Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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Edited by Robert Fitridge and Matthew Thompson

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Table of Contents

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Detailed Contents

CHAPTER 20 – PATHOPHYSIOLOGY OF PAIN

Stephan Schug, Helen Daly, Kathryn Stannard

CHAPTER 21 – POST-AMPUTATION PAIN

Stephan Schug, Gail Gillespie

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

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

CHAPTER 27 – LYMPHOEDEMA – PRINCIPLES, GENETICS AND PATHOPHYSIOLOGY

Matt Waltham

CHAPTER 28 – GRAFT MATERIALS PAST AND FUTURE

Mital Desai, George Hamilton

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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	Adrenocorticotropic 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
β2-GPI	β2-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	Calcitonic 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-1α	Interleukin-1 alpha
IL1-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 *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
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
TαCE	TNFα 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

16 • Pathophysiology and Principles of Management of Vasculitides and Raynaud's Syndrome

MARTIN VELLER

VASCULITIDES

Occlusive arterial lesions in humans are usually caused by atherosclerosis. The primary and secondary vasculitides are rare inflammatory conditions that may also cause such ischaemia as well as occasional aneurysms. These pathologies usually present with unusual manifestations of ischaemia, but may also be the cause of common symptoms such as stroke, hypertension, intermittent claudication or Raynaud's phenomenon. Delayed recognition of these diseases is often associated with severe and irreversible complications. While the vasculitides are usually managed by physicians, vascular surgeons should be able to recognise them and assist in their management when appropriate.

INTRODUCTION

The vasculitides consist of primary and secondary pathologies in which non-specific transmural inflammation occurs within a blood vessel. The consequent vascular injury can cause vessel disruption, aneurysm formation or occlusion which can affect any blood vessel. The pathogenesis of each of these diseases is unclear, although they generally fall into one of the following groups:[1]

- Immune complex vasculitides: These are induced by circulating immune complexes or histamine. This results in the activation of the complement system, cytocines and monocytes in the vessel wall.
- Pauci-immune vasculitides: The anti-neutrophil cytoplasmic antibodies (ANCA) were first described in conjunction with rapidly progressing glomerulonephritis. Cytoplasmic ANCA (c-ANCA), perinuclear ANCA (p-ANCA) and x-ANCA (which is found in chronic inflammatory GIT pathologies) have been described. In the pauci-immune vasculitides, activation of neutrophils results in vascular endothelial damage.[2]
- T-cell vasculitides: In these, vessel wall damage is caused by CD4 lymphocyte mediated immune reactions.

The primary vasculitides occur rarely – between 20 and 100 cases per million. They usually present with non-specific clinical symptoms and signs – e.g. malaise, fever, weight loss – and generally evolve over a long duration. In addition, they may overlap with the manifestations of much more common infections, connective tissue diseases and malignancy. As a consequence making the

diagnosis is challenging and is confounded by the extensive overlap in the clinical and pathological manifestations between the vasculitides.

If unrecognised, these systemic diseases may be fatal. With appropriate treatment the majority of patients will improve but relapses are common. These relapses may be the result of recurrence, worsening of the inflammatory process or may be the consequence of complications of therapy.

CLASSIFICATION OF VASCULITIDES

The heterogeneous nature and extensive overlapping clinical and pathological features have made classification difficult. Currently, the most commonly used systems take into account the size of the vessel affected, the histological findings and the aetiology (Table 16.1).[1,3-5] There is also some value in differentiating between ANCA positive (e.g. Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss vasculitis, drug induced vasculitis) and ANCA negative vasculitides.[1]

Whilst, the classification systems attempt to highlight the differences among these diseases, in clinical practice these differences are not precise – polyarteritis nodosa for example normally considered to be a primary, medium vessel vasculitis, can also be caused by chronic hepatitis B or C infections and may involve small vessels.[1,5]

Table 16.1: The major vasculitides[3,22]

Primary vasculitis
Predominantly large vessel vasculitis
Giant cell arteritis (also temporal arteritis)
Takayasu's arteritis
Predominantly medium vessel vasculitis
Polyarteritis nodosa
Kawasaki's disease
Predominantly small vessel vasculitis
Churg-Strauss syndrome
Wegener's granulomatosis
Microscopic polyangiitis
Henoch-Schönlein purpura
Essential cryoglobulinaemic vasculitis
Hypersensitivity vasculitis
No predominant vessel size
Behçet's disease
Secondary vasculitis
Vasculitis secondary to connective tissue disorders
Rheumatoid vasculitis
Systemic lupus erythematosus (SLE)
Systemic sclerosis
Scleroderma (including the CREST syndrome)
Mixed connective tissue disease
Antiphospholipid antibody syndromes
Vasculitis secondary to viral disease
Hepatitis B and C virus
Human immunodeficiency virus (HIV)
Cytomegalovirus
Epstein-Barr virus
Drug induced vasculitis
Other vasculitides
Thromboangitis obliterans (Buerger's disease)
Purpura fulminans (Waterhouse-Friderichsen)
Thrombotic thrombocytopaenic purpura

CLINICAL PRESENTATION OF VASCULITIDES

In general, vasculitis should be considered to be present when chronic systemic symptoms of inflammation, including pyrexia, malaise, fatigue, and weight loss are associated with some form of organ dysfunction. Arthralgia, myalgia, pain in the digits, rashes, anaemia of chronic disorders, pericarditis and a raised ESR and CRP are also common. The common organ specific manifestations are listed in Table 16.2.

In general, the skin and peripheral nervous system signs are particularly useful because they tend to develop early in the course of

TABLE 16.2: The common clinical manifestations of the vasculitides

Skin	Livedo reticularis, palpable purpura, nodules, ulcers, gangrene
Peripheral nervous system	Mononeuritis multiplex, polyneuropathy
Central nervous system	Stroke, seizures, encephalopathy
Eyes	Blindness, scleritis
Heart	Myocardial infarction, cardiomyopathy, pericarditis, arrhythmia
Lung	Cough, chest pain, haemoptysis, shortness of breath
Kidney	Hypertension, proteinuria, haematuria, renal failure
Gastrointestinal tract	Haemorrhage, perforation
Genitals	Testicular atrophy, reduced ovarian mass

the disease and are easily detected. Small vessel vasculitis is often first noted when palpable purpura develops while the vasculitides affecting medium vessels commonly produce nodules, ulcers and gangrene.

