What does a diagnosis of Myeloma mean in 2015

Dr Aristeidis Chaidos

Consultant Haematologist

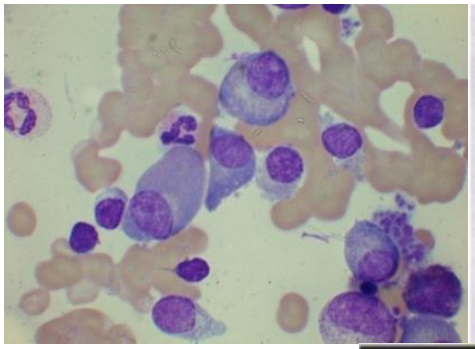
Hammersmith Hospital

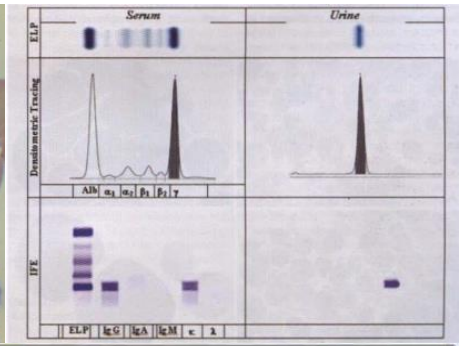
Learning objectives

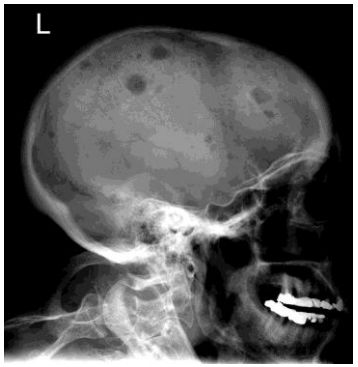
- define myeloma and related disorders
- diagnosis & disease monitoring
- “many myelomas”: staging & prognostic systems
- the evolving landscape in myeloma treatment
- principles of management with emphasis to care in the community
- future challenges and novel therapies

Myeloma – overview

- malignancy of the plasma cells (PC): the terminally differentiated, antibody producing B cells
- myeloma cells infiltrate the bone marrow
- IgG or IgA paraprotein (PP) and/or free light chains in blood and urine
- bone destruction
- kidney damage
- anaemia
- despite great advances in the last 15 years myeloma remains an incurable disease



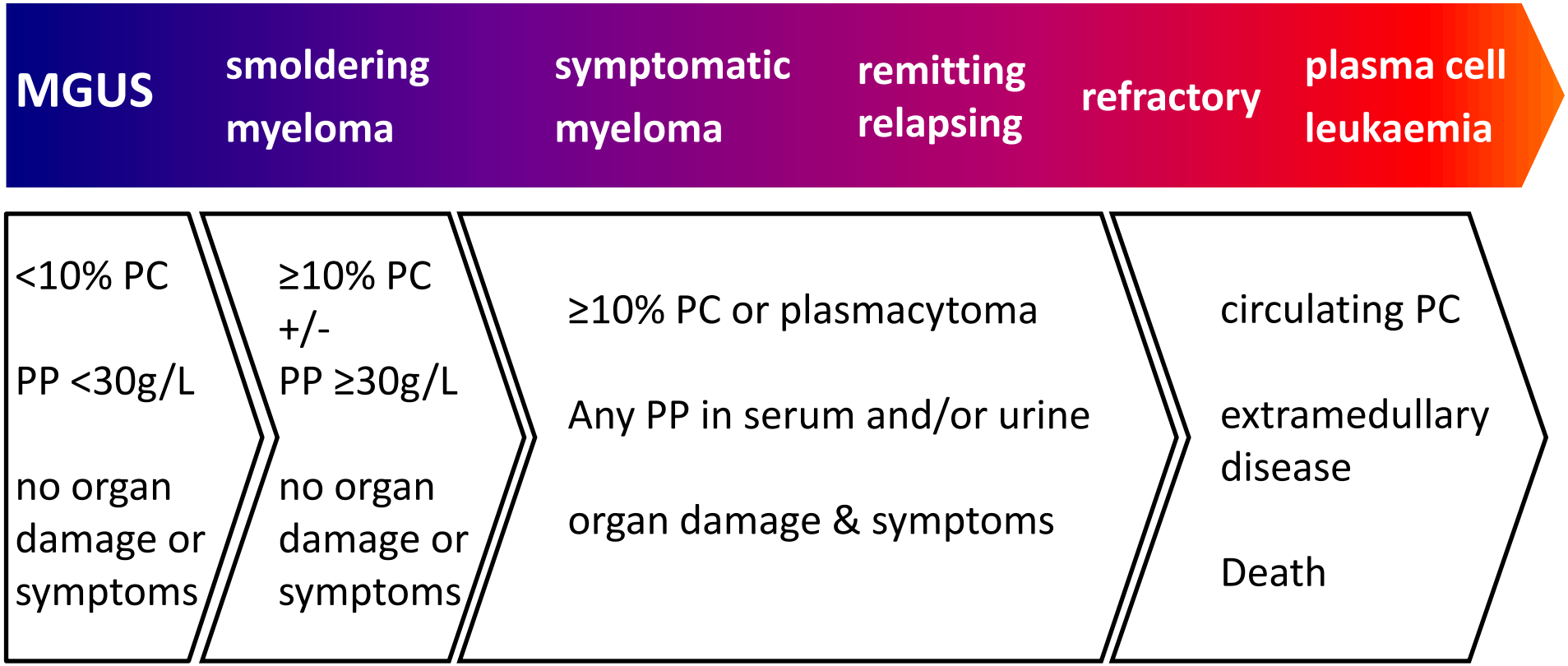




Myeloma in figures

- 1% of all cancers – 13% of blood cancers
- median age at diagnosis: 67 years
- only 1% of patients <40 years
- 4 – 5 new cases per 100,000 population annually, but different among ethnic groups
- 4,800 new myeloma patients in the UK each year
- the prevalence of myeloma in the community increases with outcome improvements and aging population

Myeloma related conditions



MGUS

monoclonal gammopathy of unknown significance

- The most common pre-malignant condition: 3% of individuals aged >50 yrs

- Average risk of progression 1% per year

- IgG and IgA MGUS → myeloma
- IgM MGUS → lymphoma
- Light chain MGUS → risk of kidney damage

- Overall survival MGUS vs general population: 8 *vs* 11 years

MGUS: prognostic systems & management

Number of risk factors	Rajkumar *et al.* (n=1148)[17] -Serum M-protein≥15 g/L -non-IgG subtype -Abnormal FLC ratio Risk of progression at 20 years	% of total	Perez-Persona *et al.* (n=276)[13] -≥95% aberrant bone marrow plasma cells -DNA aneuploidy Risk of progression at 5 years	% of total	Perez-Persona *et al.* (n=311)[30] -≥95% aberrant bone marrow plasma cells -Evolving MGUS* Risk of progression at 7 years	% of total
0	5%	39%	2%	46%	2%	49%
1	21%	37%	10%	48%	16%	45%
2	37%	20%	46%	6%	72%	6%
3	58%	5%	-	-	-	-

**Evolving MGUS is defined as an increase of M-protein of at least 10% by the third year, confirmed by two consecutive measurements separated by at least one month.*

- **Low-risk MGUS**: protein electrophoresis and serum free light chains (FLC) every 2-3 years or on myeloma-related symptoms

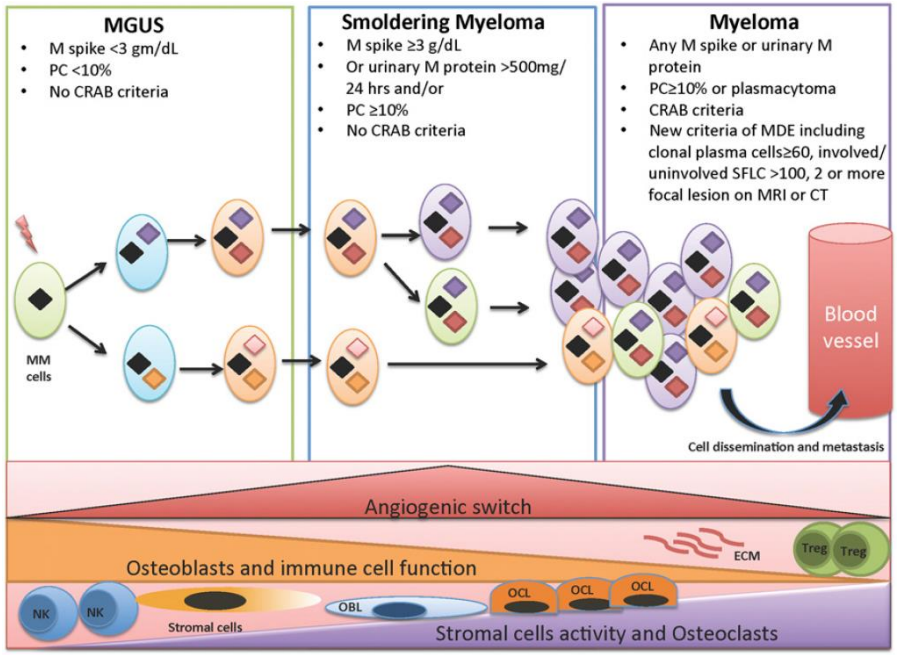
- **Intermediate & high-risk MGUS:** review every 6 -12 months

Smoldering myeloma

- Heterogeneous group

- Mayo Clinic Risk Stratification:
  - BM PC ≥10%
  - PP ≥30g/L
  - FLC ratio <0.125 or >8

- Low, intermediate risk: observation
- High risk (3 factors): ?treatment



Symptomatic myeloma

- BM plasma cells >10% or plasmacytoma
- Organ damage: CRAB or
- Myeloma defining event
  - BM PC ≥60% or
  - FLC ratio >100 / <0.01 or
  - 2 focal lesion in CT (PET) or MRI

Panel: CRAB criteria for active multiple myeloma

C: hyercalcaemia
Calcium concentration >0·25 mmol/L (>0·5 mg/dL) above normal range or >2·75 mmol/L (>10·5 mg/dL)

R: renal insufficiency
Creatinine concentration >173 mmol/L (>2 mg/dL)

A: anaemia
Haemoglobin concentration 20 g/L below normal range or <100 g/L

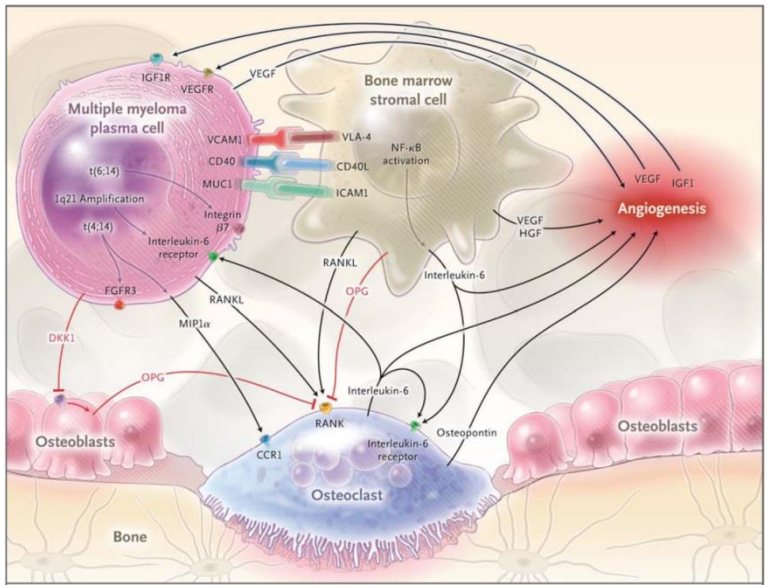
B: bone lesions
Lytic bone lesions of osteoporosis with compression fractures

Other features
Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 per year)

