THE ESSENTIAL RAPID REFERENCE FOR ALL HAEMATOLOGISTS

OXFORD HANDBOOK OF CLINICAL HAEMATOLOGY

Drew Provan | Trevor Baglin
Inderjeet Dokal | Johannes de Vos

A concise, clinical handbook covering the whole of haematology

Includes rare disorders as well as common conditions affecting both adults and children

Contains all the latest guidelines and a brand new chapter on rare diseases

Covers all major advances in the specialty including malignant haematology and transfusion medicine

Oxford Handbook of Clinical Haematology

FOURTH EDITION

Drew Provan

Reader in Haematology
Barts & The London School of Medicine and Dentistry
Queen Mary University of London, UK

Trevor Baglin

Consultant Haematologist
Addenbrooke's NHS Trust
Cambridge, UK

Inderjeet Dokal

Chair of Child Health and Centre Lead
Barts & The London School of Medicine and Dentistry
Queen Mary University of London
Honorary Consulta
Barts Health NHS T
London, UK

Johannes c

Consultant Haematologist
Royal Surrey County Hospital NHS Foundation Trust
Guildford, UK

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Preface to the fourth edition

The world of haematology has been exciting over the past few years, and we have seen major advances since the third edition of the *Oxford Handbook of Clinical Haematology* was published. These are most obvious in haemato-oncology, with the development of new agents and regimens for treating malignant haematology disorders. But there have also been advances in haemostasis and red cell haematology with the arrival of the novel oral anticoagulation drugs and new oral chelators for the treatment of iron overload, in addition to a number of other advances.

This edition sees a change of editorial team and we are very happy to have John de Vos, haemato-oncologist, on board. He has overhauled the haemato-oncology sections bringing them thoroughly up to date. We have also sought the advice of Shubha Allard, consultant in transfusion medicine, to make sure the blood transfusion section is accurate, in addition to Banu Kaya, a red cell haematologist who has brought the red cell material up to date.

For the first time, we have incorporated a new chapter on rare disorders which we hope readers will find useful.

We are very grateful to the editorial team at Oxford University Press for their patience and hard work, especially Liz Reeve and Michael Hawkes.

There may be errors or omissions from the book and we would welcome any comments or feedback (email drewprovan@mac.com). We will try to incorporate these in future editions.

DP
TB
ID
JdV

January 2014

Preface to the third edition

It is hard to believe that at least three years have passed since the second edition of the handbook. As with all medical specialties, Haematology has seen major inroads with new diagnostic tests, treatments and a plethora of guidelines. In fact, Haematology has the largest collection of guidelines covering all aspects of haematology care (http://www.bcshguidelines.com) and was the first specialty to design guidelines in the 1980s.

The book underwent a major revision with the second edition, most notably the sections dealing with malignant disease. For the new edition these have been brought right up to date by Charles Singer. Coagulation has been entirely rewritten by Trevor Baglin and now truly reflects the current investigation and management of coagulation disorders. Following the retirement of Professor Sir John Lilleyman we needed to find a new author for the Paediatric Haematology component of the book. Thankfully, we were able to persuade Professor Inderjeet Dokal to take on this mantle and he has revised this section thoroughly.

In addition to these significant changes, we have gone through the entire book and attempted to ensure that obsolete tests have been removed and that the Handbook, in its entirety, reflects contemporary haematology practice.

As ever, we are very keen to hear about errors or omissions, for which we are entirely responsible! We would also very much like readers to contact us if there are topics or subject areas which they would like to see included in the fourth edition. We also need more trainee input so if there are any volunteer proof-readers or accuracy checkers among the haematology trainee community we would very much like to hear from you.

DP
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ISD

2008

Foreword to the fourth edition

The *Concise Oxford English Dictionary* defines a handbook as 'a short manual or guide'. Modern haematology is a vast field which involves almost every other medical speciality and which, more than most, straddles the worlds of the basic biomedical sciences and clinical practice. Since the rapidly proliferating numbers of textbooks on this topic are becoming denser and heavier with each new edition, the medical student and young doctor in training are presented with a daunting problem, particularly as they try to put these fields into perspective. And those who try to teach them are not much better placed; on the one hand they are being told to decongest the curriculum, while on the other they are expected to introduce large slices of molecular biology, social science, ethics, and communication skills, not to mention a liberal sprinkling of poetry, music, and art.