The most common neurological manifestation of the vasculitides is mononeuritis multiplex. This is a distinctive peripheral neuropathy in which peripheral nerves infarct one at a time as a result of vasculitis in the vasa nervorum. Sudden, asynchronous and asymmetrical loss of function of individual nerves occurs, most frequently affecting sensory nerves. In the absence of diabetes and nerve compression syndromes, mononeuritis multiplex can usually be assumed to be due to a vasculitis such as polyarteritis nodosa or Wegener's granulomatosis.

INVESTIGATIONS OF VASCULITIDES

Haematological and serological changes will usually be present in individuals presenting with vasculitis. Chronic microcytic anaemia, a raised ESR and CRP are non-specific findings while red cell casts in urine, antinuclear antibody (ANA), complement, serum cryoglobulins and ANCA are more specific manifestations of the vasculitides.

X-rays are generally not useful other than in Wegener's granulomatosis where views of the nasal sinuses and chest, especially using computed tomography, may demonstrate diagnostic nodular lesions.

Biopsy of involved tissues is the most helpful method of making a definitive diagnosis, especially if the biopsy is taken from a symptomatic site. Occasionally a serological test, an angiogram or another investigation can be pathognomonic.

Some investigations are helpful in excluding secondary causes of a vasculitis or those conditions that may mimic a vasculitis. Examples include investigations to exclude drug reactions, syphilis, Human Immunodeficiency Virus (HIV), infective endocarditis, and antiphospholipid syndromes. By the very nature of these conditions this list is not exhaustive.

PRINCIPLES OF TREATMENT OF VASCULITIDES

While the vasculitides are usually treated by some form of immuno-suppression, the most important principle is to make sure that the treatment intensity is commensurate with

the severity of disease.[6] While most forms of vasculitis require aggressive treatment to prevent morbidity and mortality, some do not. For example, minor vasculitis limited to the skin or where the secondary cause of the vasculitis can be identified and subsequently can be withdrawn or treated, require no such therapy.

THE VASCULITIDES OF SPECIFIC INTEREST TO VASCULAR SURGEONS

Giant cell arteritis

Giant cell arteritis, which is also known as temporal arteritis, is the most common vasculitis found in adults. This panarteritis of the extracranial branches of the carotid artery occurs only in older individuals. The cause is unknown, but it is associated with the same HLAs found in rheumatoid arthritis and the disease process appears to be initiated by T cells in the adventitia responding to an unknown antigen.

The classic symptoms of giant cell arteritis are:[7]

- A temporal headache that is new or different (70%).
- Jaw claudication (50%).
- Polymyalgia rheumatica – which describes a condition that presents with acheing and stiffness of the shoulders, neck, and hip-girdle area (40%).
- Blindness (20%). This is the most significant complication of giant cell arteritis which can however be prevented by early treatment. The visual loss is caused by occlusion of the posterior ciliary branch of the ophthalmic artery. As a result, the blindness tends to be profound but fortunately is rarely the first manifestation of this complication and is usually preceded by episodes of diplopia and blurred vision.
- Malaise (50%).

The aorta and its major branches can also be involved (25%) leading to the development of thoracic aortic aneurysms some years after the first manifestation.

Giant cell arteritis is characterised by a raised ESR and CRP, and the presence of a normochromic, normocytic anaemia. Ultrasound of the affected temporal arteries can show a characteristic 'halo' of peri-vascular oedema or stenosis of the involved segments. Angiography (usually MRA or CTA) is required to demonstrate involvement of the thoracic aorta and its branches if this is suspected, while PET can demonstrate occult large-vessel inflammation. The definitive method of making the diagnosis of giant cell arteritis is by histology of the temporal artery. As a result of the risk of sudden and irreversible blindness, a temporal artery biopsy, which has a low morbidity, should be performed without hesitation to confirm the diagnosis.[8] As the artery may be affected by skip lesions a 3 to 5cm segment of artery should submitted for evaluation. The histology will demonstrate mononuclear cells infiltrating all layers of the artery with varying degrees of intimal proliferation and disruption of the internal elastic lamina.[7] In recent years the possibility of using duplex ultrasonograpy to identify characteristic features of giant cell arteritis has been raised and further research in this area is warranted.

Treatment with high doses of prednisone (40–60mg/day) and low dose aspirin should be started immediately when the diagnosis is suspected and before it has been confirmed by the temporal artery biopsy. If visual loss has been present for a few hours very high doses of intravenous methyl-prednisolone should be given as some vision may recover. Usually,

after more than 24 hours the visual loss is permanent. In the long-term, in the presence of a normal ESR and CRP, the prednisone can be tapered at a rate determined by the clinical picture and the ESR or CRP.[8] The effectiveness of methotrexate as a glucocorticoid-sparing drug for giant cell arteritis remains controversial while the role of biological therapies such as the tumour necrosis factor inhibitors, infliximab is unknown.

The majority of patients with giant cell arteritis will experience a relapse as the dose of prednisone is tapered and therefore prednisone will often need to be given for prolonged periods and with resultant frequent additional complications from the steroids therapy.

Surgical or endovascular interventions are occasionally indicated when the disease involves the aortic arch and its branches.

