The Sepsis Syndrome – Aspects of Epidemiology, Cost and Outcome in Aotearoa New Zealand

Dr Paul John Huggan
BSc (Hons) MBChB FRACP FRCP(Edin)

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Abstract

The syndrome of sepsis is a life-threatening illness caused by a dysregulated host response to infection. Little is known about the epidemiology, optimal management or cost of sepsis in Aotearoa New Zealand. A series of studies were therefore conducted to investigate the local incidence, clinical features, and cost of sepsis. Findings were used to design and evaluate a whole-of-system quality-improvement programme.

Lower socio-economic status (Age Standardized Rate Ratio (ASRR) 1.72; 95% CI, 1.5-1.97)) comparing the highest with the lowest quintile of socioeconomic deprivation, and Māori ethnicity (ASRR 3.22 compared with non-Māori; 95% CI 2.85-3.65) are independently associated with incident sepsis. The incidence of sepsis may be increasing (ASRR 1.62 (95% CI 1.18-2.24) comparing 2012 with 2007 at Waikato District Health Board). In 2016, the median national cost of a sepsis-associated hospitalisation was $10,381 (interquartile range $6,093–$10,964).

Microbiological findings stratify mortality risk. *Staphylococcus aureus* bacteriuria in patients with *Staphylococcus bacteraemia* increases the risk of ICU admission (relative risk (RR) 2.5; 95% CI: 1.06-4.36; p=0.04) and in-hospital death (RR 2.18; 95% CI: 1.05-3.75; p=0.04). Compared with patients who do not grow a pathogen in blood, the recovery of Gram-negative organisms is associated with lower mortality despite high-risk clinical findings at presentation across a range of clinical infections (odds ratio (OR) for 30-day mortality 0.2, 95% CI 0.08-0.55, p<0.001).

In a cohort of hospitalised adults with and without sepsis, treatment escalation or death were associated with a respiratory rate >30 (adjusted hazard ratio (aHR) 5.97: 95% CI 2.11-16.91; p=0.001) and systolic blood pressure <80 mmHg (aHR 3.57: 95%CI 1.26-10.11; p=0.017). Building on these observations and using markers of critical illness to define high-risk cases, a whole-of-system sepsis quality improvement intervention was associated with reduced odds of in-hospital death (OR 0.83, 95% CI 0.7-0.98, p<0.05).

The sepsis syndrome in Aotearoa New Zealand is associated with poor clinical outcomes and high in-patient costs. Sepsis and the underlying infections which cause it disproportionately harm Māori people and those exposed to socio-economic deprivation. Short term outcomes are amenable to quality improvement efforts focused on early identification and management.

Dedication

This work is for my wife, children, and family.

Ka rite ta tāua aroha ki te tau o te manawa, o te mahana o te rā, o te kahurangi o te ata.

"May the love that is between us remain as constant as the tide, as warm as the sun, and as precious as the morning."

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Glossary

ADAMTS-13: *a disinterring and metalloproteinase with a thrombospondin motif-member 13*

aHR: *adjusted hazard ratio*

ASRR: *age-standardised rate ratio*

AIM2

ALR: *AIM-Like Receptor*

APC: *activated protein C*

CI: *confidence interval*

DAMP: *damage-associated molecular pattern*

DC*: dendritic cell*

DIC: *disseminated intravascular coagulation*

HMGB-1: *high motility group box-1*

ICU: *intensive care unit*

IkB:

IKK:

IL: *interleukin*

IRF: *interferon regulatory factors*

LPS: *lipopolysaccharide*

MAPK: *mitogen-activating protein kinases*

MIF: *migration inhibitory factor*

MHC: *major histocompatibility complex*

MODS: *multi-organ dysfunction syndrome*

NFκB: *nuclear factor kappa B*

NLR: *NOD-like receptor*

NO: nitric oxide

NOS: nitric oxide synthetase

PAMP: *pathogen-associated molecular pattern*

OR: *odds ratio*

PAI-1: *plasminogen activator inhibitor-1*

RAGE:

RLR:

RNS: *reactive nitrogen species*

ROS: *reactive oxygen species*

RR: *relative risk*

SIRS: *systemic inflammatory response syndrome*

TF: *tissue factor*

TFPI: *tissue factor pathway inhibitor*

TGFb: *transforming growth factor beta*

TNFα: *tumour necrosis factor* α

TLR: *toll-like receptor*

tPA: *tissue plasminogen activator*

ULWVF: *ultra large von Willebrand factor*

VE: *vascular endothelium/endothelial*

VEC: *vascular endothelial cell*

vWF: *von Willebrand Factor*

Chapter 1: Pathogenesis and Therapy

This thesis opens with a review of contemporary findings explaining the pathogenesis of the sepsis syndrome and approaches to treatment. Chapter 2 describes the evolution of sepsis definitions, and how these are used to investigate the aetiology, epidemiology, and outcomes of sepsis in adults. The aim of these opening chapters is to highlight the enormous challenge faced by those seeking to understand, treat and catalogue the severe sequelae of common infectious disease. Prevention of infection remains key to the prevention of sepsis, particularly as no breakthrough "magic bullet" therapies have emerged over the past half century to replicate the impact of antimicrobial agents.

Sepsis Pathobiology

A complete summary of the human immune response to infection is the subject of comprehensive reviews and exists outside the scope of an introductory chapter. However, sepsis is unarguably a disorder associated with the human immune response to infection, and it would be impossible to study the subject without a working understanding of key principles and contemporary findings. Sepsis is currently defined as a *dysregulated host response to an infection.* (Singer et al., 2016) This section will therefore explore biological mechanisms which contribute to this *dysregulation*, starting with pathogen-immune system interactions, leading to the vascular endothelial response and then to changes affecting haemostasis. The chapter ends with a summary of the late determinants of outcome in patients who survive an acute septic response, divided into the risks of secondary infection and of increased cardiovascular morbidity.

Three assumptions are made in this chapter to make the topic manageable: the first, that sepsis is a *pathogen driven* process, in contrast to other forms of critical illness caused by inflammatory and immune responses; the second, that the vast majority of sepsis presentations in adults are those caused by bacteria; the third, for reasons that are expanded on below, that sepsis is a heterogenous entity, reflecting the net effect of complex interactions between underlying host

factors, the pathogen, and the evolution of the immune response. As will become clear, outside some commonalities underlying the pathogenesis of infection and organ failure, the idea that there is a single 'final common pathway' leading from infection to a specific syndrome has not been borne out in basic scientific research.

The role of the early innate immune response to infection

The immune system can broadly be considered in three parts: physical, relying on the integrity of skin, mucosae, and vascular endothelium; chemical, relying on antimicrobial products such as complement and lysozyme; and cellular, classically defined as innate (to do with recognition and early response) or adaptive (to do with consolidation and memory). In reality, all components of immunity are intimately connected in the early response to infection.(Medzhitov, 2008; Mogensen, 2009) With respect to cellular immune responses, the amplification of the inflammatory and innate immune response is counter-balanced by local and systemic anti-inflammatory processes, and is usually arrested by effective pathogen clearance and tissue healing.(Rubio et al., 2019) After all, an unpleasant, self-resolving illness accompanied by symptoms of inflammatory mediator release defines a successful immune response, where immune homeostasis has been maintained.

Whilst the most recent iteration of the sepsis definition ("a life-threatening organ dysfunction caused by a dysregulated host response to infection") focused on dysregulated host responses, a definition of *dysregulation* was not offered, nor were the components of a dysfunctional response specified. (Singer et al., 2016) The distinguishing feature of the early sepsis syndrome is the exponential amplification of inflammatory and anti-inflammatory responses to pathogen-associated proteins and tissue damage. (Rubio et al., 2019) *Dysregulation* is therefore defined in this thesis as *injurious breakdown of homeostatic processes*. *Dysregulation* of the innate immune response is further examined in terms of its interface with i) bacterial pathogens, ii) the vascular endothelium and iii) the coagulation cascade.

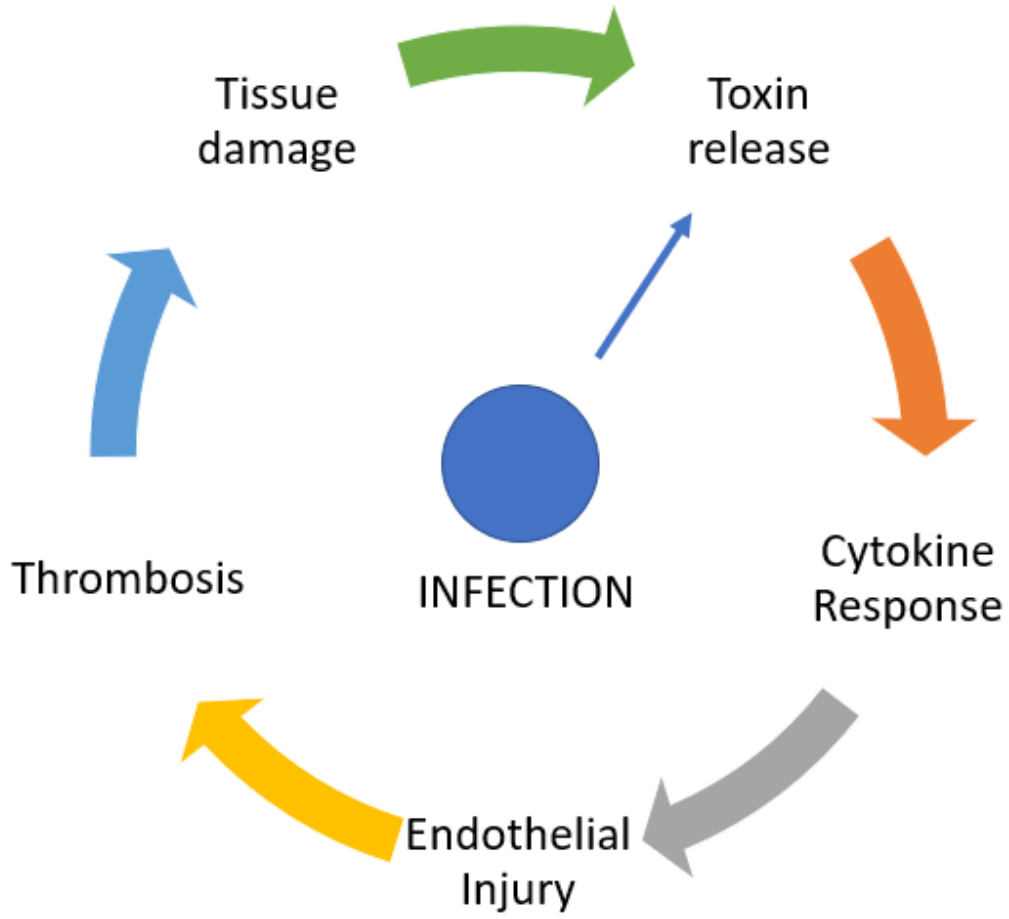


Figure 1.1. Reinforcement and amplification of processes underlying the sepsis syndrome.

Presentation of pathogen and tissue-associated molecular patterns in response to infection incites a cytokine response, causing and perpetuating endothelial and haemostatic dysregulation, further tissue damage and further toxin release.

Figure 1.1 provides a conceptual representation of the inflammatory and immune responses leading from infection to tissue injury and organ failure in sepsis. The local and systemic components of the inflammatory response are the first lines of defence when pathogens breach the various barriers to infection posed by physical and chemical immunity.(Mogensen, 2009) Inflammation results in delivery of cellular and chemical components of plasma at the site of infection or tissue injury. Acute inflammation is triggered by tissue resident mast-cells and macrophages, later engaging local antigen presenting cells (APCs) and dendritic cells (DCs) as a non-specific *inflammatory* response transitions to the *immune* response to microbial

invasion.(Nathan, 2002) These propagate a 'lag free' pro-inflammatory process through the release of inflammatory mediators.(Mukhopadhyay et al., 2004) The clinical correlates of acute inflammation are *tumor et rubor cum calor et dolore* - swelling, redness, heat and pain. Simplistically, these represent the increased endothelial permeability (swelling), blood flow (redness and heat) and pain caused by the local release of histamine, eicosanoids and other mediators. Persistent infection or injury leads to infiltration of phagocytic cells by endothelial cell adhesion, diapedesis and chemokine-induced migration.(Beekhuizen & Furth, 1998) These participate in bacterial killing through toxic degranulation and phagocytosis, which can be enhanced by complement or antibody-mediated opsonization.

Pathogen-Associated Molecular Patterns and Pattern Recognition Receptors

All of these events were known to take place long before it was understood how cells of the innate immune system could change their behaviour following exposure to pathogens and their toxins (as opposed to the effects of endogenous cytokine release). The answer to this conundrum lay in the discovery that conserved microbial molecular patterns are matched to recognition receptors located on cell and internal endosomal surfaces.(Mogensen, 2009; Mukhopadhyay et al., 2004; Nathan, 2002) *Pathogen-associated molecular patterns* (PAMPs) and *pattern recognition receptors* (PRRs) are components of *inflammatory pathways*, characterized end to end by the pairing of *inducers* with *sensors, effectors* and *mediators*. (Medzhitov, 2008) With respect to sepsis, exogenous, microbe-associated PAMPs are the most important of these.(Medzhitov, 2008; Nathan, 2002) It is worthy of note, however, that in the patient undergoing treatment for infection and sepsis, inflammatory *inducers* will also include those released by damaged tissue, or as a consequence of medical and surgical treatment.(Medzhitov, 2008) . These are described as "Damage Associated Molecular Patterns" (DAMPs) and those derived from host tissue are further referred to as *alarmins*.(D. Yang et al., 2017)

PAMPs are conserved across multiple pathogen classes and are typically essential for pathogen survival. They are also highly distinguishable from the mammalian 'self'.(Mogensen, 2009) Toll-like receptors (TLRs) are amongst the best characterized receptors for PAMPs and are

expressed on a range of cells, but particularly tissue-resident antigen presenting cells (APCs), DCs and macrophages. (Mogensen, 2009) TLRs and their associated signalling pathways are highly conserved and perform the critical function of recognizing and removing pathogens from host tissue. Some TLRs can interact with multiple structurally unrelated antigens, and still others with intermediate PAMP binding molecules. A single TLR can interact with several different pathogens, and multiple TLRs can interact with a single pathogen (as can other recognition receptor families such as RIF-I-Like Receptor (RLR), Receptor for Advanced Glycosylation End Products (RAGE) and NOD-Like Receptors (NLRs)).(Mogensen, 2009) Recognition of conserved, widely expressed, and non-self-molecular patterns obviates the need for adaptation and antigen-specific memory. However, whilst TLRs are encoded in the human germ line, broad pathogen reactivity is combined with a degree of specificity not traditionally attributed to the innate immune system.(Mogensen, 2009)

Nuclear Factor Kappa B

Engagement of a TLR activates one of three major intra-cellular signalling pathways, namely nuclear-factor kappa B (NFκB), mitogen-activating protein kinases (MAPKs) and interferon regulatory factors (IRFs).(Kawai & Akira, 2007; Mogensen, 2009) The NFκB family is described in further detail here, as it plays an important role in the clinical expression of the sepsis syndrome. NFκB is a transcription regulatory factor which amplifies and modulates expression of genes central to pathogen response.(Kawai & Akira, 2007) In the resting cytoplasm NFκB dimers are non-covalently bound to IκB inhibitors. These are phosphorylated by IκB kinase (IKK) which is released in response to TLR (and other PRR) engagement. This interaction exposes a nuclear localization sequence through which NFκB dimers move to the cell nucleus. There, NFκB interacts with multiple gene promotor regions to upregulate mediator production. Whilst all participate in the inflammatory response as mediators, some products are themselves responsible for autocrine upregulation of NFκB. (Abraham, 2003)

NFκB upregulates anti-apoptotic genes. Whilst by separate means most immune cells tend to apoptosis under systemic inflammatory conditions, the early inflammatory response itself is characterized by a NFκB and TNFα-mediated increase in the number and lifespan of neutrophils.(Abraham, 2003; Cao et al., 2019; Kawai & Akira, 2007; D. Yang et al., 2017) Mediators released by neutrophils and other immune cells transitioning to a pro-inflammatory phenotype contribute to pro-inflammatory signalling and the accumulation of intra-nuclear NFκB in multiple tissues and organs.(Schulte et al., 2013) Thus, engagement of PRRs leads rapidly to NFκB accumulation and a self-potentiating systemic inflammatory response which occurs through the interaction of 3 separate mechanisms: autocrine amplification of inflammatory mediator release, increased effector cell activity, and multi-organ involvement caused by circulating *inducers* and *mediators*.

Inflammasomes

Inflammasomes are families of protein complexes which, when stimulated, act as a scaffold for the production of caspase, which in turn cleaves the interleukin-1 and interleukin-18 family of cytokines into their active forms.(V. Kumar, 2018) There are five inflammasome complexes, four resembling NOD receptors (therefore termed NOD-Like Receptors, or NLRs) and AIM-2 (therefore termed AIM-2 like receptors, or ALRs).(V. Kumar, 2018) These exist in a resting, inhibited state in the normal cell and interact with a diverse array of exogenous and endogenous PAMPs and DAMPs. Unlike intracellular TLRs, which are confined to intracellular organelles, inflammasomes circulate freely in the cytosol, saturating the intracellular milieu with receptors capable of responding to a PAMP or DAMP-associated signal.(V. Kumar, 2018) The interaction of inflammasomes with the pro-inflammatory immune response is complex but generally leads to the key features of inflammation caused and described by TLR activation and cytokine signalling (ie chemotaxis, adhesion molecule expression, activation of the vascular endothelium, and promotion of a proinflammatory innate and adaptive immune profile). The place of the inflammasome in sepsis pathogenesis (and potentially in therapeutics) is evolving and has been reviewed in detail elsewhere.(Schulte et al., 2013)

Cytokines and Chemokines

Cytokines describe a family of low molecular weight proteins which regulate the activation and differentiation of the immune response.(Schulte et al., 2013) Activation of TLRs and nuclear accumulation of NFκB triggers production of an inflammatory "*cytokine canon",* principally consisting of tumour necrosis factor alpha (TNFα), and various interleukins (ILs) including IL-1 and IL-6.(Cao et al., 2019; Schulte et al., 2013) Soluble inhibitors of inflammatory cytokines (ie soluble TNFα receptors) and other mediators such as IL-4, IL-10 and transforming growth factor beta (TGFb) act as anti-inflammatory counter-regulators. Thus, although viewed principally as an inflammatory illness, many of the late clinical manifestations of sepsis relate to dysregulated *counter-inflammatory* processes and immunosuppressive responses to inflammation (discussed further below).(Schulte et al., 2013)

Of the proinflammatory cytokines, TNFα and IL-1 are key to the early immune response. Release of both occurs early in infection, typically within 30 minutes. Peak concentrations are reached in serum 60-90 minutes after exposure to bacterial lipopolysaccharide.(Michie et al., 1988) In experimental animals, TNFα can cause a syndrome indistinguishable from septic shock.(Okusawa et al., 1988) Experiments in humans demonstrate that infusion of recombinant TNFα and IL-1 causes fever and the systemic inflammatory response syndrome (SIRS, see *diagnosis*, below).(Cannon et al., 1990; van der Poll et al., 1990) TNFα and other pro-inflammatory cytokines interact with transmembrane receptors to initiate production and release of numerous downstream mediators and immunoregulatory proteins.(Dinarello, 1997; O'Neill, 2008) TNFα increases production of macrophages from progenitor cells and prolongs their survival.(Fahlman et al., 1994) It also interacts with the vascular endothelium to upregulate production of adhesion proteins and pro-coagulants, enabling circulating neutrophils and monocytes to leave the circulation. (Nakae et al., 1996; Schouten et al., 2008) As described above with respect to NFκB, TNFα and IL-1 exhibit autocrine and paracrine effects, contributing to *dysregulated* amplification of the inflammatory cascade and associated tissue injury.(Hotchkiss et al., n.d.; Schulte et al., 2013)