In this over-heated educational scene the much maligned 'handbook' could well stage a comeback and gain new respectability, particularly in the role of a friendly guide. In the past this genre has often been viewed as having little intellectual standing, of no use to anybody except the panic-stricken student who wishes to try to make up for months of misspent time in a vain, one-night sitting before their final examination. But given the plethora of rapidly changing information that has to be assimilated, the carefully prepared précis is likely to play an increasingly important role in medical education. Perhaps even that ruination of the decent paragraph and linchpin of the pronouncements of medical bureaucrats, the 'bullet point', may become acceptable, albeit in small doses, as attempts are made to highlight what is really important in a scientific or clinical field of enormous complexity and not a little uncertainty.

In the fourth edition of this short account of blood diseases the editors have continued to provide an excellent service to medical students, as well as doctors who are not specialists in blood diseases, by summarizing in simple terms the major features and approaches to diagnosis and management of most of the blood diseases that they will encounter in routine clinical practice or in the tedious examinations that face them. And, of equal importance, they have been able to update and summarize some of the major advances that have been made in this rapidly moving field since the appearance of the early editions of this handbook. As in previous editions they have managed to avoid one of the major pitfalls of this type of teaching: in trying to reduce complex issues down to their bare bones it is all too easy to introduce inaccuracies.

One word of warning from a battle-scarred clinician however. A précis of this type suffers from the same problem as a set of multiple-choice questions. Human beings are enormously complex organisms, and sick ones are even more complicated; during a clinical lifetime the self-critical doctor will probably never encounter a 'typical case' of anything. Thus the

outlines of the diseases that are presented in this book must be used as approximate guides, and no more. But provided they bear this in mind, students will find that it is a very valuable summary of modern haematology; the addition of the Internet sources is a genuine and timely bonus.

D. J. Weatherall
Oxford, June 2014

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We would like to acknowledge the patience and forbearance of our wives and families for the months of neglect imposed by the work on this edition. Warm thanks, as ever, are extended to Oxford University Press, and in particular Catherine Barnes, Senior Commissioning Editor for Medicine, Elizabeth Reeve, Commissioning Editor, Beth Womack, Managing Editor, and Kate Wilson, Production Manager. We fell behind schedule with this edition and are grateful to the whole OUP team for bearing with us so patiently and not harassing us! We apologize for anyone omitted but this is entirely unintentional.

Contributors

Shubha Allard
Consultant Haematologist
Barts Health NHS Trust, and NHS Blood & Transplant, UK

Banu Kaya
Consultant Haematologist
Barts Health NHS Trust, UK

Symbols and abbreviations

➔	cross-reference
↓	decreased
↑	increased
►	important
►►	very important
↔	normal
	website
♀	female
♂	male
1°	primary
2°	secondary
2,3 DPG	2,3 diphosphoglycerate
2-CDA	2-chlorodeoxyadenosine
A_2-M	alpha-2 microglobulin
6-MP	6-mercaptopurine
99mTc-MIBI	^{99m}Tc methoxyisobutyl-isonitride or ^{99m}Tc-MIBI scintigraphy
AA	aplastic anaemia or reactive amyloidosis
Ab	antibody
ABVD	adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine
ACD	acid-citrate-dextrose *or* anaemia of chronic disease
ACE	angiotensin converting-enzyme
ACL	anticardiolipin antibody
ACML	atypical chronic myeloid leukaemia
ADA	adenosine deaminase
ADE	cytosine arabinoside (Ara-C) daunorubicin etoposide
ADP	adenosine 5-diphosphate
AFB	acid-fast bacilli
Ag	antigen
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune haemolytic anaemia
AIN	autoimmune neutropenia
AITL	angio-immunoblastic T-cell lymphoma
AL	(1°) amyloidosis
ALB	serum albumin

ALCL	anaplastic large cell lymphoma
ALG	antilymphocyte globulin
ALIPs	abnormal localization of immature myeloid precursors
ALL	acute lymphoblastic leukaemia
ALS	advanced life support
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
AMP	adenosine monophosphate
ANA	antinuclear antibodies
ANAE	alpha naphthyl acetate esterase
ANCA	antineutrophilic cytoplasmic antibody
ANH	acute normovolaemic haemodilution
APC	activated protein C
APCR	activated protein C resistance
APL	antiphospholipid antibody
APML	acute promyelocytic leukaemia
APS	antiphospholipid syndrome
APTR	activated partial thromboplastin ratio
APTT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ARF	acute renal failure
ARMS	amplification refractory mutation system
ASCT	autologous stem cell transplantation
AST	aspartate aminotranferase
AT (ATIII)	antithrombin III
ATCML	adult-type chronic myeloid (granulocytic) leukaemia
ATG	antithymocyte globulin
ATLL	adult T-cell leukaemia/lymphoma
ATP	adenosine triphosphate
ATRA	all-trans retinoic acid
A-V	arteriovenous
AvWS	acquired von Willebrand syndrome
β_2-M	beta-2-microglobulin
BAL	broncho-alveolar lavage
B-CLL	B-cell chronic lymphocytic leukaemia
bd	bis die (twice daily)
BEAC	BCNU (Carmustine), etoposide, cytosine, cyclophosphamide
BEAM	BCNU (Carmustine), etoposide, cytarabine (ara-C), melphalan