Takayasu's arteritis

This large vessel vasculitis affects mostly young adult women but has been found in infants and more rarely in the aged. The cause is unknown, yet the geographic distribution (predominantly south-east Asia, India and Africa) suggests environmental or genetic factors – e.g. HLA associations have been found in Japanese patients – while the predominance in women of childbearing age points to oestrogen and progesterone playing a role.[7]

Takayasu's arteritis is a T-cell driven, non-specific granulomatous inflammation of all layers of the vessel wall which pathologically cannot be distinguished from giant cell arteritis.[9] In response to the inflammation, cellular proliferation in the intima and media may lead to occlusion and stenosis of the artery, or weakening of the media and adventitia which can result in dilation and aneurysm formation. The most frequently affected vessels are the subclavian arteries, carotid arteries and the aorta, including the origin of its visceral branches. Dilatation or aneurysm formation is usually only found in the aorta. The pulmonary and coronary arteries can be involved, albeit rarely and myocarditis associated with Takayasu's arteritis has also been described.[9,10]

The disease is usually recognised by the manifestations of the vascular disease but constitutional symptoms of inflammation – fever, myalgia, arthralgia and weight loss – are commonly the earliest feature of this illness. The vascular manifestations include those associated with occlusion of arteries supplying the limbs, hypertension caused by aortic or renal artery stenosis, cerebrovascular manifestations due to occlusion of the carotid or vertebral arteries and aortic valve regurgitation. Involvement of the coronary arteries, myocardium and pulmonary arteries may cause angina and congestive cardiac failure.[9-11] Affected blood vessels are often tender and as a result, severe back pain, similar to that seen in patients with thoracic dissection, and pain in the carotid arteries is common.

No specific diagnostic test exists. An elevated ESR and CRP are usual during active phases of the disease.[9] Microcytic anaemia develops in many patients. Some patients have an elevated serum creatinine usually associated with longstanding hypertension, while glomerulonephritis occurs rarely.

Vascular imaging is essential to delineate the full extent of the vascular involvement. Many favour MRA, as this can demonstrate changes in the vessel wall prior to luminal changes being noted. PET may detect vascular inflammation but its accuracy in diagnosing the disease has not been determined but shows promise.[12]

The histological diagnosis is based on demonstrating the typical granulomatous vasculitis with giant cells in inflamed blood

vessels. This is however rarely possible, as biopsy of an affected artery while the disease is in an active phase is usually not advisable, and when specimens become available, while the disease is in a quiescent phase, only nonspecific transmural fibrosis can be found.

Initial treatment requires high doses of prednisone in the acute phase which is then tapered to 10mg/day and continued for 4 to 6 months. This regime is usually effective in addressing the inflammation in the vascular wall and abating the constitutional symptoms but two thirds of patients with Takayasu's arteritis experience relapse of symptoms or progression of vascular disease. As a consequence life-long monitoring of this condition is mandatory.

Methotrexate or mycophenolate mofetil in combination with prednisone are occasionally needed to reduce the inflammation and are also at times used without prednisone during phases of remission in order to minimise the corticosteroid side effects. Other drugs such as cyclophosphamide are used rarely because of their side effects but on occasion are all that some patients will respond to. Agents such as infliximab have shown promise but are usually unaffordable in the countries in which this disease predominates.[9] The use of statins and low-dose aspirin is encouraged.

The renal and cardiac dysfunction and hypertension that do not rapidly resolve after initial treatment for the acute inflammatory disease are managed using standard protocols. Diagnosing and managing these can, however, be challenging because of the diffuse vascular involvement. In patients who have cerebrovascular occlusive disease it is often also necessary to maintain a high blood pressure to avoid episodes of cerebral and brainstem hypoxia. Surgical and endovascular interventions play an important role in treating occlusive and aneurysmal manifestations.[11] The indications for intervention are the same as they are for other pathologies, i.e. usually only for life or limb threatening symptoms. Fortunately, few interventions are required in the acute phase, as failure rates are high for procedures performed when acute inflammation is present, are high. Revascularisation in our practice is deferred, if at all possible, until pharmacological therapy has completely suppressed the inflammation, which we believe to be indicated by a normal CRP and ESR. This experience is shared by others.[13]

In the long-term once the active disease has been treated, most patients return to near normal lifestyles and survival rates. A significant number of patients do however die as a consequence of renal or cardiac failure,[14] or from the complications of immunosuppressive treatment which is compounded by the high prevalence of HIV infections in some of the affected populations.[11]

Thromboangiitis obliterans (Buerger's disease)

This condition usually occurs in young individuals after extended and ongoing exposure to tobacco smoke, but can affect all age groups. The reason for the relationship between thromboangiitis obliterans and smoking has not been established. There are some indications that it has an immunological background, as increased levels of cell-mediated responses to vascular collagen and raised levels of anti-endothelial cell antibodies have been described.[15] Other forms of smoking, such as cannabis, may also cause similar disease patterns.

Thromboangiitis obliterans affects medium-sized arteries, veins and nerves. The lower limbs are most frequently affected but upper limb disease is common. Pathologically, the blood vessel wall architecture is usually

intact, with preservation of the internal elastic lamina and absence of necrosis. During the acute phase of the disease a highly cellular, inflammatory thrombus is found occluding the lumen. In time this becomes a band of fibrous tissue. Involvement of superficial veins is associated with a perivascular inflammatory cell infiltrate resulting in a thrombophlebitis.

Thromboangiitis obliterans is usually first recognised by the presence of extremely painful, severe, progressive digital ischemia (often first thought to be splinter haemorrhages).[15] Occasionally, the earliest lesion may be a superficial thrombophlebitis. In advanced cases the gangrene may extend well beyond the digits. Other organs are not involved. Prior to the development of gangrene, pain in the distal extremities may be due to a neuropathy. These symptoms are due to thickening of the tissues in the neurovascular bundles as a result of perivascular inflammation.

The diagnosis is generally confirmed by identification of the typical pattern of vascular involvement, exclusion of conditions that may mimic the disease, particularly atherosclerosis, and the presence of ongoing tobacco exposure. The demonstration of typical 'corkscrew' collaterals in the neurovascular bundles is characteristic but can also be found in other conditions such as diabetes mellitus and polyarteritis nodosa.[15] While most diagnostic systems for thromboangiitis obliterans are intended to exclude the presence of atherosclerosis, both these conditions often coexist, particularly in patients over the age of 40 years.

The only effective treatment for thromboangiitis obliterans is to completely stop smoking.[15] Immunosuppression and anticoagulation have no role. Occasional patients respond partially to prostaglandins. Revascularisation, using endovascular techniques or bypass grafts, is usually not feasible from a technical perspective, as a result of the inflammatory and thrombotic processes, and occlusion of distal runoff arteries, but may play a role if haemodynamically significant atherosclerotic lesions coexist in the patient. Effective pain control is essential as patients will not be able to stop smoking without it.

