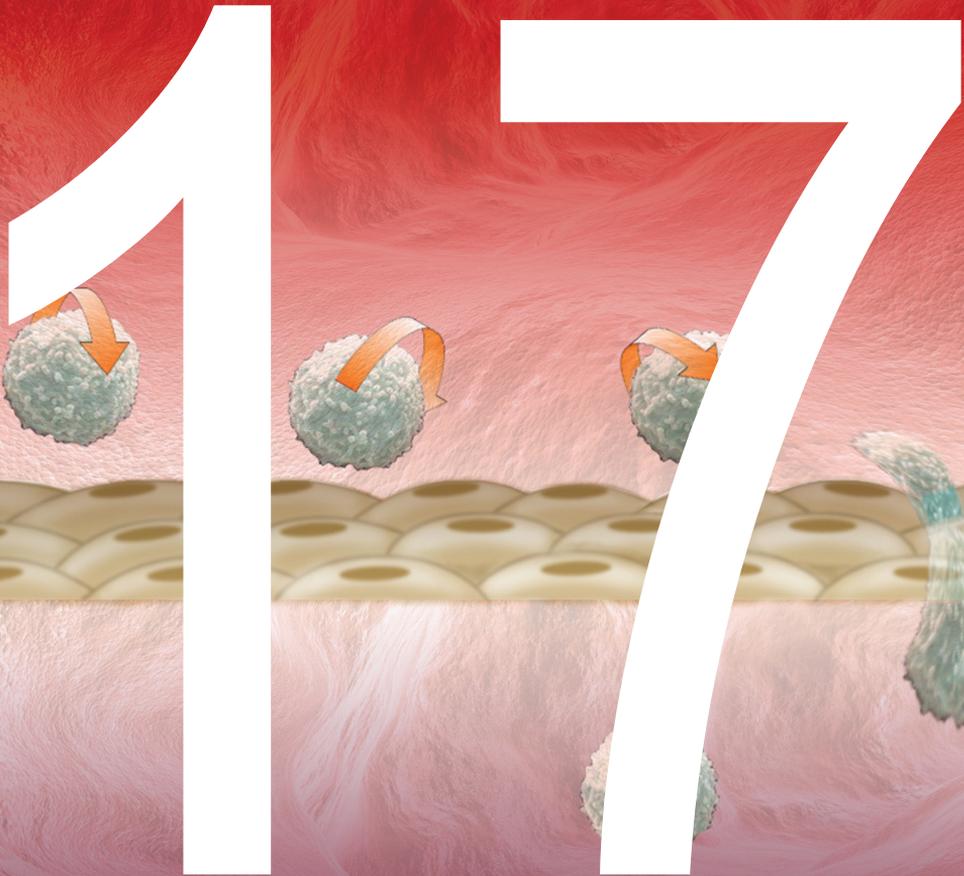


MECHANISMS OF VASCULAR DISEASE:

A REFERENCE BOOK FOR VASCULAR SPECIALISTS



EDITED BY ROBERT FITRIDGE AND MATTHEW THOMPSON
COMPLETELY UPDATED EDITION 2011

BARR SMITH PRESS

Mechanisms of Vascular Disease

Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

Robert Fitridge

The University of Adelaide, The Queen Elizabeth Hospital, Woodville, Australia

Matthew Thompson

St George's Hospital Medical School, London, UK



BARR SMITH PRESS

An imprint of
The University of Adelaide Press

Published in Adelaide by

The University of Adelaide, Barr Smith Press
Barr Smith Library
The University of Adelaide
South Australia 5005
press@adelaide.edu.au
www.adelaide.edu.au/press

The University of Adelaide Press publishes peer-reviewed scholarly works by staff via Open Access online editions and print editions.

The Barr Smith Press is an imprint of the University of Adelaide Press, reserved for scholarly works which are not available in Open Access, as well as titles of interest to the University and its associates. The Barr Smith Press logo features a woodcut of the original Barr Smith Library entrance.

© The Contributors 2011

This book is copyright. Apart from any fair dealing for the purposes of private study, research, criticism or review as permitted under the Copyright Act, no part may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior written permission. Address all inquiries to the Director at the above address.

This CIP cataloguing for this work is as follows;

Mechanisms of vascular disease : a reference book for vascular surgeons / Robert Fitridge, Matthew Thompson, [editors].

1. Blood vessels, Diseases.
2. Blood vessels, Surgery.

- I. Fitridge, Robert
- II. Thompson, M. M.

For the full Cataloguing-in-Publication data please contact National Library of Australia:
cip@nla.gov.au

ISBN (paperback) 978-0-9871718-2-5

Book design: Midland Typesetters

Cover design: Emma Spoehr, based on a diagram by Dave Heinrich of the Medical Illustration and Media Unit, Flinders Medical Centre

Paperback edition printed by Griffin Press, South Australia

Table of Contents

Contributors vii

Detailed Contents xi

1. Endothelium 1
Paul Kerr, Raymond Tam, Frances Plane (Calgary, Canada)
2. Vascular smooth muscle structure and function 13
David Wilson (Adelaide, Australia)
3. Atherosclerosis 25
Gillian Cockerill, Qingbo Xu (London, UK)
4. Mechanisms of plaque rupture 43
Ian Loftus (London, UK)
5. Current and emerging therapies in atheroprotection 79
Stephen Nicholls, Rishi Puri (Cleveland, USA)
6. Molecular approaches to revascularisation in peripheral vascular disease 103
Greg McMahon, Mark McCarthy (Leicester, UK)
7. Biology of restenosis and targets for intervention 115
Richard Kenagy (Seattle, USA)
8. Vascular arterial haemodynamics 153
Michael Lawrence-Brown, Kurt Liffman, James Semmens, Ilija Sutalo (Melbourne & Perth, Australia)
9. Physiological haemostasis 177
Simon McRae (Adelaide, Australia)
10. Hypercoagulable states 189
Simon McRae (Adelaide, Australia)
11. Platelets in the pathogenesis of vascular disease and their role as a therapeutic target 201
Sandeep Prabhu, Rahul Sharma, Karlheinz Peter (Melbourne, Australia)
12. Pathogenesis of aortic aneurysms 227
Jonathan Golledge, Guo-Ping Shi, Paul Norman (Townsville & Perth, Australia; Boston, USA)
13. Pharmacological treatment of aneurysms 247
Matthew Thompson, Janet Powell (London, UK)
14. Aortic dissection and connective tissue disorders 255
Mark Hamilton (Adelaide, Australia)
15. Biomarkers in vascular disease 277
Ian Nordon, Robert Hincliffe (London, UK)
16. Pathophysiology and principles of management of vasculitis and Raynaud's phenomenon 295
Martin Veller (Johannesburg, South Africa)
17. SIRS, sepsis and multiorgan failure 315
Vishwanath Biradar, John Moran (Adelaide, Australia)
18. Pathophysiology of reperfusion injury 331
Prue Cowled, Robert Fitridge (Adelaide, Australia)
19. Compartment syndrome 351
Edward Choke, Robert Sayers, Matthew Bown (Leicester, UK)
20. Pathophysiology of pain 375
Stephan Schug, Helen Daly, Kathryn Stannard (Perth, Australia)

21. Postamputation pain 389
Stephan Schug, Gail Gillespie
(Perth, Australia)
 22. Treatment of neuropathic pain 401
Stephan Schug, Kathryn Stannard
(Perth, Australia)
 23. Principles of wound healing 423
Gregory Schultz, Gloria Chin,
Lyle Moldawer, Robert Diegelmann
(Florida, USA)
 24. Pathophysiology and principles of
varicose veins 451
Andrew Bradbury (Birmingham, UK)
 25. Chronic venous insufficiency and leg
ulceration: Principles and vascular
biology 459
Michael Stacey (Perth, Australia)
 26. Pathophysiology and principles of
management of the diabetic foot 475
David Armstrong, Timothy Fisher,
Brian Lepow, Matthew White,
Joseph Mills (Tucson, USA)
 27. Lymphoedema – Principles, genetics
and pathophysiology 497
Matt Waltham (London, UK)
 28. Graft materials past and future 511
Mital Desai, George Hamilton
(London, UK)
 29. Pathophysiology of vascular graft
infections 537
Mauro Vicaretti (Sydney, Australia)
- Index 549

List of Contributors

David G Armstrong
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Vishwanath Biradar
Intensive Care Unit
The Queen Elizabeth Hospital
Woodville, SA
Australia

Matthew Bown
Department of Vascular Surgery
University of Leicester
Leicester
UK

Andrew W Bradbury
University Department of Vascular Surgery
Birmingham Heartlands Hospital
Birmingham
UK

Edward Choke
Department of Vascular Surgery
University of Leicester
Leicester
UK

Gillian Cockerill
Department of Clinical Sciences
St George's Hospital Medical School
London
UK

Prue Cowled
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Helen Daly
Royal Perth Hospital
Perth, WA
Australia

Mital Desai
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Robert F Diegelmann
Department of Biochemistry
Medical College of Virginia
Richmond, VA
USA

Timothy K Fisher
Rashid Centre for Diabetes and Research
Sheikh Khalifa Hospital
Ajmon
UAE

Robert A Fitridge
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Gail Gillespie
Royal Perth Hospital
Perth, WA
Australia

Jonathan Golledge
Vascular Biology Unit
School of Medicine & Dentistry
James Cook University
Townsville, QLD
Australia

George Hamilton
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Mark Hamilton
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Robert J Hinchliffe
St George's Vascular Institute
St George's Hospital
London
UK

Richard D Kenagy
Department of Surgery
University of Washington
Seattle, WA
USA

Paul Kerr
Department of Pharmacology
University of Alberta
Alberta
Canada

Michael MD Lawrence-Brown
Curtin Health Innovation Research
Institute
Curtin University
Perth, WA
Australia

Brian Lepow
The University of Arizona
Department of Surgery
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Kurt Liffman
CSIRO Material Science & Engineering
and School of Mathematical Sciences
Monash University
Melbourne, Vic
Australia

Ian Loftus
Department of Vascular Surgery
St George's Hospital
London
UK

Mark J McCarthy
Department of Surgery and Cardiovascular
Sciences
University of Leicester
Leicester
UK

