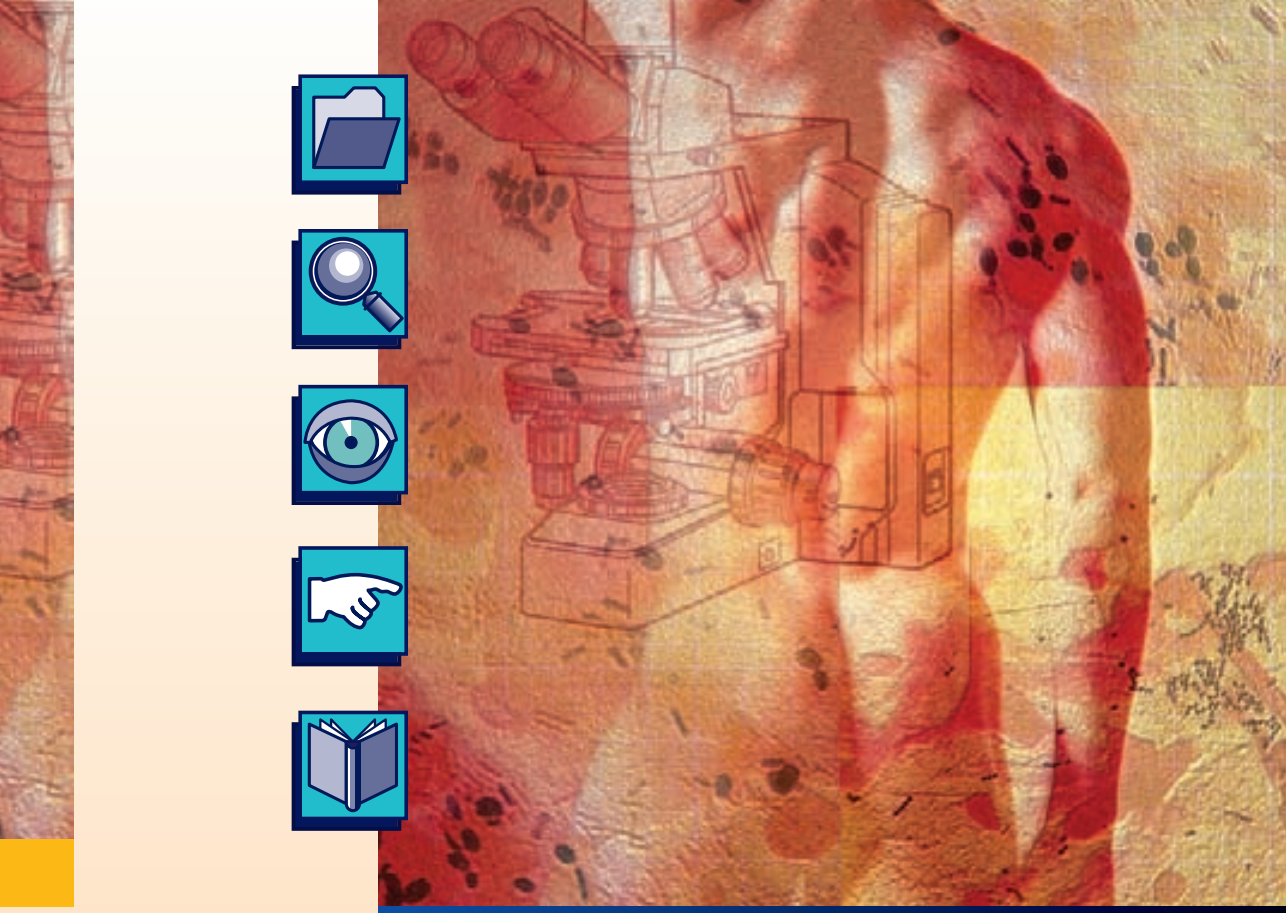

Problem Solving in Haematology

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CLINICAL PUBLISHING

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Abbreviations

ABVD	adriamycin, bleomycin, vinblastine and dacarbazine
ACA	additional chromosome abnormalities
ACD	anaemia of chronic disease
ACS	acute chest syndrome
ADP	adenosine diphosphate
AIHA	autoimmune haemolytic anaemia
ALG	antilymphocyte globulin
ALL	acute lymphoblastic leukaemia
alloBMT	allogeneic bone marrow transplantation
alloSCT	allogeneic stem cell transplantation
ALT	alanine transferase
AML	acute myeloid leukaemia
ANA	antinuclear antibody
ANC	absolute neutrophil count
APA	antiphospholipid antibodies
APC	activated protein C
APS	antiphospholipid syndrome
APTT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ASCT	autologous stem cell transplantation
ATG	antithymocyte globulin
AVN	avascular necrosis
BCSH	British Committee for Standards in Haematology
BEACOPP	bleomycin, etoposide, adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine and prednisolone
BEAM	carmustine, etoposide, cytarabine and melphalan
BMT	bone marrow transplantation
CALGB	Cancer and Leukemia Group B
CAP	cyclophosphamide, adriamycin [doxorubicin] and prednisolone
CCyR	complete cytogenetic response
2-CDA	2-chlorodeoxyadenosine (cladribine)
CEL	chronic eosinophilic leukaemia
ChlVPP	chlorambucil, vinblastine, procarbazine and prednisolone
CHOP	cyclophosphamide, adriamycin [doxorubicin], vincristine and prednisolone
CHR	complete haematologic response
CIMF	chronic idiopathic myelofibrosis
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CN	cytogenetically normal
CNS	central nervous system
COPPABVD	cyclophosphamide, vincristine, procarbazine, prednisolone and ABVD
CPHPC	R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid
CR	complete remission/complete response
CR1	first complete remission
CRAB	hyperCalcaemia, Renal dysfunction, Anaemia, Bone fractures or lytic lesions
CSA	ciclosporin
CSF	cerebrospinal fluid
CSSCD	Cooperative Study of Sickle Cell Disease
CT	computed tomography
CVP	central venous pressure
CVP	cyclophosphamide, vincristine and prednisolone
CXR	chest X-ray
CyR	cytogenetic response
DCT	direct Coombs' test
DDAVP	1-deamino-8-D-arginine vasopressin
DEXA	dual-energy X-ray absorptiometry
DFS	disease-free survival
DIC	disseminated intravascular coagulation
DLBCL	diffuse large B-cell non-Hodgkin lymphoma
DVT	deep vein thrombosis

