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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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

29 • Pathophysiology of Vascular Graft Infections

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INTRODUCTION

The introduction of prosthetic grafts has revolutionised the management of vascular disease but graft infection although uncommon, remains a dreaded complication with associated significant morbidity and mortality. Mortality occurs in approximately one third of all vascular graft infections,[1] with mortality highest when an aortic prosthesis is involved.[2,3] As many as 75% of survivors of an infected aortic prosthesis require amputation of a limb,[3] with the incidence of amputation highest when the infection involves more distal prosthetic grafts.[4] The incidence of graft infections is difficult to quantify as infection may manifest many years after implantation[1] with many reports being isolated or as part of case series. Nevertheless, the reported incidence is in the order of 5%, varying according to the site of operation, being higher when a groin incision is used, or if the procedure is an emergency or a redo procedure. Infection following endovascular stent deployment has been reported although its incidence is considered to be very low.

NATURAL HISTORY OF PROSTHETIC VASCULAR GRAFT INFECTIONS

Early prosthetic vascular graft infections typically occurring in the first four months following placement are relatively uncommon (approximately 1%) and are usually caused by the more virulent micro-organisms, such as *S. aureus, E. Coli, Pseudomonas, Klebsiella, Proteus and enterobacter*.[1] Late prosthetic vascular graft infections are the result of two possible mechanisms. Firstly, by haematogenous seeding from a septic focus elsewhere[5] or by the prosthetic graft becoming infected with enteric contents following a graft-enteric erosion.[6] In both the haematogenous and graft-enteric erosion situations the usual causative organisms are those with high virulence and clinical manifestations are signs and symptoms of sepsis. The second mode of presentation is insidious, caused by the less virulent coagulase negative staphylococci such as *S. epidermidis* with contamination likely occurring at the time of implantation.[1]

MECHANISMS OF GRAFT CONTAMINATION AT OPERATION

Prosthetic grafts most commonly become infected at the time of implantation either by contamination from the surgical team or by colonised microorganisms on the patient. It has been demonstrated that the majority of patients undergoing arterial revascularisation are colonised with coagulase negative staphylococci[7] and colonisation of patients with nosocomial bacteria is enhanced when the preoperative hospitalisation is lengthy.[8]

The incidence of infection following emergency aneurysmorrhapy has been reported to be increased to 7.5%.[9] The evidence of other potential mechanisms such as division of lymph nodes,[10,11,12] infected transudated fluid during aortic surgery[13,14,15] and infected laminated thrombus[4,14,16,17] is conflicting.

PATHOGENESIS OF GRAFT INFECTIONS

The exact aetiology of vascular graft infections is not completely understood but is likely to be multifactorial. According to Bandyk and Esses[18] the risk of vascular graft infection as demonstrated by animal models can be predicted by the formula:

$$\text{Risk of biomaterial infection} = \frac{\text{Dose of bacterial contamination X virulence}}{\text{Host resistance}}$$

The dose of bacterial contamination is dependent on the infecting microorganism. Experimentation in a canine aortic model has demonstrated that the infective threshold for bacteria to cause graft infection in over 50% of grafts was 10^7, 10^9, and 10^2 for *S. aureus, S. epidermidis and P. aeruginosa* respectively.[19] Virulence of microorganisms is often associated with the production of secreted toxins and enzymes with a resultant decline in structural integrity of the artery wall[18] and the release of toxins and enzymes to control the perigraft environment and cause graft infection.[19,20] Many bacterial strains, including *S. epidermidis, S. aureus and P. aeruginosa* are known to produce extracellular polymer substances (slime), forming a capsule incorporating the bacteria. This is referred to as a biofilm and protects the micro-organism against host defences and antibiotic therapy.[21] Biofilms allow greater adherence of the microorganism to the biomaterial[22, 23] and contribute to bacterial virulence. Multiple species of microorganisms may co-exist in a biofilm and unless the biofilm is disrupted and or the microorganism/s become planktonic the microorganism/s identification is limited. Different graft materials have varying susceptibility to infection. Dacron grafts are more likely to become infected than grafts made of PTFE (polytetrafluoroethylene).[24] The use of vein grafts instead of prosthetic material greatly reduces the risk of infection.