Although intimate with TNFα and IL-1 in the generation of an inflammatory response to infection, IL-6 mediates different aspects of the acute phase response. Its production is stimulated by IL-1 as well as by PAMPs, including LPS.(Schulte et al., 2013) Its levels peak after TNFα and IL-1, typically remaining elevated in concert with evolution of illness, in contrast to TNFα and IL-1 which decay from their peak and can even circulate at normal levels in patients with sepsis-associated multi-organ failure. (Parrish et al., 2008) IL-6 is the key cytokine responsible for mediating the "acute phase response", characterized by fever, leucocytosis, and elevated production of C-reactive protein (CRP), complement, fibrinogen and ferritin.(Schulte et al., 2013) IL-6 provides a counter-regulatory, inhibitory signal leading to reduced production of TNFα and IL-1, whilst also increasing the levels of a range of anti-inflammatory molecules such as TGFb and cortisol.(Hotchkiss et al., n.d.) Demonstrating the partitioned nature of the cytokine response, IL-6 infusion does not itself induce a septic shock-like response in animals.(Preiser et al., 1991) IL-6 knockout models suggest that the long-lived elevation of IL-6 in sepsis states make it a plausible target for control of advancing clinical manifestations of a dysregulated acute phase response.(Group, 2021)

Chemokines are a sub-group of cytokines responsible for trafficking white cells to infected tissues, of which Macrophage Migration Inhibitory Factor (MIF) is the best studied. The release profile of MIF includes pituitary as well as immune cells following exposure to exogenous (ie LPS) and endogenous (ie TNFα) inducers. (Schulte et al., 2013)The first release of MIF is not dependent on gene transcription, with pre-formed MIF stored and concentrated in the Golgi bodies of effector cells. (Merk et al., 2009) Once secreted, MIF has a wide range of actions including (predictably) the stimulation of TNFα and IL-1 release, as well as interferon-gamma (IFNγ) and the expression of TLR4 on macrophages. As its name indicates, though, the principal actions of MIF are i) to attract and enhance the activity of monocyte and macrophage cell lines, and ii) to activate T-Lymphocytes via the Major Histocompatibility Complex (MHC) Class II receptor.(Hotchkiss et al., 2016)

Experimental and clinical studies of MIF in sepsis have produced surprising results. As perhaps expected of a pro-inflammatory cytokine in a disease characterized by inflammation-associated organ damage, MIF inhibition improves survival in mouse models of sepsis. Whilst also acting

synergistically with LPS to increase mortality. In humans, MIF levels are higher in patients with sepsis than in healthy controls and, in one study, levels correlated positively with mortality.(Beishuizen et al., 2001) Subsequent to this finding, though, a large genetic study of sepsis related to pneumonia found that of 20 loci studied, upregulation of the MIF promoter was inversely associated with mortality.(Yende et al., 2009) Highlighting the complexity of cytokine pathobiology, this suggests that high upstream MIF secretion produces complex effects with respect to clinical outcomes, possibly promoting pathogen clearance or ameliorating sepsis-associated immunoparesis.(Schulte et al., 2013)

High Motility Group Box-1 and the Alarmins

Inducers of inflammation can be exogenous or endogenous. Of the endogenous inducers, tissue-derived inflammatory mediators (also known as alarmins) are of special relevance to the septic, dysregulated host response to infection.(D. Yang et al., 2017) These mediators can be defined as DAMPs, but are often referred to as *alarmins*, the term which will be used here. Alarmins are released through degranulation, cell injury or death and interact with PRRs to alter immune cell behaviour in the same manner as PAMPs.(D. Yang et al., 2017) Alarmins also interact with RAGE receptors and the CXCR4 leukocyte surface receptor. As a group, the alarmins activate and chemoattract leucocytes, activate inflammasomes, induce dendritic cells (DCs) to engage the adaptive immune response, and (outside the study of sepsis) may play a part in anti-cancer immunity.(Andersson & Tracey, 2011; D. Yang et al., 2017).

The alarmin High motility Group Box 1 (HMGB1) lies at the intersect of responses to endogenous and foreign molecules, being released by injured cells in response to PRR interactions with PAMPs.(Andersson & Tracey, 2011) As with other alarmins, passive release of HMGB1 occurs in response to cell injury. However, HMGB1 also meets the definition of a cytokine, being released by one cell type and effecting responses in a range of others through interaction with TLR4 and RAGE receptors expressed on dendritic cells, the vascular endothelium, epithelial barrier cells and cells of innate immunity.(Andersson & Tracey, 2011) HMGB1 consists of two DNA-binding transcription domains (Box A and Box B), and a C

terminal chain which is directly bactericidal. Whilst HMGB1 is released in cell apoptosis and injury-associated necrosis, only HMGB1 associated with cell necrosis incites a pro-inflammatory response.(Andersson & Tracey, 2011) This is because reactive oxygen species (ROS) released by apoptotic mitochondria inactivate HMGB1, by oxidizing cysteine at position 106 in BoxB. Box B "recapitulates" production of pro-inflammatory cytokines, whilst Box A antagonises the same.(Andersson & Tracey, 2011) The differential effects of HMGB1 are mediated by the balance of activity following binding to HMGB1 receptors. Via TLR4, both HMGB1 and LPS cause nuclear translocation of NFκB and increased TNFα, IL-1, and IL-6 activity. Counter-regulatory receptors are present which interact with BoxA to inhibit NFκB release. The net effect of HMGB1 release is therefore dependent on a range of other extra and intracellular signals and responses.(Andersson & Tracey, 2011)

HMGB1 can cause the systemic inflammatory response syndrome (SIRS) independently of other cytokines and is a key mediator of SIRS in cases of sterile tissue injury.(Kornblit et al., 2008) HMGB1 levels increase some hours after the appearance of TNFα and IL-1, and are persistently high in murine models of sepsis as well as humans who succumb to sepsis in the ICU.(Andersson & Tracey, 2011) In murine models of LPS-induced sepsis, anti-HMGB1 antibodies reduce mortality, and in contrast to anti-TNFα approaches, this effect is seen even after a prolonged delay in treatment. These and other experiments have demonstrated that HMGB1 is a late mediator of sepsis-associated tissue injury (as opposed to sterile tissue injury, where HMGB1 response precedes the release of TNFα), and one which may perpetuate the insult triggered by early cytokine responses.(Andersson & Tracey, 2011)

Cytokine production (via stimulation of TLRs and Inflammasomes) and signalling therefore plays a major role in the pathogenesis of sepsis. Why, then, has *anti-cytokine* therapy in general failed to improve clinical outcomes? In conditions where these approaches have been successful, such as rheumatoid arthritis, single or small groups of cytokines are necessary and sufficient causes of disease, such that cytokine inhibitors can resolve or substantially ameliorate symptoms.(Andersson & Tracey, n.d.; J. C. Marshall, 2014) This linearity may not exist in the acute, dysregulated immune response to tissue damage and pathogen invasion. Disruption and dysregulation of cytokine networks is best viewed as a dynamic, time-sensitive process reflecting

specific pathways and the interplay of host, pathogen and immune response.(Andersson & Tracey, 2011; Netea et al., 2000; Schulte et al., 2013) Peak exposures to key cytokines may even precede clinical evidence of the characteristic *dysregulated immune response* by several hours.(Netea et al., 2000) For anti-cytokine approaches to be effective in sepsis therapy, they need to be delivered at the appropriate point in the evolution of the underlying illness. To achieve this level of targeting, new tools may be needed to reveal the homogenous sub-groups most likely to benefit from specific treatment approaches. For example, unsupervised cluster analysis of transcriptomic data identified three distinct clusters of patients with bacterial sepsis (inflammopathic, adaptive, and coagulopathic).(Sweeney et al., 2018, 2021) Machine-learning analysis of clinical and basic laboratory suggested four distinct phenotypes, each associated with broadly recognizable signatures but with high inter-individual and inter-pathogen variation.(Seymour et al., 2019) Monte Carlo simulation revealed that variation in the proportion of each clinical phenotype within early goal directed therapy trials would have substantially changed findings, with a high likelihood of harm in patients with the δ phenotype. (Seymour et al., 2019)

Phagocytic cells and Neutrophil Extracellular Traps

Phagocytic cells, including polymorphonuclear neutrophils (PMNs) and mononuclear phagocytes (monocytes and macrophages) are the most common white blood cells in circulation, and act as the first lines of defence against bacterial infection.(Rubio et al., 2019) Vast numbers are released into the circulation as part of the acute stress response and later in in response to pro-inflammatory cytokine signalling. Rapid distribution to tissue accounts for a circulating half-life of only 6 hours.(Pérez-Figueroa et al., 2021) Monocyte migration creates pools of highly differentiated tissue-resident macrophages which defend the body in specific positions of vulnerability, such as splenic, liver and bone marrow sinusoids. This process occurs under normal conditions. By contrast, neutrophils (and activated monocytes) only transmigrate from the circulation in response to tissue damage or infection.(Pérez-Figueroa et al., 2021; Rehaume & Hancock, 2008) This migration is mediated by chemotactic factors, specifically N-formyl bacterial oligopeptide, complement-derived C5a, leukotriene B4 and IL-8. (Beekhuizen & Furth,

1998) The chemoattraction of leucocytes culminates in the outward migration of the neutrophil exclusively through the intact vascular endothelial lining of the post-capillary venule, a process referred to as diapedesis.(Brown et al., 2006; Harding et al., 2014) Diapedesis is the final step in a coordinated sequence of adhesion events that anchor and target the phagocyte to vascular endothelial cells at the site of infection. These steps are rolling (mediated by the selectin family of neutrophil surface receptors), firm adhesion (mediated by the integrin family, which interact with their counterparts intra-cellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1)), and crawling (mediated by the beta-2 integrins).(Brown et al., 2006; Harding et al., 2014)

The principal effector mechanism of neutrophils is the phagocytosis of micro-organisms which have been opsonized by complement and immunoglobulin.(Rehaume & Hancock, 2008) Resulting phagosomes are almost immediately merged with intracellular granules containing anti-microbial proteins, enzymes and reactive oxygen species.(Guthrie et al., 1984; Rehaume & Hancock, 2008) Neutrophil phagocytic function is enhanced by exposure to microbial products such as LPS.(Guthrie et al., 1984) However, it is constitutively sub-normal in the immature neutrophils which predominate in many cases of sepsis, and which also demonstrate increased production and release of neutrophil extracellular traps (NETs).(Papayannopoulos, 2018)

NETs are web-like structures consisting of chromatin, DNA, histones and granule proteins which trap large pathogens to localize immune responses and prevent dissemination.(Papayannopoulos, 2018) They are released through two pathways in response to inflammatory mediators and bacterial toxins. The slow (lytic) pathway involves an apoptotic process called NETosis, where neutrophil-derived products are released following neutrophil plasma membrane rupture.(Papayannopoulos, 2018) A non-lytic pathway leads to expulsion of neutrophil granules and nuclear chromatin in response to bacterial toxins, with surviving neutrophils continuing to participate in chemotaxis and phagocytosis.(Papayannopoulos, 2018) NETs persist for a prolonged period and are thought to degrade through exposure to DNase1. Overproduction or inadequate removal of NETs can potentiate endothelial damage, promote inflammation in the absence of a pathogen and activate the coagulation cascade to cause microcapillary thrombosis.(Papayannopoulos, 2018) NETs are therefore a key contributor to the dysregulation

of the immune response to infection, particularly as it relates to the perpetuation of vascular endothelial damage, described later in this chapter.

The role of red blood cells

Through the process of *oxycytosis,* red blood cells (RBCs) have a central role in the control of infections which breach tissue barriers and evade local innate immune responses.(Minasyan, 2019) The bacterial cell wall carries a negative electrical charge (the zeta potential) which is potentiated by friction with other cells as well as plasma and with the vascular endothelium.(Minasyan, 2018) This process of *triboelectric* charging increases the electro-attraction of bacteria to RBCs, whose biconcavity and cell wall behaviours (ie deformability) contribute to triboelectric charging, which fixes bacteria to the red cell membrane. Here, activation of TLRs triggers release of reactive oxygen species (ROS). Killed bacteria lose their electroactive state, disassociate from the RBC membrane, and undergo scavenging by splenic, hepatic and lymphoid macrophages.(Minasyan, 2019)

It has been suggested that this highly effective mechanism of oxidative bacterial clearance explains several confounding observations in human infection and sepsis. Firstly, a high proportion of patients with sepsis have negative blood cultures.(Phua et al., 2013) Whilst this may be explained in part by sampling limitations and by the regional and toxin-mediated diseases known to cause sepsis without bacteremia (ie liver abscess, lower limb cellulitis), the rapid clearance by RBCs may render samples negative in blood whilst infection in other compartments persists.(Phua et al., 2013) Secondly, the repertoire of organisms which commonly cause sepsis is extremely restricted as a function of microbial diversity, and the majority of positive blood cultures are monomicrobial.(Nannan Panday et al., 2019) Pathogens observed in sepsis-specific blood culture statistics are typically capable of surviving oxycytosis and replicating or even ‘thriving’ in the human bloodstream (see below).(Minasyan, 2019) Thirdly, infections which cause “fulminant” sepsis are capable of planktonic growth in the face of oxycytosis.(H, 2018) Fourthly, at the other end of the clinical spectrum, microbial adaptation to RBC-mediated oxidative killing typically involves evasion or attenuation of the pro-

inflammatory immune response.(Minasyan, 2019) This explains why some intravascular infections cause severe tissue damage without inciting the *dysregulated* responses which lead to clinical sepsis. Finally, it is well documented that transient bacteraemia occurs throughout life, and the vast majority never cause recognizable symptoms or disease.(Roberts et al., 2006) Oxycytosis acts to rapidly clear bacteria entering the human bloodstream, rendering the vast majority of these events harmless and asymptomatic.

The role of the pathogen

The clinically rapid and severe manifestations of sepsis, of which clinicians are rightly fearful, are mediated by a restricted repertoire of pathogens which are typically capable of thriving in the face of phagocytotic and oxycytotic defences. Common human pathogens are formidably evolved. Surface structures important for normal bacterial function can contribute to pathogenesis.(Lemichez & Barbieri, 2013) For example, the expression of Type IV pili by *N.meningitidis* allows colonization of endothelial surfaces, whilst also allowing replication under conditions of shear stress.(Coureuil et al., 2013) Bacterial *toxins*, by contrast, interact directly with the host to cause inflammation and tissue damage. They have "diverse structures and modes of action" and have been classified into four groups: those that interact with host cell receptors; those which disrupt host cell lipid-bilayer integrity; those which release toxins into the cell cytoplasm following endocytosis (known as "molecular syringes"); those synthesized inside bacteria and injected directly into host cytoplasm through modified flagellar proteins.(Sastalla et al., 2016)

Most bacterial toxins can incite inflammation by damaging host tissue. In the early stages of sepsis, and continuing in many cases even after the initiation of treatment, microbial toxins play a major role in initiating and sustaining *dysregulation* of the immune response.(Baron et al., 2006) Toxins act singly or in concert with each other and/or with cellular apparatus to evade recognition and killing, promote specific niche survival and modulate aspects of the inflammatory and immune response.(Baron et al., 2006; Lemichez & Barbieri, 2013) Some are targeted by specific TLRs, for example the lipotechoic acids and lipopolysaccharides

respectively expressed by gram-positive and gram-negative bacteria.(Mogensen, 2009) Study of two organisms, *Neisseria meningitidis* and *Staphylococcus aureus*, demonstrates the formidable complexity and specificity of toxins as determinants of outcome in human infection. These have been reviewed in summary publications and are presented in Table 1.1.(Cheung et al., 2021; Coureuil et al., 2013)

Various other mechanisms and behaviours have evolved to permit microbial survival in human tissues. These include i) capsule expression, ii) biofilm formation, and iii) L-form switching. Capsules protect bacteria from environmental stress, permit adhesion to human cell surface proteins, and reduce susceptibility to oxycytosis by reducing surface triboelectric charge.(H, 2018; Minasyan, 2019) Biofilms are proteinaceous bacterial products which permit colony formation and persistence of these colonies on organic and non-organic surfaces.(Gupta et al., 2016) L-forms are cell-wall deficient bacteria formed in response to inhibited cell wall synthesis. These are resistant to cell-wall active antimicrobials, and can persist extracellularly and also intracellularly following phagocytosis. L-forms do not incite significant immune activity and evade anti-bacterial killing, rendering them important sources of persistence and relapse.(Minasyan, 2019)

Summary

The inflammatory and immune responses to infection are complex, layered, and interdependent. The ability of pathogens to cause sepsis relates to evolutionary strategies permitting survival in human tissue and resistance to phagocytosis and oxycytosis. A no-lag inflammatory response is triggered by microbial tissue invasion, which transitions to an *immune* response as *inflammatory pathways* are engaged, made up of *inducers, sensors, mediators, and effectors*. These act in concert to amplify and coordinate pro-inflammatory signalling which, alongside non-cellular mechanisms of immunity, activate and attract immune cells. Microbes are not merely bystanders but the principal actors in the dysregulated cascade of immune-mediated events leading from infection to organ failure and death.

Table 1.1. Sample bacterial toxins and their effects on pathogenicity in humans

Toxin	Receptor/Target	Effect	Outcome
Staphylococcus aureus			
Alpha-toxin	ADAM10 receptor	Cleavage of E-cadherin disrupts adherens junctions	Breach of epithelium and endothelium
Biofilm formation/ coagulation (i.e. coagulase)	Aggregation on inanimate and damaged tissue surfaces	Adherence and survival	Immune evasion and/or reservoir of infection *in-vivo* (i.e. devices and implants)
Leukocidins	Phagocytes	Destruction of effector cell	Neutrophil evasion
Superoxide dismutase, staphyloxanthin		Resistance to intracellular killing in phagosomes	
Nucleases		Degradation of NETs	
Staphopain	CXCR2	Inhibition of chemotaxis	
Staphylococcal Protein A	Fc portion of Ig	Forms non-specific IgG 'coat' on bacterial surface	Inhibition of opsonization and complement-mediated killing
MSCRAMM	Diverse family of surface proteins involved in tissue adherence	Binding of S.aureus to collagen and fibronectin	Promotes adherence and survival in damaged host tissues
Neisseria meningitidis			
Iron chelation	Ferric ions	Survival *in-vivo*	Ability to invade, survive and replicate in human host
Polysaccharide capsule	Complement	Prevention of complement-mediated phagocytosis	
Lipopolysaccaride surface protein (endotoxin)	Complement		
Factor H binding protein (Fhbp)	Complement		

Uptake of L-glutamate	Maintenance of intracellular redox potential	Resistance to PMN oxidative burst	
Pentacylation of endotoxin	TLR4	Reduced engagement with TLR4,	
Type IV pili	Promote endothelial adhesion and bacteria-bacteria adhesion	Adhesion and replication on endothelial cell surface	Invasion across blood-brain barrier, intense replication on vascular endothelial surface leading to *purpura fulminans*

Abbreviations: MSCRAMM, Microbial Surface Components Recognizing Adhesive Matrix Molecules; CXCR2, CXC chemokine receptor2; NETs, neutrophil extracellular traps

The role of the vascular endothelium

Overview

Local activation of inflammatory and immune responses establishes a pro-inflammatory nidus in the host. It is now understood that the vascular endothelium is central in the transition to systemic *dysregulation* of the host response, through its dual role as an amplifier of inflammation, a determinant of platelet function and coagulation, and the determinant of major organ function.