With any ongoing smoking, which tends to be the norm – such patients appear to be particularly nicotine dependent – arterial disease progresses. Limb loss therefore occurs frequently. On the other hand, complete abstinence is associated with remarkably good outcomes.

Behçet's disease

Behçet's disease was originally described as a syndrome consisting of recurrent oral aphthous ulcers, genital ulcers, and ocular inflammation. This idiopathic vasculitis can however, cause inflammation in almost any organ. The most significant morbidity associated with Behçet's disease is related to ocular inflammation, which can cause blindness. Most manifestations of the disease are however episodic and become less frequent over time, but mortality may occur – mostly as a result of thrombosis, aneurysms and de novo rupture of large vessels.

Behçet's disease is common in countries along the ancient Silk Road (eastern Mediterranean countries central Asia to China) – as many as 4 per 1000 population have been described – and rare elsewhere. It mostly affects young adults and is more frequent in men. The distinct geographic distribution suggests an environmental or genetic aetiology. The pathologic changes point to an abnormal reactivity of neutrophils and lymphocytes causing damage by a vasculitic process which affects all types of arteries. Venous thrombosis is also common.[16]

Clinically, oral ulceration tends to be the earliest manifestation and must be present to make the diagnosis of Behçet's disease. These painful ulcers, which affect the mucosa from the lips to the oropharynx, can be up to 2cm in diameter and usually have a white base and a red halo around the ulcer. Between two and five lesions are usually present at a time. The oral lesions tend to heal within two to three weeks without scarring while the genital ulcers tend to be larger and deeper, and often heal with scarring. In men the genital ulcers, which develop mostly on the scrotum and less commonly on the shaft of the penis, are associated with epididymitis. In women ulcers affect the vagina and vulva. Ocular inflammation is caused by an anterior and posterior uveitis. The anterior uveitis usually presents with a red eye, photophobia and blurred vision while the less common posterior uveitis, in combination with vasculitis affecting the carotid arteries and retina, can result in loss of vision. Other regularly encountered features include erythema nodosum, migratory thrombophlebitis, arthritis, spondylitis, gastrointestinal aphthous ulcers, meningoencephalitis, stroke (thrombotic or haemorrhagic), sagittal sinus thrombosis, seizures, hearing and vestibular impairment, dementia and psychiatric conditions. Vascular manifestations, include thrombophlebitis and venous thrombo-embolism, occur in a fifth of patients while the arterial vasculitic manifestations are much less common – this arterial process particularly affects mesenteric and pulmonary arteries and may cause occlusion, aneurysm formation or primary rupture.[17,18]

The diagnosis of Behçet's disease rests predominantly on the clinical features but raised nonspecific markers of inflammation are common while the disease is active. Serum IgD levels are also often elevated. Histology of the aphthous ulcers reveals an inflammatory vascular infiltrate but a true vasculitis is rare.[16]

The oral ulcers and other aphthous lesions are treated with topical steroids or Dapsone while vision- or life- threatening complications are treated with high doses of intravenous corticosteroids and other immunosuppressive agents. Infliximab is also effective.[16] Vascular interventions are required for symptomatic life threatening occlusive arterial disease, while aneurysms are treated according to their risk of rupture. All spontaneous arterial ruptures require emergency repair. Thrombophlebitis is treated symptomatically and venous thrombo-embolism is managed by anticoagulation.

Polyarteritis nodosa

This is a vasculitis confined to small and medium-sized arteries. Men and women are equally affected and the disease occurs in all age and ethnic groups. The association with chronic hepatitis B virus infection is well established.[19]

Polyarteritis nodosa can involve virtually all organs, but spares the lungs.[20] Commonly involved organs are:

- Skin – includes livedo reticularis, nodules, papules, ulceration, and digital ischemia often associated with splinter haemorrhages which can lead to gangrene.
- Peripheral nerves – usually mononeuritis multiplex of the sural, peroneal, radial, and ulnar nerves.
- Gastrointestinal tract – commonly postprandial abdominal pain, but also mesenteric infarction or aneurysmal rupture of visceral arteries due to multiple microaneurysms.
- Kidneys – excluding glomerulonephritis.

The constitutional symptoms of inflammation and pain, caused by myalgia, arthritis,

peripheral nerve infarction, testicular ischemia, or mesenteric vasculitis, are usually found. The other vascular presentations include renin-mediated hypertension, subclinical arteriolar involvement of the cardiac circulation with occasional congestive cardiac failure and myocardial infarction, and occasional stroke.

The diagnosis of polyarteritis nodosa is generally based on histology – most frequently of skin nodules, which specifically does not demonstrate granulomatous infarction – and the demonstration of microaneurysms in the visceral arteries. The ANA and rheumatoid factor (RF) are usually negative. The ANCA tends to be positive but specific enzyme immunoassays for antibodies to proteinase-3 or myeloperoxidase – the antigens known to be associated with systemic vasculitis – are negative. Polyarteritis nodosa is therefore not considered to be an ANCA associated vasculitis.

When polyarteritis nodosa is associated with hepatitis B virus, polyarteritis nodosa tends to occur soon after the initial infection and these patients also have low complement levels.

Treatment of idiopathic polyarteritis nodosa is similar to the other vasculitides already described.[20] Cyclophosphamide is required for approximately half the patients whose disease is refractory to corticosteroids or who have significant life threatening involvement of major organs. Hepatitis B virus if present is treated with antiviral therapy which is the reason that the frequency of polyarteritis nodosa is diminishing.

The prognosis is usually favourable. Bowel perforation and rupture of a mesenteric microaneurysm however requires emergency surgical intervention which is the reason that this disease still causes mortality. Recurrence rates after successful treatment of the initial clinical manifestation are unusual.