Greg S McMahon
Department of Surgery and Cardiovascular
Sciences
University of Leicester
Leicester
UK

Simon McRae
Adult Haemophilia Treatment Centre
SA Pathology
Adelaide, SA
Australia

Joseph L Mills
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Lyle Moldawer
Department of Surgery
University of Florida
Gainesville, FL
USA

John L Moran
Faculty of Health Sciences
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Stephen Nicholls
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Ian M Nordon
St George's Vascular Institute
St George's Hospital
London
UK

Paul E Norman
School of Surgery
University of WA
Fremantle, WA
Australia

Karlheinz Peter
Baker IDI Heart & Diabetes Institute
Melbourne, Vic
Australia

Frances Plane
Department of Pharmacology
University of Alberta
Alberta
Canada

Janet T Powell
Imperial College
London
UK

Sandeep Prabhu
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Rishi Puri
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Stephan A Schug
Royal Perth Hospital
Perth, WA
Australia

Gregory S Schultz
Department of Obstetrics and Gynaecology
University of Florida
Gainesville, FL
USA

Rahul Sharma
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Guo-Ping Shi
Department of Cardiovascular Medicine
Brigham & Women's Hospital
Harvard Medical School
Boston, MA
USA

Michael Stacey
University Department of Surgery
Fremantle Hospital
Fremantle, WA
Australia

Ilija D Sutalo
CSIRO Material Science & Engineering
and Curtin Health Innovation
Research Institute
Curtin University
Highett, Vic

Raymond Tam
Department of Pharmacology
University of Alberta
Alberta
Canada

Matthew Thompson
St Georges Hospital Medical School
London
UK

Martin Veller
Department of Surgery
University of Witwatersrand
Johannesburg
South Africa

Mauro Vicaretti
Department of Vascular Surgery
Westmead Hospital
Westmead, NSW
Australia

Matt Waltham
Academic Department of Surgery
St Thomas' Hospital
London
UK

Matthew L White
Vascular and Endovascular Surgery
University of Arizona
Tucson, AZ
USA

David P Wilson
School of Medical Sciences
Discipline of Physiology
University of Adelaide
Adelaide SA
Australia

Qingbo Xu
Department of Cardiology
Kings College
University of London
UK

Detailed Contents

CHAPTER 1 – ENDOTHELIUM

Paul Kerr, Raymond Tam, Frances Plane

- Introduction 1
- Endothelium-dependent regulation of vascular tone 2
- Angiogenesis 7
- Haemostasis 8
- Inflammation 9
- Conclusions 10
- References

CHAPTER 2 – VASCULAR SMOOTH MUSCLE STRUCTURE AND FUNCTION

David Wilson

- Introduction 13
- Smooth muscle (vascular) structure
- Cytoskeleton 14
- Contractile myofilament
- Functional regulation of vascular smooth muscle: Neuronal, hormonal, receptor mediated 15
- Smooth muscle function 17
- Myofilament basis of smooth muscle contraction and relaxation
- Smooth muscle contraction and relaxation 18
- Ion channels important in the regulation of smooth muscle function
- Regulation of cellular Ca^{2+}
- Sources of cytosolic Ca^{2+} entry 19
- Potassium channels
- Endothelial regulation of smooth muscle vasodilatation 20

Smooth muscle proliferation and vascular remodeling 20

Summary 22

References

CHAPTER 3 – ATHEROSCLEROSIS

Gillian Cockerill, Qingbo Xu

Introduction 25

Atherosclerotic lesions 26

Fatty streaks

Plaque or atheroma

Hypercholesterolemia and oxidised-LDL 27

High-density lipoproteins role in atheroprotection 28

Hypertension and biomechanical stress 29

Biomechanical stress-induced cell death 30

Biomechanical stress and inflammation 31

Biomechanical stress-induced smooth muscle cell proliferation 32

Infections and heat shock proteins

Infections

Heat shock proteins 33

Infections and HSP expression

Infections, sHSP and innate immunity 34

Immune responses 36

MHC class II antigens and T cells

Oxidised LDL as a candidate antigen

HSP60 as a candidate antigen 37

B2-glycoprotein Ib as a candidate antigen

Inflammation

C-reactive protein	38
CD40/CD40L	
Summary and perspectives	39
References	

CHAPTER 4 – MECHANISMS OF PLAQUE RUPTURE

Ian Loftus

Introduction	43
Evidence for the ‘plaque rupture theory’	44
Coronary circulation	
Cerebral circulation	
The role of individual components of the arterial wall	
The endothelium	45
The lipid core	47
The cap of the plaque	49
Smooth muscle cells and collagen production	50
Macrophages and collagen degradation	51
The vessel lumen	56
The role of angiogenesis in plaque rupture	
The role of infectious agents in plaque rupture	57
Risk prediction of plaque instability	58
Imaging	
Blood markers	59
Therapy aimed at plaque stabilisation	
HMG Co-A reductase inhibitors	60
MMP inhibition	
Tissue inhibitors of metalloproteinases (TIMPs)	61
Synthetic MMP inhibitors	
Doxycycline	
ACE inhibitors	
Summary	62
References	63

CHAPTER 5 – CURRENT AND EMERGING THERAPIES IN ATHEROPROTECTION

Stephen Nicholls, Rishi Puri

Background	79
Pathology	
Risk factor modification	80
Statins, LDL lowering and C-reactive protein	
The complexity of HDL	84
The controversy of triglycerides	87
Hypertension	
Risk factor modification in the diabetic patient	89
Glycaemic control	
Global risk factor reduction in diabetics	91
The metabolic syndrome	92
Future targets	93
Conclusion	
References	94

CHAPTER 6 – MOLECULAR APPROACHES TO REVASCULARISATION IN PERIPHERAL VASCULAR DISEASE

Greg S McMahon, Mark J McCarthy

Introduction	103
Mechanisms of vascular growth	
Vasculogenesis	
Angiogenesis	104
Neovessel maturation	105
Microvascular network maturation	106
Arteriogenesis	
Therapeutic induction of vascular growth	107
Delivery of molecular activators of vascular growth	
Angiogenic activators	108
Arteriogenic activators	109
Clinical trials for angiogenic therapy of peripheral vascular disease	
Conclusions	110
References	

CHAPTER 7 – BIOLOGY OF RESTENOSIS AND TARGETS FOR INTERVENTION

Richard Kenagy

Introduction 115

Mechanisms of restenosis

Thrombosis 116

Remodelling

Intimal hyperplasia 123

Sequence of events after injury

Origin of intimal cells 125

Inflammation 126

Role of ECM production 127

The contribution of specific factors to restenosis

Growth factors/cytokines

Inhibitors 128

Coagulation and fibrinolytic factors 129

Matrix metalloproteinases

Extracellular matrix/receptors

Targets for intervention 130

Intracellular signalling molecules

mTOR and microtubules

Transcription factors

miRNA 131

Inflammation targets

Brachytherapy

Extracellular targets and cell-based therapies

Angiotensin pathway

Cell-based therapies 132

Differential effects on endothelium and SMCs

Delivery devices

Prevention versus reversal of restenosis

Conclusions 133

References 134

CHAPTER 8 – VASCULAR ARTERIAL HAEMODYNAMICS

Michael Lawrence Brown, Kurt Liffman, James Semmens, Ilija Sutalo

Introduction 153

Laplace's law of wall of tension 154

Newtonian fluid 155

Non-Newtonian fluid

Poiseuille flow 158

Bernoulli's equation

Young's modulus and pulsatile flow 159

Mass conversion 161

Reynold's number

Arterial dissection, collateral circulation and competing flows 163

Shear stress and pressure 164

Forces on graft systems 165

Case 1 – The cylindrical graft 168

Case 2 – The windsock graft

Case 3 – The curved graft 169

Case 4 – The symmetric bifurcated graft

Computational modelling 170

Recent development and future directions 171

Conclusions 172

References 173

CHAPTER 9 – PHYSIOLOGICAL HAEMOSTASIS

Simon McRae

Introduction 177

Primary haemostasis

Platelets

Platelet adhesion

Platelet activation and shape change 179

Platelet aggregation 180

Interactions between primary and secondary haemostasis 181

Secondary haemostasis

The coagulation cascade 182

Initiation 183

Amplification

Propagation 184

Normal inhibitors of coagulation

Fibrinolysis 185

Conclusions 186

References

CHAPTER 10 – HYPERCOAGULABLE STATES

Simon McRae

Introduction 189

Classification of thrombophilia

Inherited thrombophilia 190

Type 1 conditions

Antithrombin deficiency

Protein C and Protein S deficiency

Type 2 conditions 191

Factor V Leiden

The prothrombin (G20210A) gene mutation

FVL/PGM compound heterozygotes

Other inherited conditions

Acquired thrombophilia 192

Antiphospholipid antibodies

Heparin induced thrombocytopenia

Myeloproliferative disorders 193

Potential reasons for performing thrombophilia testing

Patients with venous thrombosis and their relatives

Providing an understanding of the aetiology of a thrombotic event

Determining risk of recurrence and therefore optimal duration of anticoagulation 194

Determining the need for primary prophylaxis in asymptomatic family members 195

Making decisions regarding the use of the oral contraceptive pill 196

Determining the need for thromboprophylaxis during pregnancy

Patients with arterial thrombosis

Potential detrimental effects of thrombophilia testing 197

Conclusion

References

CHAPTER 11 – PLATELETS IN THE PATHOGENESIS OF

VASCULAR DISEASE AND THEIR ROLE AS A THERAPEUTIC TARGET

*Sandeep Prabhu, Rahul Sharma,
Karlheinz Peter*

Introduction 201

Platelet function – Adhesion and activation

Platelet adhesion 202

Platelet activation 203

Mediators of platelet activation and ‘outside in’ signalling

Thrombin and collagen 204

Adenosine diphosphate (ADP)

Thromboxane A2 (TXA2)