Raab et al, The Lancet 2009

Clinical presentation

- Asymptomatic
- Anaemia
  - >70% of patients at presentation, normocytic
- Bone disease (80%)
  - Bone pain, lytic lesions, osteopenia, fractures, hypercalcaemia
- Renal impairment (20 - 40%)
  - Ig / light chain deposits
- Infections
  - Bacterial & viral



Palumbo & Anderson, NEJM 2011

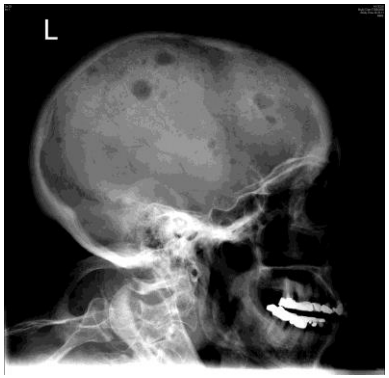
Clinical presentation

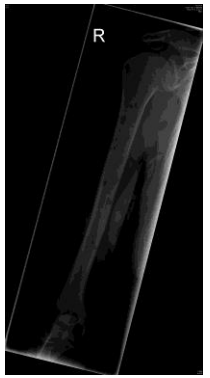
- Myeloma screening
  - FBC: Hb↓, WBC →, PLT→
  - ESR: ↑
  - Renal function
  - LFT normal, Alkaline phosphatase
  - Calcium ↑
  - Serum globulins ↑ & albumin ↓
- Serum protein electrophoresis & immunofixation
  - Paraprotein (IgG or IgA)
  - low normal Ig (immunoparesis)
- Serum free light chains
  - high level of kappa or lambda
  - abnormal ratio
- Bence-Jones protein

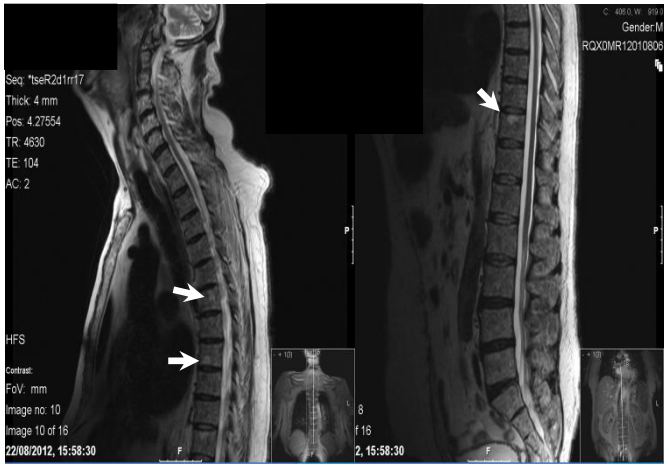
Bone disease

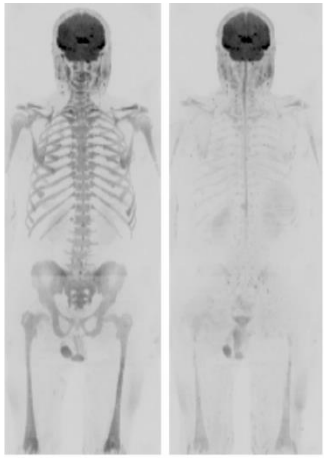
Imaging in myeloma

- Plain XR films
- CT scan including low-dose
- MRI
- PET CT
- Whole-body diffusion-weighted MRI





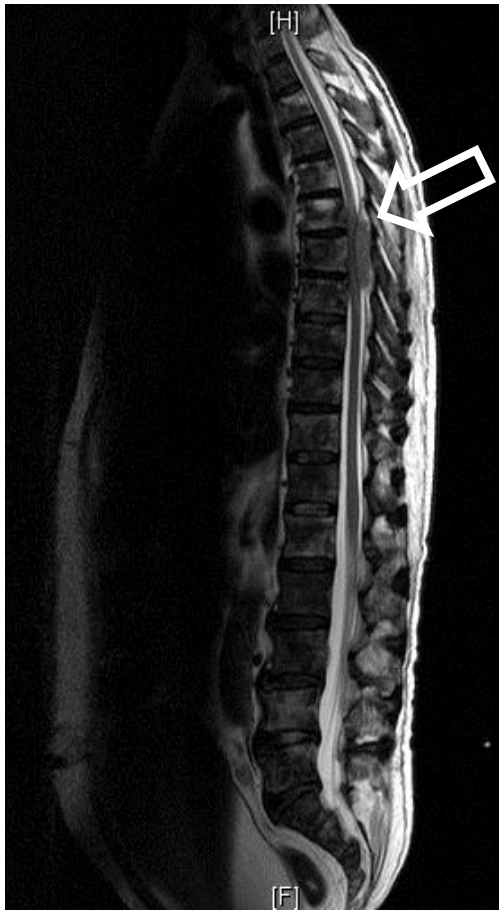




Emergencies in Myeloma

Cord compression

- Diagnosis & treatment within 24hrs
- MRI scan
- Dexamethasone 8mg iv + PPI
- Radiotherapy
- +/- biopsy
- Neurosurgery
- Stabilise unstable spine
- MDT management



Hypercalcaemia

- Fluids, steroids, zolendronic acid

Hyperviscosity

- plasmapheresis

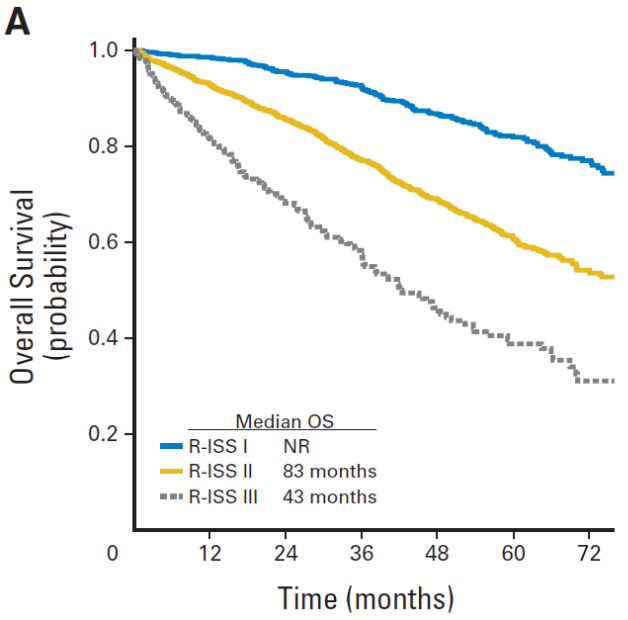
Prognosis & staging

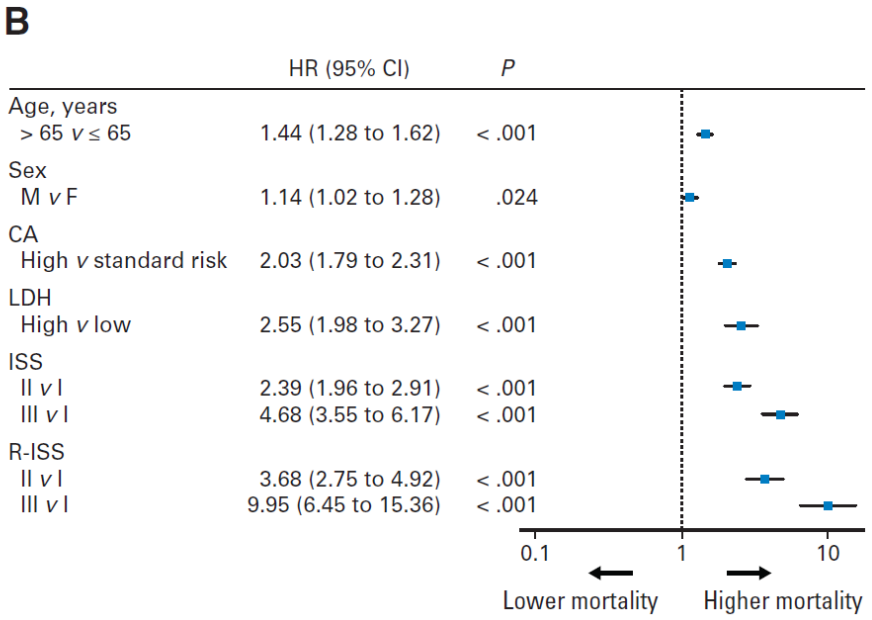
International Staging system

ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L

Revised International Staging system

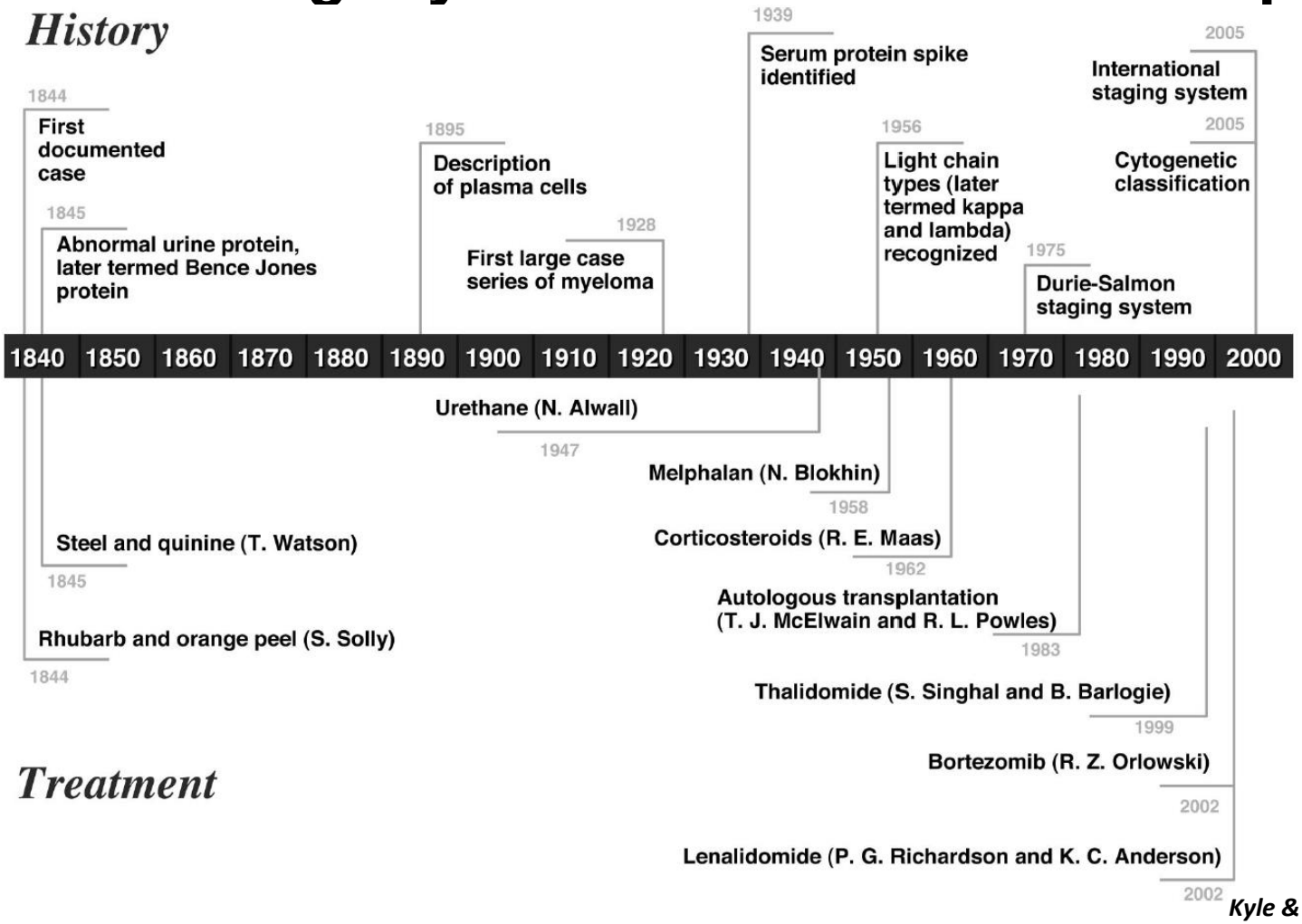
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH





Palumbo et al, JCO, August 2015

The evolving myeloma treatment landscape



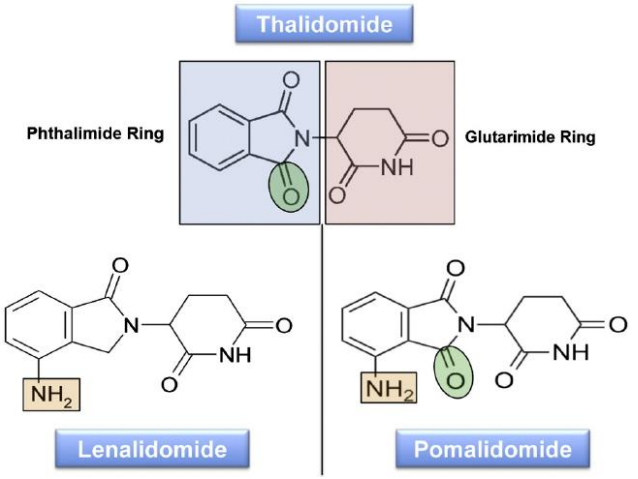
Kyle & Rajkumar, Blood 2008

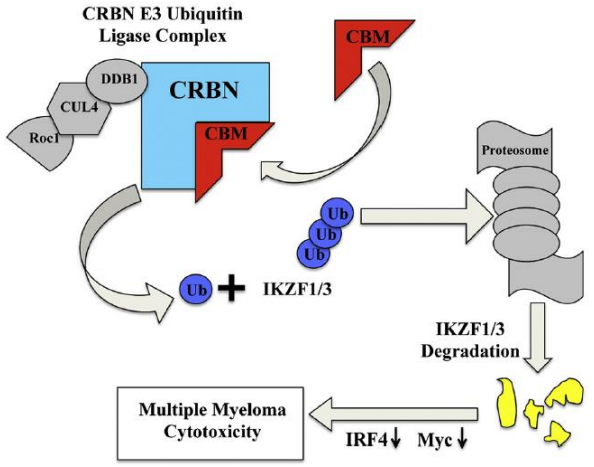
Novel agents

Cereblon binding molecules
(immunomodulatory drugs, IMiDS)

- Thalidomide
  - Approved for first line or relapse
  - neuropathy, drowsiness, constipation, thromboembolism, teratogenicity

- Lenalidomide & Pomalidomide
  - Approved for relapse
  - Neutropenia, thrombocytopenia, thromboembolism, teratogenicity



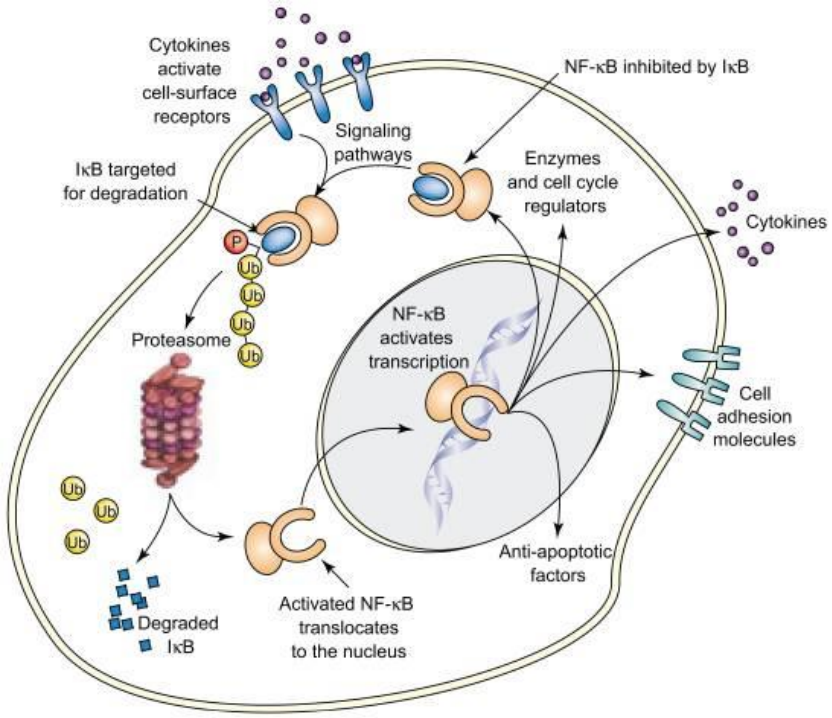


Kortum et al. Blood Reviews2014;99:232-242

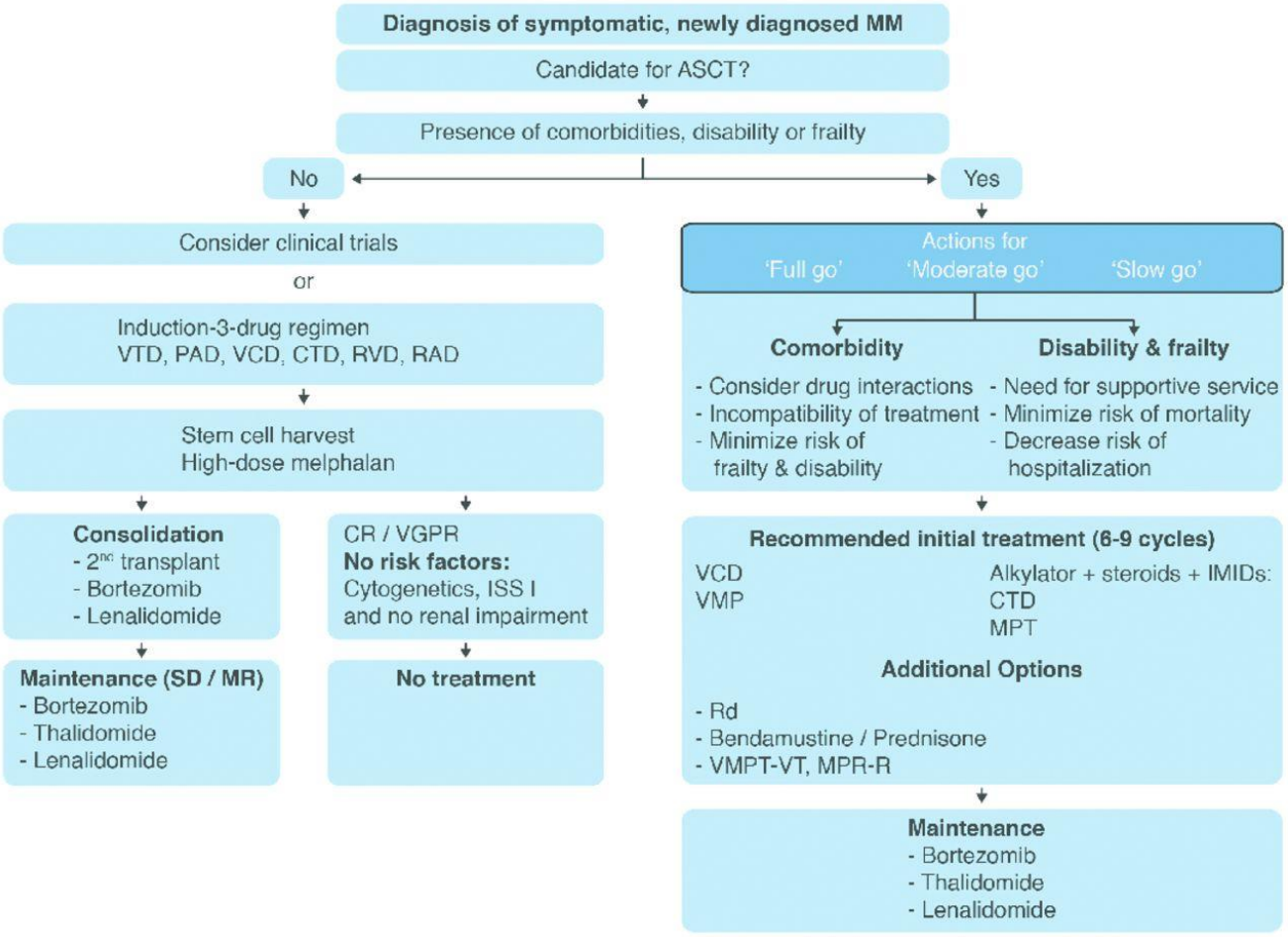
Novel agents

Proteasome inhibitors

- Bortezomib
  - Approved for first line or relapse
  - neuropathy, thrombocytopenia, infections (shingles), GI symptoms, rash
- Carfilzomib
  - Available in clinical trials only
  - thrombocytopenia, diarrhoea, respiratory symptoms, fever
- Ixazomib
  - Available in clinical trials only
  - Rash, liver, thrombocytopenia, neuropathy



Current treatment approach



Engelhardt M et al. Haematologica 2014;99:232-242

Supportive care – managing complications

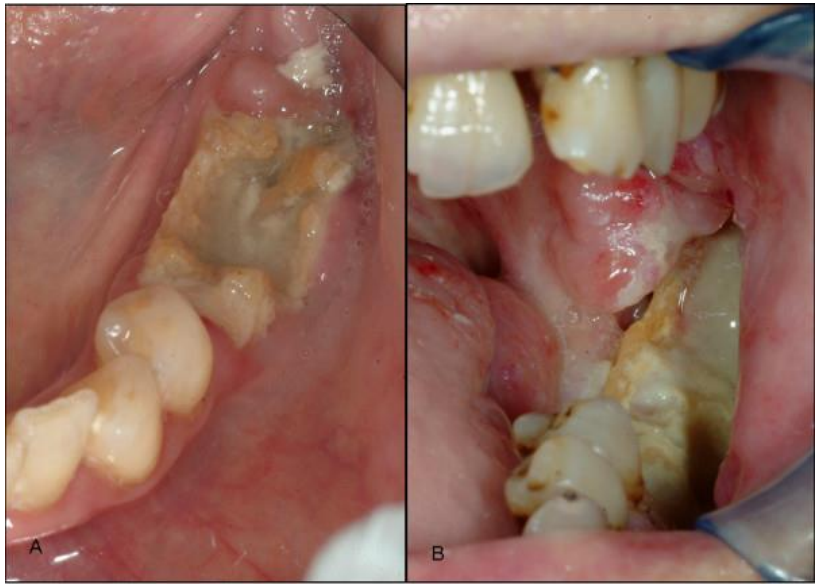
Bone disease - Biphosphonates

- Zolendronic acid and pamindronate
  - Both reduce skeletal-related events (pathologic fractures, cord compression, requirements for radiotherapy and surgery)
  - Zolendronic acid more effective than pamindronate
  - Oral biphosphonates (clodronate) are clearly inferior
- Patient population
  - Myeloma at all stages with bone disease
  - Maybe indicated in some patients with MGUS or smoldering myeloma
- Duration
  - At least 2 years in CR or long-term
- Hypocalcaemia
  - Vitamin D and calcium

Supportive care – managing complications

Bone disease - Biphosphonates

- Osteonecrosis of the jaw
  - Exposed bone in the mouth that does not heal in 6-8 weeks
  - Frequency: 4-11%, more common with zolendronic acid
  - Prevention is best strategy
  - Dental hygiene – patient education
  - Dental review before treatment
  - Avoid unnecessary dental invasive procedure
  - Interrupt treatment at least 90 days in advance of invasive dental procedures
  - if diagnosed stop biphosphonates



Supportive care – managing complications

Recommended vaccination 12 months post-transplant

- influenza
- polio
- Diphtheria –tetanus – pertussis
- H influenza
- Pneumococcal (PCV13 and PPV23)
- Meningococcal group C (often as Hib/MenC)
- Meningococcal group B