Vasculitis secondary to connective tissue diseases

Systemic lupus erythematosus (SLE)

In SLE, lupus vasculopathy is found in up to 40% of patients (mostly female). This usually is a typical vasculitis characterised by inflammation and necrosis in the vessel wall.[21] The aetiology of these changes are:

- Leucocytoclastic inflammation in 60%
- Cryoglobulinaemia in 30%
- Systemic vasculitis resembling polyarteritis nodosa in 6%.

Lupus vasculitis is also associated with thrombotic thrombocytopenic purpura, venous thrombosis, antiphospholipid syndrome and urticarial vasculitis.

Lupus vasculopathy is an immunological disease with various autoantibodies, directly or indirectly affecting endothelial cells and cell membrane phospholipids. These cause chronic vessel wall damage.[22] It is hypothesised that the endothelial deposition of circulating immune complexes causes activation of secondary inflammatory responses which then activate the complement cascade. This results in the destruction of vascular basal membranes. The expression and activation of adhesion molecules appear to also be the key factors in the pathogenesis of the vasculitis by enabling leukocyte adhesion to the vessel endothelium and allowing leukocyte infiltration into affected tissues. In addition, lupus vasculitis also initiates the development and progression of atherosclerosis.

The antibodies involved in lupus vasculitis include:[22,23]

- Anti-endothelial cell antibodies which occur in over 80% of SLE patients. It seems that their presence is typical of vasculitis, vascular thrombosis and lupus nephritis. These antibodies belong to

the IgG, IgM and IgA immunoglobins and bind to antigens through the F(ab)2 region. Multiple endothelial cell antigens react with these antibodies.
- Antiphospholipid antibodies which bind to exposed endothelial cell phospholipids. These antibodies cause vascular endothelial damage, an increased arterial and venous thrombosis risk and proliferative heart valve lesions.
- ANCA. Their role in lupus vasculitis remains unclear.
- Anti-double-stranded DNA antibodies may take part in vascular damage in SLE. They possess an anti-endothelial activity, which is directed against certain antigens on the endothelial surface.

The spectrum of the lupus vasculopathy ranges from the mild and most common form, affecting only vessels of the skin, to severe multiple organ dysfunction.[21] The cutaneous lupus vasculopathy manifests as purpura, urticaria or bullous lesions in the extremities, and livedo reticularis on the trunk. Occasionally necrosis of the nail bed and digital ulceration is also found. Lupus vasculitis in other organs can affect 20% of patients. Examples include:

- Focal segmental glomerulonephritis in the kidneys
- Necrotic inflammation in alveolar capillaries of the lungs
- Cognitive dysfunction, psychosis, convulsions and strokes in the brain
- Mononeuropathies in the peripheral nerves
- Gastrointestinal haemorrhage or perforation.

Antiphospholipid antibody syndrome (APS)

The APS is defined by the presence of at least one of the many plasma antiphospholipid antibodies and the occurrence of at least one clinical feature of which venous or arterial thromboses, recurrent foetal loss, or thrombocytopenia are the most common. The antiphospholipid antibodies, which are directed against plasma proteins bound to anionic phospholipids, are: [24,25]

- Lupus anticoagulants. These are antibodies directed against plasma proteins such as β2 glycoprotein-1 or prothrombin bound to anionic phospholipids. Despite their name, the presence of lupus anticoagulants is generally associated with thrombosis and they do not have an anticoagulant effect.
- Anticardiolipin antibodies.
- Other antibodies, e.g. those to β2 glycoprotein-I, prothrombin, annexin V, phosphatidylserine and phosphatidylinositol.

In addition to causing thrombosis, the above antibodies also increase vascular tone, thereby increasing the susceptibility to atherosclerosis, fetal loss and neurological damage.

The pathogenesis remains unclear. It appears that the antiphospholipid antibodies develop in susceptible individuals following incidental exposure to currently undefined, infectious agents. Once the antibodies are present a second hit, such as an infection, prolonged immobilisation, pregnancy, hormone replacement therapy, malignancy or nephrotic syndrome is required for the syndrome to develop.[24]

APS can either be a primary disease or can be associated with another secondary condition.[25] For example:

- Some healthy individuals have antiphospholipid antibodies but few ever get the APS.
- Autoimmune diseases – particularly SLE.

- Infections:
  - Bacterial infections: e.g. bacterial septicaemia, tuberculosis, leprosy and post-streptococcal rheumatic fever.
  - Viral infections: e.g. hepatitis A, B, and C, HIV, cytomegalovirus and Epstein-Barr virus.
  - Parasitic infections: malaria and visceral leishmaniasis
- Medications: e.g. phenothiazines, phenytoin, hydralazine, α-interferon, quinine, amoxicillin, chlorthiazide, oral contraceptives and propranolol.
- Malignancies including solid tumours of the lung, colon, cervix, prostate, kidney, ovary, breast, and bone; Hodgkin's and non-Hodgkin's lymphoma; myelofibrosis, polycythemia rubra vera, myeloid and lymphocytic leukemias.

The most common manifestations, in order of frequency, are deep vein thrombosis, thrombocytopenia, livedo reticularis, stroke, superficial thrombophlebitis, pulmonary embolism, fetal loss, transient ischemic attack and haemolytic anaemia. Rarely, APS results in ischaemic multiorgan failure. Other possible antiphospholipid antibodies related manifestations include migraine headache, Raynaud's phenomenon, pulmonary hypertension, avascular necrosis, cutaneous ulcers that resemble pyoderma gangrenosum, adrenal insufficiency and cognitive deficits.

The presence of APS should be considered in patients who have one or more otherwise unexplained thrombotic or thrombo-embolic events, one or more adverse outcomes related to pregnancy or otherwise unexplained thrombocytopenia or bleeding.

Rheumatoid arthritis

The vasculitis associated with rheumatoid arthritis occurs in patients with previously severe disease, typically in those with long-standing rheumatoid nodules, destructive joint disease, and high titres of rheumatoid factor. The development of a vasculitis is associated with new constitutional symptoms, skin ulceration, serositis, digital ischemia, and sensory and motor nerve dysfunction. It may also cause multiorgan dysfunction.