Adrenaline 206

Second messenger systems 207

Physiological consequences of platelet activation

The GP IIb/IIIa receptor and ‘inside-out’ signalling

Granule exocytosis 208

Activation-induced conformational change of platelets

Platelets and atherosclerosis 209

Role of platelets in the initiation of the atherosclerosis

Role of the platelets in the progression of the atherosclerosis

Role of platelets in vulnerable plaques and plaque rupture

Current and future anti-platelet agents 210

Aspirin (salicylic acid)

Thienopyridines 211

Clopidogrel

Prasugrel 213

Ticlopidine

Ticagrelor

GPIIb/IIIa Antagonists

Other anti-platelet agents and promising new developments 214

Platelet function testing 215

Light-transmission aggregometry

Whole blood aggregometry 217
 VerifyNow® Assay
 Flow cytometry 218

References

CHAPTER 12 – PATHOGENESIS OF AORTIC ANEURYSMS

*Jonathan Golledge, Guo-Ping Shi,
 Paul E Norman*

Introduction 227

Differences between thoracic and abdominal aortic aneurysms 228

Summary of current theories and stages of AAA evolution

Atherosclerosis and AAA

Immune mechanisms in AAA 229

Extracellular matrix dysfunction 232

Infection 233

Biomechanical forces

Angiogenesis

Intra-luminal thrombus

Extracellular matrix proteolysis 234

Genetics 236

AAA rupture 237

Biomechanical factors in aneurysms rupture

The role of enzymes in AAA rupture

Role of intraluminal thrombus in aneurysm rupture 238

Future research

References

CHAPTER 13 – PHARMACOLOGICAL TREATMENT OF ANEURYSMS

Matthew Thompson, Janet T Powell

Background 247

Screening programmes

Pathophysiology 248

Therapeutic strategies

Beta blockade

Modification of the inflammatory

response 249

Non-steroidal anti-inflammatories

Matrix metalloproteinase (MMP)

inhibition

Anti-chlamydial therapy 250

Drugs acting on the renin/angiotensin axis

HMG Co-A reductase inhibitors 251

The future – Data from recent

experimental studies

References

CHAPTER 14 – PATHOPHYSIOLOGY OF AORTIC DISSECTION AND CONNECTIVE TISSUE DISORDERS

Mark Hamilton

Introduction 255

Embryology of thoracic aorta and arch vessels

Haemodynamics of thoracic compared to abdominal aorta 257

Sizes of normal aorta

Classification of aortic syndromes

Acute/Chronic

DeBakey classification of class 1 dissection – Type 1, 2, and 3

Stanford classification 258

European task force

Pathogenesis of thoracic aortic dissection

Classical thoracic aortic dissection (class 1 dissection) 260

Intramural haematoma (class 2 aortic dissection) 261

Penetrating aortic ulcer (class 4 aortic dissection) 262

Complications of acute aortic syndromes 263

Visceral ischaemia /malperfusion syndromes

Fate of the false lumen

Aneurysmal degeneration and rupture 264

Connective tissue disorders and acute aortic syndromes

Marfan syndrome
 Fibrillin and Marfan syndrome 265
 The role of transforming growth factor
 beta in development of the vascular
 system in health and disease 266
 Ehlers-Danlos syndrome 267
 Diagnosis of Ehlers-Danlos syndrome
 268
 Loeys-Deitz syndrome 270
 Familial thoracic aortic aneurysm disease
 271
 Bicuspid aortic valve 273
 Turners Syndrome
Summary 274
Reference list

CHAPTER 15 – BIOMARKERS IN VASCULAR DISEASE

Ian M Nordon, Robert J Hinchliffe

Introduction 277
What is a biomarker?
Types of biomarkers
 A classical clinical example 278
**Potential value of biomarkers in vascular
 disease 279**
Biomarker discovery steps 280
AAA biomarkers
 Circulating extracellular matrix markers
 281
 Matrix-degrading enzymes 283
 Proteins associated with thrombosis
 Markers of inflammation 284
Biomarkers of AAA rupture 285
Biomarkers following endovascular repair
 Inflammation 287
 Lipid accumulation
 Apoptosis
 Thrombosis
 Proteolysis 288
Challenges in biomarkers discovery
Future work
Conclusion 289
References

CHAPTER 16 – PATHOPHYSIOLOGY AND PRINCIPLES OF MANAGEMENT OF VASCULITIS AND RAYNAUD'S PHENOMENON

Martin Veller

Vasculitides 295
Introduction
Classification of vasculitides 296
Clinical presentation of vasculitides
Investigations of vasculitides
**Principles of treatment of vasculitides
 297**
**The vasculitides of specific interest to
 vascular surgeons 298**
 Giant cell arteritis
 Takayasu's arteritis 299
 Thromboangitis obliterans (Buerger's
 disease) 300
 Behcet's disease 301
 Polyarteritis nodosa 302
 Vasculitides secondary to connective
 tissue diseases 303
 Systemic lupus erythematosus (SLE)
 Antiphospholipid antibody syndrome
 (APS) 304
 Rheumatoid arthritis 305
 Scleroderma
 Infective vasculitides 306
 Human immunodeficiency virus (HIV)
**Pathophysiology and principles of
 Raynaud's phenomenon 307**
 Prevalence of Raynaud's phenomenon
 308
 Clinical findings in Raynaud's
 phenomenon 309
 Diagnosis of Raynaud's phenomenon
Prognosis 310
Treatment
Recommendations 311
References 312

CHAPTER 17 – SIRS, SEPSIS AND

MULTIORGAN FAILURE*Vishwanath Biradar, John Moran***Epidemiology 315****Historical perspectives and definition 316****Risk factors for sepsis 317**

Causative agents

Pathophysiology of sepsis

innate immunity and toll-like receptors (TLRs) 319

Proinflammatory response

Coagulation cascade

Multorgan dysfunction syndrome (MODS) 320

Epithelial and endothelial dysfunction

Immune suppression and apoptosis

Sepsis, circulatory failure and organ dysfunction

Management 322

Steroids 323

Recombinant human activated protein C (rhAPC) 324

Glucose control 325

Renal replacement therapy

3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (HMG-CoA) 326

Other adjuvant therapies in sepsis

Cytokines and anticytokine therapies

Pooled immunoglobulin (IVIG)

Acute respiratory distress syndrome (ARDS) 327

References**CHAPTER 18 –
PATHOPHYSIOLOGY OF
REPERFUSION INJURY***Prue Cowled, Rob Fitridge***Introduction 331****Ischaemia**

ATP and mitochondrial function

Gene expression during ischaemia 332

Reperfusion 333

Reactive oxygen species

Eicosanoids 334

Nitric Oxide 335

Endothelin 336

Cytokines

Neutrophil and endothelial interactions 338

Complement activation 340

Tissue destruction 341

Proteases and metalloproteinases

Apoptotic cell death during ischaemia-reperfusion injury

No-reflow phenomenon 342

Therapeutic approaches to IRI

Ischaemic preconditioning

Ischaemic post-conditioning 343

Conditioning effects of volatile anaesthetics

Pharmacological treatments 344

Summary 345**References****CHAPTER 19 – COMPARTMENT
SYNDROME***Edward Choke, Robert Sayers, Matthew Bown***Definition 351****Acute limb compartment syndrome**

Incidence

Anatomy/physiology 352

Aetiology/pathophysiology

Clinical presentation 354

Investigation 355

Treatment 357

Complication of LCS 359

Outcome 360

Acute abdominal compartment syndrome

Incidence 361

Aetiology

Pathological effects of raised intra-abdominal pressure 362

Clinical presentation 363

Investigation

Treatment 364

Complications of surgical decompression

Outcome 367

References 368

CHAPTER 20 – PATHOPHYSIOLOGY OF PAIN

Stephan Schug, Helen Daly, Kathryn Stannard

Introduction 375

Peripheral mechanisms

Nociception/transduction

Conduction 376

Spinal cord mechanisms

Ascending systems 377

Descending control

Pain modulation 378

Peripheral sensation

Central sensitisation in the dorsal horn

Neuropathic pain 379

Mechanisms of neuropathic pain

Peripheral mechanisms

Spontaneous ectopic discharge

Altered gene expression

Spared sensory neurons

Involvement of the sympathetic nervous system 380

Collateral sprouting

Effects of bradykinin

Central mechanisms

Wind up

Central sensitization 381

Central disinhibition

Expansion in receptive field size (recruitment)

Immediate early gene expression

Anatomical re-organisation of the spinal cord

Contribution of glial cells to pain conditions 382

Symptoms of neuropathic pain

Stimulus-dependent pain

Stimulus-independent pain 383

Sympathetically maintained pain (SMP)

Neuropathic pain syndromes

Peripheral neuropathies

Central neuropathies 385

References

CHAPTER 21 – POST-AMPUTATION PAIN

Stephan Schug, Gail Gillespie

Introduction 389

Classification and incidence of post-amputation pain syndromes

Stump pain

Phantom sensation 390

Phantom limb pain

Pathophysiology of post-amputation pain syndromes

Peripheral factors

Spinal factors 391

Supraspinal factors

Current pathophysiological model of post-amputation pain syndromes 392

Prevention of post-amputation pain

Perioperative lumbar epidural blockade

Peripheral nerve blockade 393

NMDA antagonists

Evaluation of the patient with post-amputation pain syndromes

Examination

Therapy of post-amputation pain syndromes 394

Calcitonin

Ketamine

Analgesic and Co-analgesic compounds

Opioids 395

Gabapentin

Clonazepam

Lidocaine

Carbamazepine

Tricyclic antidepressants (TCA)

Selective serotonin reuptake inhibitors

Baclofen

Capsaicin

Symptomatic treatment of pain components 396

Neuropharmacological therapies

Invasive therapies
 Electroconvulsive therapy (ECT)
 Nerve blockade
 Spinal cord stimulation
 Implantable intrathecal delivery systems
 Dorsal root entry zone (DREZ) lesions
 Psychological therapy 397

Future aims

References

CHAPTER 22 – TREATMENT OF NEUROPATHIC PAIN

Stephan Schug, Kathryn Stannard

Introduction 401

Principles of treatment

Pharmacological treatment 402

Opioids

Recommendations for clinical use of opioids

Tramadol

Mechanism of action

Efficacy 403

Adverse effects

Recommendations for clinical use of tramadol in neuropathic pain

Antidepressants

Tricyclic antidepressants (TCAs)