BACTERIOLOGY OF VASCULAR GRAFT INFECTIONS

Gram-positive, Gram-negative, anaerobic and fungal micro-organisms all have the potential to infect a vascular prostheses but in general the majority of infections are the result of a small number of micro-organisms. Staphylococci are the most prevalent organism associated with prosthetic graft infection.[2,25,26,27] Of the staphylococci, *S. aureus* is generally regarded as the most common causative bacteria,[2,26,28,29] particularly MRSA.[27] *S. epidermidis* is now being recognised as the leading cause of vascular graft infection, particularly chronic and late onset infections.[17,29,30,31,32]

The Gram-negative organisms, *E. Coli, Pseudomonas, Klebsiella, Enterobacter* and *Proteus,* although relatively uncommon

causative organisms for graft infections are of particular interest and concern because of their high virulence and their tendency to destroy the vessel wall.[18,33,34]

Candida mycobacterium, and Aspergillus infections are uncommon but pose a significant risk to patients who are immunocompromised.[2] Although uncommon they are all expected to increase in frequency because of their increasing resistance to standard prophylactic antibiotics.[35]

There is an association between the type of infecting organism, the type of vascular complication and the arteries that are involved in the anastomosis to the prosthetic graft. Bandyk and Bergamini[2] in a collective survey of 1258 patients who had a vascular graft infection found that the majority of aortoenteric fistulas were the result of either *Streptococci or E. Coli* and if the anastomosis involved the femoral artery, the thoracic aorta, the subclavian, carotid or innominate arteries *S. epidermidis or S aureus* was the likely causative organism. *E. Coli, Enterococci and Enterobacter* were the more likely organisms to be involved in aortoiliac anastomoses.

INVESTIGATIONS FOR DETECTION OF PROSTHETIC GRAFT INFECTIONS

The diagnosis of vascular prosthetic infections can be difficult as the presentation may be subtle especially if it is a late onset infection, the prosthesis is intra-abdominal and the micro-organism is one of low virulence. Presentation is thus very dependent on the location of infection and the causative microorganism/s. The diagnosis is aided by multiple available microbiological investigations and imaging but in general is directed more at proving the absence of infection rather its presence. Not only are investigations imperative in the diagnosis of vascular graft infection but they may assist in the planned therapy including vascular reconstruction when required. At times the only means of confirming graft infection is the surgical excision of the graft and further microbiological assessment.

History and physical examination

The clinical clues suggesting graft infection especially those placed superficially include an inflammatory perigraft mass, overlying cellulitus, presence of exposed prosthetic graft, a sinus tract with persistent purulent drainage and/or bleeding and/or a palpable anastomotic pseudoaneurysm, graft thrombosis and distal septic embolisation.[2-4,36,37] The presence of intra-abdominal prosthetic graft infection may be non-specific, such as fever of unknown origin, septicaemia, or abdominal pain.[3] Upper or lower gastrointestinal haemorrhage either of an acute or chronic nature may indicate a graft-enteric fistula[17,37,38] and can only be excluded when another source of gastrointestinal haemorrhage has been identified.

Laboratory investigations

Routine laboratory studies such as white cell count and differential, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), and blood cultures are routinely obtained but the results may be non-specific and even normal if the organism is *S.epidermidis.*[2] Wherever possible pus, exudates, tissue specimens, blood and wound cultures should be analysed microbiologically to aid in microorganism identification and to allow the commencement of appropriate and specific chemotherapy.[39] To aid in the diagnosis of *S.epidermidis* all solid material should be mechanically or ultrasonically disrupted.[40-42]