The vasculitis is caused by the deposition of immune complexes and antibody-mediated destruction of endothelial cells resulting in vascular necrosis and luminal thrombosis.[22] Cigarette smoking and other factors have a significant adjunctive role.

The diagnosis should ideally be established by tissue biopsy. Deep full-thickness skin biopsies from the edge of skin ulcers, that include some subcutaneous fat, can detect the presence of medium-vessel vasculitis.

As in all the vasculitides, therapy must reflect the severity of organ involvement. When small, relatively painless infarctions around the nail bed develop, these do not necessarily require treatment. While this vasculitis does respond to therapy it generally is associated with a poor prognosis. Fortunately, with the modern more effective treatment of rheumatoid arthritis, this condition is becoming rare.[26]

Scleroderma

Scleroderma refers to the presence of thickened, hardened skin which is a common feature of a heterogeneous group of connective tissue disorders. When the characteristic skin disorder is associated with visceral organ involvement, the disease is termed systemic sclerosis. This is further subcategorised into diffuse cutaneous systemic sclerosis and limited cutaneous systemic sclerosis on the basis of the extent and distribution of the skin involvement. Limited systemic sclerosis is commonly associated with the CREST syndrome (made up of cutaneous calcification, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangectasia).

The visceral manifestations of systemic sclerosis are varied, including fibrotic and/or vascular complications of the circulatory, musculoskeletal, renal, pulmonary, and gastrointestinal systems. The characteristic clinical manifestation of vascular dysfunction is Raynaud's phenomenon.[27] Episodes of Raynaud's phenomenon may be prolonged and can result in ischemic digital ulceration or infarction. In patients with limited cutaneous systemic sclerosis, Raynaud's phenomenon generally precedes other disease manifestations, often by many years. In contrast, in patients with diffuse cutaneous systemic sclerosis, the onset of Raynaud's phenomenon generally coincides with, and in some cases may even follow, the appearance of characteristic skin or musculoskeletal manifestations. Vascular injury and consequent chronic tissue damage underlies other serious complications of systemic sclerosis, including pulmonary artery hypertension, renal crisis and gastric antral vascular ectasia, and also contributes to the pathogenesis of cardiac and other gastrointestinal complications.[28]

The presence of systemic sclerosis is suggested by the presence of skin thickening and hardening that is not confined to one area. The diagnosis is supported by the presence of other non-cutaneous features such as:

- Heartburn and/or dysphagia
- Acute onset of hypertension and renal dysfunction
- Effort induced dyspnoea and interstitial pulmonary fibrosis
- Pulmonary hypertension
- Mucocutaneous telangiectasia on the face, lips, oral cavity, or hands
- Digital gangrene

Over 95% of patients have at least one autoantibody present. These include the presence of antinuclear antibodies and more specific antibodies such as anti-topoisomerase I, anti-centromere, anti-RNA polymerase III and anti-beta2-glycoprotein I antibodies which are frequently present in patients with systemic sclerosis. The anti-topoisomerase I, anti-centromere and anti-RNA polymerase III antibodies are specific but only moderately sensitive. A skin biopsy is generally not needed to confirm a diagnosis.

Infective vasculitides

Human immunodeficiency virus (HIV)

HIV infection can cause a range of vascular diseases.[29] In the arterial system, HIV positive patients have been found to have both aneurysms and occlusive disease, mostly thrombotic disease. These vessel wall pathologies have unique histological characteristics where the inflammation is found in the vasa vasora. The inflammatory process consists of neutrophils surrounded by a cuff of plasma cells and lymphocytes. In addition, there is marked endothelial swelling with fibrin deposits on the luminal surface which leads to occlusion of the vasa vasora. In the wall of large arteries there are patches with acute inflammatory infiltrate, while in other regions there are areas of extensive fibrosis without inflammation. This suggests that there is a sequence of events starting with inflammation concentrated in the adventitia. Later in the disease this may either cause trans-mural necrosis, possibly leading to aneurysm formation, or the transmural inflammation may induce luminal thrombus.

Both HIV associated aneurysms and HIV associated arterial occlusion are considered to be Acquired Immunodeficiency Syndrome (AIDS) defining conditions as they are usually associated with low CD4 counts in patients with other manifestations of the infection.

HIV associated aneurysms have been found in most major arteries and are usually saccular in nature as a result of a localized region of cytoclastic activity in all layers of the arterial wall. Patients tend to present with multiple aneurysms. Treatment is based on the usual principles of care for aneurysms but because of the poor general condition of affected patients, endovascular modalities are favoured.

Occlusive arterial disease most commonly involves the iliac arteries, but involvement of the coronary arteries is also found in young men who also smoke.[30] Treatment of these patients is hampered by the underlying vasculitis and is generally associated with a poor outcome unless the inflammatory process is reversed by treating the HIV infection.

The association between venous thrombo-embolism and the HIV infection has also been conclusively proven.[31] The reported incidence ranges from 0.2% to 18% which is well in excess of what one would expect in a non-infected population (0.05%). At the Johannesburg Hospital 84% of patients who presented with deep vein thrombosis were found to be HIV positive. The severity of the HIV infection appears to be of significance as there is a greater incidence of venous thrombosis in patients with low CD4 counts, while the risk is even higher when individuals have confirmed AIDS. The reason for HIV infection's relationship with venous thrombosis has not yet been conclusively elucidated, but appears to be multimodal, with all three limbs of Virchow's triad being involved.

PATHOPHYSIOLOGY AND PRINCIPLES OF TREATMENT OF RAYNAUD'S PHENOMENON

In order to preserve the core temperature, the normal physiological response to exposure to a cold environment is to reduce capillary blood flow to the skin, mostly in the limbs and digits. This response is regulated by a complex interaction of neural signals, circulating hormones, and the release of local mediators mostly derived from the vascular endothelium.