Mechanism of action 404

Adverse effects

Selective serotonin re-uptake inhibitors (SSRIs)

Serotonin/Noradrenaline reuptake inhibitors (SNRIs) 405

Recommendations for clinical use of antidepressants as analgesics

Anticonvulsants

Mechanism of action 406

Individual medications

Clonazepam

Gabapentin

Pregabalin 407

Carbamazepine

Sodium valproate 408

Phenytoin

Lamotrigene

Recommendations for clinical use of anticonvulsants as analgesics

Local anaesthetics and antiarrhythmics 409

Mechanism of action

Lignocaine

Mexiletine

Recommendations for clinical use of lignocaine and mexiletine in neuropathic pain

N-methyl-D-aspartate-receptor antagonists (NMDA)

Ketamine 410

Other NMDA antagonists

Miscellaneous compounds for systemic use

Clonidine

Efficacy

Baclofen

Levodopa 411

Cannabinoids

Topical treatments

Lignocaine 5% medicated plaster

Capsaicin 412

Mechanism of action

Efficacy

Non-pharmacological therapy

Transcutaneous electrical nerve stimulation (TENS)

Spinal cord stimulation (SCS) 413

Sympathetic nerve blocks

Neurosurgical destructive techniques

Cognitive behaviour therapy

References 414

CHAPTER 23 – PRINCIPLES OF WOUND HEALING

Gregory Schultz, Gloria Chin, Lyle Moldawer, Robert Diegelmann

Introduction 423

Phases of acute wound healing

Haemostasis

- Inflammation 426
 - Neutrophils 427
 - Macrophages 428
- Proliferative phase 429
 - Fibroblast migration 430
 - Collagen and extracellular matrix production
 - Angiogenesis 431
 - Granulation 432
 - Epithelialization
 - Remodelling 433
- Summary of acute wound healing 435
- Comparison of acute and chronic wounds**
 - Normal and pathological responses to injury
 - Biochemical differences in the molecular environments of healing and chronic wounds 436
 - Biological differences in the response of chronic wound cells to growth factors 439
- From bench to bedside**
 - Role of endocrine hormones in the regulation of wound healing
 - Molecular basis of chronic non-healing wounds
 - Chronic venous stasis ulcers 441
 - Pressure ulcers
- Future concepts for the treatment of chronic wounds 442**
 - Bacterial biofilms in chronic wounds 443
- Conclusion 445**
- References**

CHAPTER 24 – PATHOPHYSIOLOGY AND PRINCIPLES OF MANAGEMENT OF VARICOSE VEINS

Andrew Bradbury

- Introduction 451**
- Anatomy**
- Histology 452**
- Physiology**

- Varicose veins 453**
- Valvular abnormalities**
- Muscle pump failure 455**
- Venous recirculation**
- Recurrent varicose veins**
 - New varicose veins
 - Persistent varicose veins
 - True recurrent varicose veins 456
- Cellular and molecular biology of varicose veins**
- Conclusion 457**
- References**

CHAPTER 25 – CHRONIC VENOUS INSUFFICIENCY AND LEG ULCERATION: PRINCIPLES AND VASCULAR BIOLOGY

Michael Stacey

- Definitions 459**
 - Chronic venous insufficiency
 - Leg ulceration
 - Assessment of cause of leg ulceration 460
- Epidemiology 461
- Pathophysiology
 - Venous abnormality
 - Effect of ambulatory venous hypertension on the tissues in the leg 463
 - Influence of venous disease on the wound healing process 465
 - Genetic associations with venous ulceration 466
- Assessment of venous function 467**
- Treatment of venous ulceration**
 - Compression therapy
 - Dressings 468
 - Surgery
 - Prevention of venous ulcer recurrence 470
 - Sclerotherapy and other techniques to obliterate surface and perforating veins
 - Other therapies 471
- References**

CHAPTER 26 –
PATHOPHYSIOLOGY AND
PRINCIPLES OF MANAGEMENT
OF THE DIABETIC FOOT

*David Armstrong, Timothy Fisher, Brian
Lepow, Matthew White, Joseph Mills*

- Introduction** 475
- Pathophysiology of the diabetic foot** 476
- Neuropathy
 - Structural abnormalities/gait abnormalities
 - Angiopathy 478
- Diagnosis**
- History and rapid visual screening
 - Neurological examination 479
 - Monofilament testing
 - Vibration testing
 - Dermatologic examination 480
 - Anatomy of occlusive disease – vascular examination
 - Prediction of wound healing: assessment of perfusion 481
 - Arterial imaging
 - Soft tissue imaging 482
- Classification systems** 483
- Diabetes mellitus foot risk classification
 - University of Texas wound classification system
- Clinical problems and principles of management** 484
- Ulceration
 - Epidemiology and risk factors
 - Offloading
 - Non-vascular surgical treatment 485
 - Class I – Elective 486
 - Class II – Prophylactic
 - Class III – Curative
 - Class IV – Emergency (urgent)
 - Post-operative management
 - Infections 487
 - Charcot arthropathy
- Prevention** 490
- Conclusion** 492
- References**

CHAPTER 27 – LYMPHOEDEMA
– PRINCIPLES, GENETICS AND
PATHOPHYSIOLOGY

Matt Waltham

- Introduction** 497
- Classification of lymphoedema**
- Classification of primary lymphoedema 498
- The genetics of lymphangiogenesis in primary lymphoedema** 500
- Milroy's disease
 - Lymphoedema – distichiasis syndrome 501
 - Hypotrichosis – lymphoedema – telangiectasia syndrome 502
 - Meige disease (primary non-syndromic lymphoedema)
 - Other primary lymphoedema disorders 503
- Structure and development of the lymphatic circulation**
- Clinical aspects of lymphoedema** 505
- Summary**
- References**

CHAPTER 28 – GRAFT
MATERIALS PAST AND FUTURE

Mital Desai, George Hamilton

- The pathophysiology of graft healing** 511
- The peri-anastomotic area
 - Healing of prosthetic grafts 512
 - The healing process of the anastomosis
 - Graft porosity and permeability
- Physical properties of prosthetic materials** 514
- Tubular compliance
 - Anastomotic compliance mismatch
 - The compliance hypothesis of graft failure
- Synthetic grafts** 515
- Newer developments of Dacron grafts
 - Modifications and newer developments of PTFE grafts 517
 - Polyurethane grafts

Newer developments of polyurethane vascular grafts	518
Biological vascular grafts	519
Newer developments of biological vascular grafts	520
Prosthetic graft modifications	
Modifications to reduce graft infection	
Modifications to improve patency	521
Nanocomposite grafts	
Endothelial cell seeding	522
Single stage seeding	
Two stage seeding	
Vascular tissue engineering	
Non-degradable polymer and cell seeding	523
Bioresorbable and biodegradable polymers	
Combined bioresorbable and tissue engineered grafts	524
Mechanical conditioning of seeded vascular cells	
Alternative scaffolds	
Tissue-engineered grafts	525
Graft materials for aortic endografts	526
The future	
References	527

CHAPTER 29 – PATHOPHYSIOLOGY OF VASCULAR GRAFT INFECTIONS

Mauro Vicaretti

Introduction	537
Natural history of prosthetic vascular graft infections	
Mechanism of graft contamination at operation	538
Pathogenesis of graft infections	
Bacteriology of vascular graft infections	
Investigations for detection of prosthetic graft infections	539
History and physical examination	
Laboratory investigations	
Diagnostic imaging	540
Management of prosthetic graft infections	
Prevention	
Reduction of prosthetic vascular graft infection with rifampicin bonded gelatin sealed Dacron	541
Established infection	
Antibiotic therapy	
Operative management	
Conclusion	542
References	

Acknowledgements

The Editors gratefully acknowledge the outstanding contributions of each Author involved in this reference book. We would also like to acknowledge the invaluable efforts of Ms Sheona Page who has worked tirelessly on this project. We would also like to thank Prue Cowled PhD and Ms Cayley Wright for their assistance.

Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotrophic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α -amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β 2-GPI	β 2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonin gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1 α	Interleukin-1 alpha
IL-1 β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC ₂₀	Myosin light chain ₂₀
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin resistant <i>Staphylococcus epidermidis</i>
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI ₂	Prostacyclin
PGG ₂	Prostaglandin G ₂
PGH ₂	Prostaglandin H ₂
PGEI ₂ /PGI ₂	Prostaglandin I ₂
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca ²⁺ APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
T α CE	TNF α converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF- α	Transforming growth factor-alpha
TGF- β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF- α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

17 • SIRS, Sepsis and Multiorgan Failure

VISHWANATH BIRADAR, JOHN L MORAN

The Queen Elizabeth Hospital, 28 Woodville Rd, Woodville South,
Adelaide, South Australia

EPIDEMIOLOGY

Sepsis remains a common reason for intensive care unit (ICU) admission and is a leading cause of mortality. This disease is now recognized to be a time-sensitive emergency, because patients stand the best chance for survival when effective therapeutic interventions are delivered as early as possible. However, consistent data are lacking regarding the incidence and outcome of sepsis in ICUs globally. Data extrapolated from a cohort study conducted by Finfer *et al* in 2004 across twenty three closed multidisciplinary ICUs showed that the incidence of severe sepsis among adult patients was 0.77 patients per 1000 population (95% CI, 0.76–0.79). There were 752 episodes of severe sepsis identified in 691 patients, equating to 11.8 patients with severe sepsis per 100 ICU admissions (95% CI, 10.9–12.6).¹ The EPISEPSIS study group conducted a nationwide, prospective, multi-centre survey of patients with severe sepsis in 206 French ICUs over two consecutive weeks. They estimated the incidence of severe sepsis to be 0.95 cases per 1000 in the French population.² In the United States between

1979 and 2000 an annualized increase of 8.7% in the incidence of sepsis was noted. (From about 164,000 cases (0.82 per 1000 population) to nearly 660,000 cases (2.4 per 1000 population)).³