EBMT	European Blood and Marrow Transplantation
EDTA	ethylenediaminetetraacetic acid
EFS	event-free survival
EMEA	European Medicines Agency
EP	extramedullary plasmacytomas
EPO	erythropoietin
ESP	erythropoiesis-stimulating protein
ESR	erythrocyte sedimentation rate
ET	essential thrombocythaemia
FAB	French–American–British
FBC	full blood count
FC	fludarabine combined with cyclophosphamide
FDG-PET	^{18}F-fluoro-deoxyglucose positron emission tomography
FFP	fresh frozen plasma
FI	full intensity
FISH	fluorescent *in situ* hybridization
FIX	factor IX
FL	follicular lymphoma
FLC	free light chain
FLIPI	Follicular Lymphoma International Prognostic Index
FNA	fine needle aspirate
FV	factor V
FVIII	factor VIII
FX	factor X
FXI	factor XI
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
GIFAbs	growth inhibitory factor antibodies
GP	General Practitioner
GPI	glycosyl phosphatidyl inositol
GvHD	graft-versus-host disease
GvL	graft-versus-leukaemia
GvM	graft-versus-myeloma
Hb	haemoglobin
HbF	haemoglobin F
HbS	haemoglobin S
HCT	haematocrit
HDAC	histone deacetylase
HDMTX	high-dose methotrexate
HES	hypereosinophilic syndrome
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNA	human neutrophil antigen
HPA	human platelet antigen
HR	haematologic response
HU	hydroxyurea
HUS	haemolytic uremic syndrome
ICH	intracranial haemorrhage
IFRT	involved field radiotherapy
Ig	immunoglobulin
IL	interleukin
IMF	idiopathic myelofibrosis
IMiD	immunomodulatory drug
INR	International Normalized Ratio
IPI	International Prognostic Index
IPSS	International Prognostic Scoring System
IR	imatinib-responsive
ITD	internal tandem duplication
ITP	idiopathic thrombocytopenic purpura
ITU	intensive therapy unit
IV	intravenous
JVP	jugular venous pressure
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
LPD	lymphoproliferative disease
LVF	left ventricular failure
M4Eo	acute myeloid leukaemia with eosinophilia
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean cell volume
MDS	myelodysplastic syndrome
β2-MG	β2-microglobulin
MGUS	monoclonal gammopathy of undetermined significance
MmolR	major molecular response
MP	melphalan and prednisone
MPL	thrombopoietin receptor
MR	minimal response
MRC	Medical Research Council
MRD	minimal residual disease
MRI	magnetic resonance imaging
MSH	Multicenter Study of Hydroxyurea in Sickle Cell Anemia
MT	massive transfusion
MUD	matched unrelated donor
nCR	near-complete response
NHL	non-Hodgkin lymphoma
NPM	nucleophosmin
OS	overall survival

PBSC	peripheral blood stem cell
PBSCT	peripheral blood stem cell transplantation
PCI	protein creatinine index
PCM	plasma cell myeloma
PCNSL	primary central nervous system lymphoma
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PEG	polyethylene glycol
PET	positron emission tomography
PFA	platelet function analyser
PMF	primary myelofibrosis
PNH	paroxysmal nocturnal haemoglobinuria
PR	partial remission/partial response
PSA	polysialic acids
PT	prothrombin time
PTD	partial tandem duplication
PV	polycythaemia vera
RA	refractory anaemia
RARS	refractory anaemia with ringed sideroblasts
RBC	red blood cell
RCT	randomized controlled trial
rFVIIa	recombinant factor VIIa
rhEPO	recombinant human erythropoietin
RIC	reduced-intensity conditioning
ROTI	myeloma-related organ and/or tissue impairment
RT–PCR	reverse transcription–polymerase chain reaction
SAP	serum amyloid P
SBP	solitary bone plasmacytomas
SC	subcutaneous
SCD	sickle cell disease
SCT	stem cell transplantation
SHOT	Serious Hazards of Transfusion
sIg	surface immunoglobulin
SLE	systemic lupus erythematosis
SM	systemic mastocytosis
SVCO	superior vena cava obstruction
TACO	transfusion associated circulatory overload
TBI	total body irradiation
TEDS	thromboembolic deterrent stockings
TF	tissue factor
TIPSS	transjugular intrahepatic portosystemic shunt
TKI	tyrosine kinase inhibitor
TOPPS	Trial of Platelet Prophylaxis
TRALI	transfusion-related acute lung injury
TRM	transplant-related mortality
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
UCB	umbilical cord blood
UFH	unfractionated heparin
VAD	vincristine, adriamycin (doxorubicin) and dexamethasone
VBMCP	vincristine, carmustine, melphalan, cyclophosphamide and prednisone
vCJD	variant Creutzfeldt Jacob Disease
VKOR	vitamin K epoxide reductase
VTE	venous thromboembolism
VWF	von Willebrand factor
WBC	white blood cell
WBRT	whole brain radiotherapy
WCC	white cell count
WHO	World Health Organization
WM	Waldenström's macroglobulinaemia
ZPI	protein Z-dependent protease inhibitor

Introduction

PROBLEM

01 The approach to the patient with an abnormal blood count

Case History

A 47-year-old female consults her doctor complaining of a sore throat of two weeks' duration, and has been aware of bruising affecting her forearms, thighs and shins, apparently developing spontaneously, for a week. She consults her General Practitioner who performs a full blood count.

What information may be gleaned from this investigation that may aid diagnosis in this case?

Background

The full blood count (FBC) is one of the most common investigations requested by doctors, and an abnormal FBC may be the first indication that a patient may have one of the primary haematological disorders discussed in this book. The test is the cornerstone of haematological diagnosis and the main test performed in haematology laboratories. Between 500 and 700 such tests will be performed daily in an average-sized district general hospital in the UK. The FBC is generated by automated instruments that count and size circulating blood cells by a variety of methods, one of the most common being 'aperture impedance' – the number and volume of cells are proportional to the frequency and height of electric pulses generated when cells pass through a small aperture. It is by this method, for example, that the mean cell volume (MCV) of red cells is determined. These machines also measure directly the haemoglobin content of the red cells, by spectrophotometric analysis after the red cells are lysed, and the haematocrit. As well as these directly measured parameters there are other calculated variables including the mean corpuscular haemoglobin (MCH) and the mean corpuscular haemoglobin concentration

(MCHC). Furthermore, such analysers can provide additional information about the various categories of white blood cells (WBCs) through complex multiparameter analysis of cell size and content, for example by assessing myeloperoxidase content that is found in neutrophils.

In interpreting a FBC, the most significant parameters to focus on are the haemoglobin – which may indicate the presence of anaemia or polycythaemia; the MCV – which will help in the classification of anaemias (see Chapter 7); the white cell count with differential – which would be important in the diagnosis of lymphoid or myeloid disorders; and a platelet count. The interpretation of any abnormality should be made in light of the knowledge that 5% of the population will display laboratory values outside the so-called normal range, and that well-recognized differences in these variables can be observed in persons of different race and between the sexes. For example, persons of African descent may have a lower white cell count (WCC), especially neutrophils, than Caucasians.[1]

Red cells – anaemia and polycythaemia

The approach to the anaemic patient is described further in Section 3, and polycythaemia in Section 6, and will not be further discussed here. The rest of this chapter will focus instead on the interpretation of an abnormal white cell or platelet count.

The history of a sore throat in this case suggests the possibility of recent infection, and the WCC may be expected to be abnormal, either as a reactive phenomenon or where there may possibly be a causative association.

White cells – leucopenia

In patients with an abnormal WCC, a 'five population' differential count should immediately tell the clinician which cell line – be it neutrophils, lymphocytes, monocytes, eosinophils or basophils – is affected.

Neutropenia

Neutropenia becomes clinically relevant only when it is severe (absolute neutrophil count [ANC] $<0.5 \times 10^9$/l) at which point there is a measurable increase in the risk of infection[2] (neutropenia of this degree is conventionally classified into congenital and acquired categories though, as already stated, 'ethnic' neutropenia in people of African origin needs to be recognized early on in the assessment of a patient). Congenital neutropenia includes Kostmann's syndrome and cyclical neutropenia.