Normal function

The vascular endothelium (VE) is composed of a single layer of vascular endothelial cells (VECs) which invest the internal surface of all blood vessels.(Ince et al., 2016) These create a parenchymal cell mass responsible for maintaining the physical integrity of the circulatory system, regulating extravasation of solutes and blood cells, directing regional blood flow and continuously balancing coagulant and anti-coagulant function.(Dolmatova et al., 2021; Ince et al., 2016; Joffre et al., 2020) As such, the VE has been referred to by some as an endocrine organ.(Ince et al., 2016) VECs maintain structural and regulatory integrity through determinants of cell to cell adhesion, signalling and basement membrane production.(Ince et al., 2016) Solute and cellular permeability is very low in all vessels other than capillaries. Outside the blood-brain-barrier these vessels demonstrate high levels of permeability and solute transfer. The behaviour of the VE contributes to specific organ functions such as nano-filtration of solutes in the kidney, micro-filtration of senescent red blood cells in the spleen, oxygen transport in the respiratory endothelium, and the docking, storage and release of marginated leukocytes and platelets in the circulation.(Ince et al., 2016; Joffre et al., 2020) Vascular tension (sometimes referred to as “tone”) and regulation of blood flow to individual organs and tissues is regulated by local and systemic mechanisms which govern the production and release of relaxing and

contracting factors such as nitric oxide (NO), arachidonic acid metabolites and numerous small peptides.(Ince et al., 2016)

Key to the function of the VE and manifestations of sepsis is the presence of a luminal glycocalyx protein matrix and cell-cell junctions (divided into *adherens junctions, tight junctions* and *gap junctions)*.(Libby & Lüscher, 2020) Glycocalyx glycoproteins and proteoglycans form a 0.2 to 0.5 μM layer. This constitutes 20% of the intravascular volume and performs important barrier functions such as the exclusion of macromolecules (>70kDa), and repulsion of red and white blood cells through maintenance of net negative charge.(Ince et al., 2016; Joffre et al., 2020) As an amphoteric molecule, albumin can bind to glycocalyx proteins, and this feature maintains interstitial hydraulic conductivity toward the circulation.(W. L. Lee & Slutsky, 2010) An intracellular VEC domain transduces mechanical sheer stress, leading to flow-induced production of NO.(Kumagai et al., 2009) Cadherin-rich *adherens junctions* join adjacent VECs preventing leukocyte emigration and vascular leak. *Tight junctions* regulate transport of water, ions, and molecules through paracellular pathways. *Gap junctions* allow cell to cell passage of small molecules and solutes.(Krüger-Genge et al., 2019) All are disrupted to a greater or lesser degree by inflammation-mediated tissue injury, leading to a loss of VE integrity.(Dolmatova et al., 2021; Ince et al., 2016; Joffre et al., 2020) Important to the clinical manifestations of sepsis are the rheological (relating to the local control of microvascular blood flow) impacts of VEC damage to oxygen delivery, and the fact that reconstitution of the glycocalyx layer takes 5 to 7 days following injury, and longer before normal function is regained. (Joffre et al., 2020)

The early reaction of the vascular endothelium to infection and inflammation

Although immune cells which are local to the initial site of infection are responsible for activating cytokine networks, this process is perpetuated by entry of *inducers, mediators and effectors* into the circulation. There they can interact with VECs, which express PRRs targeting PAMPs and DAMPs and can express cytokines through the inflammatory pathways described above.(Joffre et al., 2020) Not only does this perpetuate pro-inflammatory cytokine signalling, but the nuclear accumulation of NFκB transitions VECs to a pro-inflammatory, pro-coagulant phenotype.(Dolmatova et al., 2021)

Amongst the most important outcomes of this process is damage to the endothelial glycocalyx and adherens junctions, leading to an increase in endothelial permeability.(W. L. Lee & Slutsky, 2010) An important contributor to this process is 'glycocalyx shedding'. This occurs in the presence of oxidants, hyperglycaemia, cytokines, and bacterial endotoxins, contributes to loss of barrier function, increases exposure of the VEC to plasma constituents, and of VEC-associated adhesion molecules to circulating determinants of the innate immune response.(Ince et al., 2016) Cytokines released by VECs act as neutrophil chemo-attractants. Glycocalyx-shedding and increased expression of adhesion molecules such as VCAM (vascular cell adhesion molecule-1) facilitates neutrophil interaction with VECs leading to leucocyte diapedesis. Anchored leucocytes transmigrate into tissue where further inflammatory mediator release contributes to local tissue damage and the inflammatory cascade.(Beekhuizen & Furth, 1998) When held near VECs, neutrophils release ROS, further injuring the endothelial glycocalyx.(Ince et al., 2016; Libby & Lüscher, 2020) Disturbance of junctional protein expression and VEC apoptosis further contribute to loss of VE barrier function. Whilst potentially benefitting the immune/inflammatory response by locating plasma products at the site of tissue injury and infection, widespread loss of vascular integrity and nitric oxide (NO)-induced vasodilatation leads to loss of vascular tone, interstitial oedema and increased interstitial pressure, all of which increase tissue oxygen demands and impair organ function.(Joffre et al., 2020) Unsurprisingly, biomarkers of endothelial permeability are associated with increased risk of death in patients undergoing resuscitation with evidence of septic shock.(Hou et al., 2017)

In normal inflammation, ROS are produced in VEC signaling and angiogenesis, particularly by adenine dinucleotide phosphate hydrogen oxidase enzymes and endothelial nitric oxide synthase (eNOS).(Y.-M. Yang et al., 2009) The precursor for eNOS is tetrahydrobiopterin. As ROS production and neutrophil release exceed homeostatic tolerance, BH4 is depleted by oxidation. This leads to "eNOS uncoupling", where the lack of precursor leads to production of a superoxide radical, contributing further to oxidative stress.(Y.-M. Yang et al., 2009) Whilst the production of NO by constitutive eNOS falls, NFκB induces transcription of inducible nitric oxide synthase (iNOS). This dramatically increases overall production of NO.(Y.-M. Yang et al., 2009)

NO has a range of functions in health and disease but is a key component of the *dysregulated* host response in sepsis. It is a substrate for soluble guanylate cyclase, which produces cyclic guanylate monophosphate (cGMP) in vascular smooth muscle cells, leading to vasodilatation as a component of shear-stress response and control of vasomotor tone. Loss of VEC glycocalyx has been reported to reduce VEC sensitivity to shear stress, which stimulates NO production.(Kumagai et al., 2009) Oxidative stress is also amplified when excess iNOS-mediated NO interacts with superoxide radicals to form reactive nitrogen species (RNS) such as peroxynitrite (ONOO-). RNS increase the direct toxicity of ROS and RNS to endothelial cells and impact mitochondrial respiration. This creates a self-reinforcing, *dysregulated*, cycle of NO, ROS and RNS-induced cellular toxicity, bioenergetic failure and cardiovascular dysfunction. (Ince et al., 2016; Joffre et al., 2020)

Summary

In addition to the presence of a pathogen-driven immune response, an inflamed, vasodilated, and hyper-permeable vascular endothelium accounts for many of the key manifestations of sepsis.

The role of haemostatic dysregulation

The third and final major component of the dysregulated host response to infection, as conceived in this thesis, is the interaction of the VEC with platelets and with the coagulation cascade.(Ince et al., 2016)Together with a burgeoning systemic inflammatory response and deterioration in endothelial function, sepsis leads to important changes in platelet function and coagulation. This was demonstrated conceptually in Figure 1.1

Procoagulant effects of the vascular endothelium in sepsis

Normal haemostasis is triggered in response to endothelial injury and is tightly controlled to maintain blood flow and tissue oxygenation.(Shibata et al., 2008) The phases of normal haemostasis include i) formation of platelet plug, ii) local activation of the coagulation cascade, iii) simultaneous activity of compensatory antithrombotic proteins, and iv) removal of clot through fibrinolysis.(Shibata et al., 2008) The activation of VECs in sepsis causes a range of behaviours which create a prothrombotic milieu, both due to gain or loss of VEC function and increased mediator release from adherent leucocytes.(Joffre et al., 2020) Conceptually, this "immunothrombotic" effect might benefit the host by trapping bacteria and preventing access to the circulation. In sepsis, by definition, this potentially protective mechanism must have failed, and the systemic amplification of a procoagulant phenotype causes major changes in blood flow, endothelial barrier function, microcapillary rheology and tissue oxygentation.(Assinger et al., 2019; Ince et al., 2016; Joffre et al., 2020) The disruptions to hemostasis found in the septic patient therefore provide another example of the complex, heterogenous, layered, and non-linear processes which satisfy the definition of a *dysregulated* host response, as defined previously.

Platelets play a key part in the response to infection. They are small, anucleate cells long known to perform central hemostatic functions.(Assinger et al., 2019) More recently, the role of the platelet as an immunomodulatory agent has also come to light.(Assinger et al., 2019) Platelets can release cytokines and interact with microbes, microbial toxins and innate immune cells to form platelet-leucocyte and platelet-microbe aggregates. They can promote leucocyte transmigration whilst protecting endothelial integrity at those sites. They can induce a pro-

inflammatory phenotype by co-modulating neutrophil functions such as oxidative burst and NET formation.(Assinger et al., 2019) To do this, platelets express receptors which interact with various PAMPs, DAMPs and signalling molecules, including TLRs and Fc Receptors. Glycoproteins solely expressed by platelets (i.e. GP1b and GPIIb/IIIa) bind to exposed VEC and von Willebrand Factor (vWF), which brings platelets into proximity with the inflamed/damaged endothelium, where their pro-inflammatory and thrombotic actions can be expressed. Platelets are themselves targeted by pathogens. For example, *Staphylococcus aureus* exhibits a Clumping factor which may permit bacterial survival within dense platelet aggregates.(Cheung et al., 2021) Platelet receptor expression varies within and between humans and between mammalian species, including by copy number. For example, women express more platelet-associated TLRs than men, which has been proposed as one of the mechanisms moderating cardiovascular risk.(Koupenova et al., 2015) Whether the same effects occur in sepsis are unclear.(Assinger et al., 2019)

In sepsis, platelets circulate in an activated state, undergoing significant changes in shape and function which make them highly adhesive. After platelets or their various aggregates (ie platelet-fibrin, platelet-leucocyte, platelet-pathogen), adhere to VECs they obstruct microcapillary blood flow and cause local amplification of inflammation, either through direct toxicity (ie degranulation) or by acting as a nidus for further endothelial damage and activation of the coagulation cascade.(Joffre et al., 2020; Joffre & Hellman, 2021)

Activation of the vascular endothelium leads to a pro-coagulant, anti-fibrinolytic state which can lead to thrombotic microangiopathy. Tissue factor (TF), vWF and Plasminogen Activator Inhibitor-1 (PAI-1) are central to the coagulation cascade and are synthesized and expressed by VECs. TF is a procoagulant transmembrane glycoprotein central to activation of the extrinsic coagulation pathway through its interaction with activated factor VII.(Ince et al., 2016) This pathway is usually controlled by VEC release of TF pathway inhibitor (TFPI), which inhibits factor Xa and the TF-VIIa complex, as well as through the activation of Protein C by the thrombin-thrombomodulin complex.(Dellinger, 2003; Ince et al., 2016; Looney & Matthay, 2007) vWF is produced constitutively as a low molecular weight dimer, or inducibly as high molecular weight multimers in response to inflammatory stimuli such as TNFα and IL-6.(Ince et

al., 2016; Joffre et al., 2020) Ultra-large vWF (ULVWF) is highly thrombogenic via its central bridging function between platelets and sub-endothelial structures. Under normal conditions, ULVWF multimers are rapidly cleaved by “a disintegrin and metalloproteinase with a thrombospondin motif member 13” (ADAMTS-13). The increased expression of ULVWF leads to consumption and deficiency of ADAMTS13, which can give rise to a microangiopathy similar to that seen in other ADAMTS13-deficient states (ie thrombotic thrombocytopaenic purpura).(Levi et al., 2018) Activated endothelial cells upregulate production of Plasminogen Activator Inhibitor-1 (PAI-1), which inhibits fibrinolysis by binding to tissue plasminogen activator (tPA).

Apoptotic and damaged VECs (as well as adherent granulocytes and circulating monocytes) express TF at high concentration. TF and other anti-coagulant molecules (including activated Protein C (APC)) are depleted, and PAI-I is progressively released, amplifying procoagulant and anti-fibrinolytic function.(Dellinger, 2003; Joffre et al., 2020) These procoagulant functions are complemented by i) release (from VECs and platelets) of phosphatidylserine positive microparticles, ii) reduced production of glycophorin A on the surface of red blood cells, reducing their net negative charge and promoting adhesion to fibrin and iii) deposition of NETs.(Ince et al., 2016; Joffre et al., 2020; Mutua & Gershwin, 2021). *Dysfunctional* disorders of coagulation and thrombosis are common in sepsis. As a result, evidence of disseminated intravascular coagulation (DIC) is common in intensive care populations with sepsis.(Gando et al., 2009; Iba et al., 2019) Thrombocytopenia is also common, originating in the activation, enhanced clearance and platelet interactions with pathogens, VECs and products of coagulation.(Assinger et al., 2019) Even in those in whom platelet counts are preserved, an increase in the ratio of immature to mature platelets in circulation is common, and both the initial severity and persistence of thrombocytopenia prognosticate poor outcomes.(Koyama et al., 2018; Venkata et al., 2013)

Activated Protein C

APC is anchored to the endothelial protein C receptor. It is activated by the thrombin-thrombomodulin complex before either directly inhibiting PAI-I assembly or coupling with

activated protein S to cleave activated factors V and VIII.(Looney & Matthay, 2007) APC also exerts anti-inflammatory activity by inhibiting i) cytokine production (including TNFα), ii) modulating transcription of genes in the endothelial apoptosis pathway, and iii) preventing E-selectin binding to the sialyl-Lewis X antigen of the neutrophil cell surface.(Healy et al., 2018; Looney & Matthay, 2007) Most patients with sepsis exhibit an acquired deficiency of APC, and this finding is almost universally present in patients with septic shock caused by *Neisseriea meningitidis.*(Alberio et al., 2001)

Pre-clinical and clinical trials of recombinant APC (rAPC, also known as drotrecogin alpha) led to the registration of rAPC as a therapeutic agent in sepsis. The Placebo-controlled Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial showed a 6% absolute-risk reduction (a 20% relative-risk reduction) in mortality amongst adults with sepsis admitted to an intensive care unit.(Bernard et al., 2001) The trial suggested benefit only in those with an acute physiology and chronic health evaluation (APACHE) II score of 25 or more.(Bernard et al., 2001) rAPC was approved for use in this group in 2001 in the United States, and in Europe for patients with two or more organ dysfunctions.(Kalil & LaRosa, 2012) Due to concerns centering on trial conduct and drug production, follow-up studies were required as a condition of registration. These suggested no benefit from rAPC and an increased risk of severe bleeding, including in a meta-analysis undertaken by the Cochrane consortium.(Martí-Carvajal et al., 2012) These findings led to withdrawal of the drug by its manufacturer in 2011. Almost concurrently with this withdrawal, a second meta-analysis was published which produced robust evidence of net benefit (propensity-adjusted relative-risk of in-hospital death 0.84; $p<0.0001$; I^2=18%), and confirmed pronounced effects in patients with higher organ failure scores, and in trials with high mortality amongst controls. The authors of this study pointed to the inclusion of all analytical, controlled and single-group studies from 2001 to 2012 as the reason for the difference in findings.(Kalil & LaRosa, 2012)

A key question for sepsis therapeutics, therefore, is whether their effect is stable across a range of presenting infections and in the groups most at risk, which in this example included the elderly.(Kalil & LaRosa, 2012) Older patients exhibit reduced anti-coagulant function during periods of health, and it has been proposed that anticoagulants may have a particular role to play

in the septic elderly.(Opal et al., 2005) Though no benefit has been recorded in sepsis using non-rAPC anti-coagulant therapy, Ely and colleagues analysed outcomes of the PROWESS study based on age (75 or older).(Ely et al., 2003) In this work, the absolute reduction in 28-day mortality was 15.6% compared with placebo without survival penalty (meaning survival with increased dependency). This reduction was much higher than found in the overall PROWESS study (6%) and was closer to the overall finding in patients with higher organ failure scores (13%).(Bernard et al., 2001; Ely et al., 2003) Reductions were seen across all metrics associated with increased healthcare cost (vasopressor-free days ($p=0.006$), ventilator-free days ($p=0.001$), ICU-free days ($p=0.004$) and hospital-free days ($p=0.008$)).(Ely et al., 2003) Whilst still available, some evidence existed to suggest that rAPC was under-utilised in the elderly.(Alexander & Ernst, 2006) The issue of whether rAPC should be retained as a treatment for older, sicker patients with sepsis has not been revisited since the drug was withdrawn. rAPC remains remarkable for being the only non-antibiotic, sepsis-specific agent introduced into practice in the pre-COVID era.

Summary

Platelet and VE activation act create a pro-coagulant, pro-thrombotic state in patients with sepsis. Therapeutic attempts to modulate the coagulation cascade in patients with sepsis have produced conflicting results. As discussed below, the persistence of the pro-thrombotic, pro-coagulant effects of sepsis may have an important effect on late outcomes in early sepsis survivors.

Determinants of late morbidity and mortality in sepsis

Patients who present with invasive infection often have *a priori* vulnerabilities, and these vulnerabilities will often contribute to poor short and long-term outcomes. For example, neutropenic sepsis may complicate treatment of a haematologic malignancy, or a patient in intensive care following a road-vehicle accident may develop ventilator-associated pneumonia. However, the septic state is itself associated with the accumulation of tissue injury which predispose to death or poor recovery. The next section deals with these risks in two parts. Firstly, the increased risk of secondary infection in critically ill patient populations is described, with an emphasis on those with persistent multi-organ dysfunction. Secondly, the association between sepsis and late cardiovascular events is outlined.

Sepsis-associated immunosuppression and secondary infection

Until relatively recently, sepsis was thought of as a systemic pro-inflammatory illness.(Bone et al., 1992; Rubio et al., 2019)This paradigm has had to change to accommodate findings proving profound, synchronous release of anti-inflammatory and immunosuppressive mediators accompanying the first pro-inflammatory responses to infection.(Hotchkiss et al., n.d.; Rubio et al., 2019)

Release of the potent cytokine IL-10 accompanies release of TNFα, IL-1, IL-6 and IL-8, exerting a dysregulated *counterinflammatory and immunosuppressive* response.(Hotchkiss et al., n.d.) After this initial burst of pro and anti-inflammatory activity, cytokine production is globally reduced, and responses to new stimulation of blood and splenic tissue with LPS are diminished.(Hotchkiss et al., 2013) Downregulation of HLA-DR expression is one of the earliest findings in patients with sepsis, and fewer than 5% of monocytes in patients with established activity produce cytokines above normal levels of expression.(Hotchkiss et al., n.d.) The early period of sepsis is also characterized by the profound apoptotic depletion of cells of the innate and adaptive immune systems, reprogrammed immune cell behaviours, and changes in the ratios of memory and effector cells.(Rubio et al., 2019) Patients in ICU with sepsis frequently lose hypersensitivity responses to common antigens, and reactivation of latent viruses is common,

with CMV viraemia detected in a third of previously immunocompetent adults.(Hotchkiss et al., n.d.) Early lymphopenia is common in sepsis, caused by apoptosis, aberrant recruitment, sequestration and thymic involution.(Hotchkiss et al., n.d.)

These responses are thought to play a significant part in mediating sepsis outcomes. For example, the IL-10/TNFα ratio at presentation predicts an increased risk of death in cases of community acquired sepsis, and recovery of pro-inflammatory monocyte function in abdominal sepsis increases survival (van Dissel et al., 1998; Weighardt et al., 2000) Most patients survive the early inflammatory phase of sepsis, with most short-term deaths occurring more than 72 hours following presentation to hospital.(Hotchkiss et al., n.d.) Post-mortem studies of patients with sepsis suggest undiagnosed/unresolved foci of infection in a high proportion of late deaths, despite clinically adequate antimicrobial therapy and drainage procedures.(Torgersen et al., 2009) Secondary infections are common in patients with sepsis and are commonly due to opportunistic pathogens or those of low virulence in immunocompetent patients. Although some patients will certainly die due to incomplete source control these overall findings suggest an impaired net immune response with ongoing or secondary infection in a high proportion of those who die.(Kim et al., 2003) Although no immunomodulatory approaches or agents have yet been introduced into clinical practice, significant efforts continue to try and describe and treat net negative immune function in sepsis patients.(Hotchkiss et al., n.d.)