BFU-E	burst-forming unit-erythroid
BJP	Bence Jones protein
BL	Burkitt lymphoma
BM	bone marrow
BMJ	*British Medical Journal*
BMM	bone marrow mastocytosis
BMT	bone marrow transplantation
BNF	*British National Formulary*
BP	blood pressure
BPL	BioProducts Laboratory
BSS	Bernard–Soulier syndrome
BTG	β-thromboglobulin
BU	Bethesda units
C/I	consolidation/intensification
Ca	carcinoma
Ca^{2+}	calcium
CABG	coronary artery bypass graft
cALL	common acute lymphoblastic leukaemia
CAMT	congenital amegakaryocytic thrombocytopenia
CaPO4	calcium phosphate
CBA	collagen binding activity
CBV	cyclophosphamide, carmustine (BCNU), etoposide
CCF	congestive cardiac failure
CCR	complete cytogenetic response
CD	cluster differentiation or designation
CDA	congenital dyserythropoietic anaemia
cDNA	complementary DNA
CEL	chronic eosinophilic leukaemia
CGL	chronic granulocytic leukaemia
CHAD	cold haemagglutinin disease
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CJD	Creutzfeldt–Jakob disease (v = variant)
Cl^-	chloride
CLD	chronic liver disease
CLL	chronic lymphocytic ('lymphatic') leukaemia
CM	cutaneous mastocytosis
CMC	chronic mucocutaneous candidiasis
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukaemia
CMV	cytomegalovirus

CNS	central nervous system
COAD	chronic obstructive airways disease
COC	combined oral contraceptive
CR	complete remission
CRF	chronic renal failure
CRP	C-reactive protein
CRVT	central retinal venous thrombosis
CsA	ciclosporin A
CSF	cerebrospinal fluid
CT	computed tomography
CTLp	cytotoxic T-lymphocyte precursor assays
CTZ	chemoreceptor trigger zone
CVA	cerebrovascular accident
CVP	cyclophosphamide, vincristine, prednisolone; central venous pressure
CVS	chorionic villus sampling
CVS	cardiovascular system
CXR	chest x-ray
CyA	ciclosporin A
CytaBOM	cytarabine, bleomycin, vincristine, methotrexate
d	day
DAGT	direct antiglobulin test
DAT	direct antiglobulin test daunorubicin, cytosine (Ara-C),
dATP	deoxy ATP
DBA	Diamond–Blackfan anaemia
DC	dyskeratosis congenita
DCS	dendritic cell system
DCT	direct Coombs' test
DDAVP	desamino D-arginyl vasopressin
DEAFF	detection of early antigen fluorescent foci
DEB	diepoxy butane
DFS	disease-free survival
DHAP	dexamethasone, cytarabine, cisplatin
DI	delayed intensification
DIC	disseminated intravascular coagulation
dL	decilitre
DLBCL	diffuse large B-cell lymphoma
DLI	donor leucocyte/lymphocyte infusion
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid

DOB	date of birth
DPG	diphosphoglycerate
DRVVT	dilute Russell's viper venom time/test
DTT	dilute thromboplastin time
DVT	deep vein thrombosis
DXT	radiotherapy
EACA	epsilon aminocaproic acid
EBV	Epstein–Barr virus
EBVP	etoposide, bleomycin, vinblastine, prednisolone
ECG	electrocardiograph
ECOG	European Co-operative Oncology Group
EDTA	ethylenediamine tetraacetic acid
EEC	endogenous erythroid colonies
EFS	event-free survival
EGF	epidermal growth factor
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
EMH	extramedullary haemopoietic
EMU	early morning urine
EPO	erythropoietin
EPOCH	etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone
EPS	electrophoresis
ESHAP	etoposide, methylprednisolone, cytarabine, platinum
ESR	erythrocyte sedimentation rate
ET	essential thrombocythaemia or exchange transfusion
ETTL	enteropathy type T-cell lymphoma
FAB	French–American–British
FACS	fluorescence-activated cell sorter
FBC	full blood count
FCM	fludarabine, cyclophosphamide, melphalan
FDG-PET	^{18}fluoro–D–2–deoxyglucose positron emission tomography
FDP	fibrin degradation products
Fe	iron
FEIBA	factor eight inhibitor bypassing activity
FEL	familial erythrophagocytic lymphohistiocytosis
$FeSO_4$	ferrous sulfate
FFP	fresh frozen plasma
FFS	failure-free survival
Fgn	fibrinogen

