出血性疾病
Hemorrhagic disorder

珠江医院血液科　邓兰 2020.4

Key words

- Hemorrhage, hemorrhagic 出血，出血的
- Hemostasis, hemostatic 止血，止血的
- Blood coagulation 凝血
- Fibrinolysis, fibrinolytic 纤溶，纤溶的

Contents

Chapter 1 --Summary

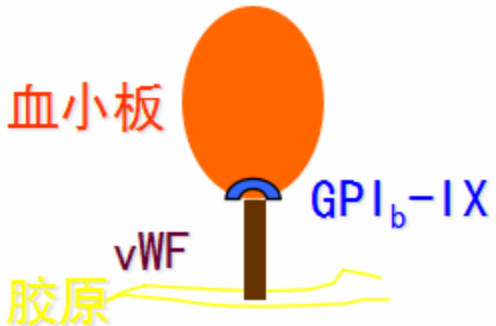
Factors of hemostasis

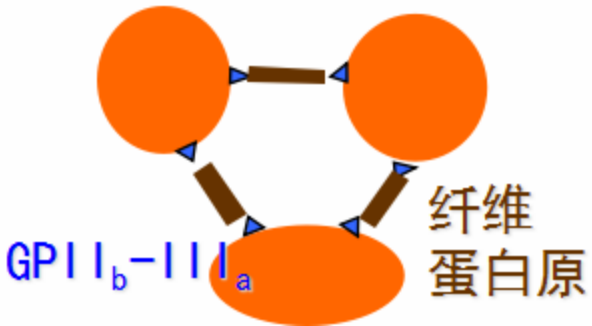
1. Blood vessel
--When it is injured

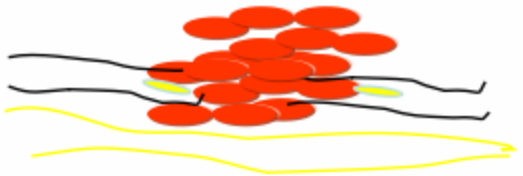
- Its endothelial cells will release vWF to make platelets adhere and aggregate there
- release TF to start extrinsic pathway of coagulation
- collagen fiber of blood vessel exposed will activate FXII, and start intrinsic pathway of coagulation

2. Platelet

- By vWF, platelets adhere to collagen fiber to form thrombus of platelets
- By fibrinogen, platelets aggregate
- Then the platelets activated excrete substance to regulate blood coagulation





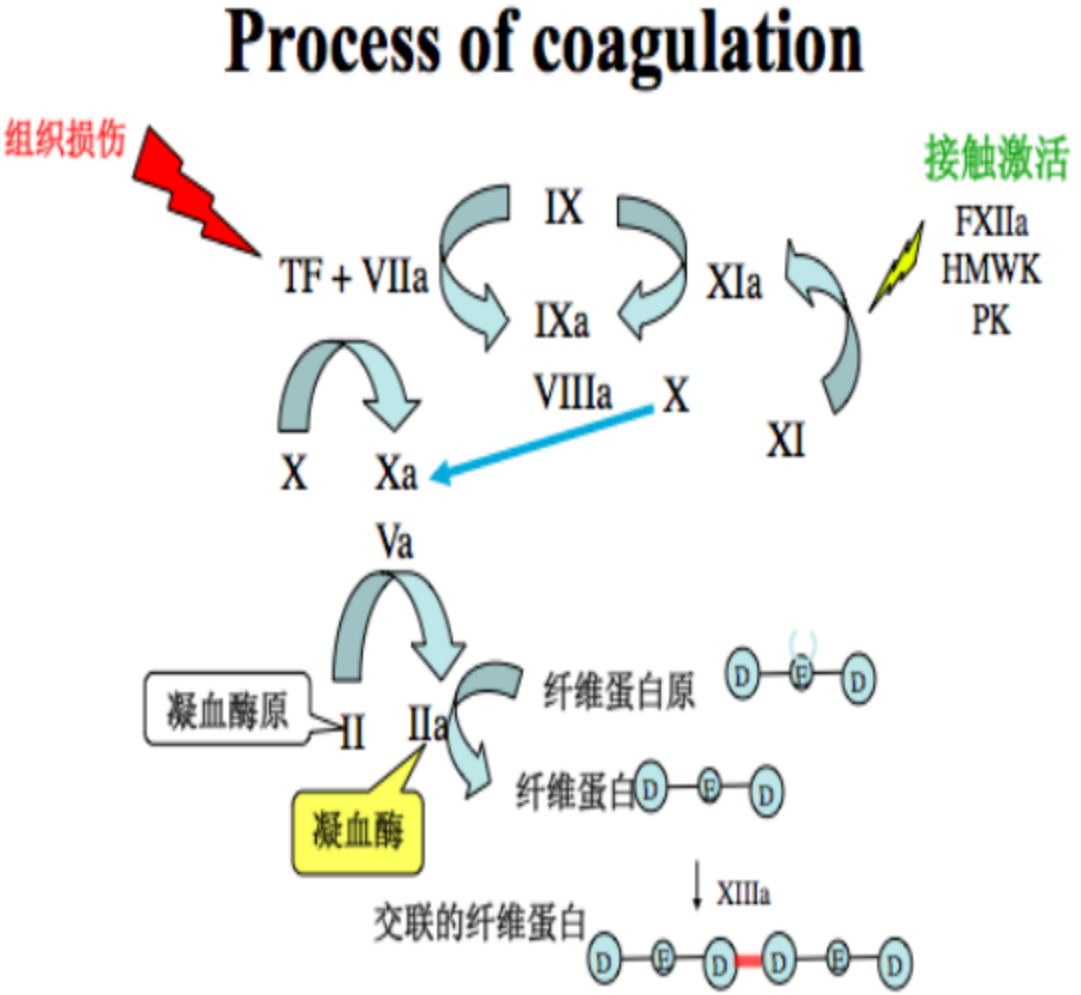


血小板聚集

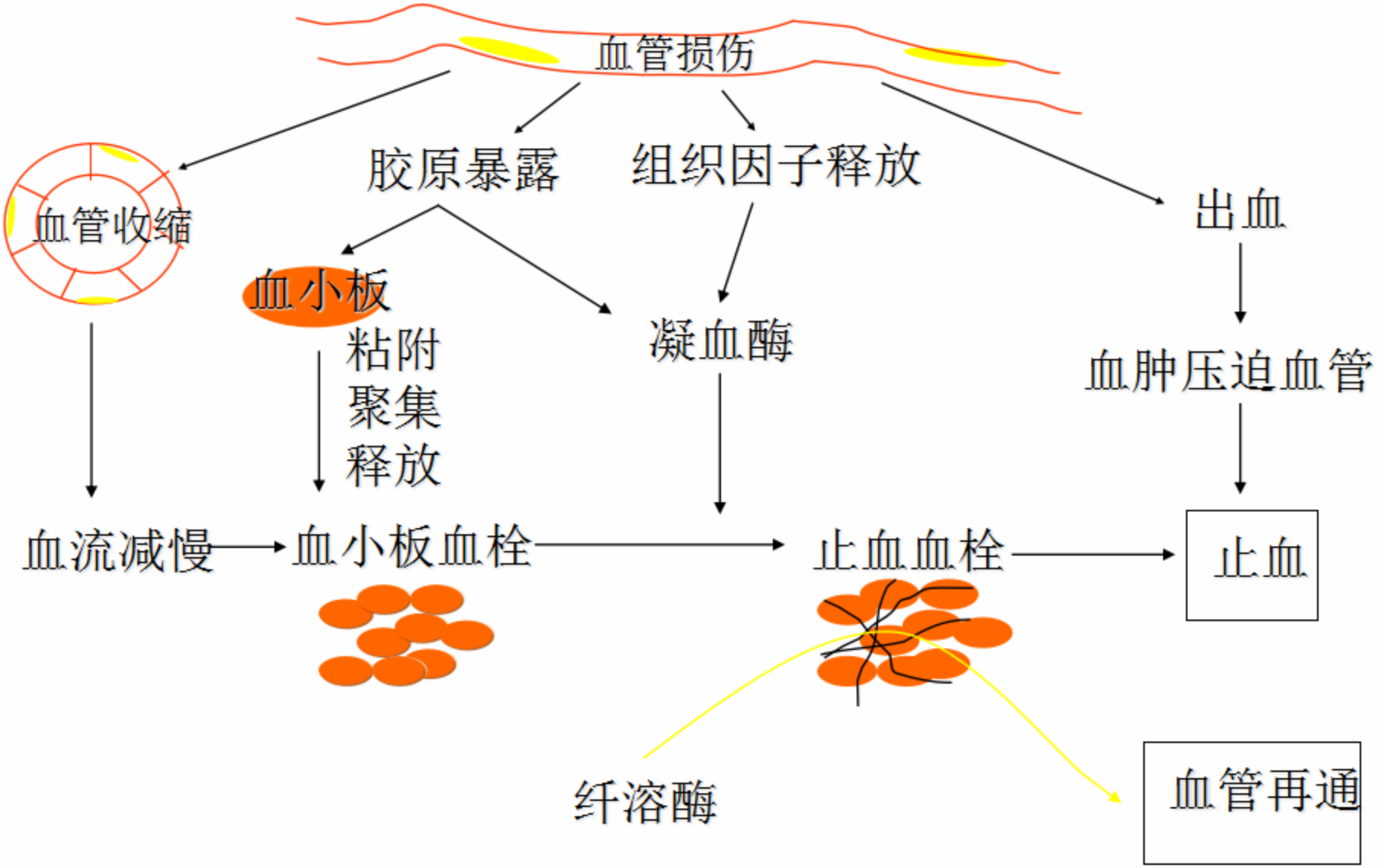
Factors of hemostasis

3.System of blood coagulation

- Blood clotting factors
- Extrinsic and intrinsic pathway of coagulation
- Form thrombus of fibrin