The most frequent cause of acquired neutropenia is drug therapy (Table 1.1) with a long list of potential offenders. In the clinical assessment of the patient the possibility of a drug-induced neutropenia means that any possible contributing drug should, if at all possible, be stopped immediately. In this setting, early use of granulocyte colony-stimulating factor (G-CSF) should be considered. Autoimmune conditions and various haematological malignancies enter the differential diagnosis. Many of these conditions are suggested by the clinical assessment of the patient but further investigations, including peripheral blood immunophenotyping, and bone marrow examination may be required.[3]

Lymphopenia

Lymphopenia is most commonly seen in the setting of recent therapy with immunosuppressive drugs including corticosteroids. Recent viral infection is also a common cause

Table 1.1 Drugs associated with neutropenia[4]

Anticonvulsants	e.g. phenytoin
Antithyroid agents	e.g. carbimazole
Phenothiazines	e.g. carbamazepine
Anti-inflammatories	e.g. phenylbutazone
Antibacterials	e.g. co-trimoxazole
Others	e.g. gold, penicillamine, tolbutamide, mianserin, imipramine, cytotoxics

and consideration should be given to autoimmune and connective tissue disease, sarcoidosis and chronic renal failure.

White cells – leucocytosis

In any patient in whom an elevated WCC is detected it is essential to examine the blood film, which would be part of standard practice in most laboratories. This simple step should immediately identify rare causes such as chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL) or the various subtypes of acute leukaemia based on the proportion of immature precursors (including blasts), or cells of lymphoid lineage.

Neutrophilia

This is either a reactive phenomenon or is due to a myeloid malignancy. It is probably the commonest abnormality seen in the white cell series and the list of possible contributions is as long as the list of inflammatory and infective disorders that can affect the human body. Rarer causes such as CML are suggested by an increase in basophils, and also a so-called 'myelocyte peak' where the myelocytes represent the second-most numerous cell after the neutrophil in the white cell differential. In such cases it is very simple to perform fluorescent *in situ* hybridization (FISH) analysis or a polymerase chain reaction (PCR) test to look for the *BCR-ABL* fusion gene associated with this condition.

Eosinophilia

As in all cases of increased white cell production, secondary or reactive causes are the most common; in this case, parasitic infection, drugs and conditions such as asthma and other allergic conditions (see Chapter 5).

Monocytosis

A persistent monocytosis, although commonly encountered in viral and fungal infections, may be associated with myeloproliferative disorders and if, in addition, there are morphological abnormalities of white cell maturation such as hypogranular neutrophils and so-called pseudo-Pelger cells, the possibility of chronic myelomonocytic leukaemia (one of the myelodysplastic syndromes) should be considered.

Lymphocytosis

In evaluating a lymphocytosis, a blood film again would be helpful in distinguishing reactive lymphocytoses such as that associated with glandular fever (and characterized by the

presence of atypical lymphocytes) from, for example, large granular lymphocyte proliferations which may be either reactive or part of a T-cell disorder. A very high lymphocyte count, with the presence of smear cells, is highly suggestive of CLL though peripheral blood immunophenotyping is required to define the specific lymphoproliferative disorder.

Basophilia

This is extremely rare. Reactive increases are sometimes seen in infections and lymphoproliferative disorders and an elevated count is of diagnostic and prognostic importance in CML.

For the woman described in the case history, the FBC result was as follows:

- Haemoglobin: 12.8 g/dl
- WCC: 6.5×10^9/l (neutrophils 3.5×10^9/l, lymphocytes 2.0×10^9/l, monocytes 0.6×10^9/l, eosinophils 0.4×10^9/l)
- Platelets: 10×10^9/l

What is the interpretation of this result?

The patient has a normal haemoglobin level and WCC. The only abnormality is an isolated low platelet count (thrombocytopenia).

Platelets – thrombocytopenia

The most important first step is to exclude a spuriously low platelet count which may be induced by ethylenediaminetetraacetic acid (EDTA) clumping of platelets. This is clarified by examination of the blood film and, if there is any doubt, repeating the FBC using citrate as an anticoagulant. However, this explanation of a low platelet count would not be associated with any evidence of clinical bleeding, as appears to be the case here. Generally speaking, the cause of a low platelet count will be either increased consumption or reduced production. It is also important to consider physiological states such as pregnancy that can be associated with moderate thrombocytopenia (levels as low as 75×10^9/l), but the platelet count in this case is much lower than would be expected if this was the cause. Increased consumption may be due to disordered autoimmunity in the case of immune thrombocytopenia, which may be idiopathic or related to drugs or infections. Other disorders that can increase platelet consumption include thrombotic thrombocytopenic purpura (TTP) – examination of the blood film to look for red cell fragmentation will help exclude this diagnosis – and platelet consumption as part of a wider derangement of coagulation such as occurs in disseminated intravascular coagulation (DIC). The clinical assessment of the patient will help exclude causes such as hypersplenism or cirrhosis and, as in the case of neutropenia, drug causes should be considered, some of the commonest culprits being medications given for cardiac disorders, including quinidine and thiazide diuretics. In a hospital setting, heparin-induced thrombocytopenia (HIT) is an important cause with significant consequences which needs early consideration and exclusion. The commonest cause of a low platelet count, that is immune (idiopathic) thrombocytopenic purpura (ITP), is often a diagnosis of exclusion but, if thought to be the explanation, contributing underlying disorders such as autoimmune disease, lymphoproliferative disorders and human immunodeficiency virus (HIV) infection need to be