FH	family history
FISH	fluorescence *in situ* hybridization
FITC	fluorescein isothiocyanate
FIX	factor IX
fL	femtolitre
FL	follicular lymphoma
FNA	fine needle aspirate
FNHTR	febrile non-haemolytic transfusion reaction
FOB	faecal occult blood
FVIII	factor VIII
FVL	factor V Leiden
g	gram
G&S	group, screen, and save
G6PD	glucose-6-phosphate dehydrogenase
GA	general anaesthetic
GCS	graded compression stockings
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GIT	gastrointestinal tract
GM-CSF	granulocyte macrophage colony stimulating factor
GP	glycoprotein
GPI	glycosylphosphatidylinositol
GPS	grey platelet syndrome
GT	Glanzmann thrombasthenia
GvHD	graft-versus-host disease
GvL	graft versus leukaemia
h	hour
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
Hb	haemoglobin
HbA	haemoglobin A
HbA_2	haemoglobin A_2
HbF	haemoglobin F (fetal Hb)
HbH	haemoglobin H
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	hydroxycarbamide *or* heavy chain
HCD	heavy chain disease
HCG	human chorionic gonadotrophin
HCII	heparin cofactor II

HCL	hairy cell leukaemia
HCO_3	bicarbonate
Hct	haematocrit
HCV	hepatitis C virus
HD	haemodialysis
HDM	high-dose melphalan
HDN	haemolytic disease of the newborn
HDT	high-dose therapy
HE	hereditary elliptocytosis
HELLP	haemolysis, elevated liver enzymes and low platelets
HES	hypereosinophilic syndrome
HHT	hereditary haemorrhagic telangiectasia
HI	haematological improvement
HIT(T)	heparin-induced thrombocytopenia (with thrombosis)
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma (Hodgkin disease)
HLA	human leucocyte antigen
HLH	haemophagocytic lymphohistiocytosis
HMP	hexose monophosphate shunt
HMW	high molecular weight
HMWH	high molecular weight heparin
HMWK	high-molecular-weight kininogen
HPA	human platelet antigen
HPF	high power field
HPFH	hereditary persistence of fetal haemoglobin
HPLC	high-performance liquid chromatography
HPP	hereditary pyropoikilocytosis
HRT	hormone replacement therapy
HS	hereditary spherocytosis
HTC	hospital transfusion committee
HTLV-1	human T-lymphotropic virus type 1
HTO	high titre antibodies
HUMARA	human androgen receptor gene assay
HUS	haemolytic uraemic syndrome
IAGT	indirect antiglobulin test
IAHS	infection-associated haemophagocytic syndrome
ICE	ifosfamide, carboplatin, etoposide
ICH	intracranial haemorrhage
ICUS	idiopathic cytopenia of uncertain (undetermined) significance

IDA	iron deficiency anaemia
IF	involved field (radiotherapy)
IFA	intrinsic factor antibody
IFRT	involved field radiotherapy
Ig	immunoglobulin
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-1	interleukin-1
IM	intramuscular
IMF	idiopathic myelofibrosis
INR	international normalized ratio
inv	chromosomal inversion
IPC	intermittent pneumatic compression devices
IPF	immature platelet fraction
IPI	International Prognostic Index
IPSS	International Prognostic Scoring System
ISM	Indolent systemic mastocytosis
ISS	International Sensitivity Index
IST	immune suppressive therapy
IT	intrathecal
ITP	idiopathic thrombocytopenic purpura
ITU	Intensive Therapy Unit
IU	international units
IUGR	intrauterine growth retardation
IUT	intrauterine transfusion
IV	intravenous
IVI	intravenous infusion
IVIg	intravenous immunoglobulin
JCMML	juvenile chronic myelomonocytic leukaemia
JML	juvenile myelomonocytic leukaemia
JVP	jugular venous pressure
KCT	kaolin clotting time
kg	kilogram
L	litre
LA	lupus anticoagulant
LAP	leucocyte alkaline phosphatase (score)
LC	light chain