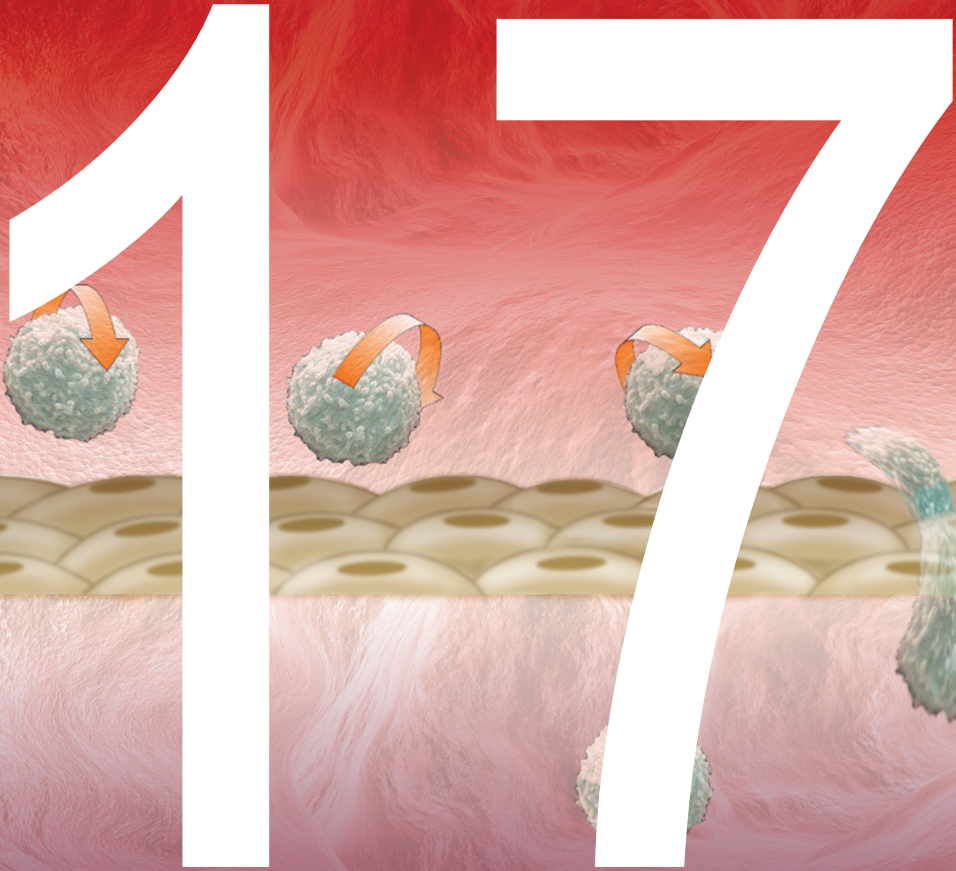


MECHANISMS OF VASCULAR DISEASE:

A REFERENCE BOOK FOR VASCULAR SPECIALISTS



EDITED BY ROBERT FITRIDGE AND MATTHEW THOMPSON
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Mechanisms of Vascular Disease

Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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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	Adrenocorticotrophic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α -amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

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

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

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

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

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

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

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

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

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

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

17 • SIRS, Sepsis and Multiorgan Failure

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EPIDEMIOLOGY

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

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

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

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

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

HISTORICAL PERSPECTIVE AND DEFINITION

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

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

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

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

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

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

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

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

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

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

RISK FACTORS FOR SEPSIS

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

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

Causative agents

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

PATHOPHYSIOLOGY OF SEPSIS

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

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

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

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

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

Innate immunity and toll-like receptors (TLRs)

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

Proinflammatory response

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

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

Coagulation cascade

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

MULTIORGAN DYSFUNCTION SYNDROME (MODS)

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

Epithelial and endothelial dysfunction

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

Immune suppression and apoptosis

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

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

Sepsis, circulatory failure and organ dysfunction

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

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

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

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

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

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

MANAGEMENT

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

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

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

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

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

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

Steroids

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

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

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

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

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

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

Recombinant human activated protein C (rhAPC)

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

FDA decision to license rhAPC for use in sepsis.

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

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

Glucose control

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

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

Renal replacement therapy

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

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

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

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

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

Other adjuvant therapies in sepsis

Cytokines and anticytokine therapies

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

Pooled immunoglobulin (IVIG)

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

Acute respiratory distress syndrome (ARDS)

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

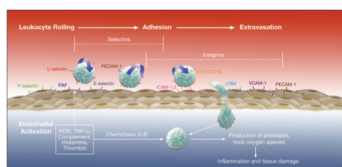
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MECHANISMS OF VASCULAR DISEASE

Edited by Robert Fitridge and Matthew Thompson

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