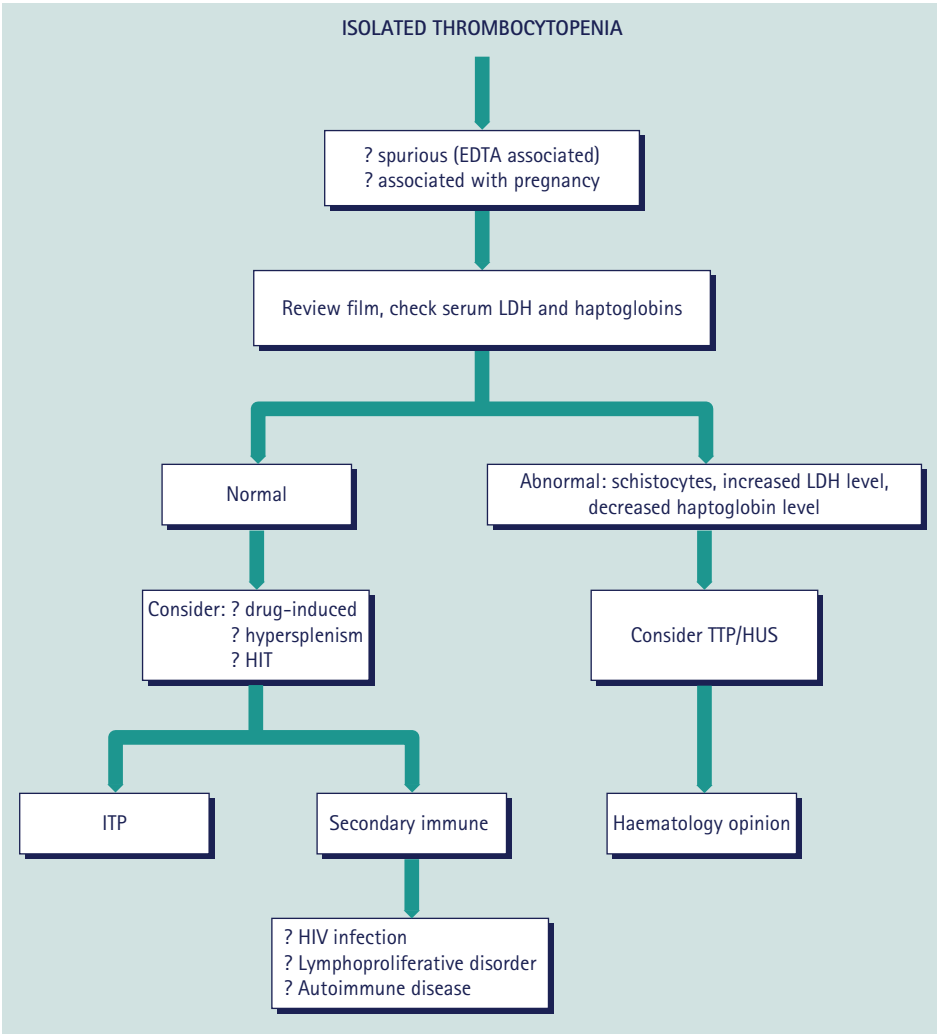

Figure 1.1 The approach to a patient with an isolated low platelet count.[5] HUS, haemolytic uremic syndrome; LDH, lactate dehydrogenase.

considered. The condition may develop following viral infections and the history of sore throat in this case may be relevant. Rarer causes of isolated thrombocytopenia include congenital abnormalities such as the May–Hegglin anomaly and Bernard–Soulier syndrome. Both are associated with large (giant) platelets on the blood film. Figure 1.1 summarizes the clinical approach to making a diagnosis, described by Tefferi *et al.*[5]

Platelets – thrombocytosis

This is usually a secondary process, again related to inflammatory conditions but also to blood loss, asplenia and infection, and hence highlights the importance of taking a full history. The differential diagnosis is primary thrombocythaemia, which may be associated with the Janus kinase 2 (*JAK2*) mutation (see Section 6).

Recent Developments

The increased sophistication of automated blood counters and parallel advances in automated biochemistry analysers have led many hospitals to house such high throughput instrumentation in joint 'core' laboratories often with the employment of a 'track-based' system in which samples move through the laboratory from a common specimen reception, where once they were sent to separate areas for analysis. Allied to this is the cross-training of staff to form a fully integrated blood sciences diagnostic facility, with increased capacity and allowing the redeployment of staff to more specialist laboratory areas.

Conclusion

The FBC is a routine part of the assessment of most patients presenting with clinical symptoms to their doctor. It is a lead-in to the majority of the blood disorders described in this book and sensible interpretation of the abnormalities in a logical way can expedite the appropriate referral and management of these cases. The key message is that the FBC findings are always reviewed in the context of the clinical history and examination. This should lead to prompt haematology consultation for those patients who need it, but equally should lead the general physician to perhaps consider non-haematological conditions and appropriate referral elsewhere based on a logical interpretation of the abnormalities that the FBC has uncovered.

In this case the test indicated immediately that the patient's bruising was due to a low platelet count. The normal haemoglobin, MCV, WCC and differential pointed to a diagnosis of ITP, and this was subsequently confirmed by bone marrow examination. There was no clinical or other evidence of an underlying lymphoproliferative disorder or autoimmune disease and it was likely that this ITP was precipitated by viral infection. Given the significant bruising, treatment was instigated with oral prednisolone 1 mg/kg, with recovery of platelets to normal within 3 days. No recurrence of thrombocytopenia occurred on tailing off steroids after 6 weeks.

Further Reading

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Haemostasis and Thrombosis

PROBLEM

02 Anticoagulation

Case History

A 39-year-old woman develops an extensive femoral vein thrombosis. She is receiving chemotherapy for carcinoma of the breast complicated by liver metastases. Haemoglobin is 11.1 g/dl, white cell count 9.2×10^9/l and platelet count 333×10^9/l. Her coagulation screen is normal, but liver function tests are abnormal with an obstructive picture.

How would you manage this case?

Background

Optimal management of anticoagulation can be a complex area. Ideally patients should have their treatment individually tailored taking into account the risks and benefits of particular therapies and complicating factors such as comorbid conditions and thrombophilia. These issues are well illustrated by the management of venous thromboembolism (VTE) in patients with cancer.

Venous thromboembolism is a common complication for cancer patients, with a reported incidence of approximately 15%. However, this figure is likely to be much higher as VTE may produce few if any symptoms, which are often attributed to the underlying malignancy. Venous thromboembolism represents an important cause of morbidity and mortality. Data have been published which estimate that one in every seven patients with cancer who require hospital admission and die, do so from a pulmonary embolus.[1]

The risk of VTE in cancer patients is highest in the first few months after diagnosis and is compounded by associated surgery, immobilization, hormone therapy, chemotherapy and central venous catheter insertion. The complications of cancer and its treatment make the management of VTE in such patients a challenge.

Initial therapy

The use of fixed-dose low-molecular-weight heparin (LMWH) has become standard practice in the initial treatment of VTE. This represents a significant therapeutic advance in terms of ease and convenience of administration. Its longer half-life and increased subcutaneous bioavailability compared with unfractionated heparin (UFH) mean that it can be administered as a single daily dose, lending itself to outpatient treatment and home therapy. There is a lower incidence of heparin-induced thrombocytopenia (HIT) compared with UFH and minimal monitoring is required.

There is still a place for UFH in initial treatment of VTE. In the cancer patient, intravenous UFH may be more appropriate if rapid reversal is required for procedures or in the face of renal impairment. Heparin is cleared by the reticuloendothelial system and renal route. Both mechanisms are important for UFH, but renal clearance predominates for LMWH. This is clinically important as accumulation of LMWH may occur in renal failure, causing an increased bleeding risk.

Long-term heparin use can cause osteoporosis but the absolute risk of symptomatic osteoporosis is unknown. Symptomatic vertebral fractures have been reported in approximately 2%–3% of patients receiving treatment doses of UFH for more than 1 month. The mechanism by which heparin exerts its effects on bone appears to be a decrease in osteoblast activity as well as an increase in osteoclast activity. An animal model has shown that the effects of heparin on bone are reversible but that this is a slow process because heparin binds to bone matrix proteins. Evidence now suggests that LMWHs are associated with a lower risk of osteoporosis than UFH. [2]

The following may be helpful to clinicians when deciding on which heparin preparation and what dose to use:[3]

- the patient's haemostatic potential and hence the intrinsic patient risk of thrombosis or bleeding (patient risk);
- the risk of thrombosis and bleeding associated with the procedure or condition of the patient (disorder risk);
- the relative efficacy of different heparin preparations and doses and the relative bleeding risk associated with these (heparin risk).

Monitoring is not routinely recommended for thromboprophylaxis or treatment with a LMWH but should be considered in certain subgroups, which include the very obese, those with severe renal failure and those in whom the pharmacokinetics of LMWHs may differ, such as infants younger than 3 months and in pregnancy. The activated partial thromboplastin time (APTT) is generally insensitive to LMWHs and cannot be used to monitor dose if this is required. The anti-Xa assay can be helpful but has significant limitations. The following issues need to be considered: the degree of anticoagulation induced by different LMWHs may not be comparable at the same plasma anti-Xa concentration; the comparability between commercially available assays is poor; and the anti-Xa assay appears to have poor correlation with bleeding or thrombosis in subjects receiving a LMWH. Accepting the limitations, monitoring 4–6 hour peak levels using the

anti-Xa assay may provide some guidance on dosage. In situations where LMWH may accumulate, such as in renal failure, a trough level may be useful.

