by reducing antibody production and preventing platelet destruction by macrophages (by reticulo-endothelial cells).	T. 6 T. 7	1. Write prescriptions for Prednisone 2. Explain mechanism of action. 2. Explain side effect

	Answer for Case study Haemophilia A: CONDUCT DIAGNOSTICS AND TREATMENT OF HEMOPHILIA A			
Stage:	Be able to:		Knows and understands:	Owns
Stage I Orientations	1. Identify the known data (on the basis of the analysis conditions): 1) A 19 years old boy; 2) complaints: • left elbow swelling for one day after hitting it against the wall while playing; 3) medical history: He was diagnosed with Haemophilia A since sixteen years of age. His father and uncle suffer from a similar illness. 3) results of physical examination: • There was a joint deformity with valgus deformity noted on his right elbow; • the left elbow, there was a swelling • On palpation, the joint was warm and tender to touch. • There is presence of moderate effusion in the left elbow joint. • There was restricted joint movement		T. 1 T. 2 T. 3	1. Discuss about past medical history, family history, social history, and drugs and allergy history; 2. Examination (demonstration of clinical skill) of patients with .Haemophilia;
Stage II: Prescribe plan of investigati	• CBC with platelet count Hemoglobin/hematocrit:	Normal (or low if	T. 4 T. 5	3. Interpret the results of

ons and interpret the results of laboratory tests		associated bleeding)		laboratory and instrumental examination
	• Platelet count:	Normal		
	• FVIII assay	decreased		
	• Prothrombin time (PT)	normal		
	• Partial thromboplastin times (APPT)	prolonged		
Stage III. Formulates the clinical diagnosis, based on the diagnostic criteria of the disease.	Clinical diagnosis: Haemophilia A based on 1. Patient complaints: - complaints: • left elbow swelling for one day after hitting it against the wall while playing; 2.Medical history: • He was diagnosed with Haemophilia A since sixteen years of age. His father and uncle suffer from a similar illness. 3. Results of physical examination: • There was a joint deformity with valgus deformity noted on his right elbow; • the left elbow, there was a swelling • On palpation, the joint was warm and tender to touch. • There is presence of moderate effusion in the left elbow joint. • There was restricted joint movement. 4. The results of laboratory tests: • Factor VIII decreased • A normal prothrombin time (PT) with • prolonged activated partial thromboplastin times (APPT)			

Stage IV Recommend Haemophilia A treatment	First-line therapy: Replacement with factor VIII concentrates	T. 6 T. 7	2. Explain mechanism of action.

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