DO NOT give live vaccines

- BCG
- Measles
- MMR
- Rubella
- Shingles
- Yellow fever

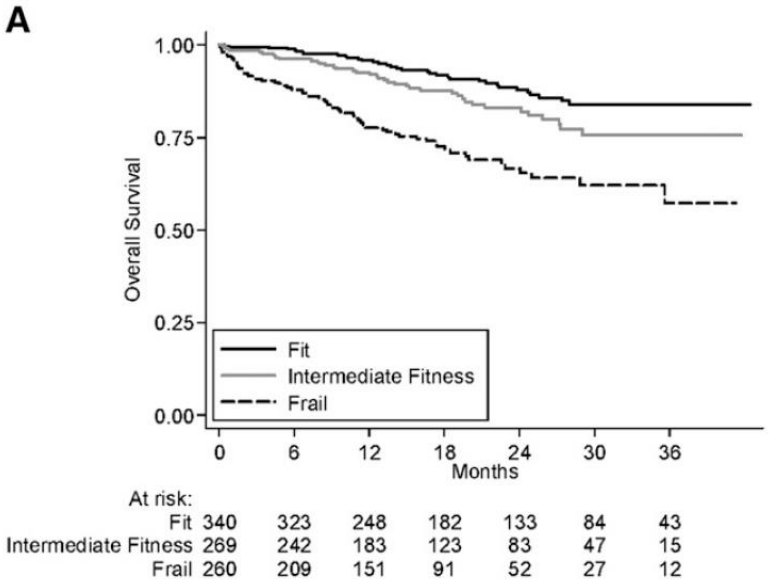
Geriatric assessment predicts survival and toxicity

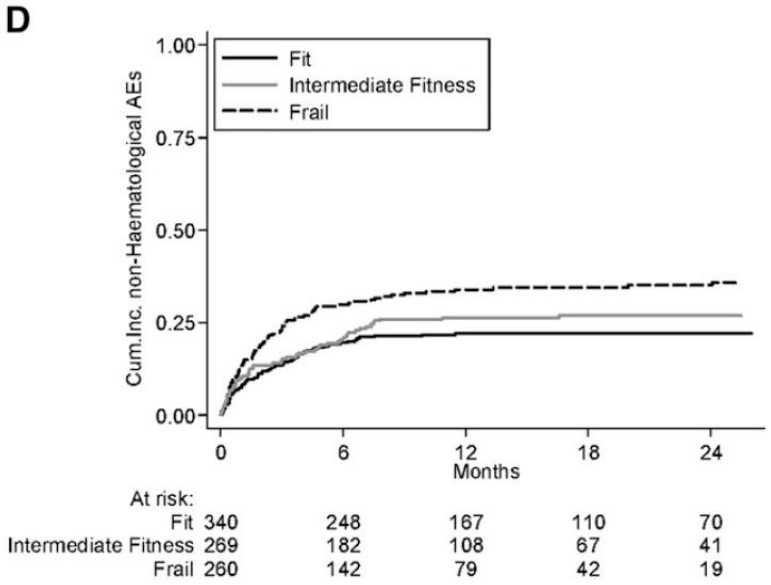
Scoring system

(Katz Activity of Daily Living, Lawton Instrumental Activity of Daily Living , Charlson Comorbidity Index)

Table 3. Additive total score and related rate of OS and PFS at 3 years

			% (95% CI)		Cumulative incidence at 12 mo, %	
Additive total score	Patient status	No. of patients (%)	OS	PFS	Treatment discontinuation	Grade 3-4 nonhematologic AEs
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate-fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34





Palumbo et al. Blood, January 2015

Myeloma clinical trials

- Myeloma remains an incurable disease
- Still unclear topics in management
- Early access to novel treatments
- Allows the use of standard therapies later in the course of disease

Myeloma clinical trials at Imperial

	MUK5 (myeloma UK)	Millenium C16019 (Millenium)	Millenium C16021 (Millenium)	Alcyone (Janssen)	BET116183 (GSK)
Phase	2	3	3	3	1
Patient population	First relapse / primary refractory	Maintenance post transplant	Maintenance in transplant ineligible	First line	Relapse - Refractory
Arms	Carfilzomib cyclo/dex vs Bortezomib cyclo/dex	Ixazomib vs placebo	Ixazomib vs placebo	Daratumumab + VMP vs VMP	BET762

Imperial Myeloma team

Consultants

- Dr Amin Rahemtulla
- Dr Holger Auner
- Dr Aris Chaidos
- Dr Lydia Eccersley (locum)

Myeloma Specialist Nurses

- Ms Vajai Glackin
- Ms Angela Daniel

Associate Specialist

- Dr Marco Bua

Ambulatory Care

Modern Management of Haemato-Oncology patients;

Patient Centred care.

Ambulatory Care

Ambulatory Care provides the opportunity for many of our patients to receive a variety of treatments, including high dose chemotherapy, without having to stay in hospital overnight.

Advantages

Cost saving

Increase of capacity

Reduction of waiting time

Patient experience

Day care services

Day care unit

Apheresis

Day care services

Day care unit

Triage & assessment

Apheresis

Ambulatory care

Day care services

Day care: 9 am – 5 pm, Mo-Fri

Ground floor Catherine Lewis building
Constance Wood Ward – chemotherapy

Day care services

Day care unit

Triage & assessment

Apheresis

Ambulatory care

Day care services

Apheresis: 9 am – 5 pm + Sat/Sun prn

Red cell exchange patients
Stem cell collections

Day care services

Day care unit

Triage & assessment

Apheresis

Ambulatory care

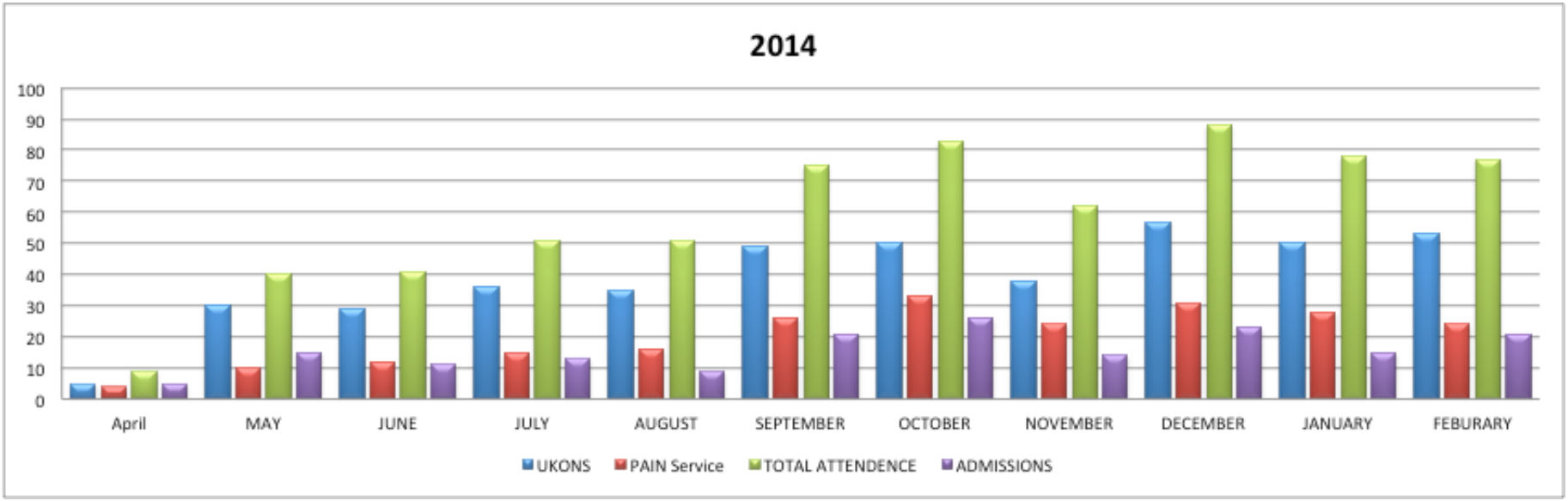
Day care services

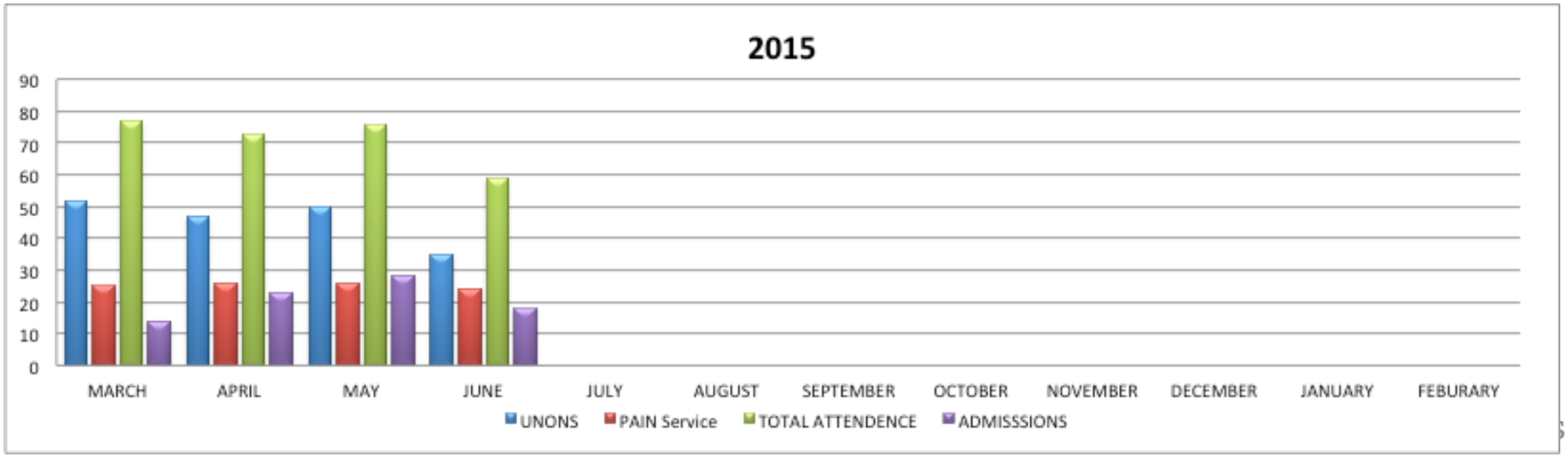
Triage & assessment

UKONS (UK Oncology Nursing Society)
Service: phone service (24 hrs)
+ assessments 8 am to 5 pm, 7 days

Day Pain Service for Sickle Cell Disease patients: phone service (24 hrs)
+ assessments 8 am to 3 pm, 7 days

T&A: attendance and admissions





Day care services

Day care unit

Triage & assessment

Apheresis

Ambulatory care

Day care services

Ambulatory care: 8 am to 20 pm, 7 days

Acute leukaemia – intensive chemotherapy except first induction
Lymphoma – salvage chemotherapy
Autologous transplantation