Secondary infection often complicates the care of patients with persistent multi-organ dysfunction following a septic insult. The concept of “multi-organ dysfunction syndrome” (MODS) has been used in an intensive care-unit environment to describe the heterogenous organ failures associated with major injury or illness, including sepsis. The MODS concept arose with the advent of antimicrobial therapy and modern methods of organ support.(J. C. Marshall & Deutschman, 2021) It has been described by some authors as a metaphor for the mixed outcomes encountered when human lives are rescued from death by advanced resuscitation techniques.(J. C. Marshall & Deutschman, 2021) MODS is shaped by the unwitting or unintended harms associated with these techniques. For example, the administration of broad-spectrum antimicrobial therapy, large volumes of crystalloid fluids, and vasoactive agents can result

respectively in gut dysbiosis, endothelial glycocalyx shedding, and mesenteric ischaemia.(J. C. Marshall & Deutschman, 2021; Meyhoff et al., 2020)

Non-iatrogenic mechanisms of organ-failure elucidated in the MODS shine some light on the complex sequelae of sepsis in those who survive with appropriate initial therapy. Inflammatory tissue damage and ischaemia are mediated by endothelial injury and microthrombosis, as described above, leading to specific regional sequelae such as the acute respiratory distress syndrome (ARDS).(Huertas et al., 2018; J. C. Marshall & Deutschman, 2021) Animal models and limited studies in humans offer that mitochondrial number and function may be depleted in MODS, potentially leading to disordered oxygen utilisation, a process described as energetic dysfunction.(Preau et al., 2021) Mitochondrial energetic dysfunction is thought to underlie late disorders of neurologic and kidney function, cardiomyopathy and diaphragmatic weakness in critical illness, and mitochondrial replacement is under investigation as a potential therapy for MODS in the setting of sepsis.(de Carvalho et al., 2021; Preau et al., 2021)

Gut microbiomic homeostasis is a key determinant of human health, is universally dysregulated in septic patients treated with broad-spectrum antimicrobial therapy and is thought to contribute to the persistence of multi-organ dysfunction in critically ill patient populations. The inflammatory response coupled with loss of microbiomic diversity leads to overgrowth of the proximal gut with organisms derived from nosocomial flora, a phenomenon described as dysbiosis.(McDonald et al., 2016) Disruption of the gut epithelial function presages translocation of these microorganisms and their toxins, including endotoxin, which can be detected in the circulation in critically ill patients following sepsis and polytrauma.(Alverdy & Krezalek, 2017)

Manipulation of the microbiome in the pursuit of improved patient outcomes is a subject of intense research. Two strategies have been investigated to address dysbiosis in critical illness, including sepsis. Firstly, selective digestive tract decontamination (using non-absorbed antibacterial and antifungal agents) aims to reduce exposure to microbe and microbial toxin translocation. A recent meta-analysis of randomised trials suggested a reduced odds for death amongst adults in ICU treated with selective digestive tract decontamination (OR 0.73 (95% CI, 0.64–0.84), and a similar effect of decontamination strategies directed only at the oropharynx

(OR 0.85 (95%CI 0.74 to 0.97).(Price et al., 2014) An alternative approach to dysbiosis is to repopulate the intestine with non-pathogenic gut commensal organisms via enteral feeding, an approach which is still being investigated. A negative multi-centre rancomised trial preceded several smaller studies assessing supplementation with *Lactobacillus rhamonsus.* These suggested beneficial effects of this approach in reducing secondary nosocomial infection, particularly ventilator associated pneumonia. Systematic review and meta-analysis of all randomised data is awaited.(Johnstone et al., 2021)

Sepsis and cardiovascular risk

Derangements in coagulation, immune and endothelial function persist well beyond the initial period of infection and treatment, affecting pathways known to contribute to the pathogenesis of cardiovascular disease (CVD). Both the acute and long-term incidence of cardiovascular disease are known to be increased in patients with sepsis .(Boehme et al., 2017; Musher et al., 2019) Myocardial infarction was found in 8% of patients hospitalized with pneumococcal pneumonia, increasing the short term risk many times over the underlying risk in the pre-infection period.(Musher et al., 2019) The risk has also been found to be proportionate to illness severity scores and the presence (or absence) of sepsis. (Musher et al., 2019) The odds of ischaemic stroke are 28 times the risk in the first 2 weeks following a sepsis diagnosis.(Boehme et al., 2017) It has been proposed that the strength of these temporal associations reflects a causal relationship, potentially accounted for in the short term by increased circulating inflammatory cytokines, the stress of acute illness (on oxygen demand and myocardial function), and locally on atheromatous plaque stability).(Musher et al., 2019) Patients with sepsis also have a high incidence of atrial fibrillation, an independent risk factor for stroke. (Xiao et al., 2021)

Sepsis has been shown to increase risk of death compared with population controls for up to five years.(H. E. Wang et al., 2014) It has been postulated that increased cardiovascular events account for a proportion of these excess deaths. Until recently, whether sepsis admissions predicted high rates of cardiovascular events in survivors beyond traditional short-term analysis was unclear. However, a recent meta-analysis suggested an association with sepsis and long term

(>30 day) stroke (adjusted hazards ratio (aHR) 1.67 [95% CI 1.37-2.05]), myocardial infarction (aHR 1.77 [95% CI 1.26-2.48]) and congestive cardiac failure (aHR 1.65 [95% CI [1.46-1.86]) through follow-up periods of up to 12 years).(Kosyakovsky et al., 2021)

Although the presence of sepsis is an independent risk for these outcomes, it may be more appropriately attributed to infection and underlying vulnerability.(Yende et al., 2014) Yende et al noted that the 1-year incidence rate of cardiovascular events in sepsis survivors was 1.9-fold higher matched with population controls, but only 1.1-fold higher matched with hospitalized infection controls.(Yende et al., 2014) This, in turn, reflects the increased risk of infectious disease admission and sepsis amongst patients experiencing high levels of socioeconomic deprivation and overlapping traditional risk factors for cardiovascular disease. In patients recruited to a large inception cohort study founded to study risk factors for stroke, the incidence of sepsis was higher in regions of the United States with high rates of stroke, and was predicted by the same palette of risk factors.(H. E. Wang et al., 2012) This and other findings generated the hypothesis that sepsis cohorts may benefit from treatments aimed at reducing cardiovascular disease risk, particularly hydroxymethylglutaryl Co-A (HMGCo-A) reductase inhibitors and aspirin.

The HMGCo-A reductase inhibitors are a family of agents with anti-inflammatory and anti-proliferative effects.(Sirtori, 2014) Early cohort studies indicated that patients with sepsis who were treated with HMG Co-A reductase inhibitors (statins) before or during a sepsis event had improved short term survival.(Chen et al., 2018; van den Hoek et al., 2011) Subsequent randomized trials provided no evidence of benefit for statins on in-hospital mortality when first prescribed during a sepsis admission, a finding repeated in a subsequent systematic review focussed on short-term outcomes. (van den Hoek et al., 2011) However, morbidity-adjusted, population-based follow-up of patients on statins prior to (and continuing after) hospital admission with bacteraemia revealed significant reductions in long term (>30 day) mortality, and that this effect may be specific to lipophilic statins such as simvastatin and atorvastatin, rather than a class effect.(Hu et al., 2019; Mermis & Simpson, 2018)

The role of anti-platelet agents is all well delineated in the management of non-sepsis cardiovascular morbidity, but there is limited support for their use in patients with sepsis outside the management of traditional cardiovascular risk profiles. Prescription of aspirin upon recognition of the systemic inflammatory response syndrome (including in those with sepsis) was shown to be associated with increased hospital survival by Eisen and colleagues.(Eisen et al., 2012) These authors proceeded to study the use of aspirin in the primary prevention of death due to sepsis in older adults (70 or older). This later study adjudicated a primary outcome of death *due to sepsis* (not the late cardiovascular outcomes being discussed here) and found no evidence of effect against this outcome.(Eisen et al., 2021) No randomized trials have investigated the prescription of aspirin to prevent longer term CVD outcomes after a sepsis episode. Many unanswered questions are left by these findings, then, but a role for enhanced (secondary) cardiovascular disease prevention may exist in patients admitted with sepsis, particularly those with traditional cardiovascular risk factors.(Mermis & Simpson, 2018)

Summary

The sepsis syndrome is characterized by early, rapid dysregulation of normal immune function, affecting every compartment of the immune system, tilting the vascular endothelial cell lining toward an inflammatory, pro-coagulant, anti-fibrinolytic state. This response is compartmentalized by organism, by organ, and by time, with late clinical manifestations reflecting nosocomial harm, secondary infection due to immunosuppression, and inflammatory damage to the vascular tree. Efforts to improve sepsis outcome will rely on improved frameworks to help understand these responses.

Sepsis Therapy

Antimicrobial therapy

Antimicrobial agents are the only treatments which can be said to have revolutionized sepsis therapy in the past century. As highlighted by Bone and colleagues, the availability of antimicrobial therapy, coupled with improvements in organ support, allowed the full evolution of sepsis-associated multi-organ dysfunction to manifest to intensive care-based clinicians.(Bone et al., 1992) This in turn drove decades of research into the late pro and anti-inflammatory cytokine response, vascular endothelial damage and deranged haemostatic function.(Bone et al., 1992) Much can be written about antimicrobial therapy, but evidence of benefit in patients with invasive infection is so overwhelming that its delivery is considered central to all patient management.(Mackenzie & Lever, 2007) However, in the context of sepsis care, important questions remain relating principally to antibiotic timing, dose and empiric choice. Table 1.2 highlights contemporary findings relating to antimicrobial therapy in patients with sepsis.

Large studies undertaken in the first decade of this century assessed the timing of antimicrobial therapy in respect to early (in-hospital) or 30-day mortality.(Ferrer et al., 2014; A. Kumar et al., 2006) These appeared to suggest that both "appropriate" (microbiologically active) therapy, and time to initiation of antibiotic therapy (appropriate or otherwise) were key determinants of early outcomes, particularly in patients with shock.(Funk & Kumar, 2011; Vallés et al., 2003) The pluripotency of antimicrobial agents with respect to underlying infections make their "appropriateness" difficult to assess. For example, in some studies, appropriateness is defined as compliance with guidelines (typically specifying very broad spectrum therapy), whereas in others, appropriateness is assessed in receipt of culture and evolving clinical data.(Sterling et al., 2015) In the small number of studies where a definition of "inappropriate" therapy equates to *microbiologic inactivity*, outcomes are clearly partitioned.(Paul et al., 2010; Vallés et al., 2003) Studies of the effect of antibiotic timing in sepsis will therefore tend towards null in less severe illness, and if a high proportion of patients receive *ineffective* empiric treatment.

Table 1.2. Contemporary findings relating to antimicrobial therapy in patients with sepsis

Author (Year)	Condition	Key findings
Potential Benefits		
Houck (2004)	Community-acquired pneumonia	Treatment within four hours of presentation reduces mortality and length of stay
Kumar (2006)	Septic shock	Time from onset of hypotension to delivery of effective antimicrobial therapy is strongly associated with increased risk of death
Harbarth (2003)	Microbiologically confirmed sepsis with organ failure	Following adjustment for comorbid conditions, illness severity and site, inappropriate initial therapy associated with increased odds of death (OR 1.8, 95% CI: 1.2-2.6)
Valles (2003)	ICU-admitted patients with community onset bloodstream infection (55% septic shock)	Following multivariable analysis, Increased risk of death in patients given inappropriate empiric therapy (OR 4.11). Inappropriate therapy most common in those with no clear source (OR 2.49). Effect most pronounced in patients with APACHE II score >25 (mortality 41% vs 11%, p<0.01)
Han X (2021)	>60,000 admissions with infection to 6 US hospitals	Delays in either ordering or administering antimicrobial therapy common (58% of patients), and associated with adjusted hourly increase in death (OR 1.07; 95% CI, 1.06-1.09)
Labelle (2012)	Blood culture positive patients with septic shock who received *appropriate* initial therapy	Antimicrobial delivery as a care process measure (given <1hour) not associated with increased survival. No statistical difference in median time from onset to antimicrobial therapy comparing survivors and non-survivors
Gaieski (2010)	Patients with sepsis + organ failure or shock receiving early goal directed therapy	Following multivariable regression, time to *guideline driven* (appropriate) therapy within 1 hour of presentation associated with improved outcomes (OR 0.3, 95% CI 0.11-0.83, p=0.02)
Sterling (2015)	Systematic review and meta-analysis (timing)	No statistical association found between mortality and time from onset of severe sepsis/shock to administration of antimicrobial therapy within 1h (n=11,017, OR 1.46 (95% CI 0.89-2.4, p=0.13))
Paul (2010)	Systematic review and meta-analysis (antimicrobial activity)	Prospective studies reporting appropriate vs inappropriate empiric antibiotic therapy (pooled adjusted OR 1.60, 95% CI 1.37 to 1.86). Number needed to treat to prevent one death=10 (95% CI 8 to 15) given baseline mortality of 36% in inappropriate treatment group.
Potential Harms		
Garnacho-Montero (2014)	Prospective enrolment of ICU-admitted severe sepsis/shock patients on broad-spectrum therapy	Multivariable analysis. De-escalation of therapy ("broad" to "narrow" pathogen and syndrome-based treatment) protective through to 90 days in patients surviving until microbiologic cultures evaluable (OR 0.54, 95%CI 0.33-0.89)
Mignon (2014)	ICU-admitted patients with severe sepsis/shock	Endotoxin measurement q4h, correlated with delivery of antimicrobial therapy – patients with higher levels of endotoxinaemia displayed temporal deterioration in organ function with administration of antimicrobial therapy
Adelman (2020)	Review of gut dysbiosis in patients with sepsis	Hypothesis generating paper suggesting that gut microbiota plays a role in predisposition to sepsis and pathogenesis of major organ dysfunction – gut flora disruption (dysbiosis) may be initiated and maintained with antimicrobial therapy
McIntyre (1997)	Systematic review of adjunctive dexamethasone in childhood bacterial meningitis	Adjunctive dexamethasone hypothesized to reduce CNS inflammation associated with antibiotic-induced bacterial lysis and toxin-release (pooled OR for severe hearing loss 0.09 (95% CI, 0.0-0.71)

Abbreviations: ICU, intensive care unit; OR, odds ratio; CI, confidence interval; CNS, central nervous system

The available evidence, coupled with common sense, does not argue that administration of *effective* antimicrobial therapy can be interminably delayed in patients who are ill.(Smith & Pell, 2003). Furthermore, prompt antimicrobial administration accompanies other aspects of assessment and treatment which contribute to outcome, such as debridement of underlying infectious foci. For these reasons, time to antimicrobial delivery in sepsis remains a key quality metric in acute care.(Rhee et al., 2014) The effect of using time to treatment as a quality measure is to rigidly dichotomise patients into those with and without sepsis based on final diagnosis, rather than on the information available to clinicians in acute settings. Decision making in the care of infection is dynamic, and in many situations, infection is one of a number of potential causes for critical illness. Initial prescribing is ultimately based on assessment of both *risk (*of a poor outcome with delayed treatment) and *certainty* of infection as a cause of illness.(Prescott & Iwashyna, 2019) Acknowledging this and the findings in Table 1.3, recent guidance from the Surviving Sepsis Campaign suggests a one-hour delivery target for patients with septic shock, and an assessment period of up to 3 hours in patients without shock.(Evans et al., 2021) Increasing emphasis is also placed on the potential harms of antimicrobial therapy, which may be more relevant to short and long-term outcomes than previously realized.

Other than to contribute to *stewardship* or *good practice* principles in the use of antimicrobial therapy, specific concerns have arisen relating to the potential for antimicrobial agents themselves to cause or potentiate harm. Experimental studies in large mammals and observational studies in ICU-treated patients suggest that antibiotic-induced endotoxin release (following bacterial lysis) could cause meaningful increases in pro-inflammatory responses.(Nau & Eiffert, 2005) Bacterial killing can cause sepsis-like presentations (termed Jarisch-Herxheimer reactions) during the management of organisms which are not in themselves causes of sepsis (ie *Treponema pallidum, Mycobacterium leprae*). Bacterial toxin release and lysis products (cell wall peptidoglycans, bacterial DNA, hemolysins etc) are PAMPs and interact with the cellular immune response via TLRs.(Nau & Eiffert, 2005) Low-dose antimicrobial therapy can cause toxin release without killing organisms, and this effect may vary depending on the affinity of antibiotics for individual penicillin binding proteins (PBPs).(Holzheimer RG, 2001) The use of dexamethasone in bacterial meningitis is the best example of anti-inflammatory therapy aimed at attenuating responses to antibiotic-induced bacterial lysis. Population heterogeneity has probably

affected trial results in adults, but dexamethasone has been found to be protective against severe hearing loss in cases of bacterial meningitis in children, which is thought to relate to suppression of the pro-inflammatory burst which follows antimicrobial therapy and bacterial lysis.(McIntyre, 1997)

Antimicrobial therapy causes major changes to the intestinal microbiota.(Adelman et al., 2020) Firstly, a high proportion of sepsis cases are temporally associated with exposure to healthcare and healthcare settings, and patient with sepsis typically exhibit high rates of co-morbid illness.(P. J. Huggan et al., 2017) These exposures associate with antimicrobial therapy and dysbiosis, leading to a preponderance of aerobic gram-positive and gram-positive pathogens, commonly carrying antimicrobial resistance determinants.(Adelman et al., 2020; Haak & Wiersinga, 2017) Reduced microbial diversity and a relative expansion of pathogenic bacteria ("pathobionts") may precede colonization and invasion events, via gut translocation or breaches of innate immune barrier functions.(Adelman et al., 2020)

A link between the microbiota and predisposition to sepsis is supported by both experimental evidence in mice, and circumstantial evidence in humans. Compared with genetically identical counterparts, mice with markers of low intestinal biodiversity exhibited high mortality in response to a caecal ligature and puncture model of abdominal sepsis.(Fay et al., 2017) Patients who have had *Clostridioides difficile* infection (CDI) or antibiotics strongly associated with CDI are at increased risk of a subsequent sepsis event.(Baggs et al., 2018; Prescott et al., 2015). Following sepsis onset, pro-inflammatory cytokine signatures are generally more pronounced in experimental animals with reduced microbial diversity, and loss of short-chain fatty acid (SCFA) production by beneficial commensals may contribute to loss of gut epithelial integrity.(Al-Harbi et al., 2018; Samuelson et al., 2015). This sets the scene for circulatory translocation of both toxins and pathobionts. For these reasons and several others, the gut has been described as the "motor" of MODS in septic and non-septic critical illness.(Klingensmith & Coopersmith, 2016) Investigations are ongoing to determine whether microbiomic effects underly the observation that antimicrobial de-escalation improves outcomes in ICU-treated sepsis, and whether microbial therapeutics have a role in improving sepsis outcomes.(Adelman et al., 2020; Garnacho-Montero et al., 2014)

Haemodynamic Management

The infusion of sterile fluids to address circulatory insufficiency and cardiovascular function is a mainstay of medical therapy. (Best & Jabaley, 2019) After administration of appropriate antimicrobial therapy, assessing and managing haemodynamic function takes priority, particularly with evidence of shock. "Haemodynamic function" is a broad term used to describe global cardiovascular and endothelial physiology and performance. This section describes major findings and approaches to haemodynamic management in sepsis following introduction of the pulmonary arterial catheter (PAC) in 1970.(Dellinger et al., 2021)

Writing on the use of the PAC in the early 1970s, Weil was the first to report the haemodynamic features of various shock states.(J. L. Vincent et al., 2012) Availability of the PAC triggered a vogue for maintaining cardiovascular measures within "therapeutic targets", a practice which persisted until the late 1990s.(Dellinger et al., 2021) By this time, evidence accumulated to demonstrate lack of clinical benefit as well as definite harms caused by PAC placement. As use of the PAC began to wane, the 2001 Rivers trial of "early goal directed therapy" (EGDT) in an urban emergency department reignited debate regarding interventions to maintain cardiac output and oxygen delivery.(Rivers et al., 2001) The EGDT protocol investigated by Rivers *et al* suggested various manoeuvres targeting oxygen delivery, including the use of blood as a resuscitation fluid and measurement of mixed venous oxygen saturation ($Scvo_2$). Large randomised controlled trials failed to replicate the earlier success of the Rivers protocol, and studies emerged which suggested increased mortality amongst those with a high positive fluid balance in the early stages of sepsis and septic shock.(Angus et al., 2015; Macdonald et al., 2017)

The principle of fluid resuscitation in sepsis rests on the crude concept of 'warm shock', where systemic vasodilatation and loss of endothelial integrity lead to inadequate intravascular volume and impaired perfusion in the face of a preserved or increased cardiac output.(Annane et al., 2005; Best & Jabaley, 2019; Lesur et al., 2018) Replacement of fluid increases cardiac preload,

and theoretically improves cardiac performance along the "Starling curve".(Best & Jabaley, 2019) Starling's work also suggested that maintenance of intravascular water (IVW) was maintained in balance between hydrostatic and oncotic forces across a semipermeable capillary membrane. In reality, myocardial function is often globally depressed in sepsis, and whilst initiation and choice of vasoactive therapy rely on identifying this, there is no routinely used point of care test that can isolate cardiac inotropy and other components of cardiac output.