The Control of Anticoagulation Subcommittee for the International Society for Thrombosis and Haemostasis has made the following recommendations on monitoring of heparin:[4]

1. Monitoring of prophylactic doses of UFH is not required.
2. Monitoring of prophylactic doses of LMWH is not required routinely. Anti-Xa assay can be employed to detect drug accumulation and risk of overdose in severe renal failure.
3. Monitoring of therapeutic doses of LMWH is not required routinely.
4. Monitoring of therapeutic doses of UFH can be achieved using the APTT. However, local calibration of the test should be employed to determine the recommended target APTT ratio.
5. Use of anti-Xa assays may provide some clue to the pharmacokinetics of LMWH when used to treat thrombosis in those in whom standard or weight-adjusted dosing is likely to be unreliable, especially subjects with severe renal failure, the obese, the pregnant, neonates and infants. Anti-Xa assay may also be of some value in the investigation of unexpected bleeding in a subject receiving a LMWH.
6. Where anti-Xa assay is employed to monitor LMWH therapy, local laboratory assay validation for the heparin in use is important and the limited predictive value of the results in terms of antithrombotic efficiency and bleeding risk of LMWH should be appreciated.

Recommendations 1–3 are based on results of randomized clinical trials of heparin/LMWH prophylaxis or treatment and are grade A. Recommendations 4–6 are based on observational and scientific data.

Long-term therapy

There are several factors to be considered in the long term. These include future antineoplastic treatment (chemotherapy, hormone therapy), presence of indwelling venous catheters, haemorrhagic risk, increased likelihood of resistance to warfarin, hepatic or renal dysfunction and the prognosis/risk of cancer recurrence.

On anticoagulant treatment, cancer patients have a two- to fourfold higher risk of VTE recurrence and major bleeding compared with cancer-free patients.[5] The increased VTE recurrence is likely to be secondary to the release of cancer procoagulants which are not inhibited by conventional anticoagulation.

Use of LMWH is convenient, flexible and does not pose a problem if there are nutrition difficulties or liver impairment but the risk of osteoporosis is not insignificant. Anti-vitamin K drugs such as coumarins can prove difficult to control, with an increased risk of over-anticoagulation and haemorrhage. However, the rate of VTE and bleeding is only increased in those patients with advanced disease when compared to non-cancer patients so warfarin could be an option for those with less advanced cancer.[5] Optimal treatment duration is for as long as the malignant disorder is active; this is lifelong for many patients.

There is some evidence for lowered cancer mortality in patients on heparin therapy and this raises the possibility of an antineoplastic effect and the possibility of cancer and thrombosis sharing a common mechanism. The increase in survival has been most

strongly linked to lung cancer. Animal models have demonstrated that UFH and LMWH interfere with processes related to tumour growth and metastasis. Retrospective meta-analysis of heparin trials shows that LMWH has been particularly associated with a trend in reducing mortality. This observation has now also been made in some small, prospective studies in which patients without VTE were randomized to a LMWH or placebo, in addition to chemo-radiotherapy.[6,7] The mechanism of action remains unclear and long-term benefit has not yet been proven. Future studies are required to confirm a beneficial effect and address issues such as patient selection, dose and duration of therapy.

In patients with cancer and acute VTE, dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.[8]

The British Committee for Standards in Haematology[3,9] recommends LMWH as first-line treatment for VTE in cancer patients but, in addition, states that heparins are not recommended for use as antineoplastic agents outside clinical trials.

Nine days after starting therapeutic-dose LMWH, the patient develops clinical signs of pulmonary emboli and extension of the deep vein thrombosis (DVT). This is confirmed radiologically. Haemoglobin is 11.3 g/dl, white cell count 12.2×10^9/l and platelet count 56×10^9/l.

What important issues need to be addressed?

The marked drop in platelet count makes HIT a strong possibility. The management of the patient needs to reflect both this and how to manage the progression of her thrombosis.

Heparin–induced thrombocytopenia

Heparin-induced thrombocytopenia is a severe complication of heparin treatment occurring with a frequency of 2.6% with UFH and 0.2% with LMWH.[10] The cause of HIT is an antibody which is directed towards the complex formed between heparin and platelet factor 4; this activates platelets and endothelial cells thereby inducing a prothrombotic state.

Heparin-induced thrombocytopenia can be associated with UFH, LMWH at prophylactic and therapeutic doses and even by the small amounts of heparin used to flush lines or impregnated in central venous catheters.

The platelet count classically falls 5–10 days after starting heparin, although in patients who have received heparin in the previous 3 months it may occur sooner because of pre-existing antibodies. The onset is rare after more than 15 days of exposure. The platelet count typically falls by >50% with a median nadir of 55×10^9/l and a platelet count of $<15 \times 10^9$/l is unusual. On average, half of the patients who develop HIT will have associated thrombosis. Those patients presenting without thrombosis have a high risk of subsequent thrombosis if heparin is not discontinued.

The probability of HIT should initially be judged on clinical grounds. There are four factors that are particularly helpful in assessing the likelihood of HIT. These are the degree of thrombocytopenia, the timing of the onset, the presence of new or progressive thrombosis and whether an alternative cause of thrombocytopenia is likely. A scoring system has been devised to assess the pre-test probability (Table 2.1).[11,12] If the pre-test

Table 2.1 Pre-test probability scoring system for heparin-induced thrombocytopenia

	Points (0, 1 or 2 for each of four categories: maximum possible score = 8)		
	2	1	0
Thrombocytopenia	>50% fall or platelet nadir 20–100 × 10^9/l	30%–50% fall or platelet nadir 10–19 × 10^9/l	<30% fall or platelet nadir <10 × 10^9/l
Timing* of platelet count fall or other sequelae	Clear onset between days 5 and 10; or less than 5 days (if heparin exposure within past 100 days)	Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other causes for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Pre-test probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low.
*First day of immunizing heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 days more until an arbitrary threshold that defines thrombocytopenia is passed).

probability is high, heparin should be stopped and an alternative anticoagulant given whilst laboratory tests are performed. Heparin-induced thrombocytopenia antibodies can be measured by immunological techniques or by platelet activation assays. However, these tests may be difficult to interpret as they can be abnormal in patients who do not have clinical HIT and *vice versa*. The diagnosis, therefore, is largely a clinical one and the pre-test probability should be considered when interpreting the results of laboratory tests.

Treatment of HIT requires the immediate cessation of heparin therapy but also the use of alternative anticoagulants. Low-molecular-weight heparin is not an appropriate alternative if HIT develops during treatment with UFH because there is a significant risk of cross-reactivity. In the UK the alternative anticoagulants licensed for use in HIT are danaparoid and lepirudin. Prospective studies in patients with HIT have shown that lepirudin reduced the occurrence of new thrombotic events by more than 90% but increased bleeding risk was recorded.[11]

The introduction of warfarin should be delayed until resolution of the thrombocytopenia as it can increase the risk of microvascular thrombosis in HIT. It can then be introduced but should overlap with the alternative anticoagulant. Bleeding is uncommon in HIT and as platelet transfusions could theoretically contribute to thrombotic risk they are relatively contraindicated.