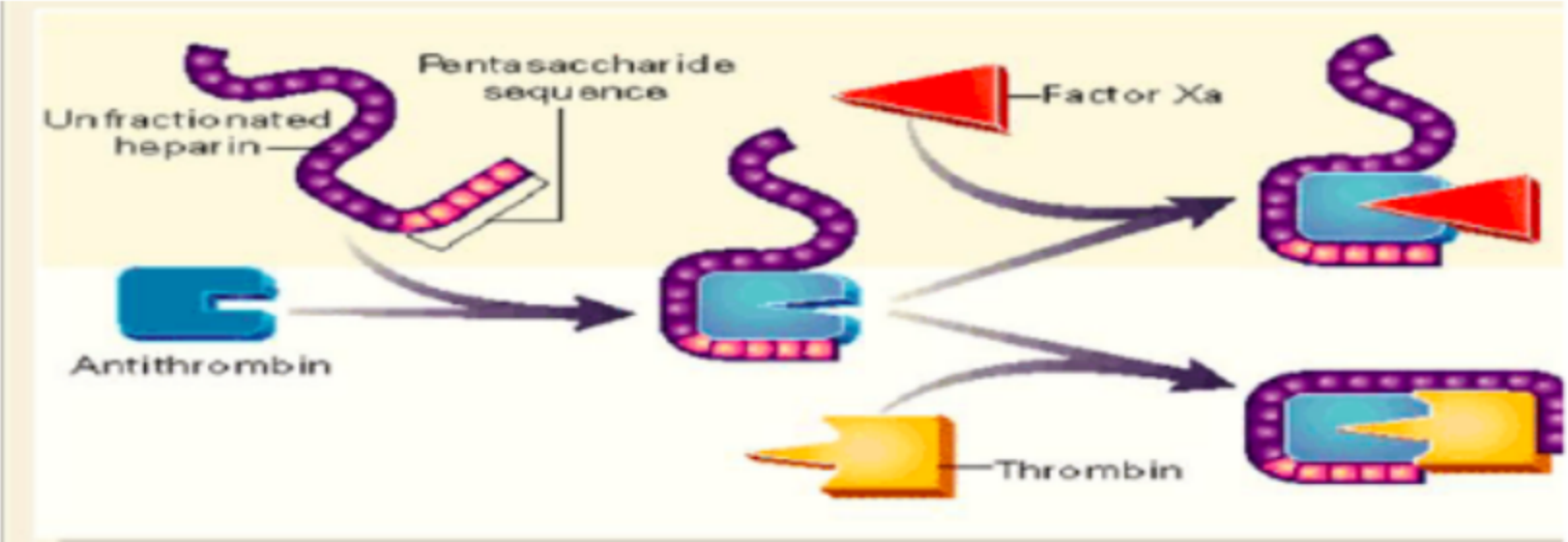
Process of hemostasis



System of anticoagulation

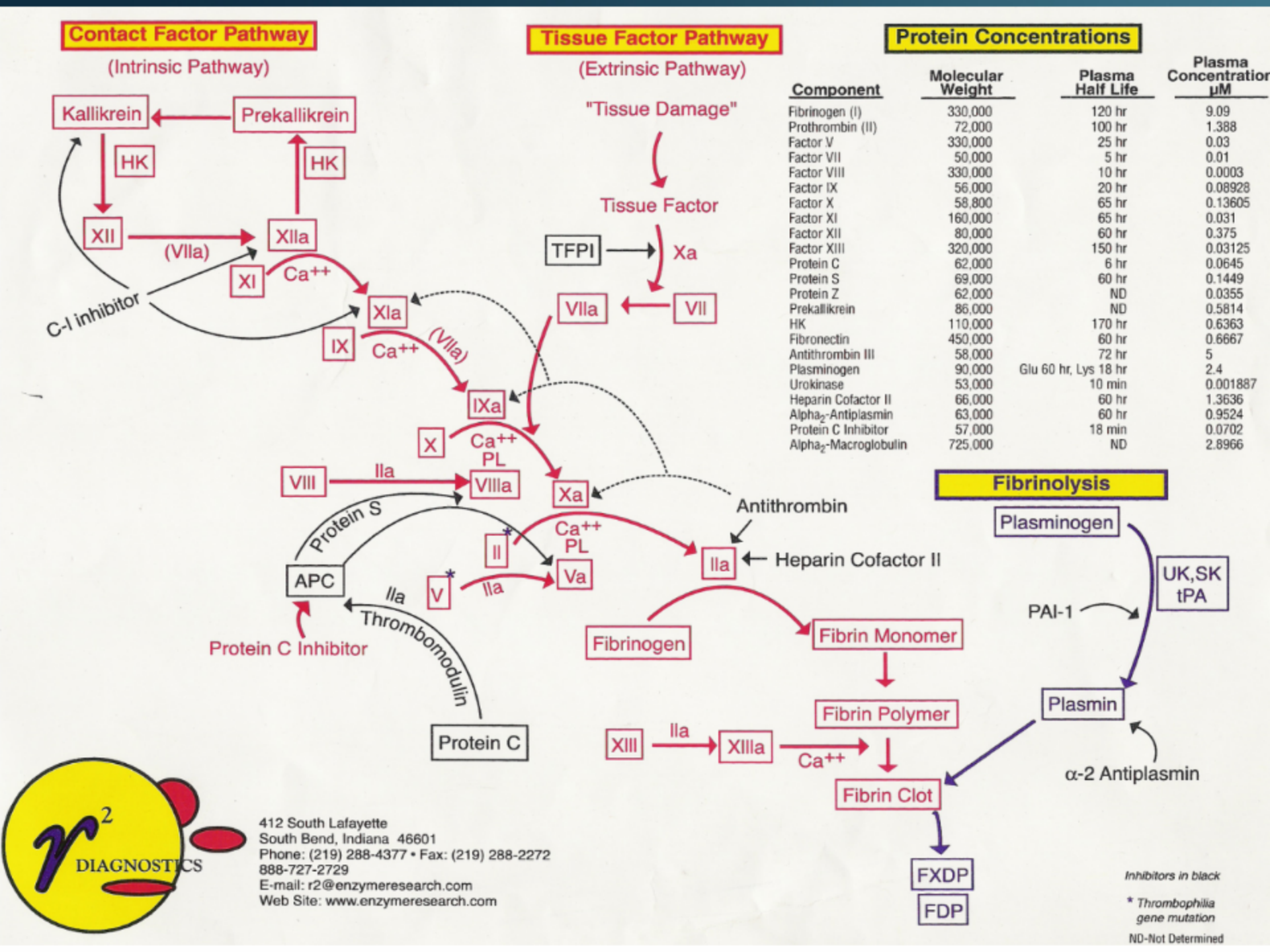
- Heparin-antithrombin (AT) system:

  AT which is the most important anticoagulant can inactivate FXa and FIIa, and **heparin** can change the configuration of AT to promote anticoagulation
- Protein C system:including PC,PS and TM
- Inhibition of TF pathway



System of fibrinolysis

- Plasminogen(PLG): It can be activated into plasmin
- t-PA and u-PA: they activate PLG into plasmin
- Inhibitions of plasmin
- Fibrinolytic system can be activated through intrinsic or extrinsic pathway
- Fibrinogen and fibrin can be decomposed into fibrinogen degradation products(FDP), D-dimer, and so on



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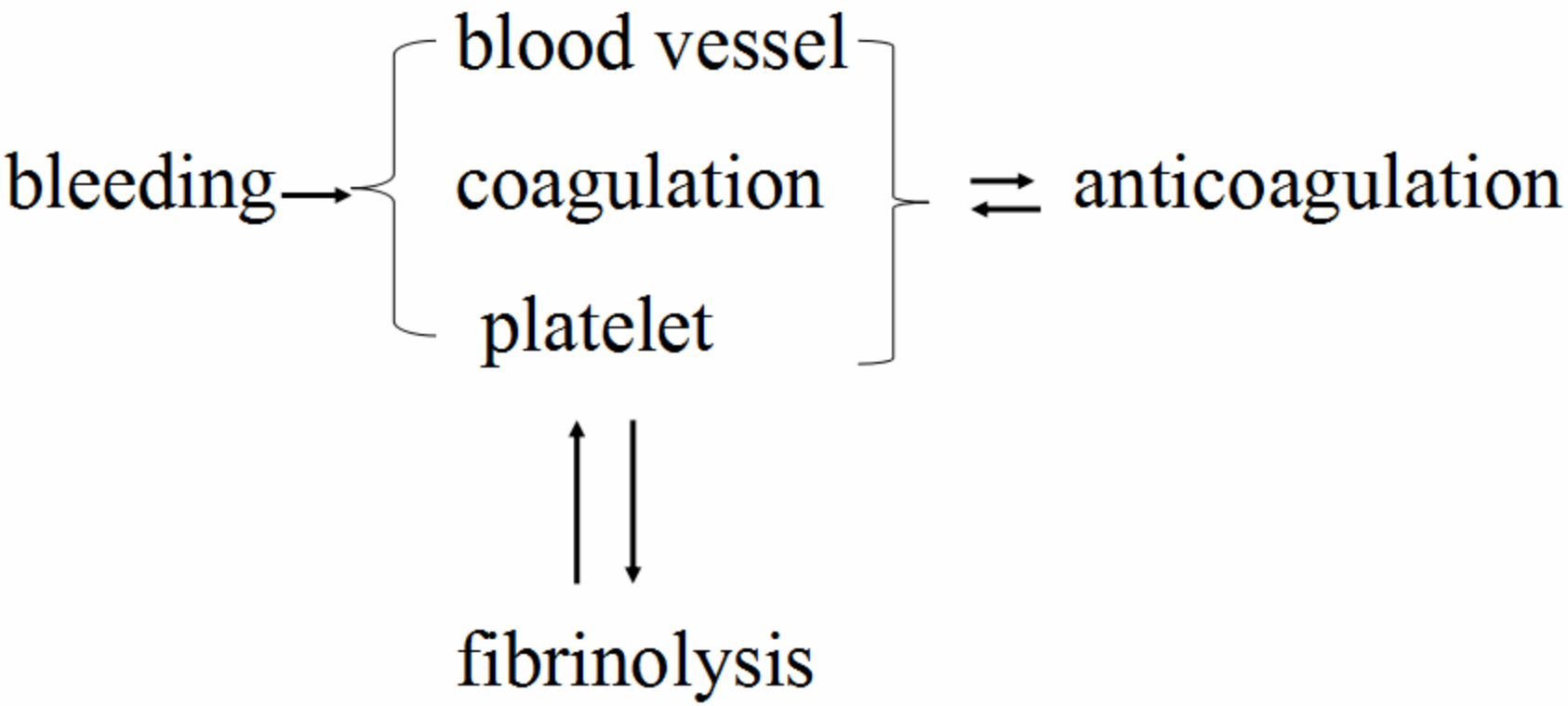
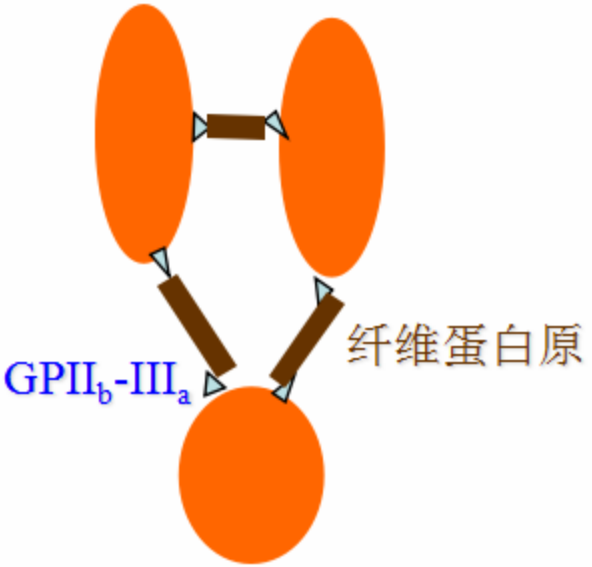
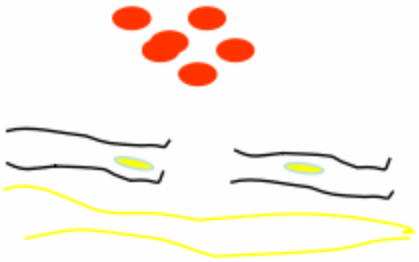

blood vessel
bleeding
coagulation
anticoagulation
platelet
fibrinolysis

Classification of disease

- Abnormality of vessel: congenital, acquired
- Abnormality of platelet: thrombocytopenia, thrombocytosis, quality abnormality
- Abnormality of blood clotting factors: congenital, acquired
- Abnormality of anticoagulation or fibrinolysis: drug, bited by snake or leech
- Abnormality of multi-factors: congenital, acquired

Abnormality of platelet





血小板减少

血小板粘附异常

GPI_b缺乏：巨大血小板病

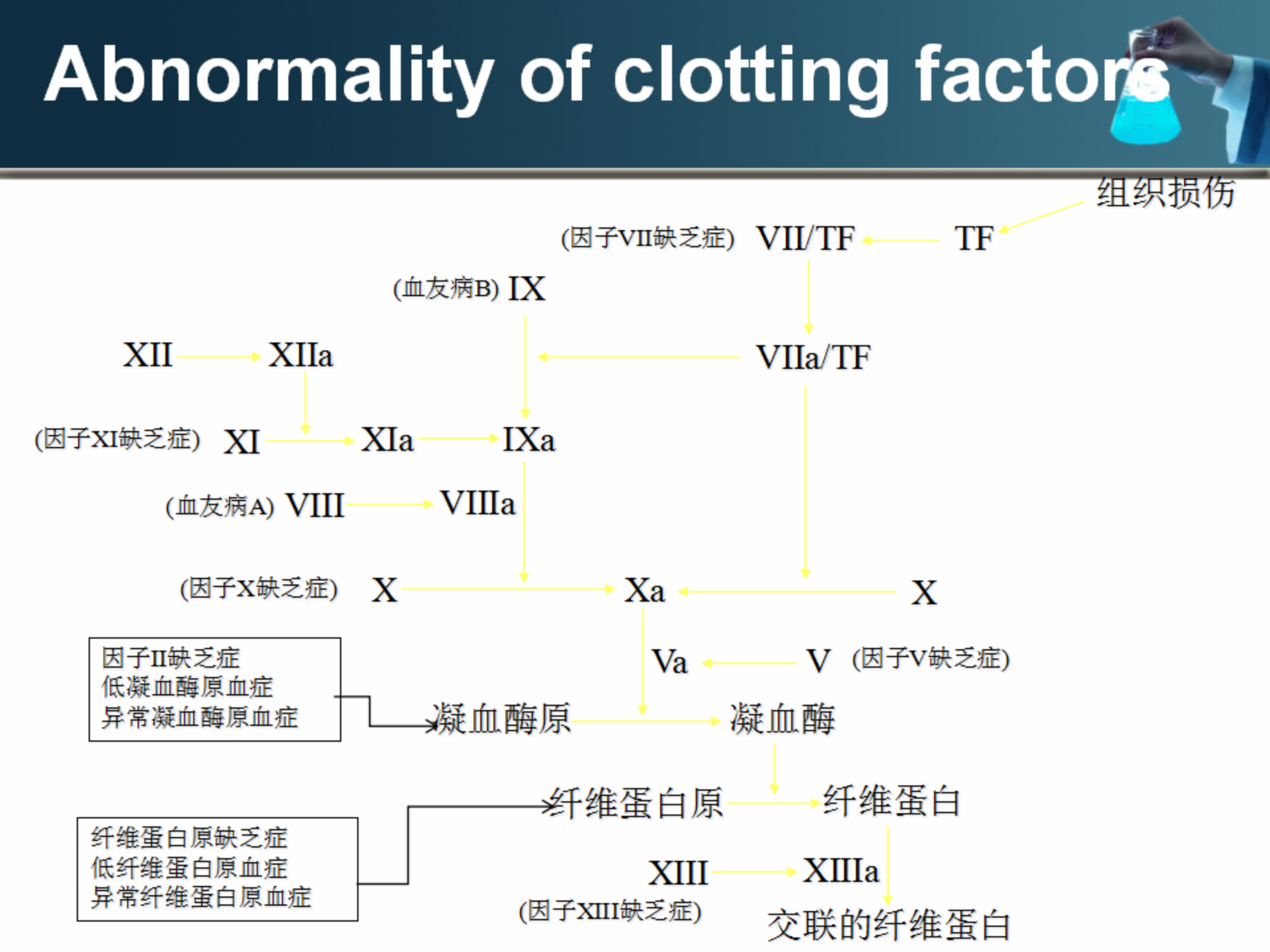
VWF缺乏：血管性血友病

血小板聚集异常

$GPII_b$-III_a缺乏：血小板无力症

纤维蛋白原缺乏：血小板聚集障碍

Abnormality of clotting factors



Diagnosis

Symptoms

- Character of hemorrhage: age, location, duration, volume.
- Cause of hemorrhage: no cause, wound, medicine
- Other disease: liver, kidney, heart, and so on
- Familial history
- Others: nutrition, occupation, circumstance

Physical examination

- Sign of hemorrhage
- Sign of disease concerned: anemia, swollen liver or spleen or lymph node, jaundice
- Vital sign