Venous capacitance is maintained under complex endocrine, autonomic and local rheologic control. Vasodilatation of medium sized arteries and veins plays a part in reducing systemic vascular resistance and increasing venous capacitance in sepsis. However, profound effects on the vascular endothelium lead rapidly to dysregulation of circulating volume.(Best & Jabaley, 2019) The endothelial glycocalyx layer (EGL) accounts for up to 20% of circulatory volume, and fixes albumin to maintain electrical repulsion of plasma proteins from the endothelial surface. Sepsis-associated EGL shedding therefore increases unstressed venous capacitance and the rate of water and solute loss to the interstitium. Under normal circumstances, increased extra-cellular water (ECW) would return to the circulation through lymphatic vessels. The lymphatic endothelial monolayer is equally affected by the processes described in earlier in relation to the vascular endothelium. Lymphatic failure ensues, increasing tissue oedema. This may play a particularly important role in the pathogenesis of sepsis-associated lung, cardiac and renal injury.(Wu et al., 2020) Clinical hypoperfusion and shock, then, can result from one or more of impaired cardiac function, loss of vascular tone, loss of the EGL layer, loss of oncotic pressure, increased ECW, and lymphatic injury. The clinician who defines "hypoperfusion", then, principally describes the net effect of endothelial failure. (Best & Jabaley, 2019)

Long ranging debates about the optimal resuscitation fluid appear to have been settled in favour of balanced crystalloid solutions, or albumin solutions if a patient with sepsis is at high risk of volume overload. These conclusions are based on large intensive care and emergency department-based studies of mixed patient populations, such that sepsis patients are analysed as sub-groups.(Rochwerg et al., 2014; Self et al., 2018; Semler et al., 2018) Hydroxyethyl starch (HES) solutions are no longer used due to an accepted increased risk of acute kidney injury.(Perner et al., 2012) An increased risk of kidney injury is also apparent in two mixed

population studies based in ED and ICU.(Self et al., 2018; Semler et al., 2018) These trials compared balanced and unbalanced crystalloid solutions. Findings favoured balanced solutions overall, with a strong signal of harm (relating to the use of unbalanced solutions and kidney injury) in the ICU subgroup with sepsis.(Best & Jabaley, 2019; Semler et al., 2018) Proposed mechanisms of kidney injury in those resuscitated with 0.9% saline include iatrogenic hyperchloremic metabolic acidosis, altered oxygen delivery due to extracellular water accumulation and venous congestion, and endothelial brush border damage. (Self et al., 2018; Semler et al., 2018; Zhou et al., 2014) Whether specific fluid strategies preserve or restore the EGL is a subject of ongoing study.(Milford & Reade, 2019) Perhaps more importantly, recent randomised trial findings have called all fluid resuscitation paradigms into question.(Levin et al., 2019)

Existing fluid resuscitation practices lack sound underpinnings in randomised trial settings. (Levin et al, 2019). The randomised FEAST study (Fluid Expansion As Supportive Treatment) was a trial conducted in febrile children with signs of hypoperfusion presenting to hospitals in Uganda, Kenya and Tanzania.(Maitland et al., 2011) Equipoise existed in those settings because administration of a fluid bolus was not routine. Although bolus therapy was available, many clinicians perceived a risk of cerebral or pulmonary oedema, an experience potentially rooted in the management of malaria.(Levin et al., 2019) The trial randomised children to routine care or a bolus of either crystalloid or albumin solution. The data safety monitoring board (DSMB) intervened after 3141 (of a planned sample of 3600) children had been enrolled due to an increased mortality in the bolus therapy arm (relative risk 1.44, 95% CI 1.09-1.9, P=0.01).(Maitland et al., 2011) Re-analysis of FEAST outcomes demonstrated clustered underlying abnormalities which explained the association of bolus fluids with mortality, including deterioration in neurologic and respiratory function, decreased haemoglobin concentration and increased chloride and base deficit.(Levin et al., 2019) These clusters were associated with increased mortality despite transient improvements in cardiovascular function. Over 50% of the children in this study had malaria, potentially predisposing to poor neurologic outcomes.(Maitland et al., 2011) Whether findings are generalizable to paediatric or adult populations in resource-rich countries (or low-income countries with different disease profiles) remains open to question.

In summary, prevailing fluid resuscitation strategies in adult patients with sepsis are based on little evidence. Abundant potential for harm exists in the type, volume, and timing of intravenous fluid. Results from the FEAST study raise the possibility that some patients may benefit from limited or even restrictive fluid strategies.(Macdonald et al., 2017) This contention forms the basis of ongoing randomised interventions based on various combinations of resuscitation and monitoring strategies. Over 400 trials relating to the choice, duration and monitoring of fluid therapy in sepsis (including in combination with various technologies and vasoactive agents) were registered on clinicaltrials.gov at the time of writing.

Glucocorticoids and Nutritional Adjuncts

The lack of success targeting individual cytokines and bacterial toxins was summarized earlier in this chapter. Of treatments which can be considered immunomodulatory, corticosteroids are advocated by many intensive care experts and consensus guidelines(Liang et al., 2021). Corticosteroids operate broadly on the immune and circulatory systems to effect the following: increase circulating volume; reduce inflammatory responses including iNOS and NFκB production; restore circulating glucocorticoid and mineralocorticoid activity in patients with sepsis-associated adrenal insufficiency; restore sensitivity to catecholamines by preventing alpha and beta adrenergic receptor down-regulation.(Annane et al., 2012; Heming et al., 2018; Liang et al., 2021) Despite these potentially beneficial effects, meta-analysis of over 50 randomised trials has failed to demonstrate a short or long term mortality benefit.(Liang et al., 2021) Low-dose (</= 200mg hydrocortisone daily) is still recommended based on the results of the recent ADRENAL study, which demonstrate earlier resolution of shock (and shorter ICU lengths of stay) in mechanically ventilated patients receiving significant doses of vasoactive agents.(Venkatesh et al., 2018)

To this canon of research focused on corticosteroids alone, some evidence (and some controversy) surrounds the potential that vitamin C in combination with hydrocortisone might play a role in improving sepsis outcomes. Ascorbic acid is a water-soluble vitamin which plays

an important part in the scavenging of ROS, in the synthesis of catecholamines, in the repair of connective tissue, in control of HIF-1 expression (a gene upregulated in response to hypoxia) and in numerous processes associated with endothelial and hemostatic function.(Kashiouris et al., 2020) It has been postulated that ascorbic acid oxidises the glucorticoid receptor's cysteine thiol group, which increases receptor performance.(Barabutis et al., 2017) SVCT-1 mediates transport of ascorbic acid across the apical intestinal epithelium and SCVT-2 mediates transport into cells. SVCT-2 is downregulated in sepsis, a process which can be attenuated or reversed by glucocorticoids.(Fujii et al., 2019) In 2017, Barabutis *et al* built on this observation with results of an *in vitro* study exposing human alveolar endothelial cells to lipopolysaccharide, alone or in combination with one or both of hydrocortisone and vitamin C.(Barabutis et al., 2017) LPS-induced endothelial dysfunction (measured using transendothelial electrical resistance) was reversed following exposure to ascorbic acid and hydrocortisone, but not following exposure to either agent alone.

Based on these findings, Marik *et al* deployed therapy with vitamin C, hydrocortisone and thiamine in the management of 47 patients with septic shock.(Marik et al., 2017) Comparing outcomes with 47 sequentially treated patients prior to introduction of the VICTAS protocol (Vitamins Thiamine and Steroids in Sepsis), mortality in the treated population was 8.5% compared with 40% at baseline. VICTAS was associated with a rapid fall in Sequential Organ Failure Assessment (SOFA) scores and rapid weaning from vasopressors, findings which justified a number of randomised trials. The eponymous VICTAS randomised controlled trial did not replicate Marik's findings.(Sevransky et al., 2021) Significant methodologic concerns were noted in the conduct of the trial, including use of a lower ascorbic acid doses, withdrawal of funding at 25% recruitment, and discretionary use of steroids in the control arm.(Sevransky et al., 2021) Compelling evidence of ascorbic acid's benefits in sepsis has not been provided by VICTAS, three contemporaneous RCTs and a network meta-analysis. (Fowler et al., 2019; Fujii et al., 2020, 2021; Moskowitz et al., 2020) Despite this, interest remains in Vitamin C due to potential benefit observed with higher doses, prevalence of vitamin C deficiency in populations at risk of sepsis, and the potential for improved response specific sepsis phenotypes (Sweeney et al., 2018, 2021).

Summary

Following the introduction of antimicrobial therapy, decades of research have failed to identify further “magic bullet” interventions which categorically improve outcomes in patients with sepsis. The harms associated with antimicrobial and fluid therapy are becoming increasingly clear, and interest in the nutritional and metabolic resuscitation of sepsis is growing, based on tantalising evidence from *in vitro* and clinical studies.

Chapter 2: The Sepsis Syndrome – History, Definitions and Epidemiology

Overview

This chapter sets clinical and basic science to one side and considers how sepsis is defined and studied in hospital-based and population-based cohorts. Aspects of sepsis in the history of medicine will be considered to inform a detailed overview of contemporary sepsis definitions. Examples are used to show how performance of different definitions and data sources produce significant variability in key epidemiologic measures, particularly sepsis incidence.

Sepsis in Medical History

Sepsis is currently understood to represent the body's "dysregulated host response to infection".(Singer et al., 2016) Throughout history this severe, systemic manifestation of infection as it progressed from symptom onset through to prostration and death would have been instantly recognizable, not to say distressing. Take the following description provided by George James Guthrie, the chief surgeon to Wellington at the time of the Napoleonic wars, who described almost 600 cases of limb injury leading to surgical amputation at the battle of Waterloo:

"Pain, heat, redness, tumefaction of neighbouring parts constituting inflammation comes on, which speedily runs into suppuration or gangrene. Fever becomes more violent and frequently ends in death in the course of a few days."(Guthrie GJ, 1827).

Table 2.1: Selected historical landmarks in the understanding of sepsis prior to general acceptance of the germ theory of disease

Era	Source or Author	Observation	Impact
3000 - 1600 BC	Papyri	Fever, and necrosis described in case series of wounds and fractures.	First use of semiotics to define prognosis and treatment
630BC	Homeric literature (The Iliad Book 24 v414)	First use of the term sepsis (σηψις)	Pre-Hippocratic recognition of decay and putrefaction in human disease
430BC	The Hippocratic Canon	Coherent description of inflammation, including recognition of loco-regional spread, secondary systemic compromise and as a prerequisite to purulence	Development of aspiration and debridement to prevent "humor afflux"
20AD	Celsus	Four cardinal features of inflammation defined – "*Notae vera inflammationis sunt quattuor; rubor et tumor cum calore et dolore"*	Key clinical findings associated with inflammation codified and propagated in medical traditions and teaching
160	Galen	Influential writings on wounds and wound healing	*Pus bonum et laudabile* leads to indiscriminate use of cautery to *promote* purulence
1440	Gutenberg	Invention of the printing press	Rapid circulation of new information and ideas
1500s	Paracelsus and Paré	Galenic teachings systematically challenged by observation	Use of dressings and ligature to avoid cautery.
1546	Fracastoro	Develops concept of contagion	Disease is carried by invisible agents in the air: *miasma*
1683	Van Leeuwenhoek	Microscopic observation of bacteria	
1815	Guthrie	Compares mortality of early vs late amputation in Battle of Waterloo	Observes 15% reduction in mortality with early amputation.
1828	Ehrenberg	First use of "bacterium"	
1837	Piorry	First use of "septicaemia"	Linguistic and conceptual link from process of putrefaction to changes carried in blood
1843	Holmes	First to suggest that contagious agent leading to puerperal fever could be spread by contaminated hands of medical staff	
1857	Tarnier	Dogs die who are injected with peritoneal fluid of women deceased with puerperal fever	Propagates theory of contagion and internal dissemination of poison as cause of "septicaemia".
1860	Nightingale	Campaigns for implementation of sanitary practice during Crimean war.(28)	Introduces data collection and scientific principles to the practice of nursing, infection prevention and hospital epidemiology.
1864	Pasteur	Disproves theory of spontaneous generation.	Builds foundations of germ theory of disease. Putrefaction may be prevented through heat, filtration, or exposure to chemical disinfectant
1867	Lister	Application of Pasteur's findings to wound care and the prevention of gangrene and sepsis, termed anti-sepsis	Revolutionises practice of surgery. Extension of anti-septic principles to the *avoidance of introduction* of bacteria during procedures, i.e. aseptic technique
1869	Feltz & Coze	Demonstrate presence of bacteria in blood during puerperal fever	

Table 2.1 elaborates selected landmarks in the study of sepsis through to the mid-19th century, the point at which the germ-theory of disease gained general acceptance. The word sepsis is derived from the Greek *sipsi,* meaning rot/putrefaction, as opposed to *pipsi,* or healthy fermentation (producing wine, for example). The term is used in the Hippocratic canon and other writings which underpin the traditions of medicine in the global West.(Hernandez Botero & Florian Perez, 2012) Although used in antiquity, the term sepsis reappeared as a descriptive term implying "rot" in massively damaged soft tissue, following the introduction of ballistic weaponry.(Hernandez Botero & Florian Perez, 2012) Through to the first half of the 19th century, sepsis was only variably used as a descriptive term for tissue putrefaction, without reference to a specific disease state. Instead, women dying from what we would now refer to as post-partum sepsis died of "puerperal fever", and soldiers dying with gangrenous wounds suffered "putrid fever".(Cavaillon & Chrétien, 2019)

By 1858, Trousseau and others already concluded that the systemic manifestations of these conditions were the same entity, and contemporaneous work by Pasteur set the scene for a revolution in the application of science to the relief of suffering.(Fitzgerald JG, 1923) Pasteur extinguished the theory of spontaneous generation, and correctly identified the role of bacteria (or "animacules") in the processes accompanying fermentation and decay.(Fitzgerald JG, 1923; Lister, 2010) Until the mid-1800s the threat of wound infection was a major barrier to therapeutic surgical intervention of any kind. Inspired by Pasteur's work, Lister published his observations on the practice of surgical *anti*-sepsis in 1867.(Lister, 2010) Combined with the use of anaesthetic agents, anti-sepsis revolutionized surgical safety and set the scene for rapid developments in medical and surgical therapy in the second half of the 19th century.

Assiduous clinical and scientific observation defined the growth of academic medicine during this period. Reflecting on the development of germ theory in 1913, Osler states that "at the middle of the last century we did not know much more of the actual causes of the great scourges of the race, the plagues, the fevers and the pestilences, than did the Greeks." He goes on to capture the excitement that accompanied discoveries in the growing field of microbiology. These followed one after the other with "bewildering rapidity", such that by the time of his writing

almost all of the most common bacterial infections in humans were linked to their underlying agent.(Osler, 1990)

Clinicians of this era became highly adept at differentiating the clinical features associated with specific bacteria, including variation in their systemic manifestations. Take the following example from 1902.(Wiggin, 1902) Having identified that puerperal endometritis and fever associated with *Staphylococcus aureus* leads to obvious clinical localization to the uterus and lower abdomen, Wiggin then offers that "when the cause of the septic trouble is due to the direct invasion of the tissues by the streptococci the constitutional symptoms are much more severe in character; the very rapid and weak pulse especially attracts attention".(Wiggin, 1902) This description precedes the discovery of streptococcal superantigens by almost a century. Nanomolar quantities of these toxins cause massive activation of pro-inflammatory pathways which we now know can lead to organ failure and death, even in the absence of significant local signs of infection.(Proft et al., 2003)

During the same period, attempts were made to define sepsis in terms which combined clinical observation with burgeoning experimental evidence. The first definition of sepsis that mirrors those developed more successfully in the second half of the 20th century was provided by Hugo Schottmüller in 1914: "sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream which leads to signs of systemic illness in remote organs".(Schottmüller, 1914) Schottmüller was writing after Loeffler and Pfieffer, who are credited with the discovery that bacterial toxins (termed exotoxins) and the breakdown products of bacterial lysis (termed endotoxin) could cause disease in the absence of viable microorganisms.(Pappenheimer, 1984; Rietschel & Cavaillon, 2002) By the middle of the 20th century significant evidence had accumulated linking inoculation of bacterial toxins to specific clinical manifestations, including the ability of endotoxin to incite cycles of fever, rigors and sweats, circulatory changes and microthrombus formation (ultimately described as disseminated intravascular coagulation).(Altschule et al., 1945; Blain et al., 1970; Dellinger, 2003)

This period was characterized by increasing interest in the clinical physiology of sepsis, whereby then modern methods of assessment were used to seek biologic correlates of the sepsis syndrome

in both humans and animals. The first controlled descriptions of the human response to endotoxin were reported, and the hemodynamic findings in hospitalized patients with septic shock were published.(Altschule et al., 1945; Blain et al., 1970) The introduction of effective antimicrobial therapy rendered treatable many conditions which had long been uniformly fatal, such as acute bacterial endocarditis. From the 1970s, with the development of molecular methods and the discovery of cytokines, an increasingly coherent map was drawn of the pathways leading from bacterial protein exposure to activation of cell-signalling, cytokine release and immune-mediated tissue injury.(Dellinger, 2003; Dellinger et al., 2008; J.-L. Vincent & Abraham, 2012) These were conceived as 'final common pathways', amenable to therapeutic blockade or augmentation, along which any exposure to an infectious agent could lead to death via stereotypical clinical responses.(Rubio et al., 2019)

At the same time, antimicrobial therapy allowed more patients to survive the early stages of sepsis. Observation under modern methods of organ support permitted complete descriptions of sepsis-associated multi-organ failure. Prior to this, patients with sepsis (and particularly septic shock) tended to succumb to acute multi-organ failure before its medium to long term impacts could be studied.(Bone et al., 1992) Identification of new therapeutic targets within immune and coagulation cascades led to the proliferation of investment in drug development and randomized controlled trials, *none* of which led to the routine use of immune-modulation as a standard approach to sepsis management. By the early decades of this century, these failures stimulated reflection on the wider opportunities to identify *dysregulated host responses* to infection earlier in the course of disease, and to improve sepsis management across the spectrum of acute care.(J.-L. Vincent & Abraham, 2012)

Thus, as with any field in medicine, whilst the disease has remained a constant, the balance of debate in relation to definitions, treatments and research priorities has shifted with time. In the positivist tradition, this is a rational response to new findings. For example, the decline of the pathogen-driven theory of sepsis occurred as evidence emerged of immune-mediated tissue injury and phenomena such as endotoxin translocation in critical illness.(Holzheimer RG, 2001) However, definitions of sepsis (and the priorities which shape our approach to its management) are better understood as shifting constructs influenced by prevailing political, cultural and

economic factors. These are the deeper, more complex underlying assumptions which allow clinicians to state something as truth (or dogma) and are referred to as *discourses*.(Burnum, 1993; Hodges B & Lingard L, 2012)

Methods of discourse analysis have been used to determine the themes which underly thinking on complex topics such as sepsis. Bostwick and colleagues used a machine learning approach to discourse analysis known as *topic modelling.*(Doran Bostwick et al., 2018) They analysed all entries in PubMed identified by the search terms “sepsis”, “septic shock”, and “septicaemia” from 1890 to 2017. Their results demonstrated transitions in discourse between the first and second halves of the twentieth century, the former characterized by a thematic focus on the pathogen, the latter period focusing on host immune response. Of relevance to this thesis, and taking only the five years from 2012-2017, core themes were found to have shifted again to early sepsis management, ICU care, cost containment, and biomarkers.