Vena cava filters

For some patients who develop a pulmonary embolus despite anticoagulation, or related to HIT as in this situation, a vena cava filter may be appropriate. It is important to establish that anticoagulation was not subtherapeutic at the time of diagnosis. An option to consider is increasing the target International Normalized Ratio (INR). Increasing the target INR to 3.5 in patients on oral anticoagulant therapy who develop recurrent VTE with a target of 2.5 and an INR greater than 2.0 at the time of recurrent thrombosis has

been suggested.[12] In the situation described in the case history above, oral anticoagulation is not appropriate given the hepatic impairment secondary to liver metastases and insertion of a vena cava filter is an option. However, in general, caval filters in cancer patients are more often associated with filter-related thrombosis.

The British Committee for Standards in Haematology has recently produced detailed guidelines on the use of vena cava filters.[13]

Recent Developments

Patients require different warfarin dosages to achieve the target therapeutic range. This is partly explained by many environmental/acquired factors such as diet, compliance, drugs and intercurrent illness. The variability is also largely genetically determined. It is partly explained by genetic variability in the cytochrome CYP2C9 locus, the liver enzyme required for oxidative metabolism of many drugs. Two variant alleles have been associated with decreased warfarin dose requirements, more time to achieve stable dosing, a higher risk of bleeding during the initiation phase and a significantly higher bleeding rate.

However, allelic variants of CYP2C9 do not explain the large interindividual variability in the dose–anticoagulant effect of warfarin, suggesting that additional factors may contribute to this variability. Recently, a novel gene responsible, at least in part, for the activity of the vitamin K epoxide reductase (VKOR) complex, the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene, has been identified.[14] Four different heterozygous missense mutations have been found in patients suffering from warfarin resistance.

Current anticoagulant drugs have limitations, which has fuelled the impetus to develop new drugs. These can be classified according to which steps in the coagulation process they act on and fall into four broad categories: inhibitors of initiation of coagulation, inhibitors of propagation of coagulation (fondaparinux), modulators of the protein C pathway and thrombin inhibitors (ximelagatran).

New anticoagulant drugs form the subject of a detailed review article.[15] Fondaparinux is a synthetic indirect inhibitor of activated factor X. It exerts its effect by selectively binding to antithrombin and producing a conformational change that increases the anti-Xa activity of antithrombin (an endogenous anticoagulant) approximately 300 fold. It is given once a day via the subcutaneous route and has a predictable anticoagulant response hence routine monitoring is not required. It does not bind to platelet factor 4 so HIT is unlikely. Trials have shown it is as effective and safe as LMWH for treatment of DVT.

Thrombin inhibitors prevent fibrin formation and thrombin-mediated feedback activation of coagulation factors. In North America, hirudin and argatroban are licensed for treatment of HIT.

Ximelagatran is the first orally available direct thrombin inhibitor. It has a predictable anticoagulant effect hence no monitoring is required. However, it is eliminated via the kidneys and may require dose reduction in patients with renal impairment. Efficacy has been demonstrated for thromboprophylaxis in high-risk orthopaedic surgery and treatment of VTE. Unfortunately it has caused significant increases in liver transaminases, often more than three times the upper limit of normal; whilst in the majority of cases this caused no symptoms and was reversible, one trial patient developed serious liver injury.

Dabigatran, another oral direct thrombin inhibitor, is under evaluation and to date has not been reported to cause liver dysfunction.

Conclusion

Venous thromboembolism is a common complication in the cancer patient and management may be complex. Low-molecular-weight heparin is the treatment of choice and the potential antineoplastic effect of LMWH confers possible additional benefit; results from further studies are awaited.

Heparin-induced thrombocytopenia is not an infrequent complication of heparin therapy. Awareness of the condition is increasing and scoring systems are now available to assess the probability of its occurrence.

Several new anticoagulants are under evaluation; oral direct thrombin inhibitors show promise. However, the precise role of these newer agents is yet to be defined and for many there is no effective reversal agent.

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PROBLEM

03 Bleeding in an intensive therapy unit patient

Case History

A 68-year-old man was admitted to Accident and Emergency with a 6-hour history of increasing abdominal pain and diarrhoea. He was a heavy smoker with a history of ischaemic heart disease. On examination he had a pulsatile mass present in his abdomen and no lower limb pulses. A computed tomography scan of his abdomen confirmed a leaking abdominal aortic aneurysm. Haemoglobin was 4 g/dl, white cell count 12×10^9/l, platelet count 432×10^9/l and coagulation screen was normal. Intra-operatively he lost approximately 10 litres of blood and was transfused 15 units of red cells. He also initially required large volumes of colloids to maintain his blood pressure. On the intensive therapy unit (ITU) post-operatively he was noted to be bleeding from drain sites at a rate that was higher than anticipated and was oozing from his arterial line and central venous pressure (CVP) line sites. Data from a repeat full blood count and coagulation screen were: haemoglobin 12 g/l, white cell count 16×10^9/l, platelet count 15×10^9/l, prothrombin time (PT) 22 seconds, activated partial thromboplastin time (APTT) 60 seconds, fibrinogen 0.8 g/l.

You are asked for your advice regarding the patient's blood results. How would you manage this case?

Background

Major bleeding, and consequently massive transfusion (MT), is a frequent complication of surgery. Massive transfusion is defined as replacement of one blood volume within a 24-hour period, the normal adult blood volume being about 7% of ideal body weight. Massively transfused patients show evidence of defective haemostasis in a high number of cases, but the incidence varies depending on the clinical context (blunt versus penetrating trauma, elective versus emergency surgery) and according to the definition of coagulopathy (clinical findings versus laboratory test results) and to the blood products administered to the patient. The cause of coagulopathy in MT is multifactorial, secondary to haemodilution of coagulation factors and platelets, disseminated intravascular coagulation (DIC), hypothermia, acidosis and hypocalcaemia.[1]

Haemodilution occurs following volume replacement with crystalloid or colloid and transfusion of red cells, and results in a reduction in the concentrations of platelets and coagulation factors. The level of fibrinogen is reduced first, with a level of 1 g/l after 150% blood volume loss, followed by a fall of coagulation factors to 25% activity after 200% blood loss. Prolongation of the APTT and PT to 1.5 times the mean normal values is associated with an increased risk of clinical coagulopathy. A platelet count of at least 50×10^9/l occurs when about two blood volumes have been replaced by fluid or red cells.

Disseminated intravascular coagulation is an acquired syndrome secondary to the systemic activation of coagulation. It is associated with the haemostatic defects related to the excessive generation of thrombin and fibrin and the excessive consumption of platelets and coagulation factors. This results in the clinical signs of end-organ damage from microthrombi in small vessels and microvascular oozing. Disseminated intravascular coagulation can be seen in a number of situations and often complicates the management of MT. Patients at risk are those with tissue damage secondary to tissue hypoxia, hypovolaemia or extensive muscle damage. A PT and APTT that are prolonged in excess of that expected by dilution, thrombocytopenia and a fibrinogen less than 1 g/l are highly suggestive of DIC. D-dimers may also be raised but are not diagnostic of the syndrome.