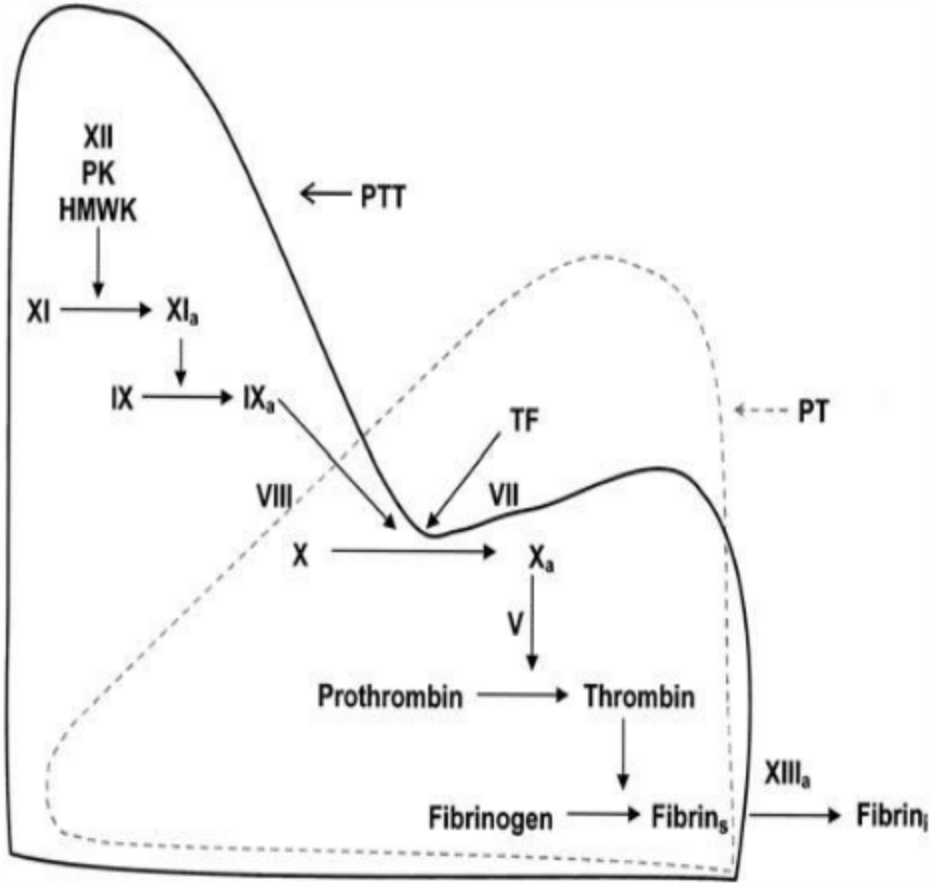
Clinical differentiation

- Disorders of vessel: female, purpura of skin
- Disorders of platelet: famale,purpura or ecchymosis of skin,common positions of bleeding are eyeground,gut,uterus
- Disorders of coagulation: male, often bleed into joints or gut, bleeding occurs after surgery or trauma

Laboratory findings

Primary test

- Vessel: BT,CRT(capillary resistance test)
- Platelet: account of platelet,CRT(clot retraction test), BT,CRT(capillary resistance test)
- Coagulation:CT,APTT,PT,PCT,TT



Laboratory findings

Diagnostic test

- Vessel:mirror of capillary, mensuration of vWF,ET-1,TM
- Platelet: account, configuration, mean volume, function, antibody of platelet
- Coagulation: mensuration of all clot bleeding factors
- Anticoagulation:AT,anticoagulation of SLE,PC, PS,TM
- Fibrinolytic:3P test,FDP,D-DI,PLG,t-PA

Steps of diagnose

- Is disease of hemorrhage?
- Disorder blood vessel? Platelet? Coagulation?
- Abnormal quantity or abnormal quality?
- Congenital or acquired?
- If congenital,test gene.

Treatment

- Inject platelets or clotting factor
- Medicine for hemostasis
- Medicine for produce more platelets
- Treatment for gene:hemophilia
- Anticoagulation or Anticongregation of platelets: DIC,TTP
- Plasmapheresis: TTP, severe ITP
- Surgery
- Chinese medicine

Chapter 2 --Allergic Purpura

Definition

- Allergic purpura (Schonlein-Henoch Syndrome) is a type of general blood vessel inflammation syndrome caused by allergen.
- Character:

1. skin purpura(the main character)
2. gall of the joint
3. Bellyache, having blood in stool
4. hematuria, albuminuria

Etiology

- Infection： bacteria, virus, parasites
- Food
- Medicine
- Other： pollen,vaccine,insect bite
- Hereditary factors

Mechanism:Type III hypersensitivity

Excessive Ag+Ab(Ig A)

↓

Medium immune complex

↓

Deposition on basement membrane

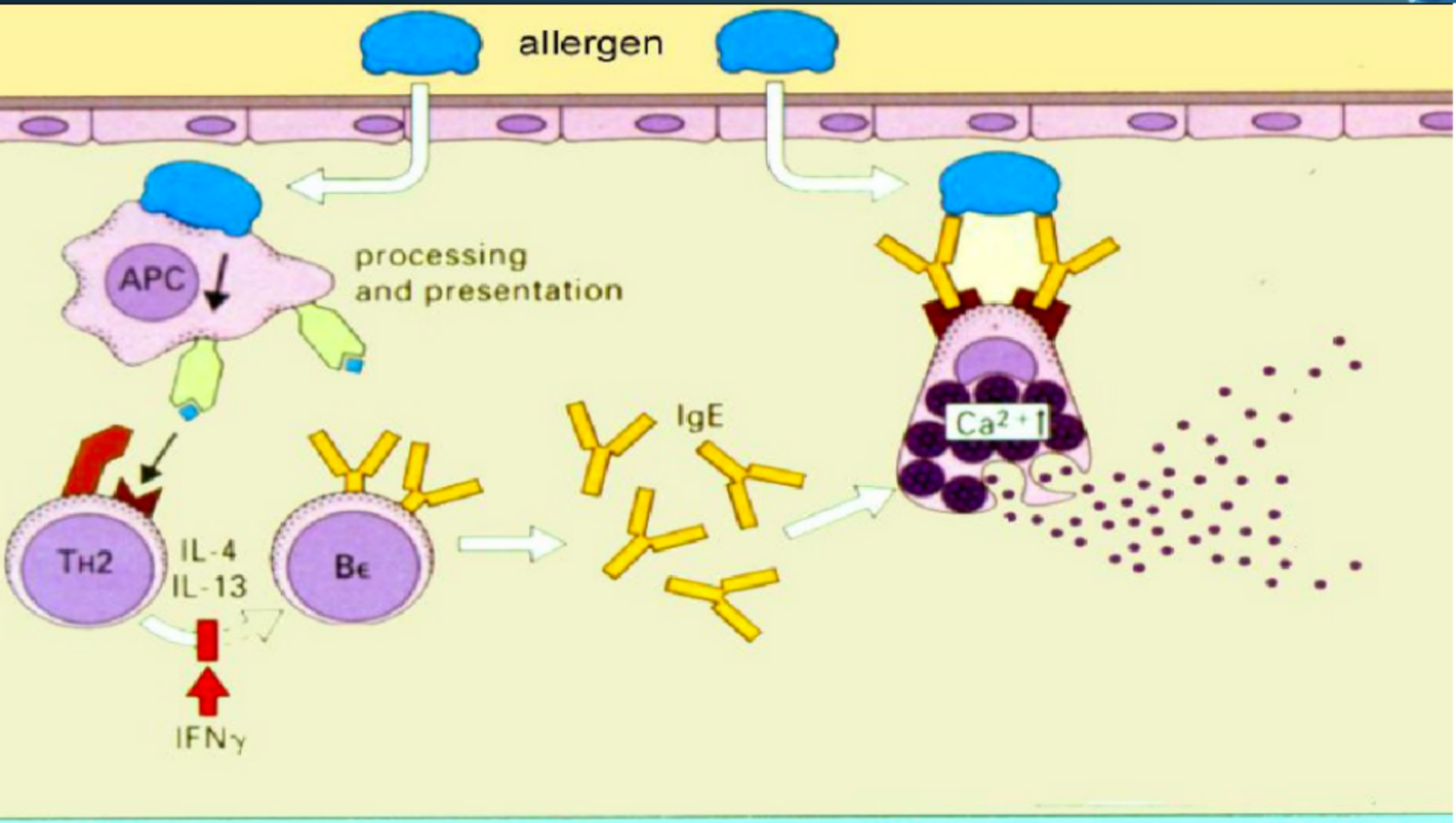
↓

Activate C by classical pathway

↓

Produce C3a and C5a

Mechanism:Type I hypersensitivity



antigen presentation → IgE production → mast cell activation → mediator release

Mechanism

Anaphylatoxin

- C3a、C5a bind to the receptors on mast cell and basophil →histamine →
  - smooth muscle contraction
  - increase vascular permeability
  - increase gland secretion

Chemotaxis

- C3a、C5a can also assemble neutrophil →lysosomal enzyme →tissue injury
- The breakage of the vascular wall can lead to the activation of coagulation pathway →assemble the platelet →thrombosis, local bleeding, necrosis