Raynaud's phenomenon describes an exaggerated vascular response to such a cold stimulus, or occasionally to emotional stress. The phenomenon is characterised by sharply demarcated colour changes of the skin of the digits. Typically these consist initially of a phase of vascoconstriction and therefore a pale appearance (white) followed in time by cyanosis (blue) as a result of deoxygenation of haemoglobin within the affected tissues. Finally, with reflex vasodilation as a result of the localised tissue ischaemia and the resultant inflow of oxygenated blood, a phase of hyperaemia (red) follows. Only the two initial phases, pallor and cyanosis, need to have been present for such an event to be recognised as a Raynaud's attack.[32]

Primary Raynaud's phenomenon describes this sequence of events in the absence of any associated disorders – occasionally called Raynaud's disease, which is inappropriate as the phenomenon only describes an exaggerated physiological response in these individuals – while secondary Raynaud's phenomenon is associated with a known disease –referred to occasionally as Raynaud's syndrome (Table 16.3).[33]

The defect in primary Raynaud's phenomenon is currently thought to be an increased vasoconstrictive response to $\alpha 2$ adrenergic stimuli, particularly at the level of $\alpha 2$ adrenergic receptors, in the digital arteries and cutaneous arterioles.[34] The exact mechanisms have however not yet been established. The vascular response to the $\alpha 2$ adrenergic agonists, serotonin and angiotensin II is increased during cooling and can be reversed by tyrosine kinase inhibitors.[35]

TABLE 16.3: Common secondary causes of Raynaud's phenomenon[32,33,36]

Connective tissue diseases and vasculitis:	
Systemic lupus erythematosus	Systemic sclerosis (scleroderma)
Rheumatoid arthritis	Giant cell arteritis
Thromboangiitis obliterans	Primary biliary cirrhosis
Diseases of arteries in the upper limbs:	
Atherosclerotic occlusive disease	Frost bite
Thoracic outlet syndrome	
Malignancies:	
Ovarian carcinoma	
Endocrine diseases:	
Phaeochromocytoma	Thyroid disease
Carcinoid syndrome	
Vasospastic conditions:	
Vibration syndromes	Migraine and Prinzmetal angina
Haematological disorders:	
Cryoglobulins and cold agglutinins	Polycythaemia
Paraproteinaemia	
Drugs and chemicals:	
Ergotamines	Polyvinyl chloride
Bleomycin and Vinblastine	

An underlying genetic mechanism is also suggested by the occasional appearance of Raynaud's phenomenon in family clusters, and because women are most frequently afflicted by this condition, suggesting that some of the relevant loci are located on the X chromosome. The effect of oestrogen on $\alpha 2$ adrenergic receptor expression may however also be a reason for the higher prevalence of this condition amongst women.[35]

In secondary Raynaud's phenomenon, the many diseases, drugs, and environmental factors that can cause the syndrome, disrupt the normal mechanisms responsible for control of vessel reactivity, each apparently in a unique manner. For example, in systemic sclerosis (scleroderma) the primary mechanism is considered to be associated with intimal fibrosis and endothelial dysfunction. In these patients, endothelin-1 levels are significantly increased. This potent vasoconstrictor is also involved in the development of fibrosis and other structural changes in blood vessels.[35] In addition, angiotensin II levels are increased, while nitric oxide levels are consistently found to be low.

Prevalence of Raynaud's Phenomenon

It is difficult to establish the prevalence of Raynaud's phenomenon because of the lack of standardisation in the diagnosis. However, when using at least pallor and cyanosis to define an episode of Raynaud's phenomenon, the prevalence ranges from 3 to 20% in women and 3 to 14% in men.[33] These wide ranges are explained by the great variation found across the world both in populations and in climate. For example Raynaud's phenomenon is common in central Europe when compared to populations in the Americas, Africa and Asia. It is also more common among women, in younger age groups (median onset 14 years), and in family members of individuals with

established Raynaud's phenomenon. About 25% of individuals first develop symptoms after the age of 40 years and rarely after the age of 60 years.[32]

Clinical Findings in Raynaud's Phenomenon

Raynaud's phenomenon most frequently affects the fingers and hands. While the toes and feet are often also affected this tends not to concern patients as much. A typical episode usually begins in a single finger and then spreads to all other digits but the thumbs are often spared. Vasospasm of the skin of the ears, nose, face, knees and nipples is also commonly described. The ischaemic phase (pallor and cyanosis) usually lasts for 15 to 20 minutes. Often when the initial phase of such an attack is prolonged, patients describe the feeling of pins and needles, numbness, and complain that the fingers are aching. These symptoms rapidly reverse in patients with primary Raynaud's phenomenon when the limb is rewarmed or the stress is alleviated. On the other hand in secondary Raynaud's phenomenon, asymmetry of symptoms, severe constant pain and ischaemic ulceration of the skin may occur, particularly when the mechanism of the underlying disease cannot be addressed.

Exposure to cold is the usual trigger and mostly occurs with rapid movement from a warmer to a cooler environment. As a consequence, air-conditioned rooms, or the mere washing of hands in cold water may be all it takes to bring on an episode. An attack is usually brought on by the distal limbs being exposed, but on occasion cooling of the trunk while the hands or feet areas are kept warm can also provoke an attack. As a consequence afflicted individuals should always ensure that all parts of their body are kept warm.

Diagnosis of Raynaud's Phenomenon

The diagnosis is mostly made when the classic symptoms are described. Confirming the diagnosis by using provocative manoeuvres such as a cold water challenge, is unhelpful due to inconsistency in producing the syndrome. As the majority of patients presenting with Raynaud's phenomenon have no other underlying disease little benefit is achieved by further evaluation.

In the small number of individuals who have a secondary cause or in whom symptoms persist, additional evaluation may be helpful, but this usually requires complex diagnostic tools that are generally not freely available. The tools used to assess the vascular responses to environmental stimuli in the skin, include nail fold capillaroscopy, angiography, laser Doppler flowmetry, and measurement of skin temperature. Generally, in patients with all forms of Raynaud's phenomenon these demonstrate that there is a delayed recovery phase of vascular flow after exposure to environmental stressors.[32,33]

Every patient with primary Raynaud's phenomenon should be carefully evaluated clinically, to exclude a secondary cause.[32] The criteria to diagnose primary Raynaud's phenomenon include the presence of symmetrical, episodic attacks, no evidence of occlusive arterial disease, no gangrene, and if there is doubt a negative nail fold capillary examination (if this is available), a negative ANA and normal ESR/CRP. The clinical clues that secondary Raynaud's phenomenon may be present include:

- Age of onset >40 years
- Male
- Pain and tissue ischemia (ulceration)
- Asymmetry

The presence of a raised ESR or CRP and autoantibodies suggests an underlying connective tissue disease.