Selected patients

Ambulatory care

Home/studio flat

Transport – taxi like

Proactive phone calls

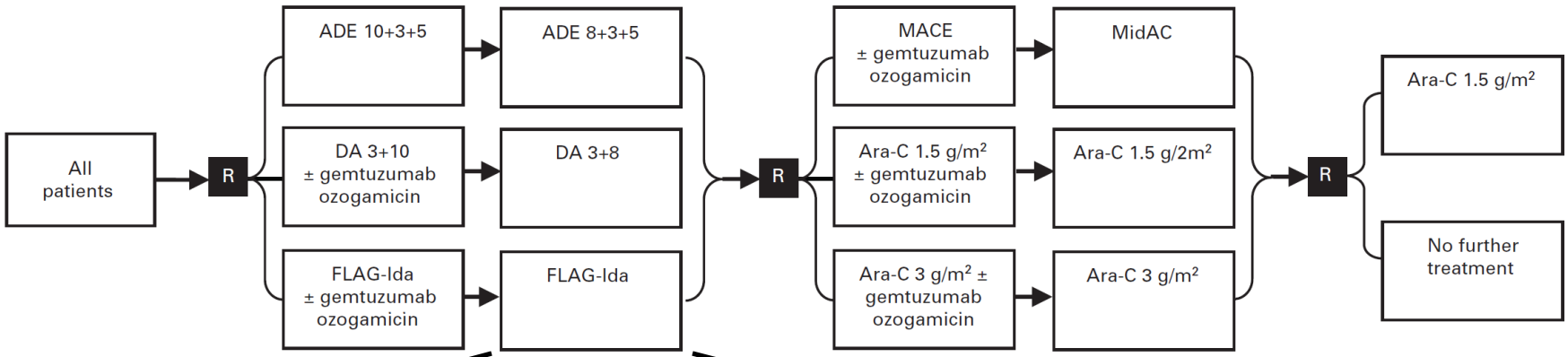
Patient education

Ambulatory care

Ambulatory care

Ambulatory care

AML



Clerking, c. line, ECHO

1-2 days

chemotherapy

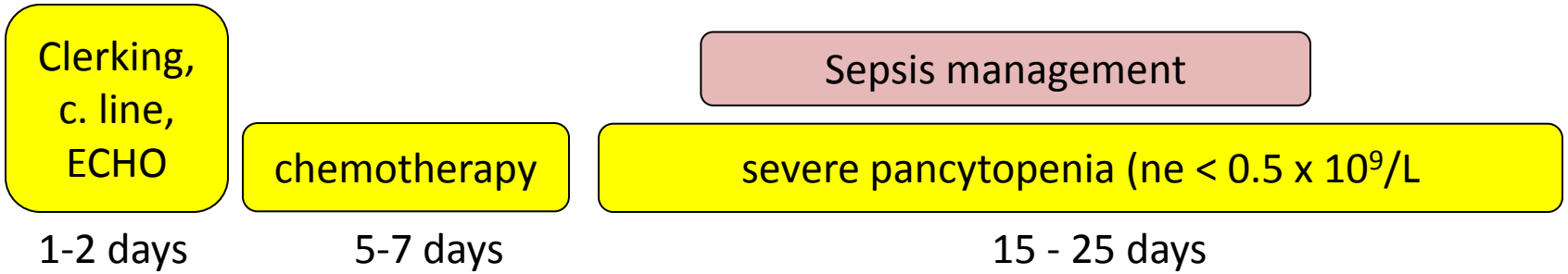
5-7 days

Sepsis management

severe pancytopenia (ne < 0.5 x 10^9/L

15 - 25 days

AML



- Daily or 2x/day attendances during chemotherapy
- 3x/week attendances during pancytopenic phase
  – for clinical review + platelet +/- blood transfusions
- Phone calls on days off

Thank you

Interpretation of coagulation tests

Prof Mike Laffan
Imperial College

Outline

- Normal coagulation / haemostasis
- The coagulation ‘screen’
- Why perform coagulation screens?
- Interpretation
- Specialist coagulation tests for primary care
- Obtaining reliable results - pre-analytical factors

Normal Haemostasis

Response to injury

Vessel constriction

↓

Formation of an unstable platelet plug

-platelet adhesion +VWF

-platelet aggregation

↓

Stabilisation of the plug with fibrin

-blood coagulation

↓

Dissolution of clot and vessel repair

-fibrinolysis

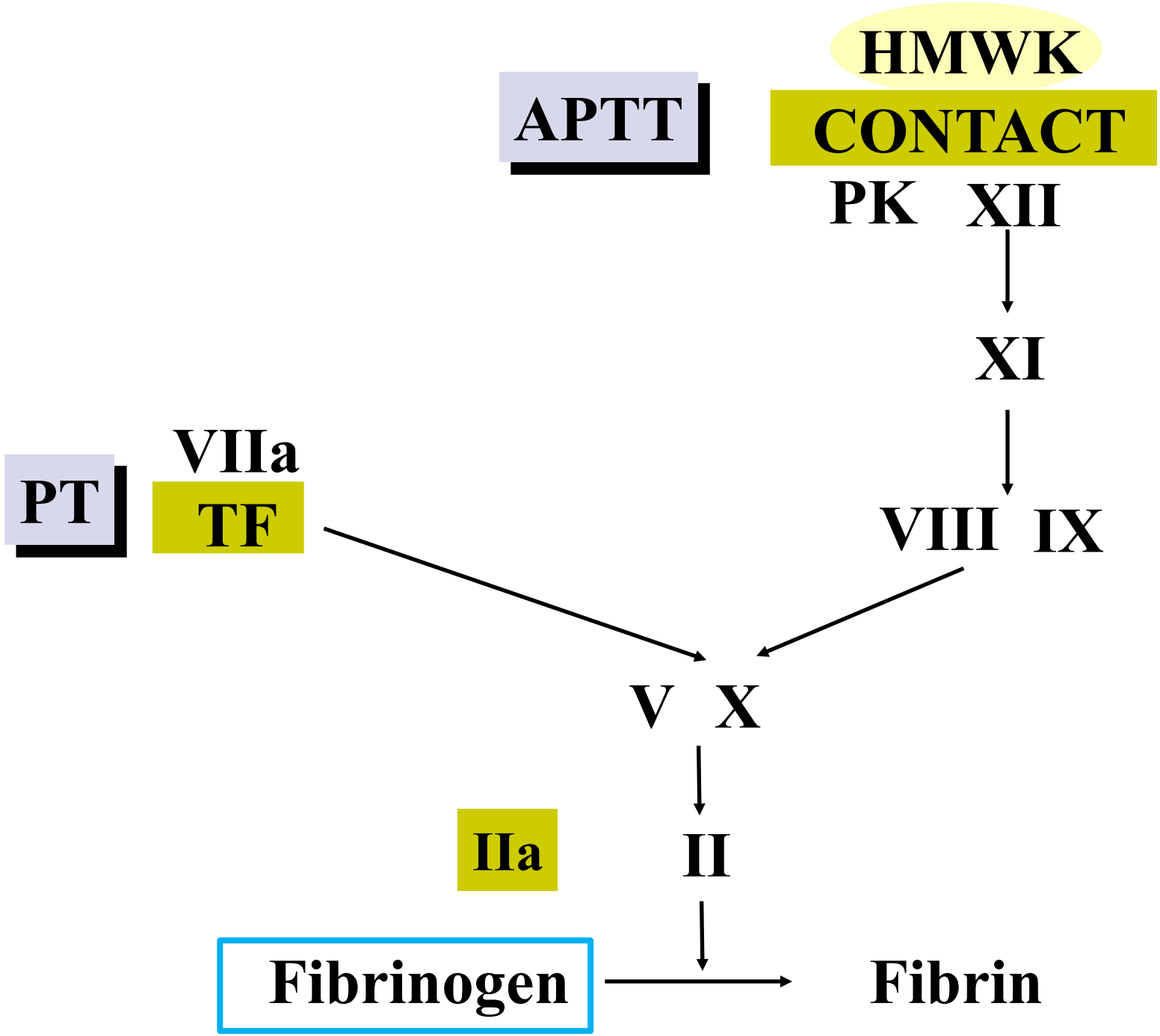
Coagulation screen

Anticoagulation systems

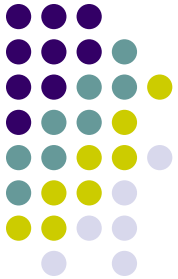
Coagulation: ‘Screening tests’

- Prothrombin time (PT)
- Activated partial thromboplastin time (APTT)
- Fibrinogen assay
- Thrombin time (TT)

- (Platelet count)


HMWK
APTT
CONTACT
PK XII
XI
VIIa
PT
TF
VIII IX
V X
IIa
II
Fibrinogen
Fibrin

Why coagulation screens?



- Detect a bleeding tendency
- Detect a cause for bleeding
- Detect a systemic disease
- Detect a thrombotic disorder
- Baseline for anticoagulation

- In fact their ability to do these is limited

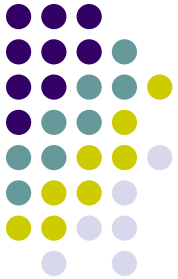
- Coagulation screens are usually performed to detect a defect in haemostasis but
  - are unphysiological
  - test a very limited portion of haemostasis
  - have limited sensitivity & specificity

Bleeding disorders not detected by routine clotting tests

- Mild factor deficiencies
- von Willebrand disease
- Factor XIII deficiency (cross linking)
- Platelet disorders
- Excessive fibrinolysis
- Vessel wall disorders
- Metabolic disorders (e.g. uraemia)
- Some anticoagulants

Normal coagulation screen ≠ Normal haemostasis

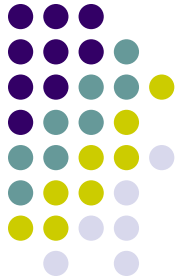
Coagulation screen and thrombotic disorders



- The coagulation screen will not detect any of the inherited thrombophilias
  - Specific tests available
  - Limited predictive value
- Current APTT reagents are insensitive to lupus anticoagulants
  - Specific testing required

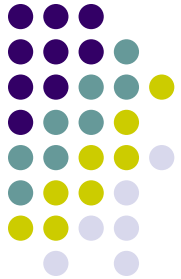
Coagulation screen: no information on thrombophilia

Coagulation screen and systemic disease



- Most coagulation factors are synthesised in the liver
  - PT and APTT are reasonable and sometimes important tests of liver synthetic function
- PT and APTT are sensitive to DIC
  - Usually in-patient problem

Coagulation screen and anticoagulation



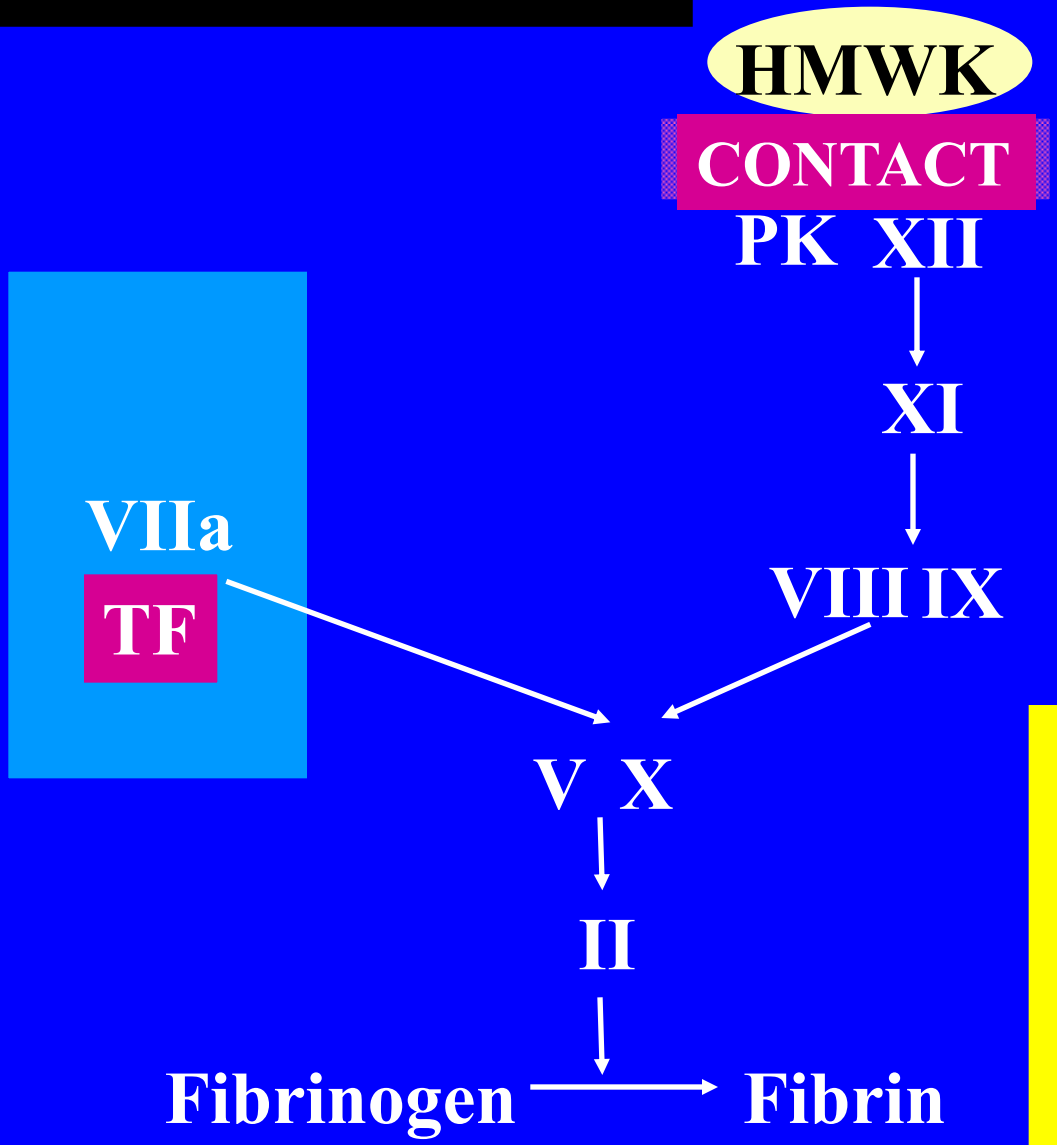
- Coagulation screen is essential baseline before beginning anticoagulation
- INR is based on the prothrombin time
  - Request specifically for calculation
- New anticoagulants may not have impact on coagulation screen.
  - Therapeutic levels reported with normal coagulation screen