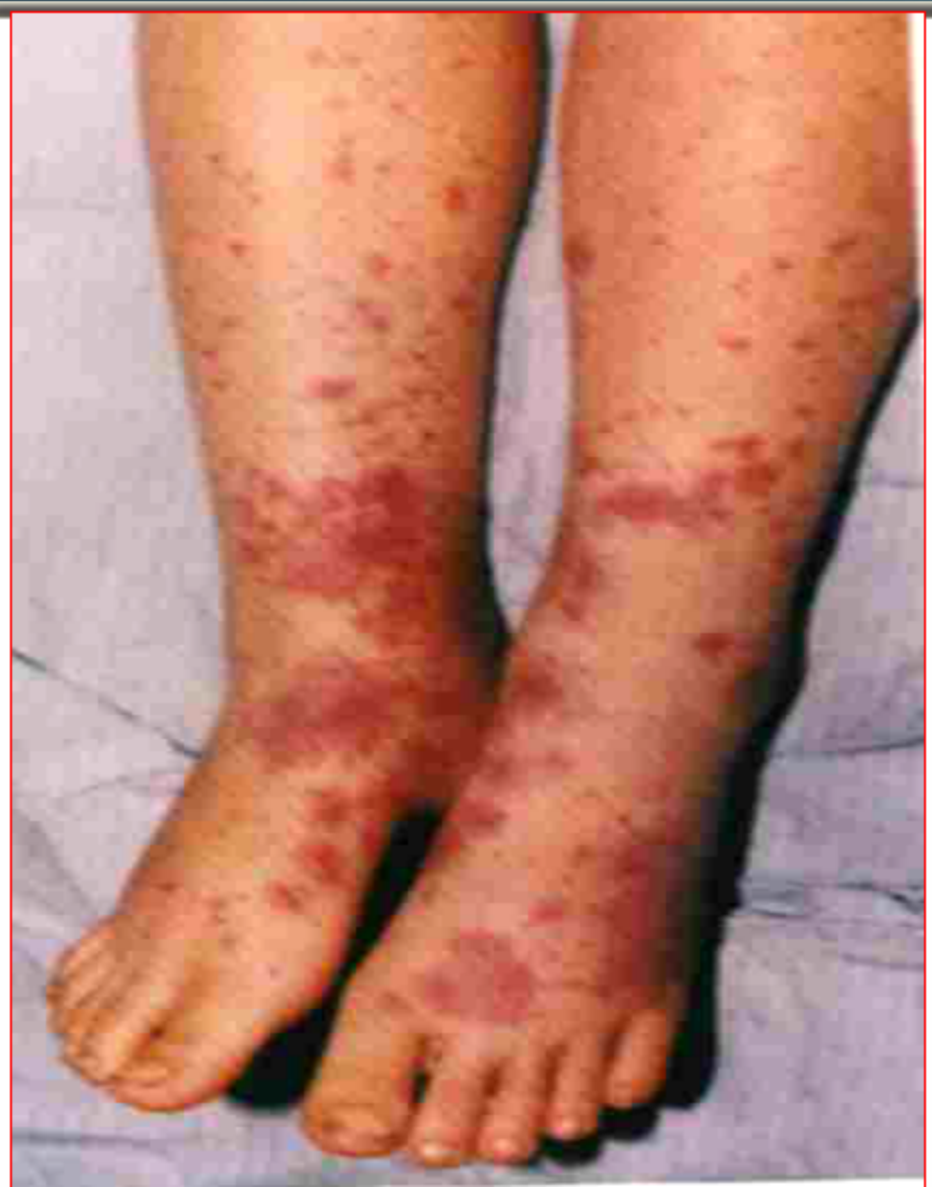
Clinic Manifestation

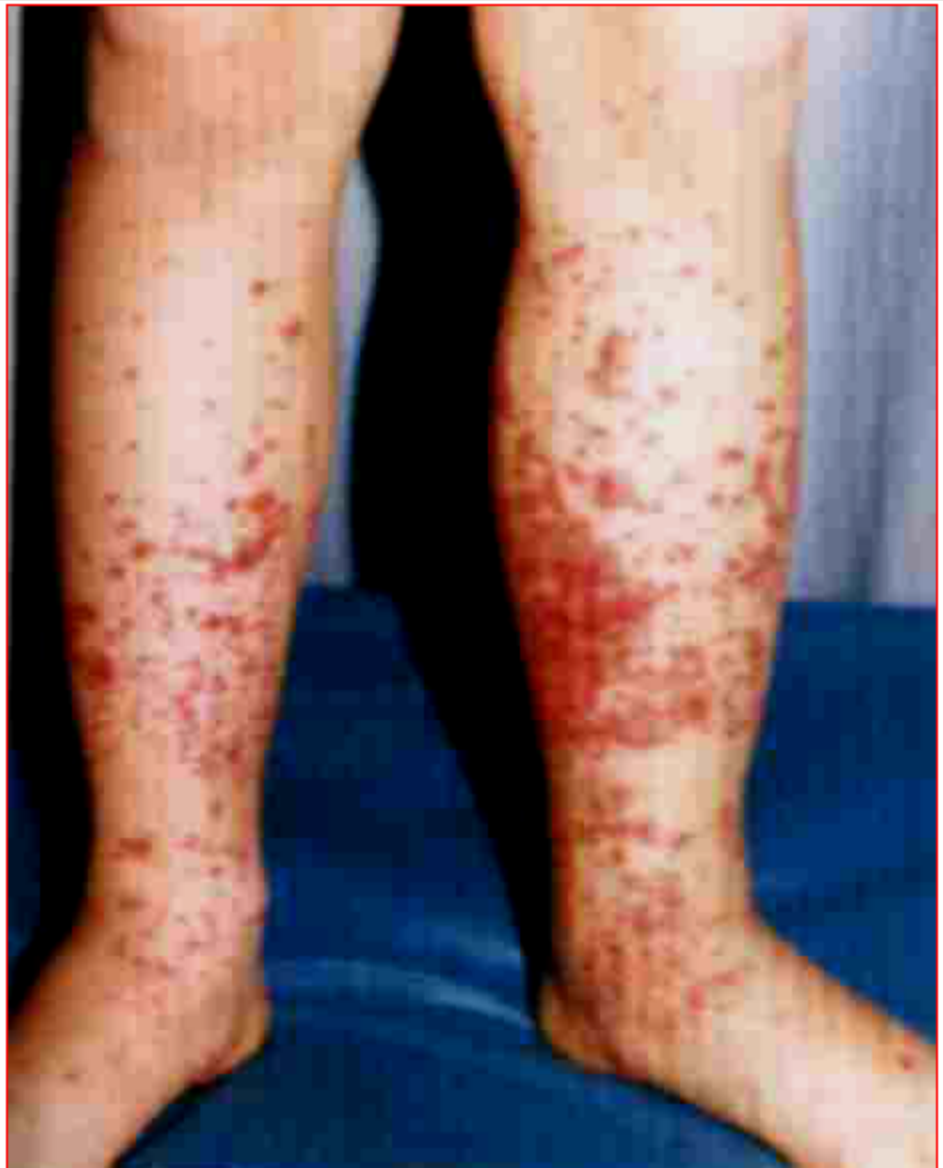
- The disease occurs most frequently in youth.
- Male>female
- Most occur in spring or autumn
- There is always URI 1~3weeks ago before break out
- Always break out acutely，symptoms including:
  - skin purpura
  - articular gall
  - symptom of gastrointestinal tract
  - symptom of kidney
  - other manifestation

Skin Purpura

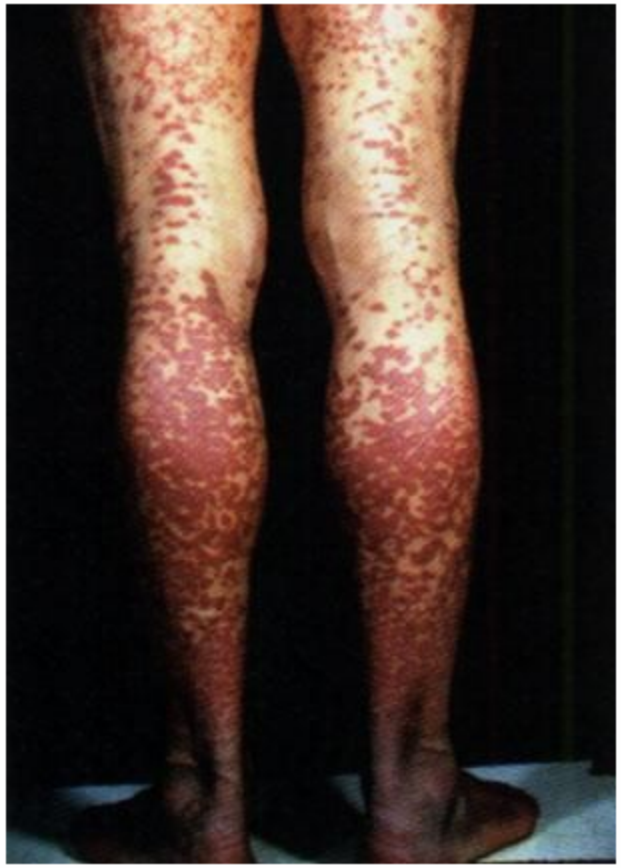
- Purpura occurs repeatedly
- most in the lower limbs and buttocks
- distributed symmetrically in groups
- can also be seen in the upper limbs and trunk in the severe case
- be of unequal size, purple, tower over the skin,
- can accompany with urticaria and erythema multiform angioedema
- a few of the reforming purpura can fuse into big vesication lead to hemorrhagic necrosis

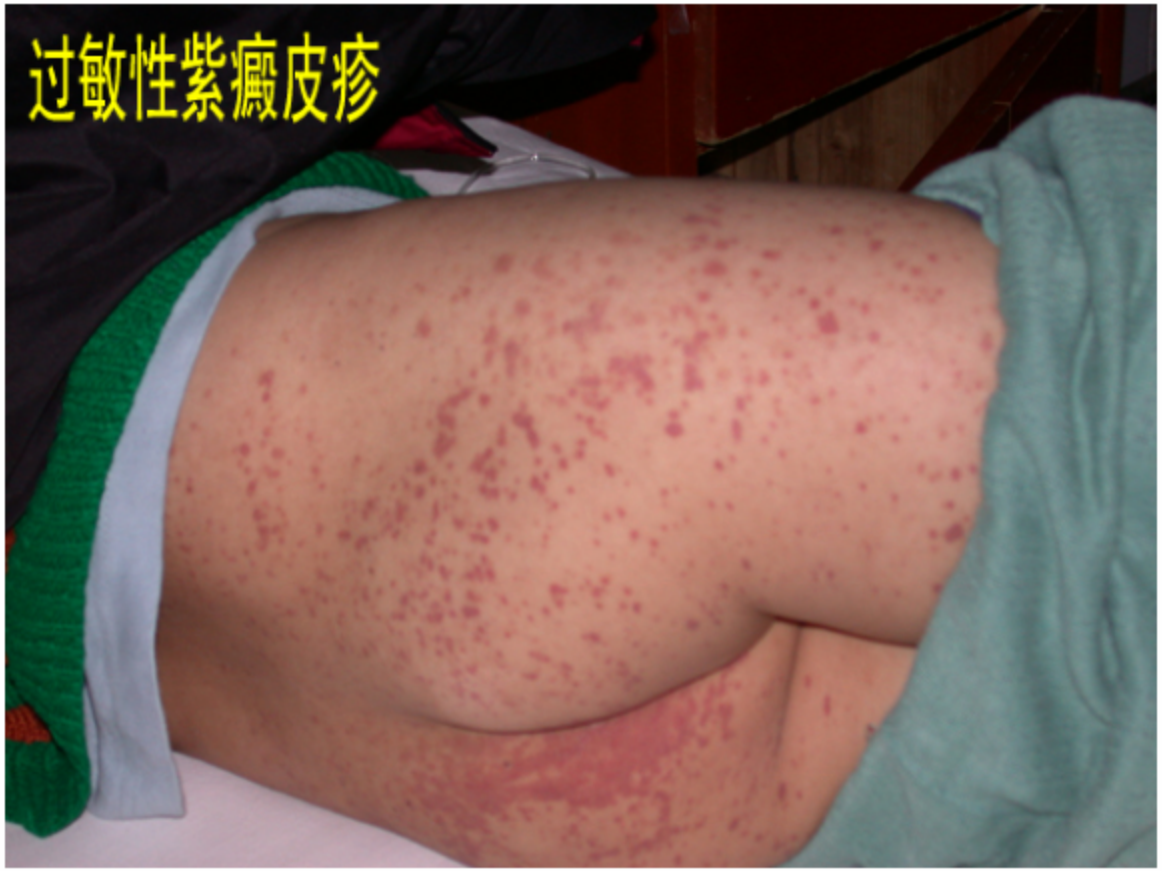
Pathoformic purpura



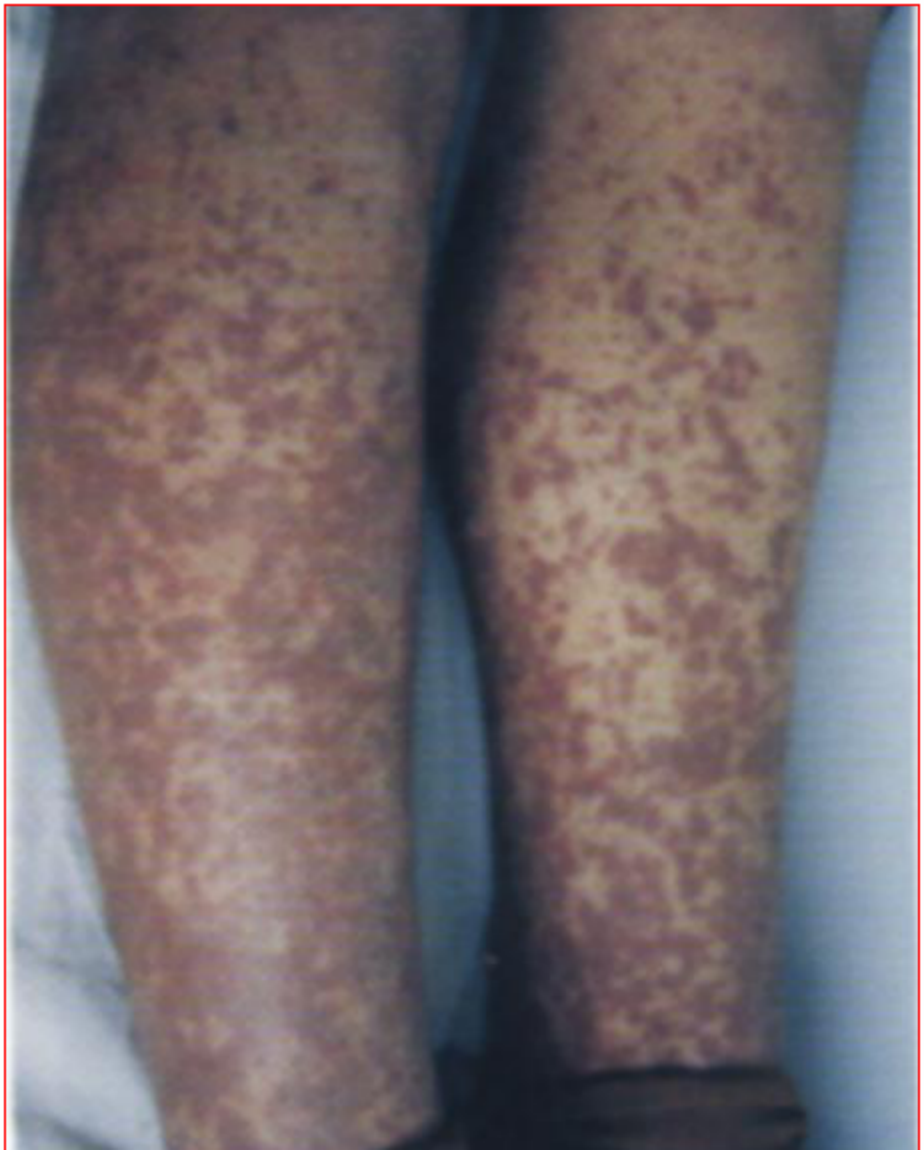


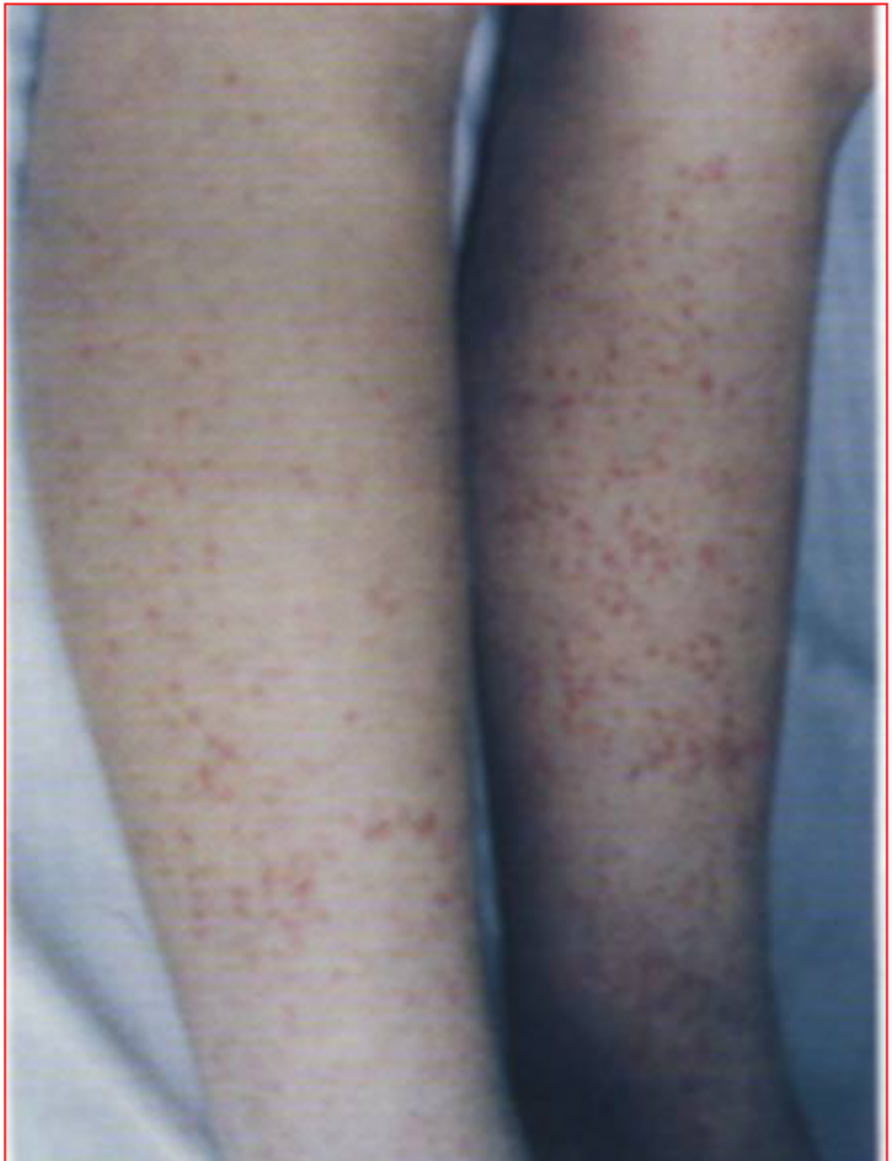
Purpura of severe case (extend to flexor aspect)