The Evolution of Consensus Clinical Definitions

In attempting to define sepsis, the following problems become apparent:

1. each definition reflects contemporary understanding and assumptions
2. some authors include (and others exclude) cases where no microbe is identified
3. tautologies arise when simple descriptors are used to describe complex phenomena (eg *people with sepsis are septic*).
4. Sepsis is an intermediate complication rather than a cause of disease

Sepsis arises from diverse underlying infections, including infectious complications of non-infectious conditions such as injuries (e.g. road traffic accidents), non-communicable morbidity (e.g. complications of childbirth) and medical therapy (e.g. surgical wounds). As described above, the dysregulated immune response involves all immune cells in all tissues, and the response is compartmentalized by organ, by time course, and by pathogen.(Rubio et al., 2019) It is unsurprising, therefore, that simplistic illness models have prevented accurate classification in health statistics. This difficulty of classification was reflected most recently in the Global Burden of Disease studies.(James et al., 2018; Rudd et al., 2020a) The first GBD publications were unable to report sepsis incidence, as initial results were drawn from International Classification of Disease (ICD)-based codes specifying *underlying cause* of death. A subsequent study used multiple cause of death analysis, an approach which was able to identify cases where sepsis was present. This showed that 20% of all global deaths are linked to underlying sepsis. Of the 11 million sepsis deaths identified in 2016, 46% were of non-communicable or injury-related *causation*, illustrating that infectious diseases are themselves common complications of non-communicable disease.(Rudd et al., 2020b)

Coherent narrative definitions of sepsis only began to arise in the early 20th century. Hugo Schottmüller, writing in 1914, described sepsis as "a state caused by microbial invasion from a local infectious source into the bloodstream which leads to signs of systemic illness in remote organs".(Schottmüller, 1914) Schottmüller was one of the early protagonists of the hypothesis that successful therapy for sepsis would be directed at bacterial toxins and secondary pathogenic processes, for example: "…therapy should not be directed against bacteria in the blood but

against the released bacterial toxins". Osler himself recognized that except on few occasions, the patient "appears to die from the body's response to infection rather than from the infection."(Osler, 1990)

The changing face of medical practice in the second half of the 20th century created a new profile of disease, such that by 1991, Bone summarized the situation thus: "Until roughly 30 years ago, sepsis, septic shock and multiple organ failure were rarely seen. Simply put, we could not keep severely ill or injured patients alive long enough for these disorders to develop. Many of the early studies of sepsis focused on patients with gram-negative bacteraemia. However, we now know that most patients with sepsis are not bacteraemic. Many of the early studies were conducted in surgical patients or trauma victims; it was not clear whether the physiologic derangements that occurred in these patients were the same as those that occurred in patients with gram-negative bacteraemia. The lack of precise criteria for *infection, sepsis, sepsis syndrome,* and *septic shock* made it difficult to assess the severity of the infectious process and the differences between study populations. The lack of precise criteria for the term *multiple organ failure* made it difficult to establish which organs were affected in patients with sepsis. It also made it more difficulty to determine whether organ failure was a cause- or a consequence – of sepsis. Only recently has the knowledge of the molecular and cellular events that occur in sepsis and its sequelae begun to shed light on the complex cascade of events underlying these disorders. Although our knowledge of these events is still incomplete, we have learned enough to make the need for more exacting definitions apparent".(Bone et al., 1992)

In response to this challenge, the first consensus conference on sepsis and organ failure was sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine. The conference introduced two explicit concepts into medical practice; the Systemic Inflammatory Response Syndrome (SIRS) and the Multi-Organ Dysfunction Syndrome (MODS) (Table 2.2). SIRS and MODS were recognized as clinical correlates of systemic inflammation and the organ dysfunction which accrues when the inflammatory cascade causes loss of organ homeostasis (MODS).(Bone et al., 1992) Importantly, the conference recognized that SIRS and MODS could be caused by acute inflammatory insults *other than* those associated with infection,

and that both were dynamic conditions in any individual patient. The conference also clearly delineated the potential for infection and bacteraemia to exist without 'sepsis'.

The Bone criteria of 1991 remain useful as a simple, elegant and robust clinical model addressing complex underlying processes.(Bone et al., 1992) They explain, in terms which are teachable and easily understood at the bedside, why the effects of invasive infection and sterile tissue damage can produce almost indistinguishable clinical syndromes of inflammation and organ dysfunction. They delineate sepsis as a discreet cause of this syndrome, caused by infection. They combine the *immune* and *microbial* paradigm of sepsis and are true to underlying pathobiology of the inflammatory, endothelial and thrombotic correlates. Finally, they provide a linear framework to define complex, non-linear events (Figure 2.2).

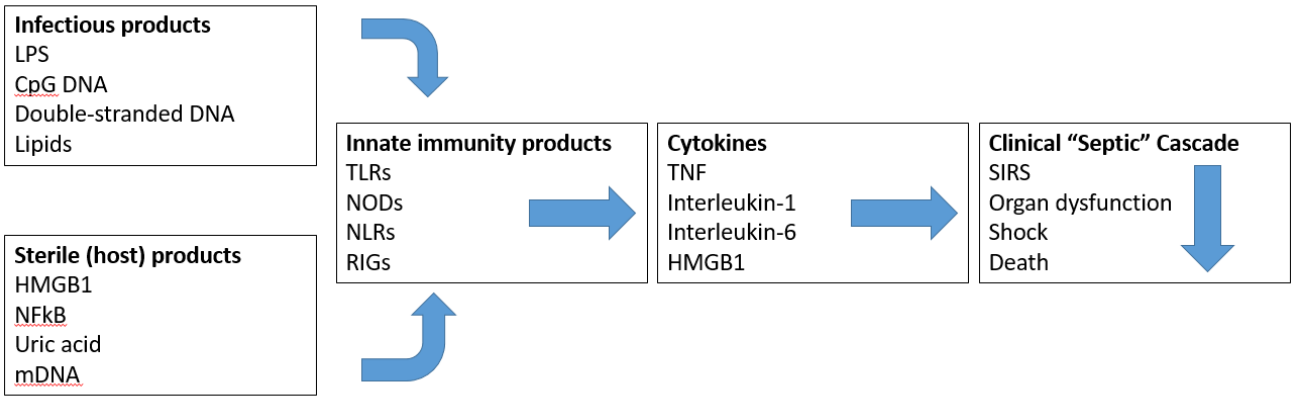


Figure 2.2. Linear representation of events leading to systemic inflammatory and septic responses

Abbreviations: LPS, lipopolysaccharide; CpG DNA, ; HMGB1, human motility group box 1; NFκB, Nuclear Factor kappa B; mDNA, mitochondrial DNA; TLR, toll-like receptor; NOD, nucleotide-binding and oligomerization domain; NLR, nod-like receptor; RIG, retinoic acid-inducible-gene; TNF, tumour necrosis factor; SIRS, systemic inflammatory response syndrome

Table 2.2. Consensus definitions of sepsis 1991-2003

Iteration	Core Sepsis Definition	Septic Shock
1st Consensus Definition (Sepsis-1)	Systemic response to infection, manifested by two or more of the following conditions *as a result of infection*: 1) temperature >38^{0}C or <36^{0}C; 2) heart rate >90 beats per minute; 3) respiratory rate>20 breaths per minute or $PaCO_2$ <32mmHg; and white blood cell count>12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms caused by infection †	"Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured"
Second Consensus Definition (Sepsis-2)	Infection, documented or suspected, and some of the following: *General variables* Fever (core temperature _38.3°C) Hypothermia (core temperature _36°C) Heart rate _90 min_1 or _2 SD above the normal value for age Tachypnea Altered mental status Significant oedema or positive fluid balance (20 mL/kg over 24 hrs) Hyperglycemia (plasma glucose _120 mg/dL or 7.7 mmol/L) in the absence of diabetes *Inflammatory variables* Leukocytosis (WBC count 12,000/L) Leukopenia (WBC count 4000/L) Normal WBC count with 10% immature forms Plasma C-reactive protein >2 SD above the normal value Plasma procalcitonin >2 SD above the normal value *Hemodynamic variables* Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age) SvO2 >70% Cardiac index >3.5 L/min/m^2 *Organ dysfunction variables* Arterial hypoxemia (PaO2/FiO2 <300) Acute oliguria (urine output 0.5 mL/kg/hr or 45 mmol/L for at least 2 hrs)	

	Creatinine increase >0.5 mg/dL
	Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count 100,000/L)
	Hyperbilirubinemia (plasma total bilirubin 4 mg/dL or 70 mmol/L)
	Tissue perfusion variables
	Hyperlactatemia (>1 mmol/L)
	Decreased capillary refill or mottling

†Severe Sepsis further defined as sepsis-associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Abbreviations: SIRS, systemic inflammatory response syndrome; MODS, multi-organ dysfunction syndrome

The appeal of the SIRS concept led to rapid adoption by intensive care clinicians and investigators, but it did not pass without criticism. Without any supporting data, the SIRS/sepsis model had been proposed in advance of the consensus event by its chair, as a set of enrolment criteria for trials assessing the role of corticosteroids in critically ill patients with infection. What came to be defined as the sepsis syndrome was "a hypothesis, not a disease".(Bone et al., 1989; J. C. Marshall, 2014) Nevertheless, by the next consensus conference, convened in 2001, authors were able to identify 800 publications in MEDLINE which mentioned SIRS in the title or abstract.(M. Levy, 2003) Adoption by other professional groups was incomplete, and clinical experience with the SIRS criteria suggested that they were too non-specific to be of broad utility in routine clinical practice.(J.-L. Vincent & Abraham, 2012) The authors also noted that the clinical criteria providing evidence for infection-associated inflammation were too narrow, and did not define specific patterns of host-response.(M. Levy, 2003) The second consensus conference (Sepsis 2) definitions expanded the grounds for definition of systemic inflammation but left the 1991 Sepsis-1 framework intact. The cumbersome clinical qualifiers for sepsis shown in Table 2.2 arose from attempts to codify all the early clinical identifiers used to determine whether a patient "looks septic". As such, Sepsis-2 provides a useful example of the problem which Bone *et al* sought to avoid through the provision of simple and robust (if non-specific) criteria.

Calls continued to exclude SIRS from the clinical definition of sepsis, essentially due to lack of specificity for the sepsis syndrome.(J.-L. Vincent & Abraham, 2012) Churpeck *et al* had shown that 15% of acute hospital admissions involved SIRS at presentation, and 47% of in-patients met SIRS criteria at least once during admission, equating to 542 episodes per 1000 hospital days in a study by Pittet et al.(Churpek et al., 2015; Pittet et al., 1995) In an ICU setting, most patients exhibit SIRS for complex underlying reasons, both infectious and non-infectious. Concerns also remained that the SIRS may be a normal or even beneficial response in some settings, and it remained unclear whether the SIRS itself *caused* organ dysfunction. Distinguishing SIRS due to infectious and non-infectious causes remained problematic in clinical practice, leading to unintended consequences such as excessive antimicrobial prescribing.(J.-L. Vincent & Abraham, 2012) The arbitrary definition of SIRS as requiring *two or more* criteria ignored the fact that even one SIRS criterion increased risk of adverse outcomes in the setting of critical illness. Finally, analysis of large, prospective ICU databases showed that one in every eight patients with organ dysfunction due to infection did not satisfy SIRS criteria.(K.-M. Kaukonen et al., 2015)

Notably, the Sepsis-1 criteria, and all those which followed, are used to dichotomise patients into those *with* and *without* sepsis. However, the 1991 conference report explicitly stated the need for sepsis definitions to accommodate baseline prognosis and to change based on dynamic reassessment and the accumulation of clinical evidence over time.(Bone et al., 1992) Simply defining the presence of sepsis and septic shock fails to allow for more precise characterization and staging, and leaves prognostication and treatment selection to the clinician. The Sepsis-2 conference sought to replicate the successes seen in oncology using disease stratification (ie the Tumour Node Metastasis system) by proposing the "PIRO" classification (Predisposition, Infection, Response, Organ Failure).(M. Levy, 2003) This proposes stratifying patients based on their underlying health state (Predisposition), the nature and extent of the infectious insult (Infection), the magnitude of the host response (Response) and the extent and type of organ dysfunction (Organ Failure). This framework explicitly allowed for change in PIRO criteria to be incorporated over time. For example, whilst present assessments of predisposition focus on co-existing disease and age, future components might include new understanding of genetic polymorphisms and biomarkers suggesting dysregulated host/pathogen interactions.(M. Levy, 2003)

In addition to providing greater nuance in clinical definitions and prognostication, the promise of the PIRO model was in the potential to direct investigation and therapy to appropriate patient sub-groups.(M. Levy, 2003) For example, in the Infection domain, pneumonia and intra-abdominal causes of sepsis are known to associate with poor outcomes. Transcriptomic studies suggest that outcomes are dependent on whether patients develop inflammatory, coagulopathic or "adaptive" phenotypes.(Sweeney et al., 2018, 2021) In the Organ failure domain, it was known that those with significant organ failure benefited most from recombinant activated protein C.(Bernard et al., 2001) Finally, the PIRO classification offered the potential to distinguish morbidity due to *infection* from morbidity due to the *response* to infection, a matter of no small significance when immunomodulatory and immunosuppressive therapies are being proposed as treatments for complications of infection.

The 2001 conference did not finalise the individual components of a PIRO classification or validate it in large patient populations. It wasn't until 2008 that the first analysis of an ICU registry attempted to characterize prognostic variables within each PIRO domain.(Granja et al., 2013) Nevertheless, well designed studies making use of regular clinical and laboratory observations over the first few days of ICU admission (as recommended by Bone *et al* in the Sepsis-1 conference) demonstrated excellent ability to discriminate for in-hospital mortality. For example, Granja et al showed that a PIRO model derived from a large population of ICU-admitted patients with community-onset sepsis in Portugal discriminated for in-hospital death with an area under the receiver operated curve (AUROC) of 0.84 (95%CI 0.81-0.87).(Granja et al., 2013) By comparison, the AUROC for the same outcome in over 180,000 patients admitted to ICUs in New Zealand and Australia using only the highest SOFA score within 24 hours of admission was 0.75 [99% CI, 0.750-0.757]. This provides evidence that the discriminative approach recommended in the PIRO framework outperforms prognostication based solely on measures of organ function (Raith et al., 2017)

In 2015, in response to the challenge of improving on existing clinical definitions of sepsis, a third consensus conference was convened by the Society of Critical Care Medicine and European Society of Critical Care Medicine.(Singer et al., 2016) A consensus approach was constructed

prospectively which incorporated Delphi methods and extensive literature review. The conference specifically tested proposed definitions in large, prospectively maintained, health record databases of patients admitted with sepsis and non-sepsis diagnoses in US and European hospitals.(Seymour et al., 2016; Shankar-Hari et al., 2016) The final diagnostic criteria (Sepsis-3) are presented in Table 2.3.

Table 2.3. Third consensus definitions of sepsis, 2016

	Sepsis	**Septic Shock**
Sepsis-3	Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection. "Organ dysfunction" defined as a SOFA score of >/=2. qSOFA score suggested as screening tool	"a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality"

Abbreviations: SOFA, sequential organ failure assessment; qSOFA, quick Sequential Organ Failure Assessment

Sepsis-3 offers a binary definition of sepsis based on the extent of organ failure, using a score designed to identify risk of death or escalation to ICU admission. The SOFA score is calculated using measures of oxygenation (PaO2/FiO2 ratio, mechanical ventilation), laboratory markers (platelet count, serum bilirubin and creatinine), conscious level (measured using the Glasgow Coma Scale), and hypotension (defined by a MAP<70mmHg or the need for vasoactive agents). This approach met with immediate criticism and outright opposition from some quarters.(Cortes-Puch & Hartog, 2016) As reported by the Sepsis-2 conference, measurement of organ function is only one component of clinical assessment (ie the Organ dysfunction domain of the PIRO classification). Practitioners in low and middle income countries objected to the focus on risk of ICU admission (a resource frequently unavailable to many patients with sepsis).(Cortes-Puch & Hartog, 2016) The severity threshold for a sepsis diagnosis (established organ dysfunction, evidenced by a SOFA score of >/=2) was high, and ignored early signs of deterioration and the prognostic value of the SIRS criteria.(Sprung et al., 2006) Perhaps the most important criticism of Sepsis-3, in a clinical setting, is the requirement for established organ dysfunction. The high mortality amongst patients meeting Sepsis-3 criteria who are admitted to an ICU is typically

20%, suggesting irreversible organ failure or critical co-morbidity placing some beyond help.(Raith et al., 2017)

In addition, the justification for adopting a new definition was not made in terms of new knowledge or improving patient outcomes, and the impact of new definitions on existing administrative and quality improvement work was not taken into account.(Cortes-Puch & Hartog, 2016) For this reason the Centre for Medicare and Medicaid Services (CMS) continues to use Sepsis-1 definitions, potentially recreating the divisions which Bone *et al* sought to resolve by convening the Sepsis-1 panel in 1991.(Motzkus & Lilly, 2017) Ultimately, these controversies continue to mean that there is no definition of sepsis which is universally accepted, and thus no gold standard against which changes in epidemiology, treatment and outcomes can be based.

The performance of administrative methods used to define sepsis in routine data

The use and performance of the international Classification of Disease (ICD) to define sepsis will be described below, followed by an assessment of definitions applied to large electronic health record databases.

Methods which use the International Classification of Disease

The ICD allows the collection and comparison of health data across time and between different countries and regions. It is one of the only uniform sources of health information available to researchers interested in defining the incidence of disease within and between populations. The ICD revision 9 (ICD-9) was introduced in 1976, and ICD-10 in 1989.(Quan, Sundararajan, Halfon, Fong, et al., 2005b) ICD-10 uses an alphanumeric coding system consisting of a letter followed by up to 3 numbers. Coding to the four-character level is universal, meaning that countries seeking to implement modifications to the ICD must do so by adding entirely new codes or additional numbers or letters. New Zealand, for example, makes use of the ICD-10-Australian Modification (ICD10-AM), whereas the United States has transitioned to the ICD-10-Clinical Modification (ICD10-CM). Thus, ICD-10-based coding algorithms which seek to define sepsis in administrative data are restricted to the use of 3- and 4-digit codes to ensure data is useful for comparison over time and location.

Various ICD-based coding algorithms have been used to define sepsis.(Mariansdatter et al., 2016) Typically, studies attempt to mirror the clinical construct of sepsis as an infection accompanied by organ dysfunction. In ICD-based studies, this means accepting explicit series codes (ie R65.2, septic shock) or infectious disease codes linked to secondary codes typical of sepsis-associated organ dysfunction (ie A481, Legionnaires' disease with E872, Acidosis).(Fleischmann-Struzek et al., 2018) Some methods qualify explicit sepsis codes by also requiring organ failure codes.(Sundararajan et al., 2005b) This approach creates numerous problems of standardization, compounded by the lack of a true clinical gold standard definition

of the sepsis syndrome. For example, Mariansdatter *et al*, identified coding strategies which varied in the number of codes used from 1 to more than 1200.(Mariansdatter et al., 2016) Unsurprisingly, higher estimates of incidence are produced in series which include more codes. Similarly, applying 4 coding strategies to a hospital administrative data in the United States, Gaieski *et al* found a 3.5-fold between method variation in estimated population incidence.(Gaieski et al., 2013) Seeking to understand this phenomenon in Sweden, Wilhelms identified that of three coding definitions studied, the patient sets identified were almost mutually exclusive.(Wilhelms et al., 2010)

Added to complexity in this area is the potential for variation in coding practice.(Rhee & Klompas, 2020a) For example, Rhee et al demonstrated that the total number of organ failures associated with coded sepsis cases increased over time in the United States, but the average threshold for coding acute kidney injury fell.(Rhee et al., 2015b) In a second example, changes in the Centre for Medicare Services (CMS) and medical severity diagnosis related group (MS-DRG) criteria were each temporally associated with increases in Californian sepsis claims data.(Gohil et al., 2016) Complex *post-diagnosis* phenomena linked to coding, collectively representing *ascertainment bias*, may also explain why incidence can increase in institutions with stable clinical markers of serious infection (ie positive blood culture rates), or in health systems seeking appropriate reimbursement for the greater costs associated with infection and organ failure.(Iwashyna & Angus, 2014; Linde-Zwirble & Angus, 2004; Rhee & Klompas, 2020a)

The explicit allegation of "up-capture" to improve financial reimbursement in the US health system, together with evidence of other forms of ascertainment bias, tend to imply declining specificity of administrative definitions. It is therefore crucial to understand the test performance characteristics of administrative codes to identify true sepsis cases, particularly in the face of reports increasing population incidence.(Fleischmann-Struzek et al., 2018; Linde-Zwirble & Angus, 2004) Several studies have in fact shown that the specificity of code-based definitions is very high. Using the 3rd consensus definitions of sepsis and septic shock as a gold standard (Table 2.3), Fleischmann-Struzek *et al* demonstrated that commonly used algorithms preserved specificity at 95% or above amongst 937 in-patient admissions to two German

hospitals.(Fleischmann-Struzek et al., 2018) Rhee et al. used a similar approach, again using Sepsis-3 definitions as a gold standard, to show that a stringent electronic health record (EHR)-based definition was only 60% sensitive for sepsis in a random sample of 510 hospital in-patients, again with high specificity.(Rhee et al., 2017)

There is abundant evidence, then, that administrative methods have high specificity but poor sensitivity, and that *no* administrative method can accurately reflect the true burden of sepsis.(Donnelly et al., 2020) This is relevant to sepsis in New Zealand. Kaukonen and colleagues applied an administrative sepsis definition to the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE) dataset, which is used extensively to investigate the population incidence of critical illness.(K. M. Kaukonen et al., 2014) This made use of the diagnostic and organ dysfunction criteria contained respectively within the APACHE-III and SOFA scores (Table 2.4). Heldens *et al* then investigated the sensitivity of the ANZICS-CORE method for detecting sepsis against PROWESS trial definitions in a large tertiary-level intensive care unit.(Bernard et al., 2001) The sensitivity of the ANZICS-CORE sepsis definition was only 52%. The implication of this finding, clearly, is that these estimates of incidence were compromised by use of a definition with poor sensitivity, applied only to the ICU-admitted population.(Heldens et al., 2018).