Sepsis is estimated to affect 18 million people worldwide each year and kill 1400 people each day. According to an epidemiological study, sepsis affects about 700,000 people annually in the United States alone, with an overall mortality rate of 30%, or more than 50% in patients with septic shock and/or multiple system organ failure.³ From a financial perspective, sepsis represents a major burden to the health care system in most developed countries since septic patients require admission and aggressive treatment in the ICUs. Table 17.1 gives the overall information on the incidence and mortality of severe sepsis in different parts of the world. Despite differences in study methodology, comparison between continents, countries and regions is possible, with some consistent themes emerging:

- 1) Severe sepsis represents a substantial health-care burden in all developed nations;

- 2) The overall incidence is increasing;
- 3) The overall mortality rate is declining;
and
- 4) The nature of infections is changing,
with infections caused by gram-positive
organisms increasing in frequency.⁴

HISTORICAL PERSPECTIVE AND DEFINITION

The word 'sepsis' [σηψις], is the original Greek word for the 'decomposition of animal or vegetable organic matter in the presence of bacteria'.⁹ The word was first noted in Homer's poems, where 'sepsis' is a derivative of the verb form sepo [σηπω], which means 'I rot'. The term is also found in the writings of the physician and philosopher Hippocrates (circa 400 BC) in his *Corpus Hippocraticum*. Hippocrates viewed sepsis as the dangerous, odiferous, biological decay that could occur in the body.¹⁰

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a 'Consensus Conference' in an attempt 'to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the

generalized term 'sepsis' and includes sepsis-associated organ dysfunction as well'.¹¹ They proposed the phrase 'Systemic Inflammatory Response Syndrome' (SIRS) which described the inflammatory process, independent of its cause. The systemic inflammatory response was seen in association with a large number of clinical conditions. Apart from infectious processes, other common non-infectious pathologic processes include pancreatitis, ischemia, multiple trauma, and tissue injury. When SIRS is the result of confirmed infectious process, it is termed 'SEPSIS', and is frequently associated with the development of multiple organ dysfunction and failure. This is the most common cause of death in patients who have severe sepsis.¹² The 1991 ACCP-SCCM Consensus Conference also introduced the term 'Multiple Organ Dysfunction Syndrome' (MODS). MODS was defined as 'the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.'¹³

In 2001, several North American and European intensive care societies agreed to revisit the definitions for sepsis and related conditions. This international sepsis definitions conference (Group of experts and opinion leaders represented by SCCM,

TABLE 17.1: Reported Incidence and Outcome of Severe Sepsis in Different Parts of the World.

Country of origin	Severe sepsis per 100 ICU admission	Incidence per 1000 population	ICU mortality	Hospital mortality
Australia & New Zealand ⁴	11.8	0.77	26.5 ¹	37.5 ¹
United States ³	11.8 ⁵	2.4	NR	17.9*
France ²	15.3 ⁶	0.95	NR	41.9
United Kingdom ⁷	28.7	0.66	30.8	44.7
Brazil ⁸	17.4	NR	NR	47

* Sepsis overall (not severe sepsis), NR: Not Reported

ACCP, The European Society of Intensive Care Medicine (ESICM), The American Thoracic Society (ATS), and the Surgical Infection Society (SIS)) revisited the 1992 sepsis guidelines. They expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience; no evidence exists to support a change to the definitions.¹⁴ Infection was defined as a microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by microorganisms.

The SIRS concept is valid to the extent that a systemic inflammatory response is non specific and can be triggered by a variety of infectious and non-infectious conditions.

Current definitions do not allow for precise staging of the host response to infection and categorical definitions, such as SIRS, severe sepsis, and septic shock, have important limitations. Despite this, the SIRS concept has been globally adopted by clinicians and investigators, Table 17.2.

RISK FACTORS FOR SEPSIS

Factors which are potentially responsible for the growing incidence of sepsis and septic shock include:

- 1) Increased awareness and sensitivity of the diagnosis,
- 2) Increased use of cytotoxic and immunosuppressant agents,
- 3) Malnutrition,
- 4) Alcoholism,
- 5) Malignancy,
- 6) Diabetes mellitus,
- 7) Increasing number of transplant recipients and transplantation procedures,
- 8) Increasing number of patients who have compromised immune status,
- 9) Acquired immunodeficiency syndrome,
- 10) Increasing use of aggressive invasive procedures in patient management and diagnosis,
- 11) Increasing number of resistant microorganisms and
- 12) Increasing number of elderly patients.

Causative agents

Gram-positive organisms, endotoxin-containing Gram-negative organisms, fungi and other microbial pathogens can trigger sepsis. Gram-negative bacteria are responsible for most clinical sepsis, although in the past decade the spectrum of invading microorganisms appears to be shifting to Gram-positive bacteria and fungi. In a recent Australian study, infection was confirmed by positive culture in about 58% of episodes. Of the organisms cultured, 48.3% were gram-positive and 38.5% gram-negative; other organisms, including yeasts, fungi, legionellae and mycobacteria accounted for the remaining 13.2%.

PATHOPHYSIOLOGY OF SEPSIS

The pathophysiology of sepsis is a complex process. Pertinent factors include the bacterial density of contamination and the underlying immune status. SIRS is a result of uncontrolled activation of innate immune effector mechanisms which serve to localize and control bacterial invasion and to initiate repair of injured tissue. The innate immune system, comprising cellular (polymorphonuclear leukocytes, macrophages, natural killer cells, dendritic cells) and humoral components (complement and coagulation systems), is activated in early sepsis. Components of the innate immune response from the first line of defence are involved in the recognition and destruction of pathogens and allow time for acquired immune response to be effective. The host–microbe interaction leads to the

TABLE 17.2: Definitions of Systemic Inflammatory Response Syndrome (SIRS) and Different Degrees of Severity of Sepsis.¹⁵

Condition	Description
SIRS	Two or more of the following conditions: <ul style="list-style-type: none"> • Temperature >38.5°C or <35.0°C; • Heart rate of >90 beats/min; • Respiratory rate of >20 breaths/min or PaCO₂ of <32mmHg; and • White blood cell count of >12,000cells/mL, <4000cells/mL, or >10% immature (band) forms
Sepsis	SIRS in response to documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection)
Severe sepsis	Sepsis and at least one of the following signs of organ hypoperfusion or organ dysfunction: <ul style="list-style-type: none"> • Areas of mottled skin; • Capillary refilling of ≥3 seconds; • Urinary output of <0.5mL/kg for at least 1 hour or renal replacement therapy; lactate >2mmol/L; • Abrupt change in mental status or abnormal EEG findings; • Platelet count of <100,000cells/mL or disseminated intravascular coagulation; • Acute lung injury/Acute Respiratory Distress Syndrome; and • Cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and one of the following conditions: <ul style="list-style-type: none"> • Systemic mean blood pressure (BP) of <60mmHg (<80mmHg if previous hypertension) after 20 to 30mL/kg starch or 40 to 60mL/kg saline solution, or pulmonary capillary wedge pressure (PCWP) between 12 and 20mmHg. • Need for dopamine of >5mcg/kg/min, or nor adrenaline or epinephrine of <0.25mcg/kg/min to maintain mean BP at >60mmHg (80mmHg if previous hypertension)
Refractory septic shock	Need for dopamine at >15mcg/kg/min, or nor adrenaline or adrenaline at >0.25mcg/kg/min to maintain mean BP at >60mmHg (80mmHg if previous hypertension)

activation of several mediators within the innate immune system, including proinflammatory and anti-inflammatory cytokines and the coagulation cascade. The consequences of a systemic proinflammatory reaction include endothelial damage, microvascular dysfunction, impaired tissue oxygenation and organ injury. The consequences of an excessive anti-inflammatory response include anergy and immunosuppression. In addition,

pro- and anti-inflammatory processes may interfere with each other, creating a state of what has been termed destructive immunologic dissonance.¹⁶ The entire process is often described as uncontrolled, maladaptive, or dysregulated. Sepsis may therefore pathologically be described as an autodestructive process that permits the extension of a normal pathophysiologic response to infection that can result in MODS.¹⁷

Innate immunity and toll-like receptors (TLRs)

SIRS is a consequence of uncontrolled activation of innate immune responses triggered when 'pattern recognition' receptors sense the presence of molecular signatures that are present in the pathogens. Pre-eminent among such pattern recognition receptors are TLRs which serve as primary sensors of the innate immune system.¹⁸ Various TLRs have been identified in humans; TLR4 is expressed on the cell surface and serves as the primary sensor for endotoxins (also called lipopolysaccharides (LPS)) which are a constituent of the outer membrane of Gram-negative bacteria. The exoskeleton of Gram-positive bacteria is comprised of peptidoglycan (PGN) and lipoteichoic acid (LTA) which is sensed by TLR2.¹⁹

Proinflammatory response

The primitive, but effective, local inflammatory processes (adherence, chemotaxis, phagocytosis, bacterial killing) are highly regulated at various levels, mainly through the production of macrophage cytokines. Once a macrophage has been triggered and activated during the invasion of tissue by bacteria, it secretes cytokines (tumor necrosis factor (TNF), interleukins (IL)) and other mediators into the cell's microenvironment. These cytokines and other multiple mediators act in concert, initiating and then amplifying the resultant generalised inflammatory processes. The overwhelming systemic inflammatory response that follows manifests itself in the shock syndrome characterised by endothelial damage, coagulopathy, loss of vascular tone, myocardial dysfunction, tissue hypoperfusion, and MODS. However, several randomised human clinical trials involving antagonism of pro-inflammatory cytokines and anti-endotoxin strategies have

either failed to improve survival, or reported worsened survival. A potential reason for failure of these immunomodulatory strategies could have been that sepsis is a heterogeneous disorder, and the timing of the intervention(s) may have been inappropriate.