Diagnostic imaging

Various diagnostic modalities (Computerised Tomography (CT), ultrasonography, Magnetic Resonance Imaging, Leucocyte or immunoglobulin labelled scanning, Positron Emission Tomography (PET) scanning +/- CT, angiography and/or endoscopy) may assist the vascular surgeon in determining the presence and extent of prosthetic graft infection. Not infrequently, a combination of the diagnostic modalities to improve sensitivity and specificity are utilised to confirm the presence or absence of a vascular prosthetic graft infection.[43] These modalities are also helpful in planning definitive surgery. The utility of CT angiography with the capability of vascular three dimensional reconstructions has largely replaced digital subtraction angiography as the method of diagnosis and therapeutic planning. CT guided aspiration is also of benefit in diagnosis. In general the features suggestive of graft infection include perigraft fluid and/or gas, graft disruption, absence of graft incorporation, pseudoaneurysm formation. The presence of periprosthetic gas more than six weeks following graft implantation is an abnormal finding and should alert the physician to the likelihood of a graft infection.[44]

MANAGEMENT OF PROSTHETIC GRAFT INFECTIONS

The general principles in the management of prosthetic graft infections are initially preventative, but in the event of a vascular graft infection, therapy needs to be individualised accounting for clinical findings, graft material (prosthetic versus autogenous graft material), site of infection, microorganism/s involved and patient co-morbidities. It is imperative that not only is graft infection eradicated but recurrent infection be minimised with avoidance of significant morbidity and/or mortality.

Prevention

Preventive measures such as the routine use of skin preparations,[45] the use of a depilatory agent,[46] limiting the length of preoperative hospitalisation,[8] operating time and intensive care stay all contribute to the reduction in wound infection and more importantly the chance of developing resistant multiple nosocomial infections.[45] Antimicrobial prophylaxis has been shown to reduce wound infections in vascular surgery[47] and ideally should be given as close to the time of incision and repeated in the event of haemorrhage and lengthy operations every four hours. Prophylatic antibiotics are also indicated with percutaneous punctures of existing prosthetic grafts and the implantation of stents. Decolonisation of nasal carriers of *S. aureus* has been shown to significantly reduce the number of surgical site *S. aureus* infections especially deep surgical-site infections.[48] Institutional prevalence of resistant organism may also dictate antibiotic prophylaxis especially when prosthetic grafts are to be implanted.

As a preventive measure host resistance may be enhanced by the antimicrobial impregnation of grafts. A number of novel combinations of grafts and antibiotic with or without various forms of treatment have been trialled at both the *in-vitro* and *in-vivo* levels.

Rifampicin, a known anti-staphylococcal agent, particularly methicillin resistant,[49] is a hydrophobic semisynthetic substance with a high affinity for gelatin.[50] It inhibits DNA dependent RNA polymerase activity in bacterial cells without affecting mammalian cells[51] and has been passively incorporated into gelatin sealed Dacron grafts as a mode of staphylococcal protection at the time of implantation. It has been shown to be resistant to experimental bacterial contamination[52-55] with in-vivo bioactivity

to 22 days,[56] and *in-vitro* bioactivity to 4 days.[57-59] It is these qualities plus its excellent tissue and intracellular penetration[59] that make rifampicin an ideal antibiotic to be bonded to prosthetic grafts in order to prevent subsequent graft infection.

Reduction of prosthetic vascular graft infection with rifampicin bonded gelatin sealed Dacron

Using an established sheep model[60] we replaced a segment of sheep carotid artery with a rifampicin soaked Gelsoft graft. At the time of graft removal microscopic assessment (perigraft abscess formation, presence of anastamotic disruption and graft thrombosis) and microbiological assessments (cultures of perigraft tissues, graft external and internal wall and total graft cultures) were recorded. We showed that, following direct inoculation of the rifampicin (1.2mg/ml or 10mg/ml) soaked graft with 10^8 colony forming units of either methicillin resistant *Staphylococcal aureus* (MRSA) or methicillin resistant *Staphylococcal epidermidis* (MRSE), the rifampicin soaked graft offered significant prophylaxis.[61-63]

For the MRSE arm, in the 10mg/ml rifampicin group there was a significant reduction in graft infection when compared to both the control group ($p < 0.05$) and the 1.2mg/ml group ($p < 0.05$).[63] Similarly, for the MRSA group, in the 10mg/ml treatment group there was a significant reduction in the total number of positive cultures when compared to the control group ($p < 0.05$) and the 1.2mg/ml group ($p < 0.05$).[63]

ESTABLISHED INFECTION

Antibiotic therapy

Once the diagnosis or suspicion of prosthetic vascular graft infection is made then broad spectrum antimicrobial therapy is initiated and subsequently converted to organism specific antibiotics.[3] The length of antibiotic therapy following excision of the infected graft is unclear but Bergamini and Bandyk[2] advocate parenteral antibiotics for two weeks and oral for six months.