INTERPRETATION OF COAGULATION SCREENS

PT

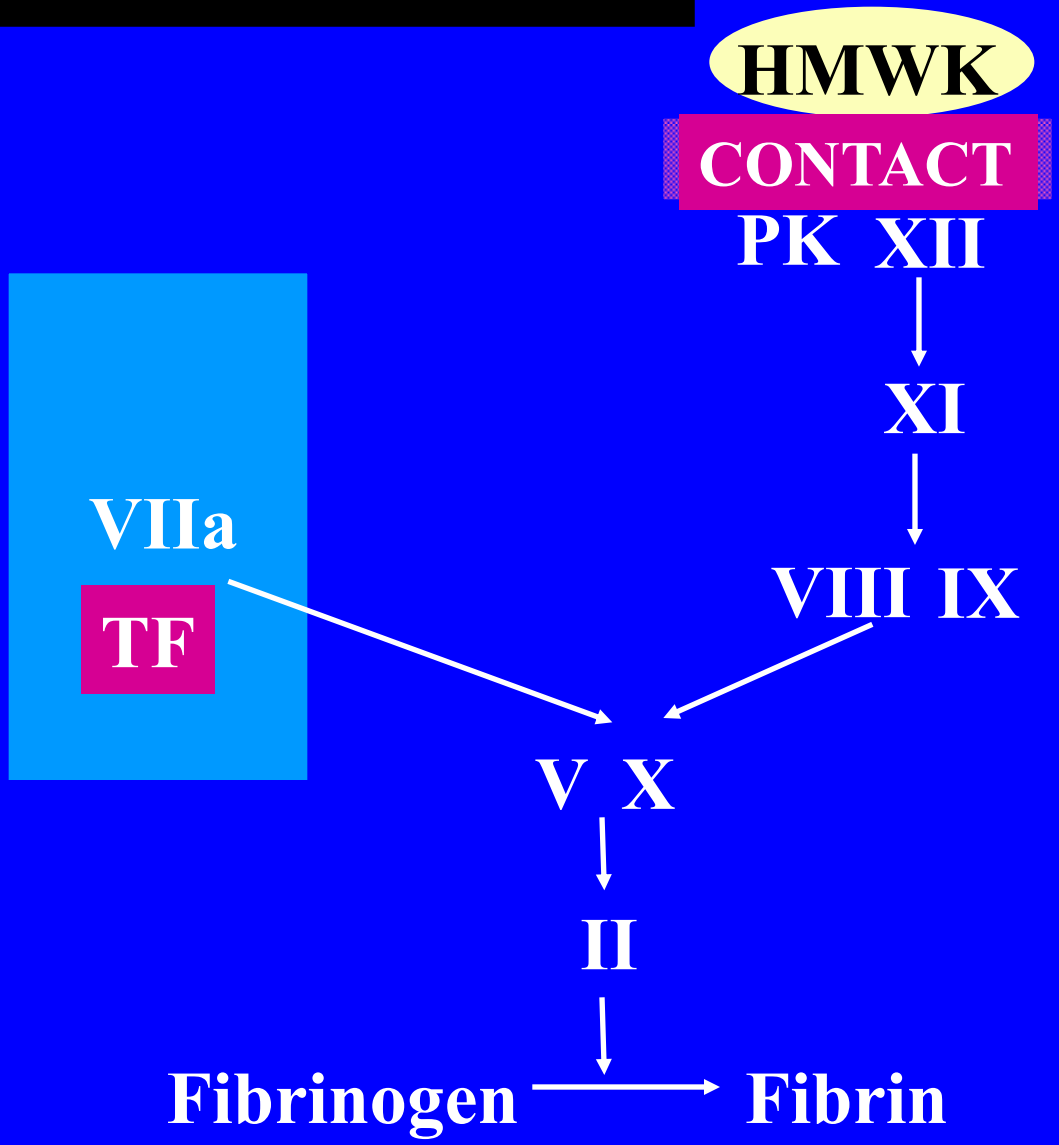
APTT

PROLONGED PT



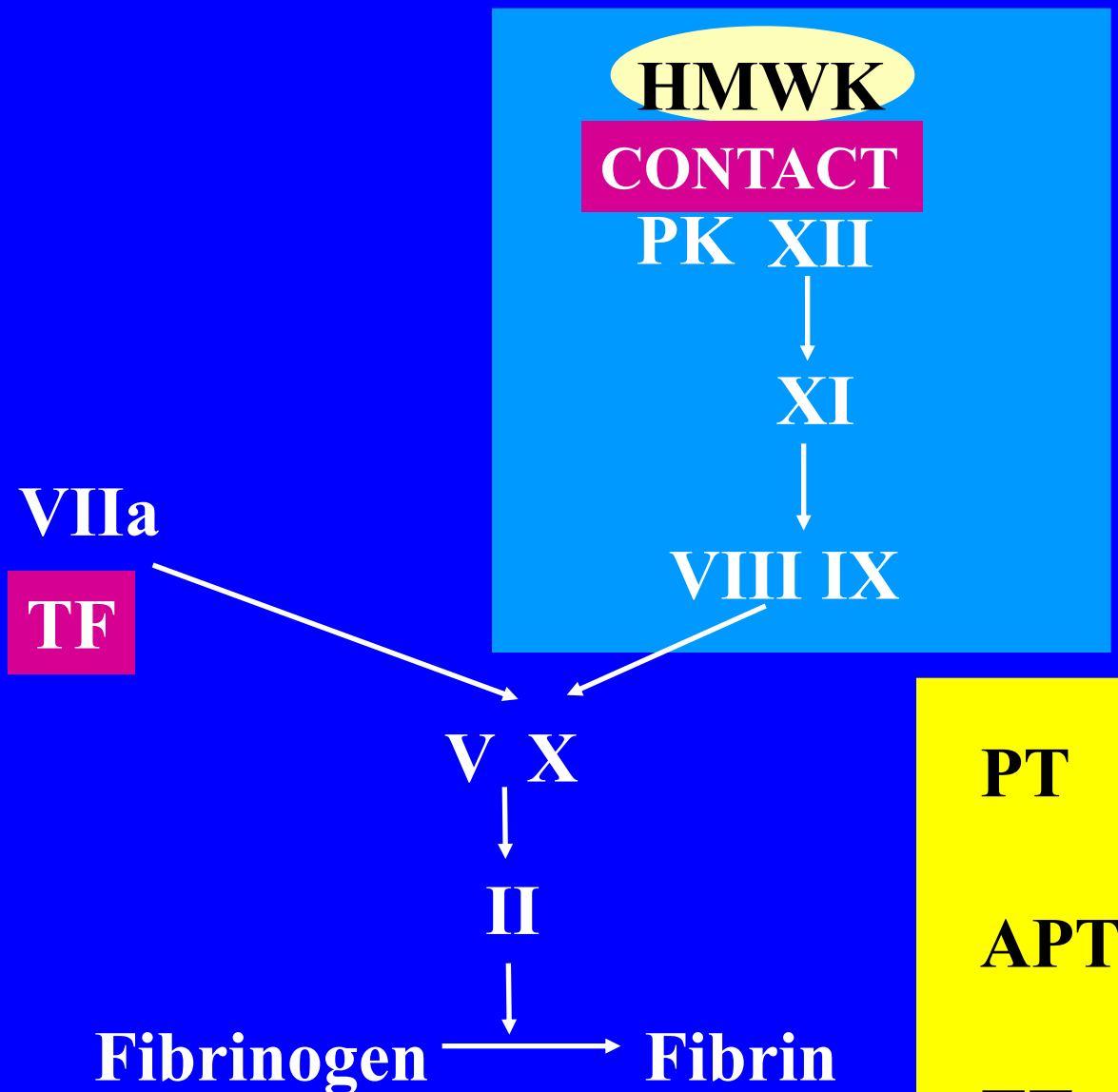
PT	22	(9.6-11.6)
APTT	28	(26-32)
TT	16	(15-19)

PROLONGED PT



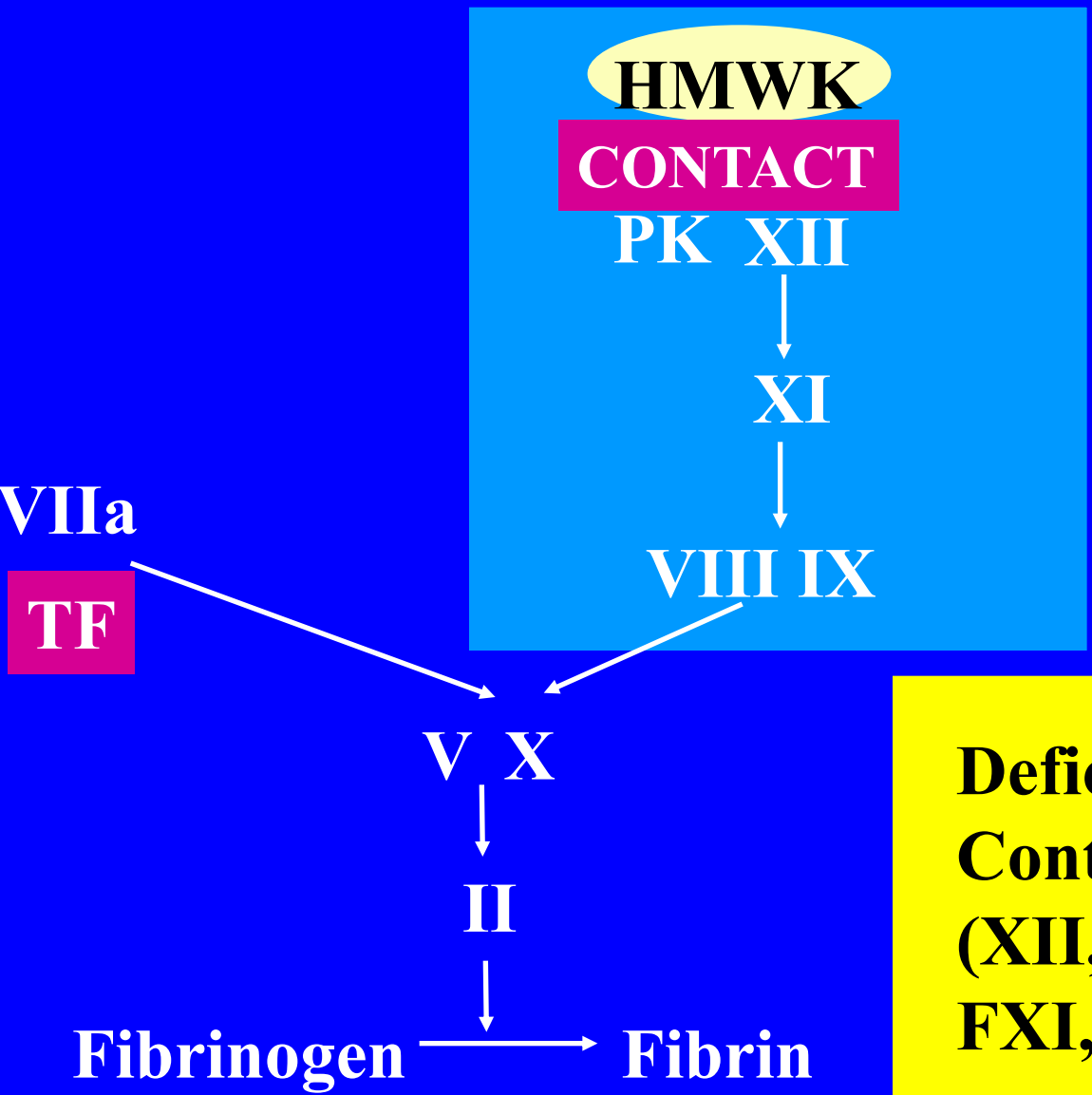
FVII deficiency

PROLONGED APTT



PT	10.6	(9.6-11.6)
APTT	65	(26-32)
TT	16	(15-19)