Table 2.4. Comparison of Clinical and ANZICS-CORE database definitions of sepsis and septic shock

Clinical definition of sepsis (A, B, C required)(Bernard et al., 2001)	**ANZICS CORE database definition of sepsis (A and B, or A,C,D required)**
A. The presence of a documented or suspected infection B. Receiving intravenous antibiotics C. Organ dysfunction related to the infection	A. A Two or more SIRS criteria B. APACHE III admission diagnosis consistent with sepsis C. APACHE III admission diagnosis consistent with infection accompanied by organ dysfunction D. Organ dysfunction (SOFA score ≥3, except for cardiovascular organ failure)

SIRS, Systemic Inflammatory Response Syndrome; ANZICS CORE, Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation; APACHE III, Acute Physiology and Chronic Health Evaluation, version 3.SOFA, Sequential Organ Failure Assessment.

Methods which make use of electronic health records

The many limitations of administrative data have led to greater interest in the analysis of electronic health records (EHRs), the use of which promises the routine prospective surveillance of hospital admission data to determine trends in sepsis incidence and underlying cause.(Rhee & Klompas, 2020a) The ubiquity of EHRs in the United States allowed Rhee and co-authors to explore the performance of clinical-EHR definitions of sepsis in the United States based on Sepsis-3 definitions.(Rhee et al., 2009; Rhee & Klompas, 2020b) Development and validation of an EHR-based surveillance definition was undertaken in two large US hospitals covering the period 2003-2012. This EHR method was superior to, and stable against, administrative definitions of sepsis. including coding applied to septic shock using ICD-9-CM.(Kadri et al., 2017) A final iteration of this method was subsequently adopted by the US Centre for Disease Control, an abbreviated summary of which is shown in Table 2.5.(Rhee & Klompas, 2020a)

Use of EHR-based surveillance is not without its challenges. The administration of antibiotics and blood culture sampling do not in themselves prove the presence of infection. Case delineation can still be influenced by local capability (ie ability to treat with vasopressors), and alternative administrative methods are still needed where EHRs are not in use. The theoretical

and practical barriers to defining sepsis therefore continue to impact the study of its epidemiology.

Table 2.5 Abbreviated Adult Sepsis Event Criteria for use in Electronic Health Record-based surveillance

A and B Required	
Evidence of Infection (all critera required)	Organ dysfunction (≥1 criteria required)
1. Blood culture obtained (irrespective of result) 2. At least 4 days of antimicrobial therapy	1. New vasopressor infusion 2. Initiation of invasive mechanical ventilation 3. Acute kidney injury 4. Increased bilirubin 5. Thrombocytopenia 6. Serum lactate ≥2 mmol/L

The application of sepsis definitions to the study of sepsis epidemiology

This section describes the how various definitions of sepsis have been applied to the study of its epidemiology, as shown in Table 2.6. Case definitions can be categorised as *administrative* (using routinely collected administrative data) or *chart-based* (retrospective assessment of records include clinical and physiological findings). Numerator data is sometimes limited to specific organisms or clinical syndromes (ie pneumonia). Selection of denominator data is determined by the investigators based on the population of interest and the availability of data. For example, in low- and middle-income countries where hospital data is either unavailable or unreliable, death certification data can be used as a numerator, against census/population denominators.(Rudd et al., 2020b) Unsurprisingly, the potential variation introduced by these approaches (and combinations of these approaches) has led to some difficulty providing accurate estimates of hospital and population incidence.

Hospital-incidence of sepsis

The most comprehensive hospital-incidence data is derived from claims and EHR surveillance data in the United States. Rhee and colleagues compared EHR records with data submitted for reimbursement (based on ICD-9 codes for "severe sepsis" and "septic shock" only).(Rhee et al., 2009) In a sample of almost 3 million admissions to 409 hospitals from 2009-2014, the EHR-based definition was satisfied in 6% of hospital admissions, and present during admission in 37% of recorded deaths. Clinical criteria were more sensitive than claims data in identifying sepsis than claims (69.7% [95% CI, 52.9% to 92.0%] vs 32.3% [95% CI, 24.4% to 43.0%],P< .001), but both under-estimated true sepsis incidence when compared with a clinical validation sample.

Table 2.6. Sources of variation in the study of sepsis incidence

Approach	Data Product	Definition used	Numerator	Denominator
Administrative Chart-based	ICU diagnostic data Hospital discharge diagnosis codes Cause of death data Antimicrobial consumption data Blood culture results Clinical notes review	1991 criteria 2001 criteria 2016 criteria Composite administrative definitions Composite clinical definitions (ie EHR-based)	All sepsis cases Specific infectious diseases	Census population Population segment -adults (vs children) -ICU -Hospital -Hospital system -Region -Country Specific groups i.e. -oncology patients -surgical patients

Abbreviations: ICU, Intensive care unit

Population incidence

Mariansdatter *et al* conducted a systematic review of all studies estimating the rate of sepsis expressed in population person-years.(Mariansdatter et al., 2016) Identifying only 12 code-based

studies which satisfied their inclusion criteria, estimates of population incidence ranged from 135 to 1074 cases per 100,000 in the United States alone. This range contains the globalised estimate for the incidence of hospital-treated sepsis provided in a separate systematic review conducted by Fleischmann and colleagues (288 sepsis cases per 100,000 person-years (95% CI, 215–386, $\tau = 0.55$)). (Fleischmann et al., 2016b) Both groups noted the scarcity of data outside the United States and in low and middle-income countries specifically. Most estimates derived from chart-based studies, and one prospective study which identified cases amongst people treated with intravenous antibiotics in Sweden. (Ljungström et al., 2019). Mariansdatter *et al* also described an increase in reported incidence over time.(Mariansdatter et al., 2016)

As mentioned above, epidemiological studies of sepsis traditionally focus on adults hospitalized in high-income countries. Different approaches are therefore needed to address the burden of sepsis in low and middle income countries. The Global Burden of Disease, Injuries and Risk Factors study (GBD) makes use of cause of death data collected from 195 countries, coding death in all age groups against 282 underlying causes (injury and morbidity, further divided into communicable and non-communicable disease). As sepsis is considered an intermediate event (between a death and its underlying cause), it was not reflected as a cause or contributor to death in earlier GBD reports.(James et al., 2018) Rudd *et al* therefore estimated the global, regional and national burden of sepsis by applying an ICD-10-based algorithm to the GBD repository.(Rudd et al., 2020b) Countries were divided by deprivation index (based on income, education and fertility rate) and redistribution was used to allocate cause of death in cases of uncertainty. Results were aggregated by underlying cause, age, sex, year, location and sepsis status. Sepsis was documented in 11 million records in 2017, and in 20% of total deaths reported in that year. Death data was used to model estimates of total age-standardised incidence for the year 2017. The global incidence of sepsis contributing to death fell from 1074.7 to 677.5 per 100,000 between 1990 and 2017. The modelled age-standardised incidence rate (ASIR) of sepsis in New Zealand in 2017 was 164 per 100,000.(Rudd et al., 2020b)

The GBD sepsis study also showed that administrative methods can demonstrate underlying differences in population health which are known to be present based on other findings and clinical experience. For example, it shows: two peaks in sepsis incidence, one in the very young,

and one in the very old; that diarrhoeal diseases and pneumonia remain serious causes of harm amongst children, and that sepsis mortality is highest overall in in the areas of high deprivation and low health spending.(Rudd et al., 2020b). 46% of all sepsis-associated deaths in 2017 were associated with an underlying non-communicable or injury-related cause, and this proportion increased as deprivation fell.

The background to sepsis research in New Zealand

In lieu of any original studies specifying sepsis outcomes in New Zealand, some conclusions can be made about the *likely* importance of sepsis by studying i) intrinsic health factors known to contribute to incident sepsis, ii) hospitalization data relating to infectious disease and iii) the epidemiology of specific infections known to cause sepsis. The clustering of epidemiologic risk factors coupled with the high incidence of infectious disease in New Zealand suggest that sepsis and its associated morbidities are common. Despite the face validity of this assumption, remarkably little is known about the cause, distribution, clinical features, cost, and outcomes of the sepsis syndrome here, nor whether sepsis outcomes can be improved in our acute health settings.

The intersect of infection and chronic co-morbidity

In attempting to explain inexorable rises in the incidence of infectious disease hospitalisation, Baker *et al* make reference to (and ultimately criticise) a dominant discourse on the cause of human morbidity and mortality: Omran's transition theory. Omran's work described great ages of human morbidity, leading from "pestilience and famine", through "receding pandemics" to "degenerative and man-made diseases".(M. G. Baker et al., 2012a; Mackenbach, 1994) By the time of Omran's writing in the early 1970s, vaccination, sanitation, nutrition, and antimicrobial therapy had substantially controlled epidemic infectious diseases. Healthcare investments in high-income settings transitioned to management of residual, chronic morbidities such as cancer and cardiovascular disease.(Lakdawalla et al., 2010) These changes were met with great optimism at the time. For example, in a much-repeated quote misattributed to the US Surgeon General William Stewart, it was "time to close the book on infectious diseases and declare the war against pestilence won".(Spellberg & Taylor-Blake, 2013) Stewart in fact correctly identified that static mortality rates from 1950 were due to i) residual morbidity due to infection, following spectacular gains in survival following the introduction of antibiotics and 2) the rise of chronic disease and accidents as "the great undertone of mortality".(Spellberg & Taylor-Blake,

2013) Omran's transition theory recognised the former but not the latter.(Mackenbach, 1994) In his view, infections were seen as random events belonging to a previous age, unrelated to other morbidities, receding into history as chronic, degenerative disease and frailty exacted their toll on human existence.

This view is now being seriously challenged. Testing whether chronic morbidities are associated with an increased risk of infection and sepsis, Wang and colleagues evaluated predictive risk factors for sepsis admissions in a large, longitudinal cohort of adults living in the United States. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort was recruited preferentially from the south-eastern states of the United States with high stroke incidence. By substituting hospital admissions with stroke for admissions with sepsis, the association of pre-sepsis factors with incident sepsis could be tested, and a risk score derived from this information.(H. E. Wang et al., 2012)

Using the Sepsis-1 definition of sepsis (admission with infection and the systemic inflammatory response syndrome), traditional risk factors for cardiovascular morbidity were found to substantially account for incident sepsis risk. Refinement of the study to include only patients with sepsis and organ dysfunction (ie severe sepsis) allowed a risk score to be tested in non-REGARDS longitudinal cohorts, amounting to 25,000 adults followed for over a decade.(H. Wang et al., 2018) This work suggests that a 60 year old male diabetic with stage III chronic kidney disease would have a "medium" 10 year risk of severe sepsis of 12%, or 3 times the rate of the referent population. Plasma markers of chronic inflammation (Cystatin-C, CRP and albumin to creatinine ratio) are included in this predictive score, suggesting that vulnerability to sepsis correlates with a predisposition to inflammatory and endothelial damage in the host.(H. E. Wang et al., 2013a)

Although "aggressive" targeting for sepsis prevention using these scores has not been studied, the finding that traditional non-communicable disease endpoints elevate sepsis risk is an important observation, given its implications in ageing populations with high rates of co-morbid risk factors. The burden of chronic non-communicable disease in New Zealand has been well reviewed elsewhere, at a time when the concept of international disease "syndemics" is gaining

popularity and relevance.(Swinburn et al., 2019) A syndemic refers to the aggregation of two or more diseases in a person or a population that interact and amplify disease outcomes.(University of Otago, 2021) In New Zealand, the accumulation of chronic co-morbid illness is well documented, concentrating in the same populations which experience high rates of infectious disease.(Steyn N et.al., 2021) Confluent increases in rates of comorbidity and infectious disease therefore set the scene for a significant growth in sepsis cases.

Finally, the study of associations between comorbidity and sepsis have the potential to generate surprising findings. For example, it has been shown that increased waist circumference increases the risk of sepsis, but that obese patients have higher survival following a sepsis event.(H. E. Wang, Griffin, et al., 2013; S. Wang et al., 2017) This "obesity paradox" has also been observed in patients with acute coronary syndrome, raising the possibility that shared protective mechanisms underlie this observation.(P. Y. Ng & Eikermann, 2017; Niedziela et al., 2014; S. Wang et al., 2017)

Infectious disease hospitalisation data

Baker *et al* explored rates of admission to New Zealand hospitals with infectious diseases between 1989 and 2008 using ICD-9 and ICD-10 discharge codes submitted to the National Minimum Data Set (NMDS).(M. G. Baker et al., 2012a) "Serious infection" in this study was based on the need for hospitalization rather than on specific clinical findings or the presence or absences of sepsis. Infectious diseases were also included which were attributed as underlying (rather than immediate or intermediate) causes of disease. For example, cervical cancer admissions were included due to the close link to infection with human papilloma virus. Therefore, whilst the population reported in this study is not a proxy for sepsis, important trends were reported which serve as a basis for concern that the impact of sepsis may be growing disproportionately in New Zealand.

Baker and co-authors revealed that between 1989 and 2008, there was a 44% relative increase in all-cause hospitalization but a 76% relative increase in admissions attributed to infectious

diseases.(M. G. Baker et al., 2012b) Infectious diseases were the most common cause of hospital admission in 2008, with important rate differences based on age, ethnicity, and exposure to socioeconomic deprivation. Across all age groups, the most common infection-related causes of admission were lower respiratory tract infection, enteric, and skin and soft tissue infection. With respect to age, the admission rate ratio comparing those over 70 with the 15–29-year age group grew from 2.9 to 4.1. With respect to ethnicity, the age standardized rate ratios for Māori and Pacific populations (compared with "European and other") were 2.15 and 2.35 respectively. The impact of ethnicity was most noticeable in the highest quintile of socioeconomic deprivation. Over the whole study period the age-standardised rate ratio (ASRR) for infectious disease hospitalisation was 2.8 comparing the highest and lowest deprivation quintiles. This effect became more pronounced over time amongst people of Māori and Pacific ethnicity, such that infectious disease admissions effectively doubled over the 20 year period studied (a 78% relative increase amongst Māori, and a 112% relative increase amongst Pacific people).

If sepsis affects a relatively stable proportion of people hospitalized for management of infectious diseases, it seems likely that the incidence of sepsis will have risen over the period reported. Furthermore, the admissions reported above were *attributable* to infectious diseases, but infections are also common complications of hospital-based care. In a 2003 study reporting the cumulative results of 7 point prevalence surveys undertaken between 1996 and 1999, nosocomial infection was found in 10% of patients admitted to Auckland City Hospital with an estimated incidence of 6.3%.(Graves et al., 2003) Based on these findings and local modelling, the cost to the New Zealand healthcare system was estimated to be over $130 million annually.

Individual infectious disease epidemiology

Some infections such as rheumatic fever are entrenched in deprived, indigenous communities living in New Zealand.(Bennett et al., 2021; Oliver et al., 2021) This is likely to be due in large part to changes in the availability, cost and quality of housing.(M. Baker et al., 2010) Colonisation and transmission of Group A streptococcus (the causative agent of rheumatic fever) is associated with household overcrowding.(Carapetis et al., 2005) This, and the effects of poor

housing on health across lifespan are well documented in seminal papers by New Zealand-based researchers. For example, Professor Phillipa Howden-Chapman's group has documented how poor housing contributes to ill-health in childhood, and that direct interventions to improve housing conditions reduce childhood hospitalisation.(Fyfe et al., 2020) In a multi-year epidemic of *Neisseria meningitidis* serogroup B, Baker et al demonstrated that household overcrowding, second-hand smoke exposure and respiratory illness were strongly associated with disease.(M. Baker et al., 2000, 2001) Expanding this observation to a collection of infections with shared risk factors for transmission, termed 'close contact infectious diseases' (CCID), the same author demonstrated that CCID made up the bulk of infectious disease admissions, and that half of these were respiratory infections. Over the period reviewed, rates of CCID admissions climbed steadily to account for 10% of hospital admissions by 2008.(M. Baker et al., 2010)

The high and rising rates of skin and soft tissue infection in the *same* disadvantaged indigenous populations points again to the disproportionate burdens of infectious disease in New Zealand. *Staphylococcus aureus* and group A beta-haemolytic streptococci are the principle agents of skin and soft tissue infection (SSTI). Hospitalisation rates for childhood SSTI almost doubled between 1990 and 2007.(O'Sullivan et al., 2011) In all age groups from 2000 to 2011, the rate of hospitalization with *S.aureus* SSTI rose by 5% per year, from 81 to 140 per 100,000 population. This was driven by admissions amongst Māori and Pacific people living in the upper North Island, whose age-standardized rate ratios approximated 3 and 5 times those of other ethnicities.(Williamson et al., 2013). In 2006, defined by the prospective identification of Group A *Streptococcus* (GAS) in normally sterile tissues, the incidence of invasive Group A streptococcal disease (iGAS) in the greater Auckland region was 8.1/100,000 overall but 20/100,000 and 24/100,000 amongst Māori and Pacific people respectively, with 50% of cases arising in people living in the highest quintile of socioeconomic deprivation.(Safar et al., 2011)

In addition to gradients in incident risk from north to south, by ethnicity and by deprivation, GAS strain typing identifies different patterns of colonization and disease at a molecular level. For example, Williamson *et al* compared GAS isolates in a population of high risk children living in South Auckland, with those identified in a low-risk population living in Dunedin.(Williamson et al., 2016) Using community-based collection of skin and pharyngeal

isolates coupled with GAS typing based on the M protein gene (*emm*), Auckland-based children were shown to have a much higher proportion of skin-trophic *emm*-pattern D/D4 in both skin *and* pharyngeal isolates, suggesting specific spread of these clones within populations which share other risk factors for close-contact infectious diseases. Incidence of acute rheumatic fever (ARF) is plausibly linked to the incidence of iGAS (Williamson et al., 2016) The incidence of first episode of ARF was 3.4 per 100,000 over the period 2000-2018.(Bennett et al., 2021) 94% of these cases were amongst Māori and Pacific people <30 years old. The highest age-specific rate was 80 cases per 100,000, seen in children of Pacific ethnicities between the ages of 5-14 years. ARF increases vulnerability to endocarditis or infection complicating corrective cardiac surgery.(Wilson et al., 2008)

Similar patterns of disproportionate incidence have been observed for pneumococcal disease in adults and children.(Eichler et al., 2019; Milne & vander Hoorn, 2010) In effect, New Zealand appears to be divided by ethnicity into indigenous and Pacific Island immigrant populations who experience rates of infection similar to those seen in low to middle income countries, and others that enjoy outcomes aligned with those documented in high income economies.(Steyn et al., 2020) Various strands of evidence therefore point to the potential for sepsis incidence to be high and increasing in New Zealand, a country whose infectious disease epidemiology starkly demonstrates the inequities in health outcomes which persist for indigenous and Pacific communities.