Operative management

The 'gold standard' treatment although technically challenging is the removal of all infected tissue and revascularisation extra-anatomically.[64] A number of more conservative approaches have been advocated depending on the site of the infection and the microorganism involved. The most conservative of treatments is aggressive local wound care with graft preservation (prosthetic/autologous) providing that the graft and anastomoses are intact and the patient has no systemic features of sepsis.[65] Calligaro *et al*[34] in a report of a series of patients who had graft preservation concluded that with the exception of *Pseudomonas*, vascular graft infections could be managed with debridement, antibiotic therapy and wound closure. The skeletonized prosthetic graft can be covered using viable regional rotational flaps.[66] Others have proposed graft excision and replacement with cadaveric arterial allografts,[67] venous autografts,[68] cryopreserved saphenous vein homografts,[69] autogenous arteries and/or veins[70] or prosthesis.[71] The major drawback with in-situ reconstruction is recurrent graft sepsis[72] with potential limb and/or life threatening graft and/or anastomotic disruption.

Schmitt, *et al*.[22] in an *in- vitro* model comparing the bacterial adherence of four strains of bacteria (*S. aureus*, 'mucin' and 'non-mucin' producing *S. epidermidis* and *E. coli*) to ePTFE, woven Dacron and velour knitted Dacron found that bacterial adherence was greatest to velour knitted Dacron

and least compared to ePTFE. In addition Schmitt, *et al*.[73] found that 'mucin' producing *S. epidermidis* adhered to Dacron in 10 to 100 fold greater numbers compared to PTFE. Bandyk and Bergamini[2] have postulated that the differential adherence of staphylococci relates to capsular adhesins.

Using the established sheep model[60] we have set out to determine if the replacement of a staphylococcal infected vascular graft with a graft impregnated with rifampicin would be considered appropriate surgical management in preventing early recurrent infection. Gelsoft grafts without any antibiotic treatment were infected with overwhelming concentrations of either MRSA or MRSE. The grafts were removed at three weeks and replaced with either control (no rifampicin) grafts or grafts soaked in either 1.2mg/ml or 10mg/ml of rifampicin. The replacement grafts were removed 3 weeks following placement.

For MRSA[74] there were no statistical significant differences between the groups for any of the macroscopic or microbiological parameters recorded.

For *S.epidermidis*[74] there were no statistical differences between the rifampicin concentrations for macroscopic findings. There were however, statistically significant reductions in the number of total infected specimens in the 10mg/ml group when compared to both the control, ($p<0.001$) and the 1.2 mg/ml groups ($p<0.005$).[74]

The conclusions from the studies[74] were that established *S. epidermidis* bacterial biofilm graft infections model can be treated by the in-situ replacement of the infected prosthesis with a 10 mg/ml rifampicin impregnated Gelsoft graft. However, such management for MRSA established infections cannot be recommended from the results obtained in this particular animal model.

To date a number of groups[75,76] have successfully managed prosthetic graft infections with rifampicin impregnated grafts with zero mortality, no requirement for limb amputation and to date no recurrence of infection.

CONCLUSION

The future management of vascular graft infections will be reliant on a better understanding of the interaction between the micro-organism, the prosthesis and the immune system. This will allow a more directed approach towards prevention and treatment. Possibilities would include more powerful antibiotics either administered parenterally or incorporated into the prosthesis, acting as a local delivery system for prolonged periods of time. The role of the biofilm in the pathogenesis of graft infection needs further understanding from both a molecular and an immune level.

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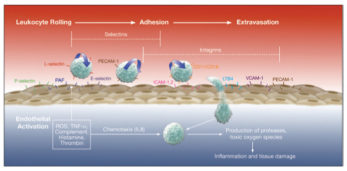

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