PROGNOSIS

Approximately 50% of individuals with primary Raynaud's phenomenon will have a reduction in the frequency and severity of their symptoms over time, particularly if the onset of symptoms occurs in adolescence.

Occasionally, Raynaud's phenomenon is the first manifestation of an underlying disease. The frequency at which individuals thought to initially have primary Raynaud's phenomenon are found to have a underlying cause identified is in the region of 1% per year, but is usually only noted 10 years or more after the primary presentation. The best predictor that this may happen is an abnormal nail fold capillary pattern.[36]

TREATMENT

The initial management of patients with primary Raynaud's phenomenon is to promote lifestyle changes and to avoid the use of medication.[36] The advice usually given includes:

- Keeping the whole body warm by:
  - Avoiding sudden exposure to cold
  - Dressing warmly
  - Keeping all digits warm even in very cold environments
  - Avoiding rapidly changing temperatures
- Reducing emotional stress
- Avoid smoking and using drugs that cause vasoconstriction

If an attack occurs, the patient should be advised to go to a warm room and to place the hands under warm water, or to swing the upper limbs like a windmill.

In patients with secondary Raynaud's phenomenon the above measures are less helpful, as a result of more severe attacks. For this reason, and because of the progression of the ischaemia, they will usually require pharmacological intervention as do some patients with primary Raynaud's phenomenon in whom severe symptoms persist.

Multiple classes of drugs are used in the management of Raynaud's phenomenon. The medications used are:[37]

- Calcium channel blockers. Approximately 60% of patients have a clinically significant improvement of their symptoms (both in the reduction of the severity and frequency).[7] Not all calcium channel blockers are effective. Nifedipine in relatively small doses given three to four times per day is the one most frequently used. These drugs are introduced slowly in order to reduce the chance of patients experiencing headaches. Secondary Raynaud's phenomenon is also less likely to benefit from this class of drugs.
- Many direct and indirect vasodilators have some effect but few are freely available for the management of this condition. The serotonin reuptake inhibitors (such as fluoxetine), angiotensin receptor blockers (losartan) and other vasodilators such as buflomedil have demonstrated similar response rates when compared to the effective calcium channel antagonists.
- Prostaglandins. Prostaglandin E1 (PGE1), prostacyclin (PGI2), and iloprost (a PGI2 analogue) are the most frequently used. The response rate in severely affected patients is in the region of 60%. Infusions given over a few days often have benefit that often lasts several months.
- The phosphodiesterase inhibitors, sildenafil and tadalafil. The current data

supporting the use of these agents is sparse but promising.
- Endothelin receptor antagonists e.g. bosentan which acts as an antagonist of endothelin-B receptors, has been demonstrated to significantly reduce the number of new ulcers forming in patients with systemic sclerosis.
- Antioxidant agents, such as zinc gluconate and N-acetylcysteine have demonstrated some improvement in small studies
- Atorvastatin does reduce the severity and frequency of Raynaud's events and of ulcer formation in patients with scleroderma.

In addition, multiple antithrombotic agents have been utilised in patients with significant complications associated with Raynaud's phenomenon. These include aspirin, dipyridamole, systemic anticoagulation, and thrombolytic therapy. The benefit of antiplatelet therapy with aspirin (75 or 81mg/day) is uncertain but use of this agent should be considered in all patients with secondary Raynaud's phenomenon.

The role of sympathectomy has recently again been considered in the management of severe Raynaud's phenomenon mostly as a result of the development of less invasive and more focused procedures being available.[36] These include:

- A local chemical sympathectomy using a long acting local anaesthetic agent to achieve a wrist or digital nerve block which can reverse vasoconstriction and relieves pain.
- Intradigital botulinum toxin A has been used to achieve a chemical sympathectomy. While this is an interesting option, the current described experience is limited.[37]
- Cervical sympathectomy is likely to result in the immediate improvement in blood flow, but the degree and duration of improvement is very variable and long term outcomes particularly in patients with secondary Raynaud's phenomenon are poor.
- Localised microsurgical digital sympathectomy has been introduced as an alternative to proximal sympathectomy. This option appears to have more durable outcomes and is often now the choice when sympathectomy is the last treatment modality available, particularly only after vasodilator drugs and after specific treatments for any reversible cause, such as vasculitis, have failed.

RECOMMENDATIONS

All patients with Raynaud's phenomenon should avoid cold temperatures, stress, and vasoconstrictors, while always being dressed in warm clothing, and should warm their hands in order to terminate an attack.

Most importantly, patients with primary uncomplicated Raynaud's phenomenon should not be over-treated. Therapy should only be initiated in those patients with primary uncomplicated Raynaud's phenomenon in whom non-pharmacologic measures have failed. These medications should be introduced in a step wise manner and should only be continued if appropriate symptom relief is achieved. Parenteral medications and sympathectomy are usually not indicated.

Patients with secondary Raynaud's phenomenon may require more aggressive therapy. The major goal is to reduce the frequency of attacks, and to prevent digital ulceration. It is unlikely that any medical therapy on its own will completely terminate attacks. In general, a step wise escalation of therapy, initially using the oral vasodilators, followed by parenteral medications and lastly localised digital sympathectomy, should be used in accordance to the level of symptoms

and the extent of digital ulceration and gangrene. All such patients should also have the underlying disease addressed, which in patients with the vasculitides include the use of a statin and an antiplatelet agent. In addition appropriate and effective analgesia will be required. Such pain control and surgical amputation may be the only option in patients with late stage ischemia or severe structural arterial disease.

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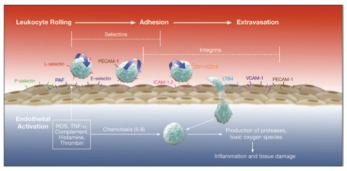

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