Stale purpura vs purpuric subsidence





Symptoms

Symptoms of arthrosis

- swollen or gall of arthrosis, often involve knee,ankle,elbow,etc
- It may occur in one or more arthrosis，can be wandering, without abnormality of arthrosis

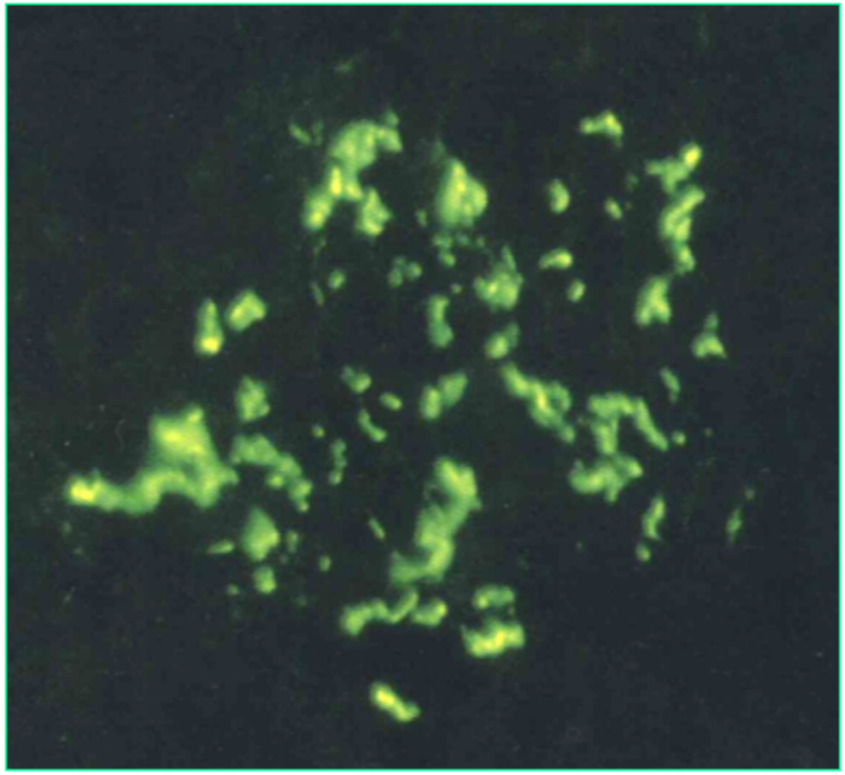
Symptoms of Gastrointestine Tract

- Paroxysmal abdominal pain, nauseating, vomiting and hemafecia can occur repeatedly,some will occur before the appearance of purpura
- Abdominal pain located on periumbilical region or hypogastric region because of the enhancement of enterokinesia or spasm
- Indigitation ,intestinal obstruction and intestinal perforation appear occasionally

Symptoms

Symptoms of kidney

- in 30%~50% of the sick children
- often occurs in 1st~8th week
- The symptoms can be slight or severe. Most have hematuria, albuminuria, or cylindruria; accompany with elevation of blood pressure and edema, called Purpuric nephritis
- Most have favorable prognosis, about 6% develop into chronic nephritis, few develop into acute renal failure, and at last die of uraemia



Immunofluorescence of purpuric nephritis: IgA in glomerulus deposit clumping-like in mesangium region

Symptoms

Other symptoms

- The pathogenic changes of central nervous system is the potential threat of this disease
- Sometimes happens encephalic hemorrhage, and inducing logomania, paralysis, coma, eclampsia, pantomime, anaesthetization

Clinical typing

- Pure type
- Joint type
- Abdominal type
- Renal type
- Mixed type

Laboratory examine

- Capillary fragility test: about half of the patients is positive
- Blood test: CBC is always normal, eosinophils can raise. Function of platelet, time of bleeding and blood coagulation, gore retraction test, marrow test are all normal. Blood IgA↑，IgE、IgG、IgM can keep normal or raise，blood sedimentation can speed up
- Urine test：hematuria and albuminuria in different level, cylindruria, urine FDP(+)
- feces occult blood(+)

Diagnosis

1. History of URI
2. Typical dermal purpura ± other symptoms
3. Platelet is normal + coagulation is normal
4. Exclude other diseases

Differential Diagnosis

1. ITP

	allergic purpura	*ITP*
Distribution of purpura	**symmetrical**	**Not always**
tower above the skin	**always**	**no**
Manifestation of joint	**possible**	**no**
platelet	**normal**	**decrease**

Differential diagnosis

- **acute abdomen :** Patients with a symptom of bellyache should be examined to confirm whether there is purpura on his leg, if not , then consider acute abdomen, enterospasm and other medical and surgical disease

- **rheumatoid arthritis:** Patients with a symptom of arthroncus should be examined to confirm whether there is purpura on his legs,if not,then consider other arthritis

- **Other nephritis：** Patients with a symptom of nephritis or nephrotic syndrome should be examined to confirm whether there is purpura on his legs , if not , then consider other pathological changes of kidney

Treatment

- **wipe off pathogeny**: to avoid allergen
- **Heteropathy:** nonspecific antianaphylactic treatment, stanch, deallergization, anticoagulation, decrease the penetrability and brittleness of capillary wall
- **glucocorticoid:** Have functions of antianaphylaxis and decreasing pentrability of vessel, which can ease arthralgia and symptom of gastrointestinal tract
- **immunosuppressor**

Course and Prognosis

- Slight case→recover in 7～10 days；
- General case→ recover in 1～6 weeks;
- Severe case→lasting several months;

- Some people who is recovered still suffers from repeated attack for several years.
- Prognosis of most patients are favorable
- prognosis of patients who suffer from renal failure and the prognosis of intracranial hemorrhage are unfavorable.

Case 1

- 患者男性，47岁，反复皮肤紫癜10余年，再发伴腹痛8天，呕血1天于2015-7-17入院。
- 1999年无明显诱因出现双上肢皮肤紫癜，伴阵发性腹痛，无腹泻、黑便、关节痛、血尿、泡沫尿等，诊断为“过敏性紫癜”，在当地医院予“激素”治疗3天，皮疹及腹痛好转。后多次因食用面粉后再次出现皮肤紫癜，当地医院予地塞米松5mg*2d治疗后皮疹消褪。
- 2015-7-9再次出现双上肢紫癜，伴轻微腹痛，解黄黑色稀便3次，量不多，排便后腹痛好转。
- 2015-7-11双上肢紫癜消褪，继而双下肢出现紫癜，再次出现轻微腹痛，解成形便2次。
- 2015-7-12出现腹痛加重，脐周为主，呈阵发性绞痛，解黄色水样便2次/天，大便后腹痛略缓解，伴有右踝关节肿痛。
- 于2015-7-13就诊于当地医院，诊断为“胃肠炎，过敏性紫癜”，予以头孢类抗生素，维生素C治疗，皮肤紫癜有所消褪，腹痛未缓解。

Case 1

- 2015-7-15凌晨患者出现全腹持续性绞痛，再次就诊于当地医院，予开瑞坦等治疗，效果差，于2015-7-16晨至我院消化门诊，诊断为急性胃肠炎，予以甲硝唑、环丙沙星、头孢呋辛、奥美拉唑、曲美布汀治疗。症状未缓解。
- 11：00至我院急诊科，予间苯三芬、头孢孟多、生长抑素、泮托拉唑治疗，腹痛好转，出现心悸、解少量稀便，带血丝。当日下午14：00少量呕血，并解红色水样便，120再次至我院急诊科。
- 粪便常规：隐血试验+，RBC满视野，WBC：20-30/HP。
- 血常规：WBC：30.46G/L,GRAN：25.95G/L,RBC ：5.79T/L,Hb：185g/L，PLT：290G/L。生化：K：2.85mmol/L，Glu:9.9mmol/L。
- 18：00再次呕吐，为红黑色液体，约1000ml。
- 血常规WBC：37.11G/L，GRAN：32.66G/L，Hb：193g/L，PLT：248G/L。凝血功能Fg：4.11g/L。
- 予生长抑素、解痉、止血、甲强龙等治疗，腹痛好转，未再呕血解黑便。

Case 1

- 18：00再次呕吐，为红黑色液体，约1000ml
- 血常规WBC：37.11G/L，GRAN：32.66G/L , MONO：3.19G/L, RBC：6.01T/L, Hb：193g/L，PLT：248G/L。
- 凝血功能Fg：4.11g/L
- 予生长抑素、解痉、止血、甲强龙等治疗，腹痛有所好转，未再呕血及解黑便。
- 2015-7-17拟“过敏性紫癜”收入我科。本次发病以来，3天未进食，精神差，体力尚可，体重无明显变化。

Case 1

- 2015-7-17拟“过敏性紫癜”收入我科。本次发病以来，3天未进食，精神差，体力尚可，体重无明显变化。
- 体格检查：体温：37.4℃，脉搏：94次/分，呼吸：20次/分，血压：135/75mmHg。被动体位，急性痛苦病容，双下肢散在紫癜，微突起于皮面，压之不褪色。全身浅表淋巴结未触及。口唇红润。双肺呼吸音清晰，双肺未闻及干、湿罗音及胸膜摩擦音。心率94次/分，心律齐，未闻及早搏，各瓣膜听诊区未闻及病理性杂音。腹部平坦，腹软，剑突下压痛，无反跳痛。肝、脾肋下未触及，肝颈回流征阴性，莫非氏征阴性。

诊断？治疗？

Case 1

- 予禁食、甲强龙60mg、解痉、抑酸、抑制消化液分泌、止血，营养支持等治疗。患者仍反复腹痛、解黑便及血便。7-21查胃镜：1、十二指肠降部糜烂及多发小溃疡；2、慢性非萎缩性性胃窦炎伴糜烂。改甲强龙为地塞米松10mg治疗，患者腹痛逐渐缓解。
- 8-3开始大便正常，无柏油样便。当日开始进全流饮食。
- 8-2查24小时尿蛋白：3120mg/24h，8-8复查24小时尿蛋白：5660mg/24h。

Chapter 3--id~~iopathic~~ic （immune）thrombocytopenia ~~Purpura~~(ITP)

Case 2

- 患者女性，68岁，因牙龈出血1周，头痛1天于2016-3-6入院。病程中无发热、咳嗽、咳痰，无腹痛、腹泻，但有黑便，质软成形。
- 入院查体：Bp：180/110mmHg，神志清楚，口腔、舌体可见多个血疱。颈软。心、肺、腹部查体未见异常。神经系统查体阴性。
- 血常规WBC：8.9G/L, HB：126g/L，PLT：2G/L
- 肝肾功能正常，自身抗体阴性
- 骨髓涂片：巨核细胞增多，伴成熟障碍，血小板少见

Outline

- The most common(5-10 /100,000) cause of thrombocytopenia
- An autoimmune bleeding disorder due to a variable combination of increase platelet destruction and impaired platelet production
- Acute and self-limiting but may be recurrent or chronic disorder
- Female ≈ Male
- Morbidity： women in childbearing>men;

  >60yrs = <60yrs*2

Pathogenesis-Ab

- **In 1951 Harrington** showed that the infusion of plasma from ITP patients into normal controls caused thrombocytopenia, thus imputing the cause of ITP to a plasma-derived factor
- This "factor" was identified as an IgG anti-platelet antibody, directed against platelet glyco- protein (GP) **IIb/IIIa and/or the GPIb-IX-V complex**. Very rarely, antibodies against GPIa-IIa or GPIV can be found (5%).
- Antibody-opsonized platelets are recognized through the Fcγ-R by macrophages in the **spleen, liver and bone marrow**, phagocytized and prematurely destroyed
- Antibodies can mediate platelet destruction are **complement** deposition with intravascular lysis and induction of platelet apoptosis