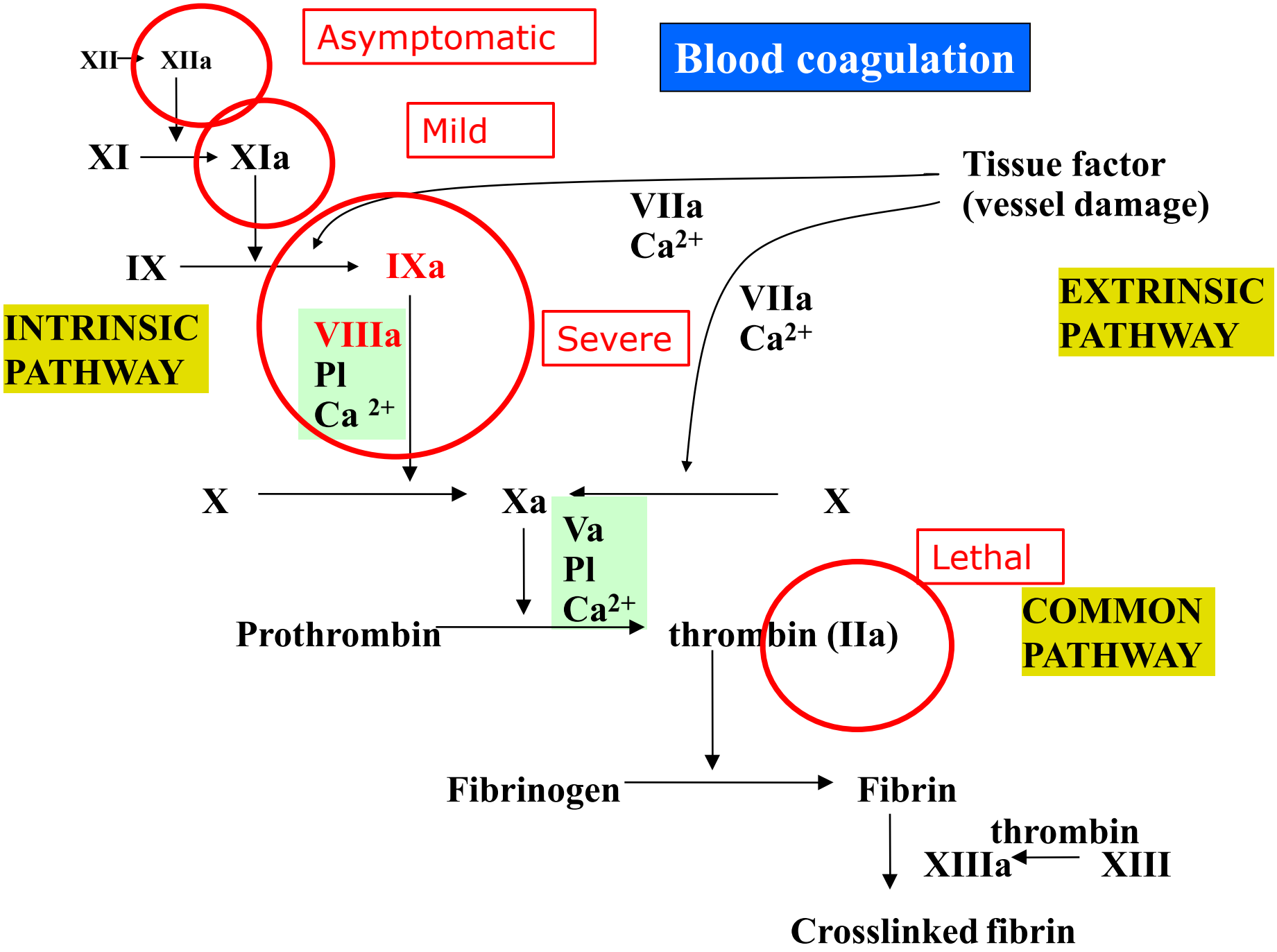
PROLONGED APTT



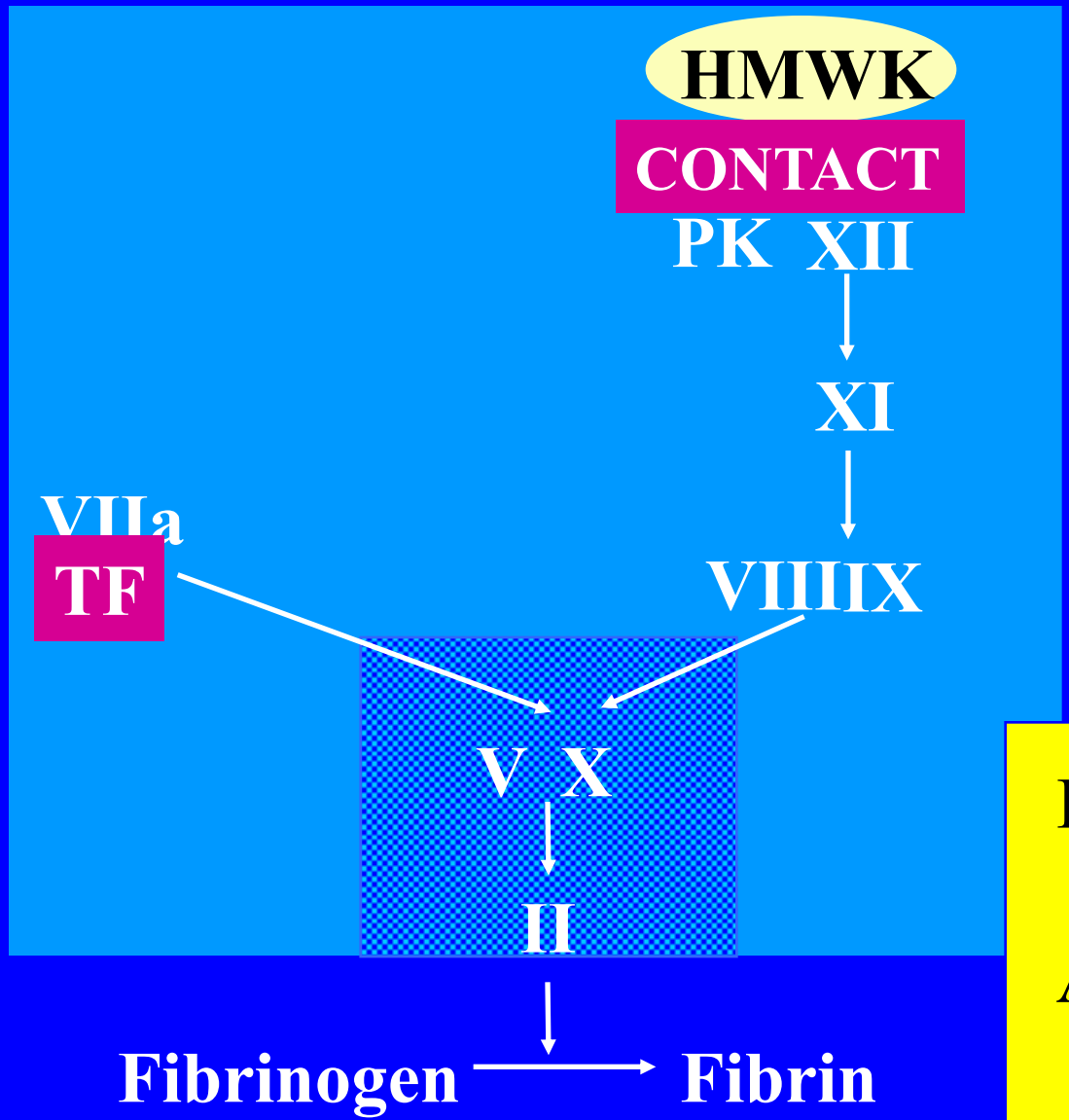
Deficiency of Contact factor (XII, PK, HMWK) FXI, FIX, FVIII

Coagulation factor deficiencies are not all the same

- Factor VIII and IX (Haemophilia)
  - Severe but compatible with life
  - Spontaneous joint and muscle bleeding
- Prothrombin (Factor II)
  - Lethal
- Factor XI
  - Bleed after trauma but not spontaneously
- Factor XII
  - No excess bleeding at all

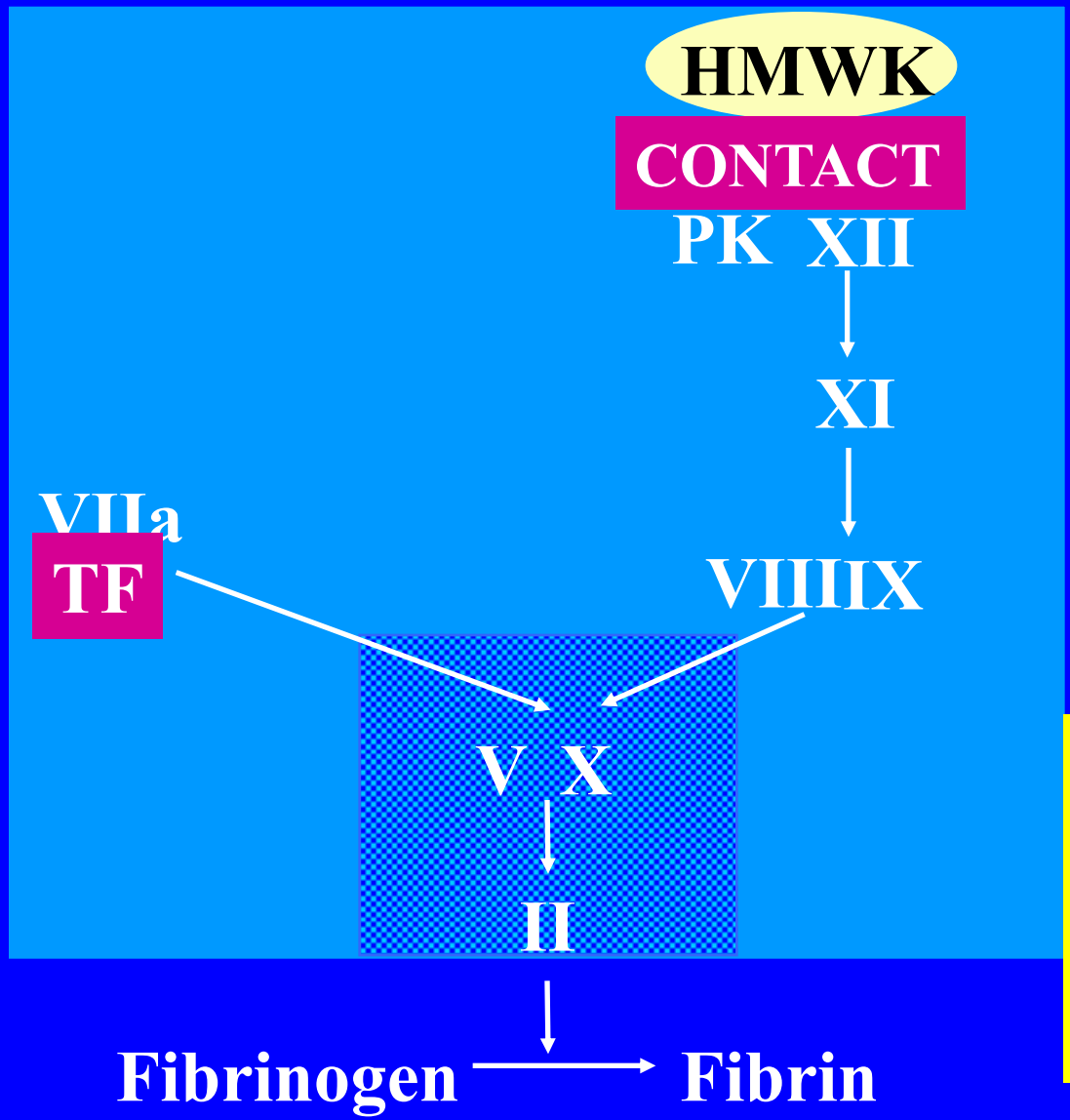

Blood coagulation
Asymptomatic
Mild
Severe
Lethal
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Pl
Ca 2+
INTRINSIC PATHWAY
Tissue factor
(vessel damage)
VIIa
Ca2+
VIIa
Ca2+
EXTRINSIC PATHWAY
X
Xa
X
Va
Pl
Ca2+
Prothrombin
thrombin (IIa)
COMMON PATHWAY
Fibrinogen
Fibrin
thrombin
XIIIa
XIII
Crosslinked fibrin