Coagulation cascade

Inflammatory mediators, such as TNF, initiate coagulation through the induction of tissue factor expression, primarily on monocyte/macrophages, polymorphonuclear and endothelial cells. The activation of the coagulation cascade leads to fibrin and clot formation. There is also loss of native anticoagulant function, indicated by decreased activity and circulating levels of protein C. A cross-talk between inflammatory and coagulation pathways leads to self-amplifying loops of activation of endothelium, leading to the formation of microthrombi and further endothelial damage, thus setting the stage for the development of consumptive coagulopathy. Despite improved understanding of the coagulation pathway, it remains unclear why Activated Protein C improved 'survival' in a landmark clinical trial,²¹ while strategies targeted at other components of the coagulation cascade, such as tissue factor pathway inhibitor and antithrombin III, had no impact on mortality.²² In addition to the complex coagulation cascade and hyperpermeable state of endothelium, vasomotor tone of the vessel is also affected. Vasoconstrictive (endothelin, thromboxane A2, and platelet activating factor (PAF)) and vasodilatory (nitric oxide and prostacyclin) metabolites are produced in certain circumstances with important consequences in terms of microcirculatory homeostasis and maintenance of tissue perfusion.¹⁹

MULTIORGAN DYSFUNCTION SYNDROME (MODS)

The precise mechanisms of cell injury and resulting organ dysfunction in sepsis are not clearly understood. Multiorgan dysfunction syndrome is associated with widespread endothelial and parenchymal cell injury, some of which can be explained by hypoxic hypoxia, direct cytotoxicity or apoptosis.

Epithelial and endothelial dysfunction

Epithelial cells line the organs involved in MODS, including liver, lung, and intestines. Increased permeability and loss of the epithelial cell barrier is hypothesized to play a role in MODS. Increased permeability of the lung epithelial cells leads to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The reactive oxygen species, lytic enzymes, and vasoactive substances (nitric oxide, endothelial growth factors) lead to microcirculatory injury, which is compounded by the inability of the erythrocytes to navigate the septic microcirculation. These changes are accompanied by peripheral vasodilatation, hypotension, tissue hypoperfusion, increased permeability, and increased peripheral oedema leading to hypoxic hypoxia frequently observed in severe sepsis. Direct cytotoxicity due to endotoxin, TNF-alpha, and nitric oxide may cause damage to mitochondrial electron transport, leading to disordered energy metabolism. This is called cytopathic or histotoxic anoxia which is an inability to utilize oxygen even when it is available.

Immune suppression and apoptosis

Few patients die shortly after the onset of sepsis due to profound hypotension or hypoxemia whilst many will have prolonged

ICU course and may die following nosocomial infection. The interaction between proinflammatory and anti-inflammatory mediators plays an important role in determining the outcome of sepsis. Activated CD4 T cells are programmed to secrete cytokines with either of two distinct and antagonistic profiles. They secrete cytokines with inflammatory (type 1 helper T-cell [Th1]) properties, including TNF, interferon-1 and interleukin-2, or cytokines with anti-inflammatory (type 2 helper T-cell [Th2]) properties for example, interleukin-4 and interleukin-10. The factors that determine whether CD4 T cells have Th1 or Th2 responses are currently unknown but may be influenced by the type of pathogen, the size of the bacterial inoculum, and the site of infection.¹⁷ Programmed cell death (apoptosis) is a normal cellular process. Sepsis is accompanied by increased apoptosis of lymphoid cells, and, to a lesser extent, parenchymal cells. Ingestion of apoptotic cells by macrophages may lead to a Th2 response, while ingestion of necrotic cells favours a Th1 response, thus apoptosis contributes to immunosuppression. The proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, but other tissues, such as the gut epithelium, may undergo accelerated apoptosis. Endogenous release of steroids during stress increases apoptosis. Therefore, derangement of apoptosis appears to play a critical role in the tissue injury involved in sepsis.

Sepsis, circulatory failure and organ dysfunction

The widespread disruptions in severe sepsis can result in profound cardio-circulatory dysfunction. This manifests itself as shock. The dysfunction involves the cardiac, peripheral vascular (macrovascular) and

microcirculatory elements of the circulation, depending on the degrees of cardiac or vascular dysfunction and the volume status of the patient. The clinical picture ranges from cold, clammy and under-perfused to one of hyperdynamic shock. However in clinical practice, hyperdynamic shock is seen much more frequently.²³

Landry and Oliver²⁰ enumerated the primary mechanisms for vascular smooth muscle relaxation in sepsis to include activation of ATP-sensitive potassium channels in the plasma membrane, activation of inducible nitric oxide synthase, and vasopressin deficiency. There are numerous vasoregulatory mediators in septic shock, and distant organs, including the brain, adrenal glands, liver, and heart; all influence vascular tone.²² Another potential factor that may contribute to persistence of vasodilation is impaired compensatory secretion of anti-diuretic hormone (vasopressin). Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits. However, the recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 units/min, showed no difference in outcome in the intent to treat population.²⁴

The situation in septic shock is further complicated by widespread microcirculatory dysfunction, further impairing tissue oxygen delivery, and diminished mitochondrial activity resulting in impaired oxygen extraction. The microcirculation is a key target organ for injury in the sepsis syndrome. Sepsis is associated with a decrease in the number of functional capillaries (capillarity), which causes an inability to extract oxygen maximally. These changes may be due to extrinsic compression of the capillary by tissue oedema, endothelial swelling, and plugging of the capillary lumen by leukocytes or red blood

cells (which lose their normal deformability properties in sepsis). Nitric oxide plays a pivotal and multifaceted role in the complex pathophysiology of sepsis in maintaining microcirculatory homeostasis and patency, especially when the microcirculation sustains an insult (as with sepsis).²⁵ In the healthy state and under pathologic conditions, NO maintains microcirculatory homeostasis by regulating microvascular tone, leukocyte adhesion, platelet aggregation, microthrombi formation, and microvascular permeability. Direct or indirect effects of one or more circulating myocardial depressing substances results in myocardial depression, ventricular dilatation and/or decreased left ventricular ejection fraction further affecting circulation.²⁶

Endothelial injury and the inflammatory process due to neutrophil entrapment in the pulmonary vasculature leads to disturbed capillary blood flow and enhanced microvascular permeability, resulting in interstitial and alveolar oedema.²⁷ ARDS is a frequent and well described manifestation of severe sepsis. Mechanisms by which sepsis and endotoxemia might lead to acute renal failure are incompletely understood. Sepsis often results in acute renal failure due to acute tubular necrosis and systemic hypotension, direct renal vasoconstriction and release of various cytokines are contributing factors.²⁷ Nervous system involvement in sepsis can be central, causing encephalopathy, or peripheral resulting in neuropathy. At least 25% of patients admitted to medical or surgical intensive care units for more than seven days have some degree of acquired paresis. Neurological manifestations of sepsis includes limb muscle weakness and atrophy, reduced or absent deep tendon reflexes, loss of peripheral sensation to light touch and pin prick with relative preservation of cranial nerve function.²⁸

MANAGEMENT

Treatment of sepsis and septic shock rests upon the triad of hemodynamic resuscitation, antimicrobial therapy and source control. Establishing vascular access and initiating aggressive fluid resuscitation should be the initial priority when managing patients with severe sepsis or septic shock. Relative intravascular hypovolaemia is common and rapid large volume infusions of intravenous fluids, appropriate vasopressor and inotropic support are indicated as initial therapy unless there is coexisting clinical or radiographic evidence of heart failure. Rivers *et al.*²⁹ in a single centre randomised controlled trial (RCT) demonstrated decreased mortality by initiating protocolized resuscitation of patients with sepsis induced shock in the first 6 hours. The goals of initial resuscitation involved the use of crystalloids or colloids to maintain central venous pressure of 8–12mmHg and a mean arterial pressure (MAP) of at least 65mmHg with fluid and norepinephrine or dopamine as the initial vasopressor of choice. Dobutamine may be indicated in patients with myocardial dysfunction as indicated by elevated cardiac filling pressures and low cardiac output. Treatment goals, assuring vital organs are perfused are; to maintain a urine output 0.5mL/kg/hr and a superior vena caval oxygen saturation (ScvO₂) or mixed venous oxygen saturation (SvO₂) less than 70% or 65% respectively. Rivers *et al* reported a mortality reduction from 47% in the control group to 31% in the treatment group. There is no evidence for the use of dopamine to increase urine output as a treatment goal. The Saline versus Albumin Fluid Evaluation (SAFE Study) was the largest randomised controlled trial ever performed in the critical care population. It involved almost 6997 critically ill patients (that is, not specifically with sepsis), run by the Australian and New

Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). Patients were eligible if clinicians judged that fluid was needed to treat intravascular volume depletion, and were treated with either 4% albumin (n = 3497) or 0.9% (n = 3500) saline. The two groups had similar baseline characteristics. Death from any cause during the 28 days after randomisation was the primary outcome measure. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95% CI, 0.91 to 1.09; P = 0.87). There were no significant differences between the groups in the mean (\pm SD) numbers of days spent in the ICU (6.5 ± 6.6 in the albumin group and 6.2 ± 6.2 in the saline group, P = 0.44), days spent in the hospital (15.3 ± 9.6 and 15.6 ± 9.6 , respectively; P = 0.30), days of mechanical ventilation (4.5 ± 6.1 and 4.3 ± 5.7 , respectively; P = 0.74), or days of renal-replacement therapy (0.5 ± 2.3 and 0.4 ± 2.0 , respectively; P = 0.41).³⁰

The Surviving Sepsis Campaign (SSC), an initiative of the ESICM, the International Sepsis Forum and SCCM was developed to improve the management, diagnosis, and treatment of sepsis. The most recent version was published early in 2008.³¹ As per these SSC guidelines, the Rivers study was considered as Grade B evidence. However, there were also concerns raised regarding the widespread implementation of this study into practise in other jurisdictions. One of these was the high mortality in the control group (47%). Mortality in other studies reporting severe sepsis has been quoted as 30–35%,^{7,32} which could suggest that while Early Goal Directed Therapy may have a beneficial effect when baseline mortality is high, it may be less effective when baseline outcomes are better. The other concern was that introduction of this treatment paradigm would have huge implications for staffing and infrastructure

in the emergency department and ICU. The ScvO₂ may be used as warning signal in critically ill patients and act as a marker instead of SvO₂ in emergency departments and ICU in the early stages of hemodynamic optimisation. Following initial resuscitation, it is uncertain whether goal-directed therapy should be based on ScvO₂ instead of SvO₂. Studies have provided indirect support for the use of lactate in goal-directed therapy, but there is as yet insufficient evidence for its use as a resuscitation end point. Single centre studies frequently either lack the scientific rigor or external validity required to support widespread changes in practice and their premature incorporation into guidelines may make the conduct of definitive studies more difficult.³³ ARISE (Australasian Resuscitation In Sepsis Evaluation) is a phase III, multi-centre, ANZICS CTG (Australia, New Zealand Intensive Care Society- Clinical Trails Group) endorsed, randomised, controlled study evaluating early goal-directed therapy in 1600 patients presenting to the Emergency Department with severe sepsis across Australian, New Zealand and Hong Kong hospitals. The study is being conducted over 2.5 years through the Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University. This study will hopefully provide more directions towards this topic.