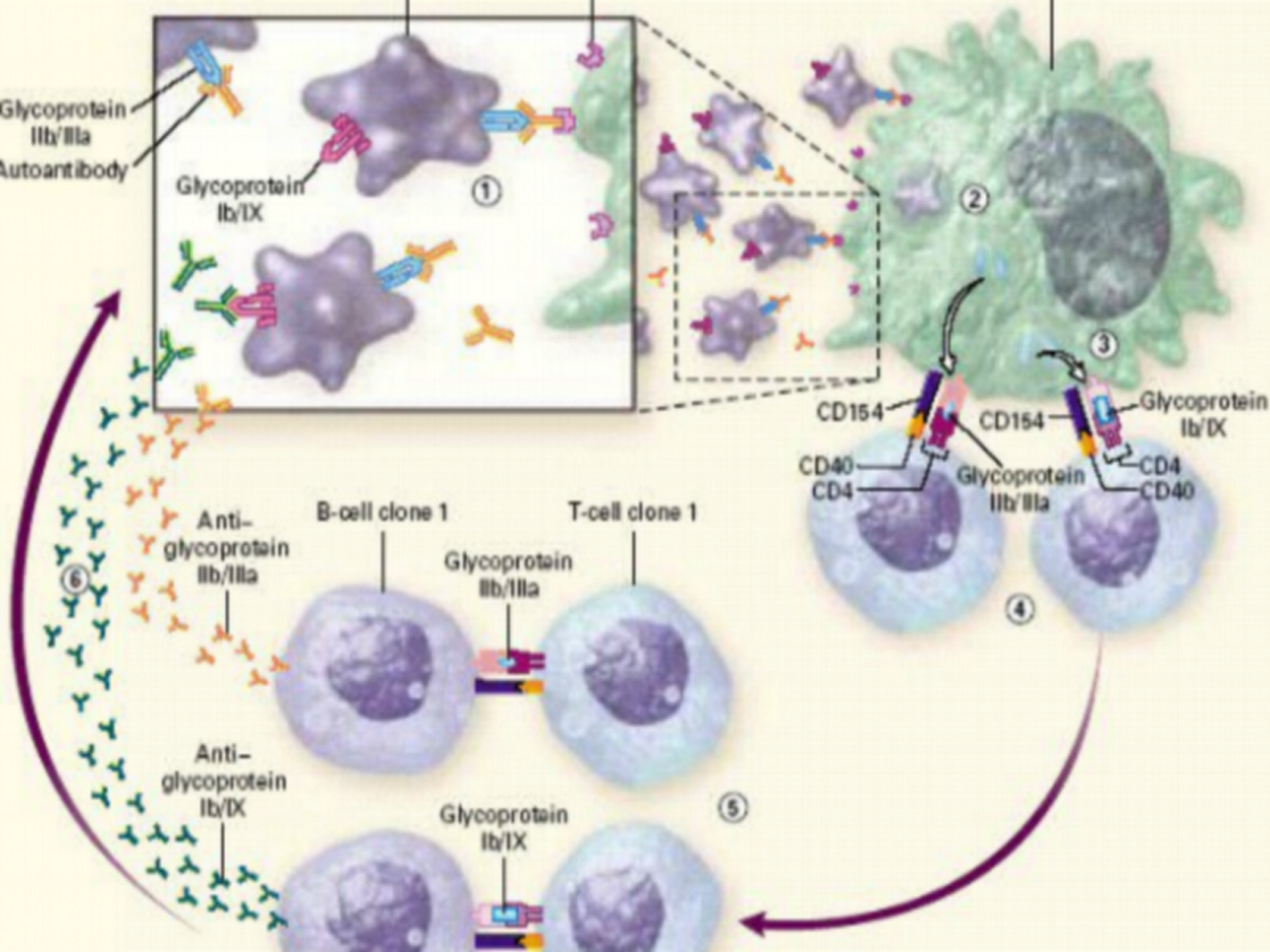
pathogenesis

viral infection

immune complexes on the platelet surface

destruction and removal by the reticuloendothelial system

cause thrombocytopenia


Glycoprotein IIb/IIIa
Autoantibody
Glycoprotein Ib/IX
1
2
3
CD154
CD40
CD4
Glycoprotein IIb/IIIa
CD154
Glycoprotein Ib/IX
CD4
CD40
B-cell clone 1
T-cell clone 1
Anti-glycoprotein IIb/IIIa
Glycoprotein IIb/IIIa
4
5
6
Anti-glycoprotein Ib/IX
Glycoprotein Ib/IX

Pathogenesis—T cell

- Plasma from patients with ITP also inhibits **megakaryocyte** growth and function in the BM.

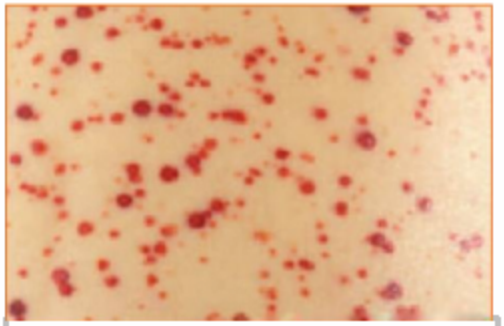
- An altered Th1/Th2 balance, with **an increased number of Th1 cells and a decrease in the number and function of Treg cells**.

- The abnormal activation of **cytotoxic CD8+ T cells** may also have a role in the pathogenesis of ITP, contributing to both platelet destruction and impaired platelet production

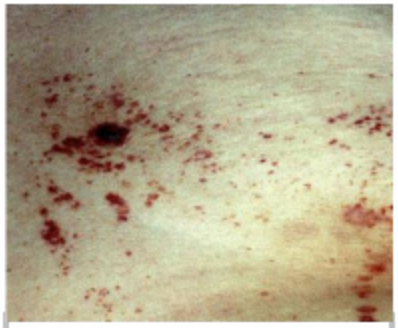
Clinical manifestations

- Develop insidiously
- Sudden onset of petechiae or purpura. Some may be accompanied by bleeding from mucosal surface, hemorrhagic bullae of gums and lips, nosebleeds(epistaxis)
- The most important potential complication is intracranial hemorrhage - rare (<1%)but serious
- Weak, fatigue
- Anemia

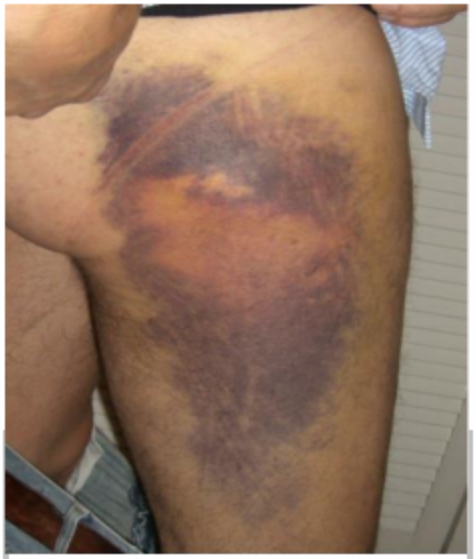
Clinical manifestation-hemorrhage



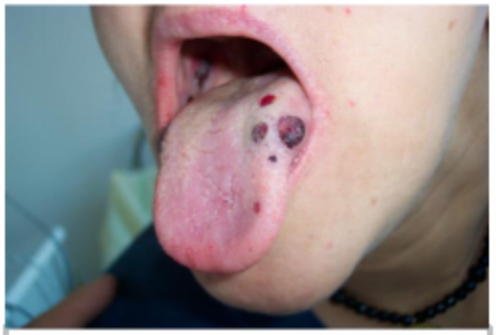
瘀点



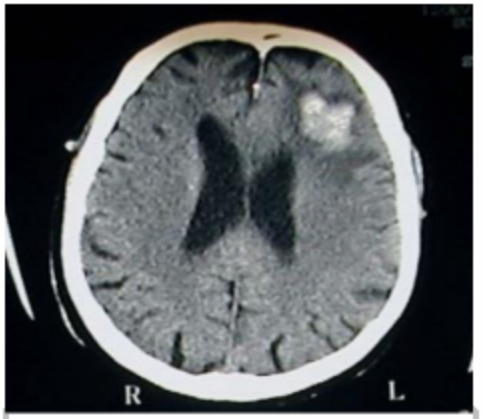
紫癜



广泛的瘀斑与
潜在的皮下血肿



口腔血疱



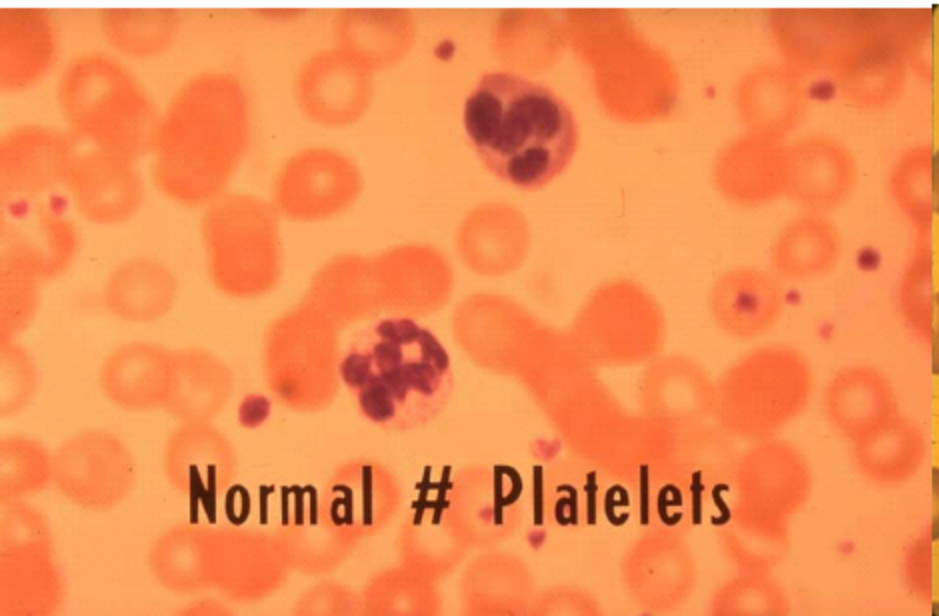
颅内出血

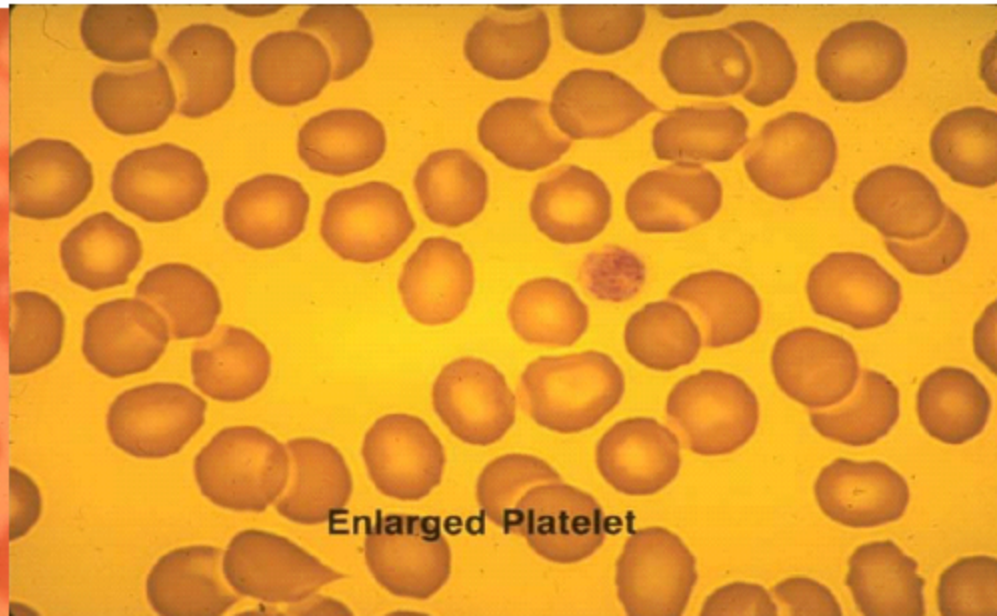
Clinical manifestations

- The liver and spleen may be palpable in a minority patients
- May be anemic if they were hemorrhagic severely
- Case fatality is approximately 0.5~1%, the principal factor is intracranial hemorrhage

Laboratory studies

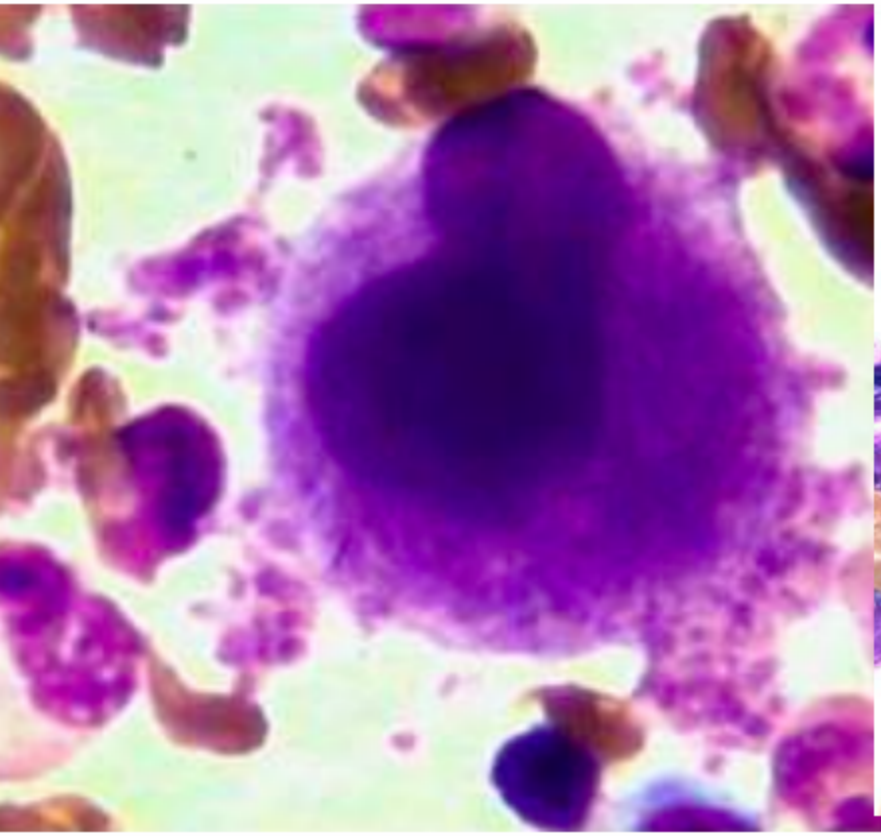
- PB smear: an isolated thrombocytopenia with no other abnormalities. platelet count $<100 \times 10^9$ /L, the few circulating platelet may be quite large (megathrombocytes)
- CBC：PLT↓,RBC,WBC
- PT and APTT are normal, bleeding time would be prolonged