Hypothermia (temperature below 35°C) impairs thrombin generation and the formation of platelet plugs and fibrin clots, and increases clot lysis.

A summary of the interplay between the various factors associated with massive blood loss and MT is shown in Figure 3.1.

Management

In addition to addressing any surgically remediable cause of bleeding, the appropriate use of blood component therapy is indicated in correcting the coagulopathy. Close liaison is required between clinicians and laboratory staff in this regard, in order that a rational approach to treatment is adopted. Regular checks of laboratory parameters are important in order to assess the efficacy of component replacement and guide future therapy. Importantly, the measurement of fibrinogen should be performed using the Clauss method, and not derived from the PT, as this is more reliable.

It is now recognized that patients receiving a massive red cell transfusion should also receive platelets, fresh frozen plasma (FFP; as a source of coagulation factors) or cryoprecipitate (as a source of fibrinogen). There are no universally accepted guidelines for the replacement of these blood components and recommendations are largely made based on consensus opinion rather than from evidence from controlled trials. Moreover,

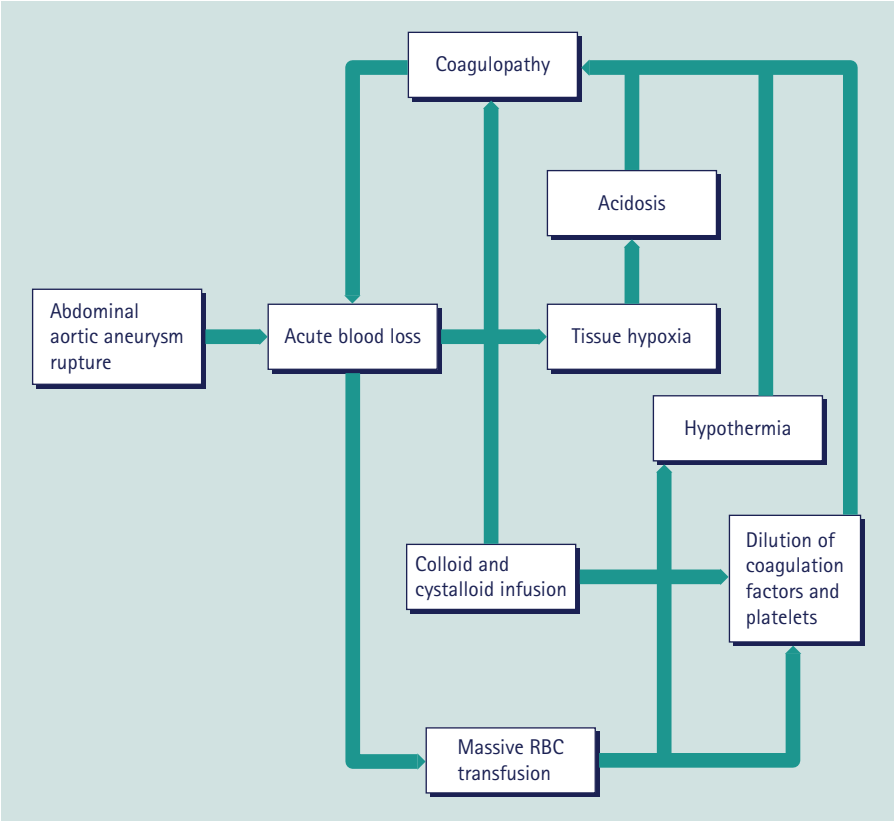

Figure 3.1 A summary of the interplay between the various factors associated with massive blood loss and massive transfusion. RBC, red blood cell.

whether this replacement should be done prophylactically after a certain number of units of red cells or only when there is clinical or laboratory evidence of coagulopathy, as in this case, is open to some debate.

The British Committee for Standards in Haematology (BCSH) guidelines on MT advise that the platelet count should not be allowed to fall below 50×10^9/l, and that a trigger of 75×10^9/l be observed when there is ongoing bleeding in order to provide a margin of safety.[2] The guideline from the American Society of Anesthesiology also uses 50×10^9/l as a cut-off for platelet transfusion.[3]

The BCSH guidelines recommend that FFP (at 12–15 ml/kg) should be given after one blood volume is lost, and that the dose should be large enough to maintain coagulation factors above the critical level to ensure that the PT and APTT are less than 1.5 times the mean control level. When the fibrinogen level is critically low (<1 g/l), as in this case, it is advised that fibrinogen be replaced (two packs of pooled cryoprecipitate for an adult). Cryoprecipitate is a better source of fibrinogen than FFP and should be used.

There are data available to suggest that a minimal haematocrit (HCT) is required to achieve haemostasis. This level remains unknown, although an HCT of about 35% is often quoted. Finally, maintaining the patient in a normothermic state is also an impor-

Table 3.1 Summary of recommendations for replacement of blood products in patients with massive bleeding

Goal	Procedure	Comments
● Maintain platelets $>75 \times 10^9$/l	● Anticipate platelet count $<50 \times 10^9$/l after 2 × blood volume replacement	● Allows margin of safety to ensure platelets $>50 \times 10^9$/l ● Keep platelets $>100 \times 10^9$/l if multiple or CNS trauma or if platelet function abnormal
● Maintain PT and APTT <1.5 × mean control	● Give FFP 12–15 ml/kg (l litre or 4 units for an adult) guided by tests ● Anticipate need for FFP after 1–1.5 × blood volume replacement	● PT/APTT >1.5 × mean normal value correlates with increased microvascular bleeding ● Keep ionized Ca^{2+} >1.13 mmol/l
● Maintain fibrinogen >1.0 g/l	● If not corrected by FFP give cryoprecipitate (two packs of pooled cryoprecipitate for an adult)	● Cryoprecipitate rarely needed except in DIC
● Avoid DIC	● Treat underlying cause (shock, hypothermia, acidosis)	● Although rare, mortality is high

APTT, activated partial thromboplastin time; CNS, central nervous system; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; PT, prothrombin time.

tant measure in the management of the coagulopathy and in achieving haemostasis. A summary of the recommendations for blood product replacement is given in Table 3.1.

The patient continues to bleed approximately 500 ml/hour into the wound drain. He has received 2 l of FFP, four packs of pooled cryoprecipitate and four pools of platelets. He is taken back to theatre for an exploratory laparotomy, but no obvious bleeding point is identified. His coagulation profile is now normal and his platelet count is 76×10^9/l.

What would you advise regarding the management of the bleeding?

Background

The patient has 'normal' haemostasis based on the laboratory parameters but continues to bleed, with no surgically correctable cause found. This refractory coagulopathic bleeding is not uncommon, with approximately 50% of the mortality in patients with traumatic bleeding attributed to it. The limitations of conventional blood products emphasize the need for additional haemostatic agents. Antifibrinolytic agents such as aprotinin, tranexamic acid and ε-aminocaproic acid have been shown to reduce surgical blood loss. In addition, 1-deamino-8-D-arginine vasopressin (DDAVP) can improve haemostasis in patients with uraemia and hepatic failure. Finally, fibrin glue has been used effectively when applied directly to a bleeding point. However, none of these agents has been shown to be effective in stopping coagulopathic bleeding. Rather, they have been shown to be most effective at prevention of rebleeding.