PROLONGED APTT AND PT



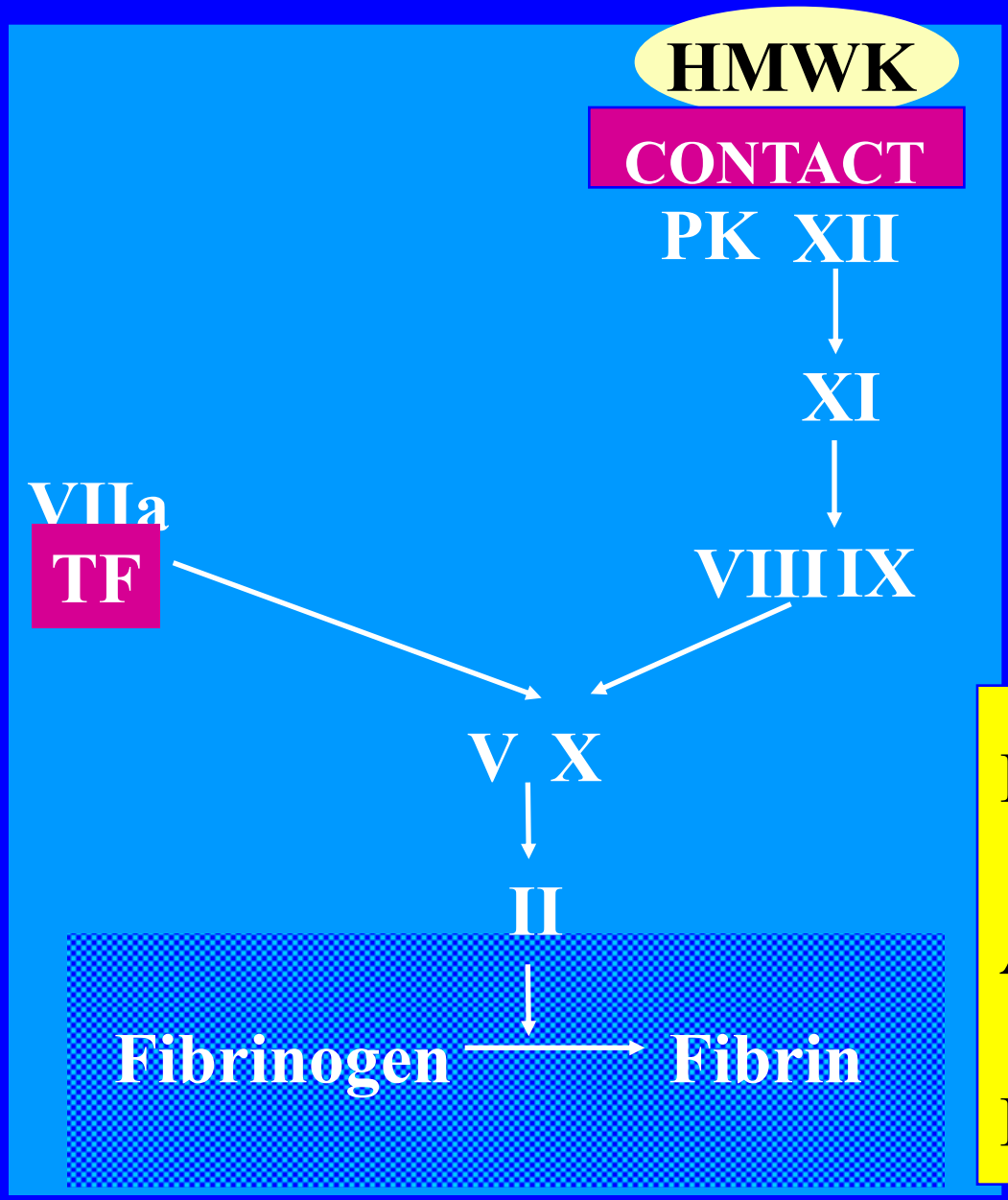
PT	19.3	(9.6-11.6)
APTT	45	(26-32)
TT	16	(15-19)

PROLONGED APTT AND PT



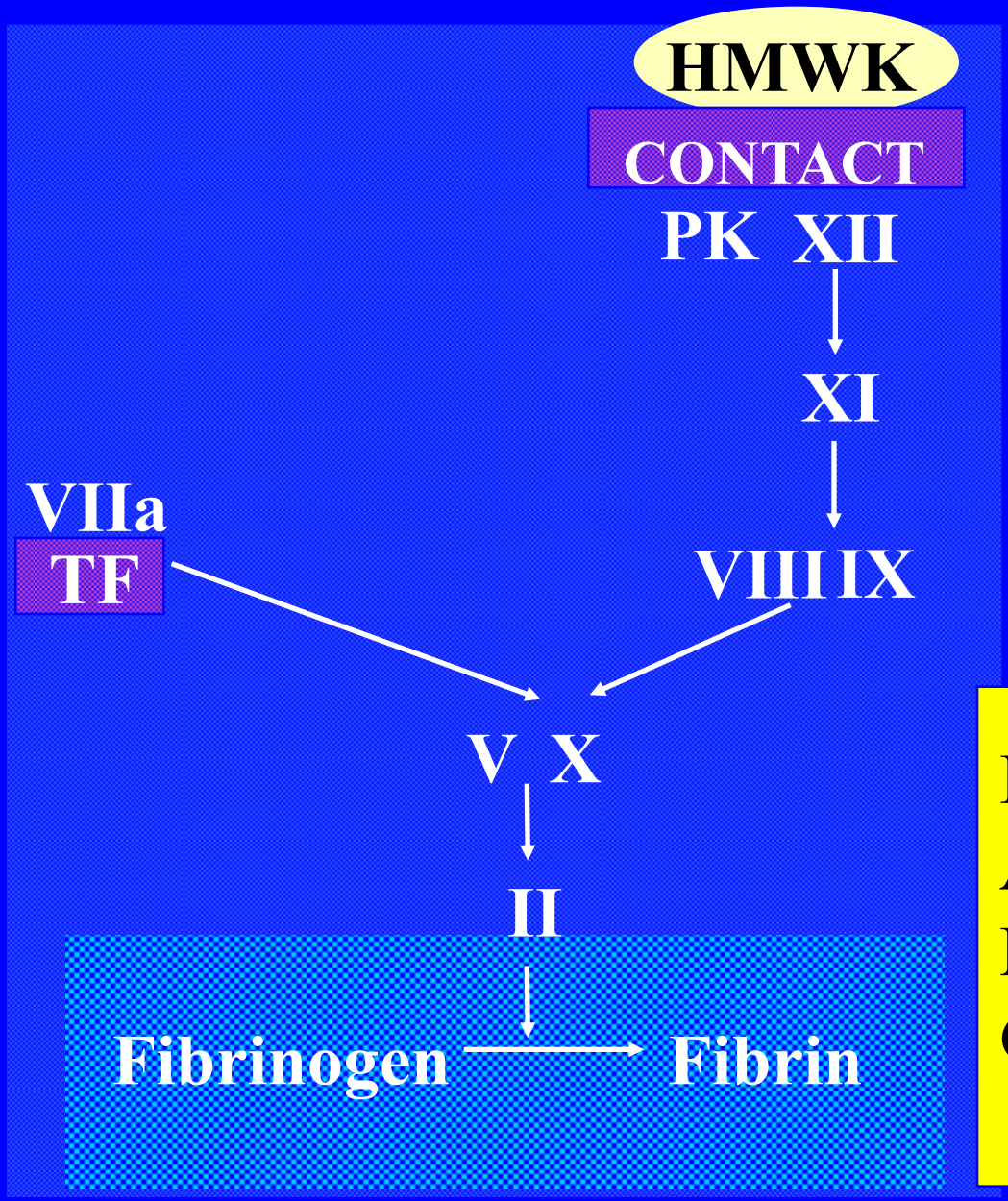
Deficiency
FV, FX, Prothrombin
OR
Multiple deficiencies

ALL TESTS PROLONGED + low fibrinogen



PT	18.5	(9.6-11.6)
APTT	45	(26-32)
Fgn	0.93g/l	(1.8-3.6))

ALL TESTS PROLONGED + low fibrinogen



Fibrinogen deficiency
Abnormal fibrinogen
Multiple deficiencies
Combination (DIC)

What can you learn from the coagulation screen?

- Significant coagulation factor deficiency
  - Children with unusual bruising/bleeding
    - Inherited factor deficiency eg haemophilia
  - Adults with new onset bleeding/bruising
    - Acquired haemophilia
    - Coagulopathy: malignancy, liver disease, DIC
- Significant synthetic defect
  - Liver disease
  - Vitamin K deficiency

What can you learn from the coagulation screen?

- Normal baseline for anticoagulation
  - Monitoring will be reliable
  - Assist in assessing risk

- Anticoagulant effect
  - Inappropriate consumption
  - Not for monitoring

What can you learn from the coagulation screen?

- The tests are designed to detect deficiencies, inhibitors and anticoagulants
  - Prolonged results are significant
  - Shortened results are not significant
    - May indicate problem with the sample

Follow-up for abnormal screens

- Unexpected abnormal coagulation screen
  - Refer for further testing
- Significant symptoms and normal coagulation screen
  - Refer for further testing (platelets, VWF, f assays)

- Specialist tests are available
  - Eg coagulation factors, lupus anticoagulant, thrombophilia screens

But….

  - More susceptible to pre-analytic effects
  - Interpretation is complicated

QUALITY CONTROL AND RELIABLE RESULTS

PRE-ANALYTICAL VARIABLES
How to ensure meaningful results

- Patient factors
  - Factor VIII & VWF rise with exercise
  - Haematocrit
- Blood sample collection
  - Venepuncture Technique
  - Blood sample containers
  - Choice of anticoagulant (Citrate)
  - Correct filling of tube
    - Citrate has significant volume

PRE-ANALYTICAL VARIABLES

- Sample transport to the laboratory
  - The in vitro half-life of FVIII is 10 hours
- Centrifugation (Speed, temperature and time)
- Storage of plasma (Temperature and time)

Underfilled, Haemolysed and a good quality citrate sample

Summary

- Good quality sample essential
- Coagulation screen informative
  - Factor deficiency, anticoagulation, liver disease, baseline
- Normal screen ≠ normal haemostasis
- No information on thrombophilia
- Shortened tests generally ignore
- Specialist tests difficult from primary care
- Coagulation consultant on call
- GP advice email