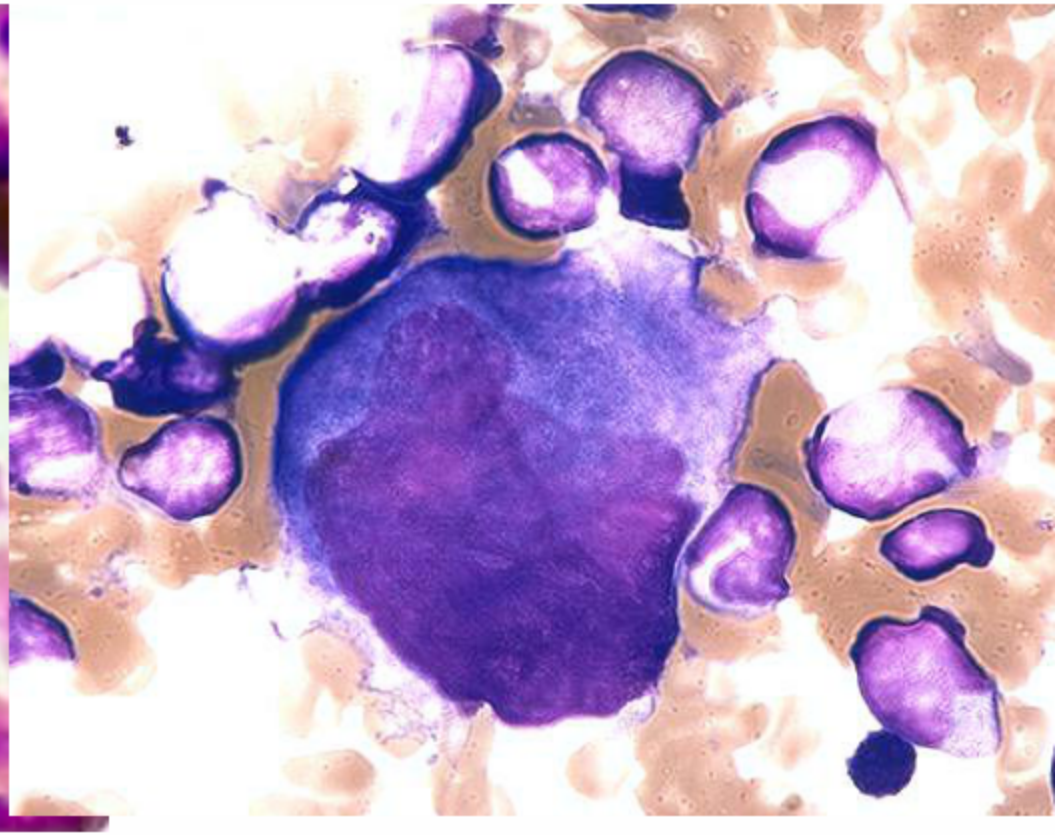




Laboratory studies

- Bone marrow: contains normal or increased numbers of megakaryocytes with dysmaturity





Laboratory studies

- Measuring antiplatelet antibodies
- Including the measurement of the amount of platelet-associated IgG(PAIgG) and direct assay of specific platelet antibodies
- However, these tests lack both specificity and sensitivity in acute ITP

Diagnosis

- Thrombocytopenia ≥twice
- physical examination: not splenomegaly commonly
- BM: megakaryocyte
- Exclude the secondary thrombocytopenia

由于ITP机制多样化， ITP具有诊断价值的检查几无进展

血清学检查特异性高，但敏感性低

ITP的诊断要点：ITP是临床排除性诊断

必须排除的其他继发性血小板减少症

- 自身免疫性疾病
- 甲状腺疾病
- 淋巴系统增殖性疾病
- 骨髓增生异常（AA和MDS）
- 恶性血液病
- 慢性肝病脾功能亢进
- 普通变异性免疫缺陷病（CVID）
- 感染等所致的继发性血小板减少
- 药物诱导的血小板减少
- 同种免疫性血小板减少
- 妊娠血小板减少
- 假性血小板减少
- 先天性血小板减少

"…the diagnosis can only be reached by the exclusion of all factors known to cause purpura…" **-Elliott, 1939**

"…little progress has been made towards making ITP anything other than a diagnosis of exclusion…" **-Provan et al, 2010**

"…the diagnosis of ITP is made by exclusion of secondary causes of thrombocytopenia…" **-Neunert et al, 2011**

中华医学会血液学分会止血与血栓学组. 中华血液学杂志, 2016, 37(2):89-93.

Differential Dignosis

- **Acute leukemia：** Acute leukemia patients with normal white blood cell counts may be to confuse, leukemic cell in blood smear or bone marrow can be to make a definite diagnosis
- **Aplastic anemia:** anaemic, hemorrhagic patients with normal liver and spleen are similar to ITP patients associated with anaemia. But anaemia in aplastic anemia patients are severity, white blood cell counts are decreased, megakaryocytes in bone marrow are also decreased
- **Allergic purpura:** hemorrhagic erythra , symmetric distribution,always in both lower extremities and haunch.platelet count is normal, it's easy to differentiate.

Types of diseases

- New ITP: <3 mons
- Lasted ITP: 3-12mons
- Chronic ITP(cITP): >12mons
- Severe ITP: PLT<10G/L,hemorrhagical syndrome, or new hemorrhage during routine treatment
- **Refratory ITP**: post-splenectomy

Refractory ITP

2009

- 国际ITP 工作组对于难治性ITP 的定义为：(1) 脾切除无效或术后复发；(2) 需要治疗以降低临床严重出血的风险；(3) 确诊为ITP

2011

- 2011 年美国血液学会制定的指南也采纳了国际ITP工作组的定义

2016

- 2016 年中国成人ITP专家共识再次强调必须是脾切除无效或术后复发的患者才能定义为难治性ITP

新声音

由于新型药物的问世，最近国外有学者建议对于难治性ITP 的定义要更加严格，提出只有那些接受脾切除、利妥昔单抗和TPO-RA治疗均无效的患者才能定义为难治性ITP。

新声音

也有学者从临床实际出发，提出可适当放宽，将那些不愿意接受脾切除术或者身体不能耐受手术者，维持治疗又无效的患者也可以纳入难治性ITP 的范畴。

杨仁池. 难治性原发免疫性血小板减少症定义及临床处理[J]. 中国实用内科杂志, 2017(02):13-15.

Treatment

1.General treatment

- Therapy is indicated if there is extensive cutaneous and particularly mucosal bleeding and a platelet count $< 20 \times 10^9/L$
- No treatment is usually indicated for patients with platelet counts $> 30 \times 10^9/L$

2.Intravenous immunoglobulin (IVIG)

Mechanisms:

- Blocking Fc receptor of the RE (reticulo-endothelium) phagocytes
- Preventing antibody from binding and destroying platelets.

Treatment

3.Corticosteroids

- Reducing capillary fragility
- Improve platelets release
- Have a rapid, dose-dependent action that reduce RE destruction of antibody-coated platelets
- Also more slowly reduces antibody production.

4. Splenectomy

- Beneficial in children with chronic, symptomatic ITP.
- About 70% of patient with chronic ITP achieve a complete remission following splenectomy, and most of the other show some improvement in platelet counts.
- Disadvantage: surgical mobidity and risk of postsplenectomy sepsis

Treatment

5.other treatment

- Anti-CD20 antibody
- TPO,TPO-RA
- Immunosupperessive drugs including vincristine(VCR) , azathioprine, and (CTX), CsA
- Absorption Ab removal have been used with limited success in refractory cases.

6. Life-Threatening Hemorrhage

- IVIG--May be given concomitantly
- High dose corticosteroid
- Multimodality Therapy--Is frequently necessary
- Emergent Splenectomy--Sometimes necessary
- Plasmapheresis--May also be beneficial
- Platelet infusions:<20 x 10^9 /L

ITP的诊疗流程

病史、查体、血常规、血涂片、B超、风湿系列、抗磷脂抗体、HIV/HCV、抗甲状腺抗体、骨髓象等

ITP

PLT ≥ 30 x 10⁹/L 无出血 → 观察

PLT < 10 x 10⁹/L 严重出血 → 紧急治疗

一线治疗：糖皮质激素或IVIg

PLT ≥ 30 x 10⁹/L且无出血 → 观察

PLT ≤ 30 x 10⁹/L，有出血 → 二线治疗

二线治疗
1. 促血小板生成药物（TPO-RA、rhTPO等）
2. 抗CD20单克隆抗体
3. 脾切除

PLT ≥ 30 x 10⁹/L且无出血 → 观察

PLT <30 x 10⁹/L，有出血 → 其他二线治疗

其他二线治疗
硫唑嘌呤、环孢素A、达那唑、长春碱类

PLT ≥ 30 x 10⁹/L且无出血 → 观察

PLT < 30 x 10⁹/L，有出血 → 临床试验

IVIg：静脉丙种球蛋白；rhTPO：重组人血小板生成素

成人原发免疫性血小板减少症诊断与治疗中国专家共识(2016年版)[J]. 中华血液学杂志, 2016, 37(2):89-93.

Case 2

- 患者女性，68岁，因牙龈出血1周，头痛1天于2016-3-6入院。病程中无发热、咳嗽、咳痰，无腹痛、腹泻，但有黑便，质软成形。
- 入院查体：Bp：180/110mmHg，神志清楚，口腔、舌体可见多个血疱。颈软。心、肺、腹部查体未见异常。神经系统查体阴性。
- 血常规WBC：8.9G/L, HB：126g/L，PLT：2G/L
- 肝肾功能正常，自身抗体阴性
- 骨髓涂片：巨核细胞增多，伴成熟障碍，血小板少见

诊断？治疗？

Case 2

- 甲强龙80mg/d，IVIG20g/d，TPO，PLT
- CsA
- Rituximab100mg / w＋维A酸

- 三周后血小板升至90G/L

Case 3

- 患者男性，65岁，因反复牙龈出血2月于2016-3-10入院。病程中无发热、咳嗽、咳痰，无腹痛、腹泻，但有黑便，质软成形。外院曾应用地塞米松、甲强龙、IVIG治疗。
- 入院查体：生命体征正常，神志清楚，口腔、舌体可见多个血疱。颈软。心、肺、腹部查体未见异常。神经系统查体阴性。
- 血常规WBC：8.9G/L, HB：126g/L，PLT：3G/L
- 肝肾功能正常，自身抗体阴性
- 骨髓涂片：巨核细胞增多，伴成熟障碍，血小板少见

Case 3

- TPO、PLT、CsA
- Rituximab+维A酸

- 三周后血小板9G/L

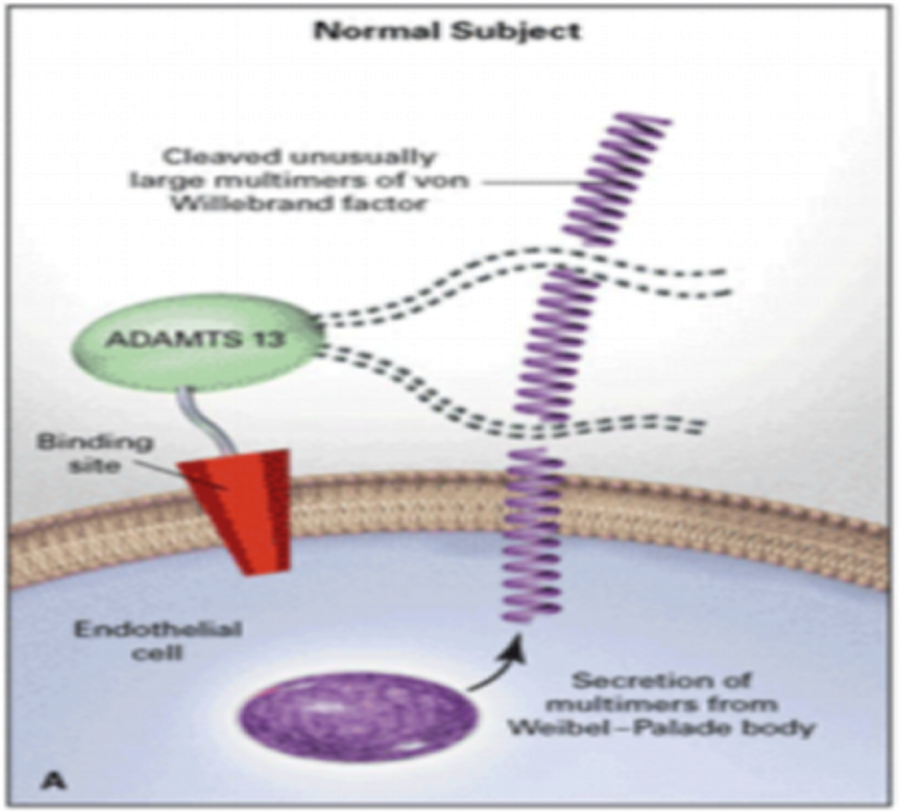
Chapter 4-- thrombotic thrombocytopenic purpura (TTP)