Appropriate cultures should properly be obtained before initiating antibiotic therapy but this should not prevent administration of antimicrobial therapy. It is recommended that empiric antibiotic therapy be administered within 1 hour of the identification of severe sepsis. In the presence of septic shock, each hour delay in achieving administration of effective antibiotics appears to be associated with a measurable increase in mortality.³⁴ Rapid diagnostic methods (polymerase

chain reaction, micro-arrays) might aid in the earlier identification of pathogens.³⁵ Specific anatomical diagnosis of infection and measures to control the source within the first 6 hours following presentation is recommended.³¹ A procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical patients in intensive care units could also reduce antibiotic exposure with no apparent adverse outcomes. A multicentre, prospective, parallel-group, open-label, randomised trial demonstrated procalcitonin guided strategy resulted in significantly more days without antibiotics when compared with control group (14.3 days [SD 9.1] versus 11.6 days [SD 8.2]; absolute difference 2.7 days, 95% CI .0.4 to 4.1, p<0.0001).³⁶

Steroids

Use of corticosteroids in patients with septic shock has been controversial for several decades and continues to be controversial despite the publication of several trials including two recent large RCT's. Sepsis may be associated with relative adrenal insufficiency in a substantial subset of patients.

Annane *et al*³⁷ in a multi-centre French trial, randomised 300 patients with septic shock to receive either placebo or hydrocortisone 50mg intravenously every six hours (plus fludrocortisone 50mcg enterally once a day) within eight hours of onset of septic shock. Treatment continued for seven days. Based upon a high-dose (250mcg) ACTH (adrenocorticotropic hormone) stimulation test, the patients were classified as having adequate adrenal reserve (maximum increase in serum cortisol of >9mcg/dL) (248nmol/L) or inadequate adrenal reserve (maximum cortisol increase of ≤9mcg/dL (248nmol/L). This study showed significant shock reversal and reduction

of mortality rate in patients with relative adrenal insufficiency. Based on this study many clinicians still use steroids in certain subsets of septic patients.

However, a recent large, European multicenter trial CORTICUS,³⁸ which was a double blinded randomised trial assigning 499 patients with septic shock to receive hydrocortisone or placebo intravenously every six hours for five days, followed by a tapering regimen, failed to show a survival benefit with steroid therapy for septic shock irrespective of the presence or absence of relative adrenal insufficiency. The therapeutic guiding role of the ACTH stimulation test was cast into doubt by this trial.

Similarities between the two studies included a beneficial steroid effect on time to shock reversal, no evidence for increased risk of neuromuscular weakness, and no hyperglycaemia. Differences between the two studies Annane³⁷ and CORTICUS trial³⁸ respectively include: Entry window (8 vs. 72 hours; SBP <90mmHg (>1 hour vs. <1 hour); additional treatment with (fludrocortisone vs. no fludrocortisone); treatment duration (7 vs. 11 days); weaning (none vs. present); differences in steroid effects according to the response to ACTH test (yes vs. no) and increased risk of superinfection (no vs. yes).

Another major difficulty regarding the use of steroid is the lack of definitive data regarding the appropriate cutoff values for 'relative' adrenal insufficiency in the shock state. Significant variability exists in the results of cortisol assay among research centres and whether they estimate free or total cortisol assay. Free and total cortisol may vary significantly based upon the protein concentration. Which steroid is also a pertinent question; there is little evidence for steroids other than hydrocortisone.

Recombinant human activated protein C (rhAPC)

Coagulation plays a central role during inflammatory processes, particularly those due to infection. Drotrecogin alfa (activated) or recombinant human activated protein C is a 54 kilodalton recombinant glycoprotein with antithrombotic, profibrinolytic, and anti-inflammatory properties. Protein C is an inactive zymogen synthesized in the liver. When coupled to thrombomodulin on the endothelial surface, protein C is converted to Activated Protein C by thrombin. Significant decreases in protein C levels have been well documented in sepsis and specifically in septic shock.³⁹ The conversion of protein C to activated protein C may be impaired during sepsis as a result of the down-regulation of thrombomodulin by inflammatory cytokines. This led to interest in therapeutic administration of activated protein C (and similar agents) in early sepsis. It has now become the first biological therapy to report a mortality benefit in human RCT of sepsis. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS)²¹ was a randomized, double-blind, placebo-controlled, multicenter trial. Patients with systemic inflammation and organ failure due to acute infection were randomised to placebo or to receive rhAPC (24µg/kg/hr) for 96 hours. The primary end point was death from any cause at 28 days. Nearly 1700 patients were randomized but the study was stopped early when an interim analysis showed a survival benefit in the treatment arm. Based upon post-hoc analyses of the study data, drotrecogin alpha was of greater benefit in the most severely ill patients, including those with an APACHE (Acute Physiology and Chronic Health Evaluation) II score ≥ 25 and patients with multiple organ dysfunction. This formed the basis for the

FDA decision to license rhAPC for use in sepsis.

A subsequent trial of rhAPC in patients with a low risk of death was halted after an interim analysis for lack of effectiveness.⁴⁰ Another trial, involving the paediatric population who had severe sepsis, was stopped after approximately 400 patients had been enrolled, again because of futility. The Surviving Sepsis Guidelines³¹ suggest its use (if there are no contraindications) in adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have Acute Physiology and Chronic Health Evaluation (APACHE) II >25. However, there has been considerable criticism of the PROWESS trial and Australian and New Zealand Intensive Care Society does not recommend the use of rhAPC within practice guidelines.⁴¹ The decision regarding administration of rhAPC is likely best made based upon clinicians assessment of high risk of death due to multiorgan failure versus the risk of bleeding complications.

Currently another trial 'Efficacy and Safety of Drotrecogin Alfa (Activated) in Adult Patients with Septic Shock' is in progress. The purpose of this placebo-controlled study is to determine if drotrecogin alfa (activated) treatment provides significant mortality reduction and organ function improvement in patients with septic shock compared with placebo treatment in patients receiving the current standard of care for septic shock. This study will also assess the effectiveness of drotrecogin alfa (activated) in reducing 28-day mortality in patients with septic shock and concomitant severe protein C deficiency at baseline.

Glucose control

Hyperglycaemia is reported to be associated with poor clinical outcomes in critically

ill patients. In 2001, Van Den Berghe and colleagues⁴² demonstrated significant mortality benefit by intensive insulin infusion titrated to strict euglycaemia in critically ill surgical patients. However, a second study by the same author which targeted medical ICU patients using the same strict glycaemic control failed to show survival benefit. With the available evidence, most clinicians agree that glycaemic control is a desirable intervention in critically ill patients although the optimal blood glucose range is still controversial. A blood glucose level of 140 to 180 mg/dL (7.7 to 10mmol/L) appears to be an acceptable target. A more stringent target (80 to 108mg/dL [4.5 to 6mmol/L]) was associated with higher incidence of hypoglycaemia and significantly higher 90-day mortality in the recently published (Australasian based) NICE SUGAR trail. This study randomised 6104 patients; 3054 were assigned to undergo intensive control 81 to 108mg/dL (4.5 to 6.0mmol/L) and 3050 to undergo conventional control blood glucose \leq 180mg/dL (<10.0nmol/L). Severe hypoglycaemia was reported in 6.8% of the intensive-control group and 0.5% of the conventional-control group ($P<0.001$).⁴³

Renal replacement therapy

Continuous Renal Replacement Therapy (CRRT) involves either dialysis based solute removal) or filtration (convection-based solute and water removal) treatments that operate in a continuous mode. Haemofiltration (HF) refers to the use of a hydrostatic pressure gradient to induce the filtration (or convection) of plasma water across the membrane of the hemofilter. Hemofiltration has been described as a technique which can lower cytokine levels. In a single-centre, randomized, controlled study in which continuous renal-replacement therapy was the sole treatment approach, survival improved

when the intensity of therapy was increased from an assigned effluent rate of 20ml/kg/hr to either 35 or 45ml/kg/hr.⁴⁴ Bellomo and colleagues recently reported the results of the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study, which was conducted at multiple centers in Australia and New Zealand. In the RENAL Study,⁴⁵ 1508 patients with severe acute kidney injury who required intensive care were randomly assigned to receive continuous venovenous hemodiafiltration at a total effluent flow rate of either 25ml or 40ml/kg/hr. In both treatment groups, 44.7% of patients died in the first 90 days after randomization (odds ratio, 1.00; 95% CI, 0.81 to 1.23). Overall, 94.4% of patients who were alive after 90 days no longer required dialysis, with similar rates of recovery of kidney function in both treatment groups.

3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (HMG-CoA)

The therapeutic use of HMG-CoA reductase inhibitors, also known as statins, has become widespread as lipid lowering agents in the prevention and treatment of major cardiovascular diseases. There is evidence that statins have beneficial effects on the perioperative risk of cardiac complications and sepsis. Statins appear to have actions on vascular nitric oxide through the balance of inducible and endothelial nitric oxide synthase. Statins also have anti-inflammatory properties, exemplified by reduced plasma concentrations of the inflammatory cytokines tumour necrosis factor (TNF- α) and interleukin (IL-6). Various cohort studies have been published in favour of statins reducing mortality in sepsis. A meta-analysis of cohort studies (including one randomised trial) demonstrated a protective effect for

statins in patients with sepsis and/or other infections compared to placebo for various infection-related outcomes; (0.61 (95% CI, 0.48-0.73) for 30-day mortality).⁴⁶ Current ongoing RCTs of statins in sepsis are to be watched with interest.