Recombinant factor VIIa (rFVIIa) was first used in the 1980s as a haemostatic agent. Since then it has been licensed for use in haemophilic patients with inhibitors to coagulation factors VIII or IX and in patients with platelet function defects. However, more recently its off-license use has been extended to include treatment of massive bleeding in a number of different clinical situations. Based on the current cell-based model of

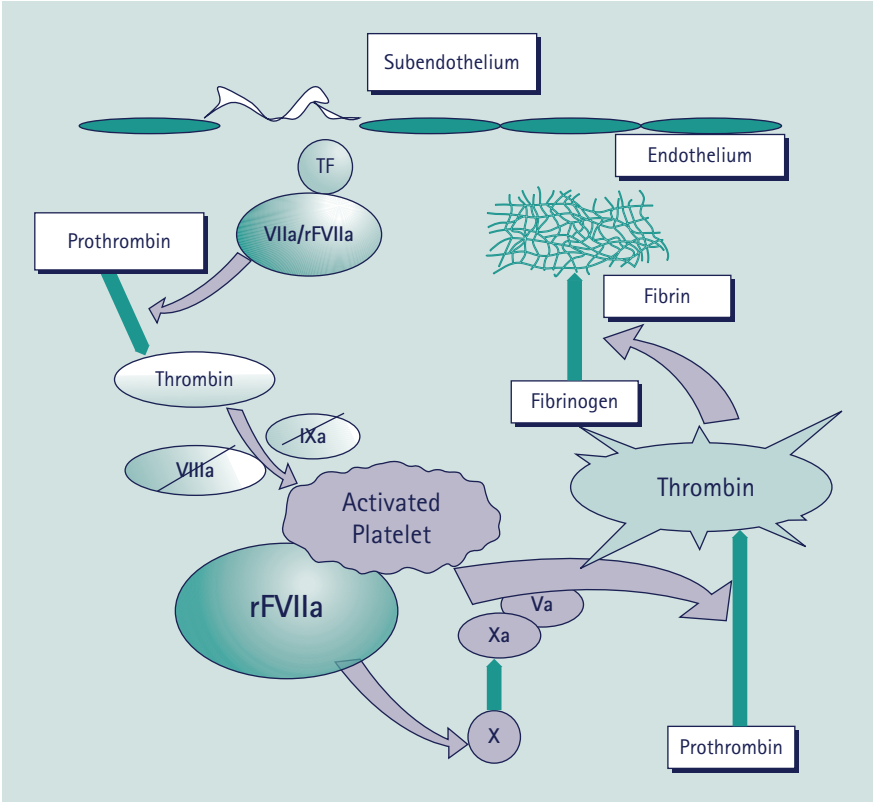

Figure 3.2 Cell-based model of coagulation and the mechanism of action of rFVIIa.

coagulation,[4] rFVIIa is thought to act locally at the site of tissue injury rather than systemically. It binds to exposed tissue factor (TF), and the rFVIIa–TF complex initiates coagulation by activating factor X (FX) and factor IX (FIX). Factor Xa then forms a complex with its cofactor factor V (FV) on the surface of activated platelets. This is sufficient to activate prothrombin and produce a small amount of thrombin. This is insufficient to convert fibrinogen to a fibrin clot, but further accelerates the coagulation cascade by activating FV, factor VIII (FVIII), factor XI (FXI) and additional platelets. This results in production of a large amount of thrombin, the so-called 'thrombin burst', which changes soluble fibrinogen into insoluble fibrin. Administration of pharmacological doses of rFVIIa causes faster and higher thrombin generation. It also binds to the phospholipid membrane of activated platelets and activates FX and FIX in a TF-independent manner, which further accelerates the coagulation process. This process is illustrated in Figure 3.2.

There has been an increasing number of case reports and case series on the use of rFVIIa in various clinical situations since the first report of its use in a trauma patient in 1999.[5] However, evidence from controlled trials is lacking. In one trial, 36 patients underwent abdominal prostatectomy and were randomized to a single injection of

rFVIIa (20 or 40 μg/kg) or placebo during the operation.[6] Administration of 40 μg/kg of rFVIIa at the beginning of the operation resulted in a 50% reduction of blood loss compared to placebo, and reduced the need for blood transfusion. Another controlled trial of 301 patients with blunt or penetrating trauma showed that red cell transfusion was reduced in the rFVIIa arm, and that there was a trend towards lower mortality rates when rFVIIa was used.[7] Despite this, however, there is conflicting evidence to support the use of rFVIIa as a 'last-ditch' treatment for massive haemorrhage. A recent review of the use of rFVIIa for treatment of severe bleeding concluded that it appeared to be relatively safe with 1%–2% incidence of thrombotic complications based on published trials.[8]

Management with recombinant factor VIIa

The BCSH guidelines on MT suggest that, until more evidence is available from controlled trials, rFVIIa should be considered for use where there is blood loss of >300 ml/hr.[2] Moreover, it should only be used when there is no evidence of heparin or warfarin effect, where surgical control of bleeding has been explored and when adequate replacement of coagulation factors (FFP, cryoprecipitate and platelets) and correction of acidosis have been achieved. The guidelines also recommend that local policies and guidelines should be in place to aid decisions regarding treatment with rFVIIa.

There is no agreed dosage, schedule or timing for the administration of rFVIIa in the massively bleeding patient. In the UK, the licensed dose for patients with haemophilia and inhibitors is 90 μg/kg. The same dose has been used in patients with massive bleeding. However, guidelines produced by the Israeli Multidisciplinary rFVIIa Task Force suggest that the dose may need to be higher (100–140 μg/kg).[9] A repeat dose of 100 μg/kg should be administered if bleeding persists beyond 15–20 minutes after the initial dose. A third dose should only be given after coagulation has been rechecked and corrected with blood products or empirical treatment given. Currently there are no laboratory methods for monitoring efficacy of rFVIIa. Response should be judged based on clinical response, although techniques such as thromboelastography and thrombin generation measurements could be used as objective measures of response in the future.

Recent Developments

The use of rFVIIa in non-haemophiliac patients anticipated to be at risk of major bleeding (prophylactic) or who have uncontrolled bleeding (therapeutic) has been a subject for debate. Review of randomized controlled trial (RCT) evidence for effectiveness of rFVIIa in these situations has been undertaken.[10] In particular, the effect of rFVIIa on blood loss and transfusion requirement was analysed. A significant reduction in transfusion requirements and/or blood loss in the rFVIIa-treated groups were recorded, but has not been confirmed in large randomised trials. Use in intracranial haemorrhage showed both bleed progression and mortality were reduced although preliminary results from a subsequent phase III trial have found no outcome benefit. The thromboembolic adverse event incidence in subjects who received rFVIIa is of concern and occurred despite exclusion criterion of patients with a history of previous thromboembolic or vasoocclusive disease. Further evidence is needed from appropriately designed clinical trials to better assess the optimal dose, efficacy and the safety of rFVIIa in critical bleeding conditions.

Conclusion

Bleeding in the ITU patient is a common problem and can be seen in a number of different clinical situations. The case presented here is of a patient undergoing an emergency aortic aneurysm repair. It highlights the importance of systematic review of the patient and of looking for surgically correctable causes and deranged coagulation profiles that can be reversed by the administration of fractionated blood components. Only after these avenues have been explored should the use of newer haemostatic agents, which have yet to prove their efficacy in this area, be considered.

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