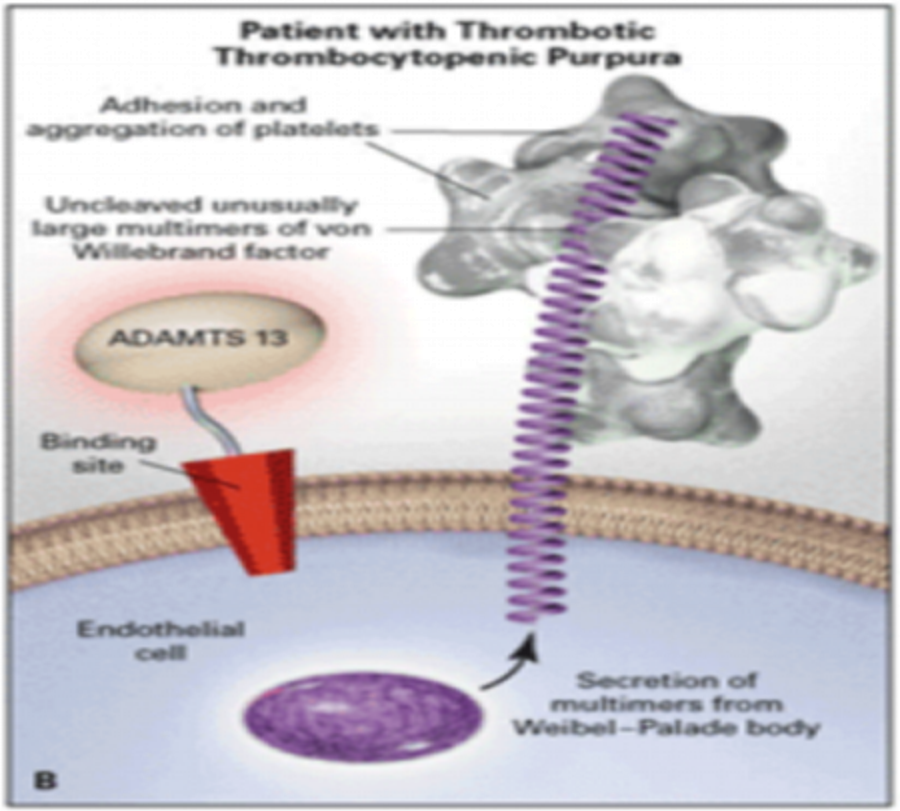
CASE 4

- 患者女性，39岁，因皮肤巩膜黄染3天，意识障碍3小时于2007-11-9入院；
- 患者于2007年6月因上感自服安乃近后出现口周发紫、肿胀、溃烂。
- 入院前4天出现头晕、乏力、纳差、咳嗽，自服安乃近，逐渐出现皮肤巩膜黄染、腰痛、牙龈出血、尿色加深。
- 当地医院血常规WBC:8.6G/L，Hb:52g/L，PLT:15G/L；肝肾功能正常，Tbil:133.8μmol/L，Dbil：23.6μmol/L，Ibil：110.2μmol/L，LDH:1548IU/L。
- 查体：生命体征平稳，神志模糊，疼痛刺激时烦躁，呼之不应。全身皮肤黄染，可见散在出血点，双上肢肌力减弱，四肢肌腱反射减弱，双侧巴彬斯基征阳性。
- 入院后患者出现反复全身抽搐、高热，小便呈酱油色。
- 头颅CT未见异常

What is TTP?

- First described by Moschcowitz in 1924
- A microvascular occlusive disorder characterized by systemic or intrarenal aggregation of plateletes, thrombocytopenia and mechanical injury to erythrocytes
- In TTP, systemic microvascular aggregation of platelets causes ischemia in the brain and other organs.





1. In normal subjects, ADAMTS13 molecules attach to binding sites on endothelial-cell surfaces and cleaves unusually large multimers of vWF as they are secreted by endothelial cells.
2. The smaller vWF forms that circulate do not induce the adhesion and aggregation Of platelets during normal blood flow.
3. Absent or severely reduced activity of ADAMTS13 in pts. with TTP prevents timely cleavage of UL-vWF resulting in the adhesion and aggregation of platelets.
4. A congenital deficiency of ADAMS13 activity or an acquired defect of ADAMS13 due to autoantibodies or by a change in the production or survival of the protein leads to TTP.

Clinical picture

Pentad of signs

1. Thrombocytopenia
2. Microangiopathic hemolytic anemia
3. Neurologic abnormalities
4. Renal Failure
5. Fever

In actual practice suspect if triad of:

1. Thrombocytopenia
2. Fragmentation of red
3. Increased LDH

Diagnosis

- Peripheral smear:

  reveals microangiopathic hemolytic anemia serum lactate dehydrogenase (LDH) level is typically extremely high.

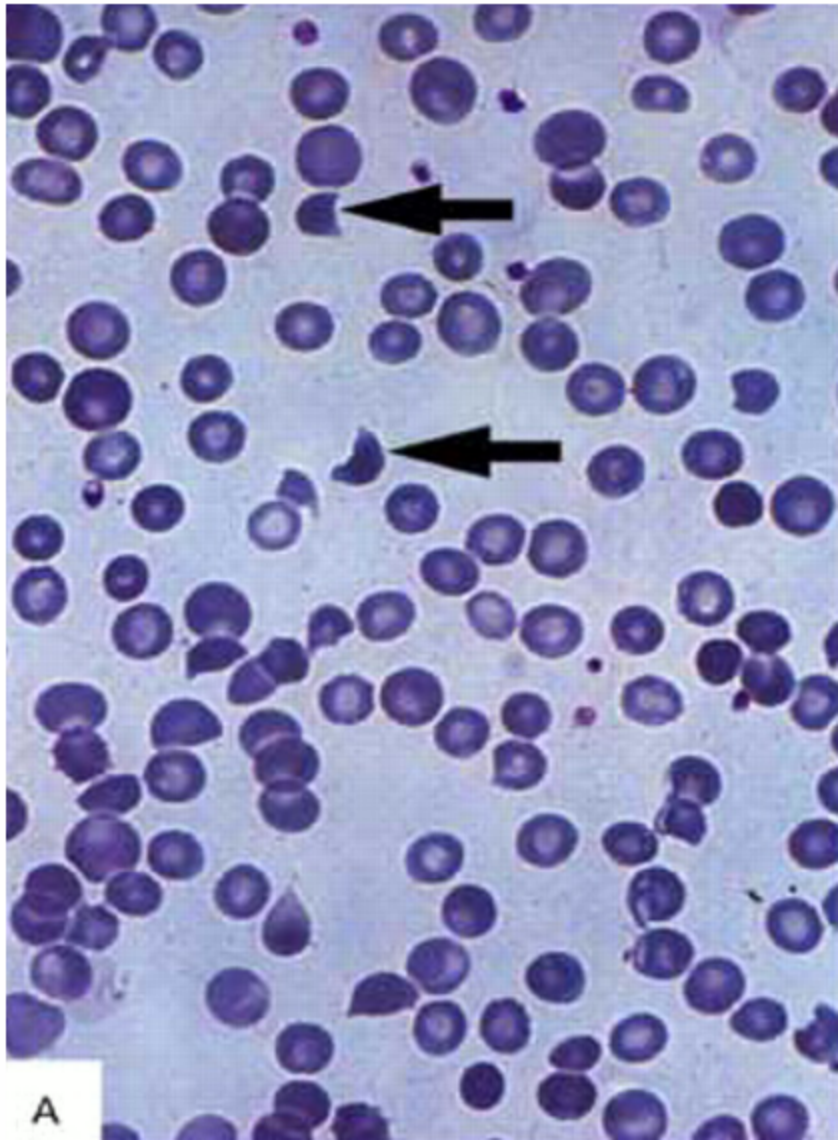
- CBC

  Thrombocytopenia, which maybe severe.

- Renal Disease

  glomerulonephritis or vasculitis may be suspected in some cases, since red cells and rarely red cell casts may be seen and hypocomplementemia occurs in approximately one-half of patients.

- ADAMTS13 level less than 5% of the normal.



Plasmapheresis

- Reverses the platelet consumption that is responsible for the thrombus formation and symptoms that are characteristic of TTP.

- A deficiency of or an autoantibody directed against a specific von Willebrand factor-cleaving protease (ADAMTS-13) is responsible for some cases of TTP-HUS, leading to the accumulation of unusually large von Willebrand factor multimers and platelet aggregation.

- In such patients, plasma infusion presumably supplies the missing enzyme, while plasma exchange can remove the acquired autoantibody and the very high molecular weight von Willebrand factor (VWF) multimers.

Corticosteroids, IVIG, VCR, CsA, CTX, rituximab

CASE 4

- 患者女性，39岁，因皮肤巩膜黄染3天，意识障碍3小时于2007-11-9入院；
- 患者于2007年6月因上感自服安乃近后出现口周发紫、肿胀、溃烂。
- 入院前4天出现头晕、乏力、纳差、咳嗽，自服安乃近，逐渐出现皮肤巩膜黄染、腰痛、牙龈出血、尿色加深。
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- 查体：生命体征平稳，神志模糊，疼痛刺激时烦躁，呼之不应。全身皮肤黄染，可见散在出血点，双上肢肌力减弱，四肢肌腱反射减弱，双侧巴彬斯基征阳性。
- 入院后患者出现反复全身抽搐、高热，小便呈酱油色。
- 头颅CT未见异常

Chapter 5-- Hemophilia

Outline

- Hereditary bleeding disorder
- Lack of particular clotting factors
- bleeding from injury
- Including:

  Hemophilia A - FVIII deficiency

  Hemophilia B – FIX deficiency

  Factor XI deficiency

- Hemophilia A is most common, about 80%
- Hemophilia A occurs in about 1 in every 5,000-10,000 male births
- Hemophilia B accounts for 15%
- Factor XI deficiency is very rare

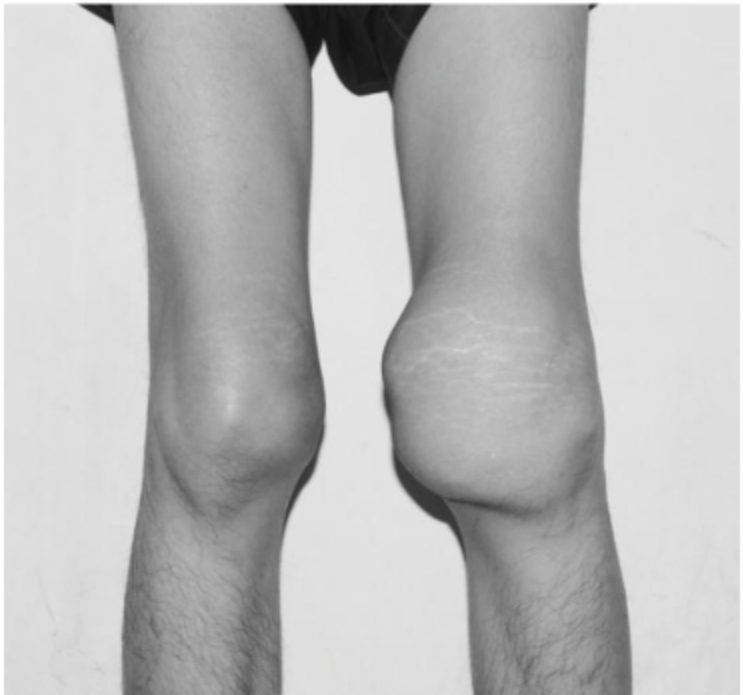
- Hemophilia is a genetic disease
- Hemophilia A/B is passed on by the X chromosome, so females are carriers.It only affects males
- Gene of factor XI is on common chromosome, so females and males both can be affected.

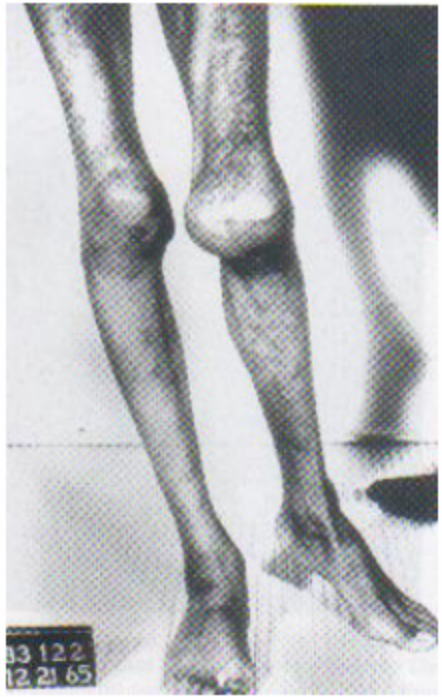
Signs and symptoms

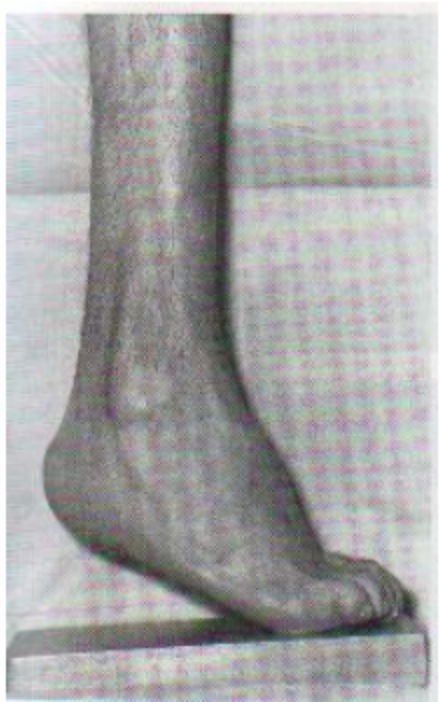
- The major signs and symptoms are excessive bleeding and easy bruising
- Signs of excessive external bleeding:
  - Bleeding in the mouth(cut, bite, losing a tooth)
  - Nosebleeds for no reason
  - Heavy bleeding from minor cut
  - Bleeding from a cut that resumes after stopping for a short time

Hemophilic Arthropathy

- As blood is catabolized, it is absorbed by synovium
- Iron is toxic to cells – synovial cells disintegrate releasing lysosomes which destroy cartilage and inflame synovium
- Hypertrophic, hypervascular synovium
- Chondrocytes also affected
- FIBROSIS







Diagnosis

- Atypical bleeding at circumcision or bruising at neonatal vaccines
- Toddlers with lip bleeding or unusual bruising when learning to walk
- Affected males on mother's side
- Elevated APTT
- Factor assays

Factor Replacement

- For routine muscle or joint bleed give 25 U/kg to maintain levels >1% for 48 hours
- Preoperatively:
  - Screen for inhibitors
  - Elevate F VIII levels to >100% 1 hr preop
  - Maintain at 60%
  - If vigorous PT required, transfuse to 50% pretreatment

Thank You !