Other adjuvant therapies in sepsis

Cytokines and anticytokine therapies

Granulocyte Colony Stimulating Factor (G-CSF) is a cytokine involved in myelopoiesis with a predominant effect on the polymorphonuclear leukocyte (PMN). Studies in humans with pneumonia have had encouraging results but with no mortality benefit. TNF plays a central role in the inflammatory process; but phase III clinical trials of TNF antibodies and TNF fusion proteins led to negative results. Similarly, studies on antagonising interleukin-1, a cytokine with similar properties, also led to negative results.

Pooled immunoglobulin (IVIG)

Immunoglobulin has been used for sepsis states such as meningococcal and pneumococcal infections with some documented survival benefit. The mechanism of action is most likely immunomodulatory and binding and inactivation of the bacterial derived superantigen. Its use has been suggested in toxic shock syndrome due to *Streptococcus pyogenes* and *Staphylococcus aureus*. A large randomised trial of 653 patients with severe sepsis failed to demonstrate any benefit of IVIG. The 28-day mortality rate was 37.3% in the placebo group and 39.3% in the IVIG group and thus not significantly different ($p = 0.6695$).⁴⁷ Many clinical studies and meta-analyses have examined the utility of IVIG, but there exists insufficient data to make a firm recommendations for its use in sepsis and septic shock.

Acute respiratory distress syndrome (ARDS)

ARDS is an acute (rapid onset) syndrome with bilateral infiltrates on chest x-ray; no evidence of elevated left atrial pressure (the pulmonary capillary wedge pressure is ≤ 18 mmHg if measured) and a ratio of arterial oxygen tension to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) is less than 201 mmHg. Conventional therapy, aimed at tidal volumes (V_T) of 12–15 ml/kg, generated lung volumes that overstretched alveoli resulting in volutrauma (secondary lung injury). The landmark Acute Respiratory Distress Syndrome Network multicenter trial randomly assigned 861 mechanically ventilated patients with ARDS and acute lung injury to receive low tidal volume ventilation (tidal volume of 6 mL/kg) or conventional mechanical ventilation (tidal volume of 12 mL/kg). Mechanical ventilation using a lower tidal resulted in decreased mortality and an increase in the number of days without ventilator use.⁴⁸ The overall goal was to maintain acceptable gas exchange and avoid alveolar over-distension, tolerating hypercapnia if indicated; thus minimizing the adverse effects of mechanical ventilation.

REFERENCES

1. Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med* 2004; **30**: 589–596.
2. Brun-Buisson C, Meshaka P, Pinton P, et al. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med* 2004; **30**: 580–8.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**: 1546–54.
4. Craig JF. The epidemiology of sepsis – is Australasia different? *Crit Care Resusc* 2006; **8**: 219–222
5. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical intensive care unit patients. *Intensive Care Med* 1995; **21**: 302–9.
6. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French Intensive Care Unit Group for Severe Sepsis. *JAMA* 1995; **274**: 968–74.
7. Harrison D, Welch C, Eddleston J. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004; secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006; **10** (2): R42.
8. Silva E, Pedro Mde A, Sogayar AC, et al. Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care* 2004; **8**: R251–60.
9. Geroulanos S, Douka ET. Historical perspective of the word ‘sepsis’ [letter]. *Intensive Care Med* 2006; **32**: 2077.
10. Duane JF, Joseph E, Parrillo, Kumar A. Sepsis and Septic Shock: A History. *Crit Care Clin* 2009; **25**: 83–101.
11. Bone RC, Balk RA, Cerra FB, et al: American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; **101**: 1644–1655,

12. Balk RA. Severe Sepsis and Septic Shock. Definitions, epidemiology, and clinical manifestations. *Crit Care Clin* 2000; **16**(2): 179–192
13. Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74.
14. Mitchell M, Levy, Mitchell P. Fink, John C. Marshall, Edward Abraham, Derek Angus, Deborah Cook, Jonathan Cohen, Steven M. Opal, Jean-Louis Vincent, Graham Ramsay. 2001 SCCM/ESICM/ACCP/ATS/ SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; (31)**4**: 1250–1256.
15. Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet* 2005; **365**: 63.
16. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS). *Ann Intern Med* 1996; (15)**125**: 680–687.
17. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; **348**: 138: 150.
18. Kumagai Y, Takeuchi O, Akira S. Pathogen recognition by innate receptors. *J Infect Chemother* 2008; **14**: 86–92.
19. Sunil AD. Inflammatory and immune responses in sepsis. *Critical Care Update* 2009; V Nayyar, JV Peter, R Krishen, S Srinivasan (Eds). Jaypee Bros Medical Publishers ltd New Delhi 2010; **13**: 143–151.
20. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; **345**: 588–595.
21. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein c for severe sepsis. *N Engl J Med* 2001; **344**: 699–709.
22. Curtis NS, Shepherd W. New concepts in sepsis. *Current Opinion in Crit Care* 2002, **8**: 465–472.
23. O. Okorie Nduka, Joseph E. Parrillo. The pathophysiology of septic shock. *Crit Care Clin* 2009; **25**: 677–702.
24. James AR, Keith RW. et al. Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. *N Engl J Med* 2008; **358**: 877–887.
25. Trzeciak S, Cinel I, Dellinger P et al. (Microcirculatory Alterations in Resuscitation and shock (MARS) Investigators) Resuscitating the Microcirculation in Sepsis: The Central Role of Nitric Oxide, Emerging Concepts for Novel Therapies, and Challenges for Clinical Trials. *Acad Emerg Med* 2008; **15**(5): 399–413.
26. Bone RC. The pathogenesis of sepsis. *Ann Intern Med* 1991; **115**: 457–69.
27. Ghosh S, Latimer RD, Gray BM, et al. An Endotoxin-induced organ injury. *Crit Care Med* 1993; **21**: S19–24.
28. Deem, S, Lee, CM, Curtis, JR. Acquired neuromuscular disorders in the intensive care unit. *Am J Respir Crit Care Med* 2003; **168**: 735–739.
29. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368–1377.
30. The SAFE Study Investigators. A Comparison of Albumin and Saline

- for Fluid Resuscitation in the Intensive Care Unit. *N Engl J Med* 2004; **350**: 2247–56.
31. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2008; **34**: 17–60.
 32. Abraham, E., K. Reinhart, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003; **290**(2): 238–47.
 33. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-centre trials. *Crit Care Med* 2009; **37**(12): 3114–3119.
 34. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589–1596.
 35. Tenover FC: Rapid detection and identification of bacterial pathogens using novel molecular technologies: Infection control and beyond. *Clin Infect Dis* 2007; **44**: 418–423.
 36. Bouadma L, Luyt CE, Tuback F et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *The Lancet* 2010; **375**(9713): 463–474.
 37. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288**: 862–871.
 38. Sprung CL; Annane D; Keh D; Moreno R. et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358**(2): 111–24.
 39. Mesters RM, Helter brand J, Utterback BG, et al. Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. *Crit Care Med* 2000; **28**(7): 2209–2216.
 40. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; **353**: 1332–1341.
 41. Peter H and Cooper DJ. The Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 and the Australian and New Zealand Intensive Care Society (ANZICS). *Crit Care Resusc* 2008; **10**: 6–8.
 42. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359–1367.
 43. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**(13): 1283–97.
 44. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. *Lancet* 2000; **355**: 26–30.
 45. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361**: 1627–38.
 46. Tleyjeh IM, Kashour T, Hakim FA et al. Statins for the Prevention and Treatment of Infections: A Systematic Review and Meta-analysis. *Arch Intern Med* 2009; **169**(18): 1658–1667.
 47. Werdan K, Pilz G, Bujdoso O, et al. Score-based immunoglobulin G

- therapy of patients with sepsis: The SBITS study. *Crit Care Med* 2007; **35**(12): 2693–2701.
48. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**(18): 1301–8.



Cover diagram by David Heinrich of the *Medical Illustration and Media Unit, Flinders Medical Centre*. (See chapter 18)

MECHANISMS OF VASCULAR DISEASE

Edited by Robert Fitridge and Matthew Thompson

Chapter 1: Endothelium **Chapter 2:** Vascular smooth muscle structure and function **Chapter 3:** Atherosclerosis **Chapter 4:** Mechanisms of plaque rupture **Chapter 5:** Current and emerging therapies in atheroprotection **Chapter 6:** Molecular approaches to revascularisation in peripheral vascular disease **Chapter 7:** Biology of restenosis and targets for intervention **Chapter 8:** Vascular arterial haemodynamics **Chapter 9:** Physiological haemostasis **Chapter 10:** Hypercoagulable states **Chapter 11:** Platelets in the pathogenesis of vascular disease and their role as a therapeutic target **Chapter 12:** Pathogenesis of aortic aneurysms **Chapter 13:** Pharmacological treatment of aneurysms **Chapter 14:** Aortic dissection and connective tissue disorders **Chapter 15:** Biomarkers in vascular disease **Chapter 16:** Pathophysiology and principles of management of vasculitis and Raynaud's phenomenon **Chapter 17:** SIRS, sepsis and multiorgan failure **Chapter 18:** Pathophysiology of reperfusion injury **Chapter 19:** Compartment syndrome **Chapter 20:** Pathophysiology of pain **Chapter 21:** Postamputation pain **Chapter 22:** Treatment of neuropathic pain **Chapter 23:** Principles of wound healing **Chapter 24:** Pathophysiology and principles of varicose veins **Chapter 25:** Chronic venous insufficiency and leg ulceration: Principles and vascular biology **Chapter 26:** Pathophysiology and principles of management of the diabetic foot **Chapter 27:** Lymphoedema – Principles, genetics and pathophysiology **Chapter 28:** Graft materials past and future **Chapter 29:** Pathophysiology of vascular graft infections



BARR SMITH PRESS

An imprint of
The University of Adelaide Press