Summary

As a poorly defined, intermediate cause of morbidity and mortality, the sepsis syndrome is under-recognised and under-reported in health statistics. This under-reporting and under-recognition mean that sepsis is poorly prioritised in the planning and provision of health services. Data specific to New Zealand are lacking. This highlights the need to provide reliable data on sepsis admissions, and to use this to inform the provision of health services. This is especially important given the rising tide of infections linked to socioeconomic deprivation and the association of ageing and chronic morbidity with sepsis risk.

Chapter 3: Programme of Research

Thesis Aims and Overview

The data presented in this thesis were collected during research and quality improvement activities undertaken in my role as a clinical infectious disease and acute medicine physician working in two countries, New Zealand and Singapore. The first part of the thesis, reported in Chapters 4 to 6, was undertaken in post-Fellowship physician training in clinical infectious disease, and involved describing the epidemiology and outcomes of disease caused by *Staphylococcus aureus* and by the genus *Fusobacterium*. This work involved poring over hundreds of individual clinical records, all detailing the individual impacts of infection on people, their families and on whānau (in Māori culture, an extended network of family and kin). Sepsis, severe morbidity, and mortality were commonly described. It was not the purpose of these studies to describe it, but many cases were associated with delays in presentation, recognition, and appropriate antimicrobial therapy.

In response to this, I became interested in how recognition and response to acute illness might be improved by prioritisation of care based on clinical findings. Chapter 7 describes work exploring how baseline assessment at admission to hospital might be used to predict outcomes in a population of patients admitted to a general medicine service. During this work I was struck by the potential for improvements in the acute recognition of severe disease to improve longer term outcomes. As an infectious disease physician, sepsis lay at the natural intersect of infection and this work on acute assessment, leading to further work in this area.

Returning to a position in New Zealand, I undertook the first study attempting to describe the incidence of sepsis in the Waikato region. This work is presented in Chapter 8 and formed the basis of further work aiming to systematically reorganize, improve, and evaluate sepsis care in Waikato District Health Board facilities. The “Raise the Flag” programme was the first whole-

of-system sepsis quality improvement intervention conducted in a New Zealand healthcare setting. Its impact is assessed in Chapter 9. In both chapters, the effect of health inequity in New Zealand is observed, with Māori presenting more frequently with sepsis, and at a younger age.

Finally, recognizing the need to quantify various dimensions of societal impact, the national burden of sepsis was explored in relation to the costs of acute in-patient care, as reported in Chapter 10. Taken together, Chapters 9 and 10 provide clinical validation of an administrative method for the measurement of adult sepsis in New Zealand hospitals.

In summary, this thesis reports a stepwise enquiry into the nature and frequency of severe infection and sepsis in New Zealand, with the following aims:

1. To investigate the epidemiology of severe infections and associated outcomes
2. To investigate risks for poor clinical outcome in hospitalized adults
3. To determine whether sepsis outcomes can be improved in acute care settings
4. To describe the epidemiology and cost of sepsis to New Zealand

My role

I had the following roles in the development of this work:

- Involvement in all aspects of study design, execution, and reporting, either under supervision (Chapters 3 to 5) or as a lead investigator (Chapters 6 to 9).
- Conducting literature reviews, either to frame this thesis and/or as part of writing papers for publication (Chapters 3 to 7)
- Submitting ethics applications
- Developing guidelines and resources for clinicians, patients and whānau (Chapter 8)
- Collecting, managing, cleaning, coding and analysis using data management tools and statistical software packages

- Ensuring that this work contributes to the health and wellbeing of New Zealand and New Zealanders, through advocacy and awareness (www.sepsis.org.nz)

Chapter 4: Population-based epidemiology of *Staphylococcus aureus* bloodstream infection in Canterbury, New Zealand

Abstract

Aim: To describe longitudinal incidence of *Staphylococcus aureus* bloodstream infection (SABSI) in a region of New Zealand with low MRSA prevalence.

Methods: Blood cultures growing *S.aureus* were identified from hospital laboratories between 1 July 1998 and 30 June 2006. Record linkage was used to combine information from local and national databases into a single patient event record. Information from the New Zealand census was used to determine regional incidence of disease. An address-based measure of deprivation was used to analyse the relationship between incidence and socioeconomic status. Morbidity data were not collected.

Results: 779 patients with SABSI were identified (482/779 (62%) male, 297/779 (38%) female). The crude incidence of *S.aureus* bacteraemia varied between 18.5–27.3/100 000 per annum. Three of 779 isolates (0.4%) were MRSA. Two hundred and seventy-seven of 776 (36%) patients with complete records had hospital-acquired SABSI. One hundred and forty-one of 778 patients (18%) died within 30 days and 235/778 (30%) died within a year. Proportional hazards survival models significantly associated age, male sex and more than 14 days of hospitalization in the year prior to index culture with adverse outcome. Higher socioeconomic status was associated with lower rates of SABSI (adjusted rate ratio 0.74, 95% confidence interval: 0.56–0.98, p=0.007 after adjustment for age and sex, and comparing the highest and lowest deprivation quintiles).

Conclusion: Population factors significantly influence SABSI incidence and survival. Further research is required to determine whether these have the potential to invalidate inter-hospital comparison of SABSI incidence as a measure of health-care quality.

Introduction

SABSI is a major cause of infectious morbidity in high income countries.(Gould, 2006; Laupland & Church, 2014) Significant and sustained increases in SABSI occurred from the 1960s onwards in association with changes in health-care delivery. (P. Collignon et al., 2005; Steinberg et al., 1996; Wyllie et al., 2006) In particular, vascular catheter-associated SABSI persists as a significant cause of health care-associated infection despite increased awareness of this problem. (P. Collignon et al., 2005; Steinberg et al., 1996) Where prevalent, methicillin resistant *S.aureus* (MRSA) appears to contribute directly to increases in hospital-acquired SABSI (HA-SABSI).(Wyllie et al., 2006) Similar SABSI incidence estimates have, however, been obtained from areas of both high and low MRSA prevalence. (P. Collignon et al., 2005; Lyytikäinen et al., 2005; Wyllie et al., 2006) Surprisingly, few studies report longitudinal population-based data, which might illuminate trends or the effect of demographic factors on incidence.

To address this, we undertook a retrospective population-based study in our region of New Zealand (NZ) to determine the following: (i) yearly incidence of community and HA-SABSI between 1 July 1998 and 30 June 2006 analysed by age, sex, ethnicity and a census-based measure of socioeconomic status and (ii) mortality following SABSI.

Methods

Data sources and population at risk

The Canterbury District Health Board (CDHB) provides comprehensive publicly funded health care to a population of approximately 478 000 people, 74% of whom live in the regional centre of Christchurch (NZ Census data, 2006). Acute secondary and tertiary level services in all specialties of medicine and surgery (excluding heart, lung and liver transplantation) are based at Christchurch Hospital. A number of other facilities is maintained by the CDHB, which provide elective, rehabilitative, and psychiatric services. Ashburton Hospital, to the south of

Christchurch, is the only sizeable secondary care facility outside the city limits. Local private hospitals do not offer emergency inpatient care.

Centrally maintained patient administration systems have been used to collect comprehensive, standardized demographic details for all patients on admission to CDHB facilities since 1 July 1997. Records are linked with national mortality data distributed by the New Zealand Health Information Office (Wellington). Canterbury Health Laboratories performs all blood cultures for the CDHB using automated techniques and maintains a computerized record of all positive blood culture results. Two other laboratories in the region offer automated blood culture to primary care and private health facilities. One (Southern Community Laboratories) contracted this service to a CDHB geriatric unit from 1998 to 2001 and provided blood culture records for this period.

The New Zealand Deprivation index (NZDep) is a geocoded census-based measure, which represents a weighted composite of nine variables reflecting socioeconomic status.(Salmond et al., 2006) In 2006, these were (in order of decreasing weight): (i) people aged 18–64 years receiving a means tested benefit, (ii) people living in equivalized households with income below an income threshold (equivalization controls for household composition), (iii) people not living in own home, (iv) people <65 years in a single parent family, (v) people aged 18–64 years unemployed, (vi) people aged 18–64 years without any qualifications, (vii) people living in equivalized households below a bedroom occupancy threshold (a measure of living space), (viii) people with no access to a telephone and (ix) people with no access to a car. Census meshblocks are geographical units defined by Statistics New Zealand each of which contains a median of 90 people. At census, meshblocks are grouped into Census Area Units. The NZDep index attributed to each Census Area Unit, from 1 to 10, divides NZ into deciles of deprivation with 1 being least deprived and 10 being most deprived.(Salmond et al., 2006)

Estimates were obtained for the CDHB population by sex and 5-year age group on 30 June of each study year (supplied by Statistics New Zealand). Population by age and sex within each NZDep decile was obtained from 2001 and 2006 census results (Public Health Intelligence, Health and Disability Systems Strategy Directorate, Ministry of Health, Wellington, New Zealand).

Data collection and definitions

All patients with at least one blood culture growing *S.aureus* during the study period were identified from the laboratory database. The administrative database was then used to determine the following for each patient: age at index culture, sex, ethnicity, number of inpatient days spent in CDHB hospitals in the year preceding index culture, duration of index hospitalization, details of admitting specialty and date of death if recorded. Cause of death could not be determined. Each patient was assigned an NZDep decile by combining their last recorded address with Census Area Unit data from the 2001 census. Institutionally licensed software (Excel and Access for Microsoft Windows, Microsoft, Seattle, WA, USA) was used to create a single patient event record.

Index blood culture (and hence the index episode of SABSI) was defined as the first isolate yielding *S.aureus* from a patient's blood during the study period. Each patient was included once only, but note was taken of recurrent SABSI, defined as a blood culture growing *S.aureus* more than 3 months after the last positive blood culture. In the absence of clinical and strain typing data this time interval was arbitrarily chosen to separate discrete bacteraemic episodes from cases of early treatment failure. HA-SABSI was defined as an index culture (i) occurring in hospital more than 48 h after admission or (ii) within the first 48 h of admission for patients previously discharged from hospital within 7 days.(Lyytikäinen et al., 2005) Community-acquired SABSI (CA-SABSI) was defined as an index culture occurring less than 48 h after admission without record of prior hospitalization within a 7-day period. Within this group the term health care-associated community onset staphylococcal infection (HA-COSI) was applied to cases of SABSI of community onset occurring in a patient with a documented admission to hospital in the preceding year.(Morin & Hadler, 2001) Four ethnic groups were described using the primary ethnicity listed in administrative data; NZ Māori, Pacific Island, NZ European and Other. Time until death was defined as the number of whole days between index blood culture and the date of death recorded in the hospital administration database.

Incidence rates were calculated by financial year. Incidence was calculated as the first event of SABSI divided by the estimated mid-study year population. The study was approved by the Ministry of Health Upper South A Regional Ethics Committee.

Statistical analysis

Poisson regression was used to model SABSI rates by 5-year age group, by sex and either (i) year of episode or (ii) NZDep score. Census Area Unit data were only available for census years, with 183 surveyed in 2001 and 196 in 2006. The deprivation deciles were grouped into quintiles for analyses, the first quintile representing the least socio-economic deprivation over time. In calculating incidence by NZDep, adjustment had to be made for changes in the denominator both in increasing population size and proportionate changes in deprivation. Deprivation quintiles were therefore used instead of deciles to minimize these differences. Population estimates were available for each study year, but NZDep data only for census years (2001 and 2006). In the model, 2001 NZDep data were therefore used in calculating incidence for the first 5.5 years of the study and 2006 NZDep data for the remainder. Incidence was modelled using 18 age categories. For analysis of patient data alone categorical variables were analysed using chi-squared tests for contingency tables. Survival analysis used Kaplan–Meier curves and proportional hazards models. Modelling was carried out using SAS 9.1 (SAS Institute Inc., Cary, NC, USA) PROC GENMOD, PROC LIFETEST and PROC PHREG.

Results

Incidence of SABSI

A total of 905 separate cultures from 779 patients was identified. In 161/779 cases (21%), penicillin-sensitive *S.aureus* was identified, and 3/779 (0.4%) were MRSA. The laboratory records of one female patient could not be linked to the administrative database. Selected demographic characteristics and mortality rates among the remaining 778 patients are shown in Table 4.1. The crude incidence rates per 100 000 for each year were: 18.5, 27.3, 27.3, 19.3, 17.0, 21.9, 20.3, and 21.1, with an overall rate of 21.5 over the whole period. There were 482/778 male patients (62%) and 297/778 female patients (38%). The median age of the cohort, as a whole, was 64 years (range, 0–98). There were 46/778 patients (6%) of Māori descent and 15/778 (2%) of Pacific Island descent. Twenty-nine episodes of recurrence occurred in 23/778 patients (3%).

Figures 4.1 and 4.2 show crude summary and annual incidence of SABSI per 100 000 persons. An apparent peak in incidence of SABSI occurred in the year 2000–2001, which was most noticeable among elderly patients because of their higher rates (Fig. 4.2). In Poisson regression models, SABSI rates fell significantly after this time ($c2 = 5.03$, d.f. = 1, $P = 0.02$ for 1999 and $c2 = 4.66$, d.f. = 1, $P = 0.03$ for 2000 across all age groups compared with 2005). Age was very strongly related to incidence. Male patients had higher rates than female patients in all age groups ($c2 = 89.71$, d.f. = 1, $P < 0.0001$). In spite of an apparent slight trend for higher rate ratios between sexes in older age groups, this was not statistically significant ($c2 = 23.08$, d.f. = 17, $P = 0.15$).

Hospital and community acquisition

A complete record could not be created for 3/779 patients (0.4%) because the patient either could not be identified in the administrative database or had never been admitted to a CDHB facility. Of the 776 patients with a complete record, 277/776 (36%) had HA-SABSI (Figure 4.3). In this group, the index culture was obtained more than 48 h after admission in 201/277 (72%) cases. Of

the 76 remaining cases of HA-SABSI, 66/277 (24%) had been discharged from a regional hospital within seven days and 10/277 (4%) had been transferred between institutions. CA-SABSI occurred in 499/776 patients (64%) among whom 254/449 (51%) had HA-COSI.(59) Thus, by the definitions used in this study, 531/776 (68%) patients had hospital or health care-associated bacteraemia.

The 10 services with the highest rates of nosocomial bacteraemia per 1000 bed-days are shown in Table 4.2.

Mortality

Survival curves following SABSI by age and prior hospitalization are shown in Figures 4.4 and 4.5. Cumulatively, 141/778 patients (18%) died within 30 days of their index blood culture and 235/778 (30%) died within a year. Case fatality increased with age. Relating individual deaths to population data, the average annual 30-day mortality rate associated with SABSI was 3.9 per 100 000 population. However, this varied from 0.6 per 100 000 population aged under 55 to 34.2 per 100 000 population aged 75 years and over.

Figures 4.4 and 4.5 show Kaplan–Meier curves for survival by age group and by bed-days in hospital in the previous year. In a proportional hazards survival model with age (11 decade categories), sex and bed-days, all three predictors were significantly associated with mortality. There was almost a 100-fold increase in the hazard ratio with age, comparing those aged 0–9 years with those aged 85+ years (Hazard Ratio (HR) = 0.008, 95% confidence interval (CI): 0.001–0.061, c2 = 22.4, P < 0.0001). Even those aged 80–84 years were significantly less likely than those aged 85+ years to die (HR = 0.68, 95% CI: 0.47–0.97, c2 = 4.5, P = 0.03). Compared with those with 0 bed-day in the previous year, the hazard of death did not increase significantly for those with 1–7 days (HR = 1.1, 95% CI: 0.8–1.5) or 8–14 days (HR = 1.2, 95% CI: 0.9–1.8), but was higher for those with 15–30 bed-days (HR = 1.8, 95% CI: 0.8–1.5, c2 = 11.8, P = 0.0006) or 31 days or more (HR = 2.6,, 95% CI: 1.9–3.7, c2 = 31.2, P < 0.0001). Women were less at risk of death than men (HR = 0.7, 95% CI: 0.6–0.9, c2 = 8.3, P = 0.004).

To aid comparison of patient survival with that for the general population, further survival analysis was carried out on those patients who survived 30 days after their first culture. Although no detailed regional data are available, the average 1-year survival for 80-year-old NZ adults in the general population is 92.9% in men and 95.5% in women (Statistics New Zealand). For male patients aged 75–79 and 80–84 years surviving 30 days after index blood culture, subsequent 1-year survival was 66.8% (standard error (SE) = 7.7) and 72.0% (SE = 9.0) respectively. For women, respective rates in these groups were 79.3% (SE = 7.5) and 62.4 (SE = 9.7).

Effect of socioeconomic deprivation on SABSI incidence and mortality

SABSI incidence and crude rate ratios between NZDep quintiles are shown in Table 4.3. After adjusting for age and sex, the incidence of SABSI in the least deprived NZDep quintile was significantly lower than the most deprived quintile (adjusted rate ratio 0.74, 95% CI: 0.56–0.98, P = 0.007). There was no linear increase in incidence across quintiles and no effect of NZDep quintile on mortality was observed in regression models.

Table 4.1 Selected demographic characteristics of 778 patients with *Staphylococcus aureus* bloodstream infection.

Characteristic	Category	n(%)	Average rate/10^5/year	Relative Risk
Sex	Male	482 (62)	27	1.7
	Female	296 (38)	15.8	1.0
Age (years)	0-14	89 (11)	12.6	1.3
	15-54	210 (27)	9.9	1.0
	55-74	235 (30)	39.6	4.0
	>75	77 (32)	34.2	5.77
Ethnicity	Non-Māori	717 (92)	21.5	1.2
	Māori	46 (6)	17.9	1.0
	Pacific Island	15 (2)	23.08	1.3

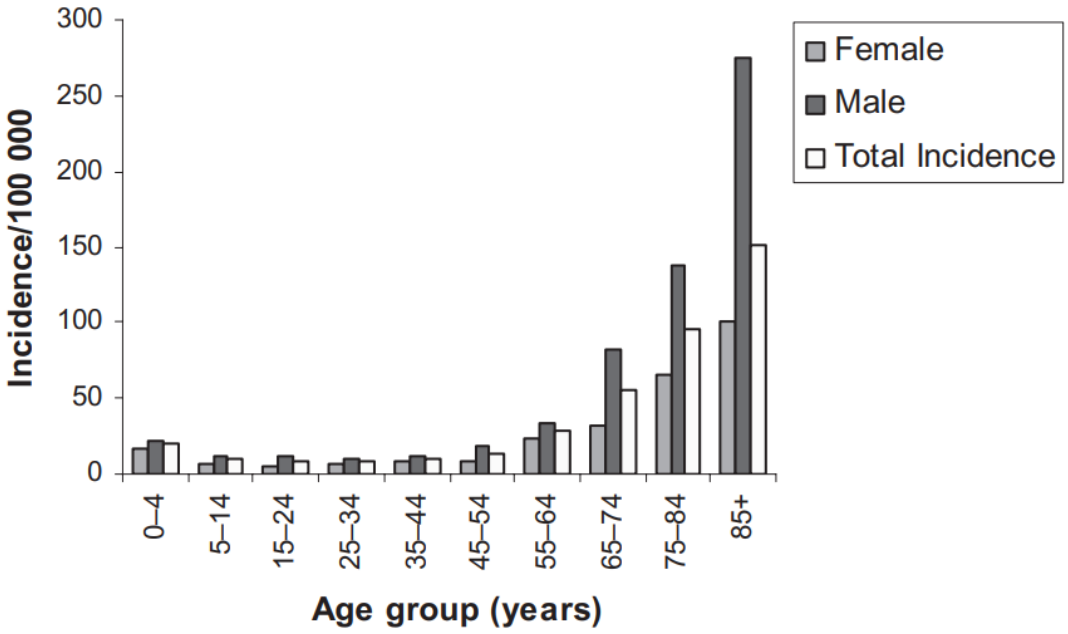


Figure 4.1 Incidence of *Staphylococcus aureus* bloodstream infections in Canterbury by sex and age group.

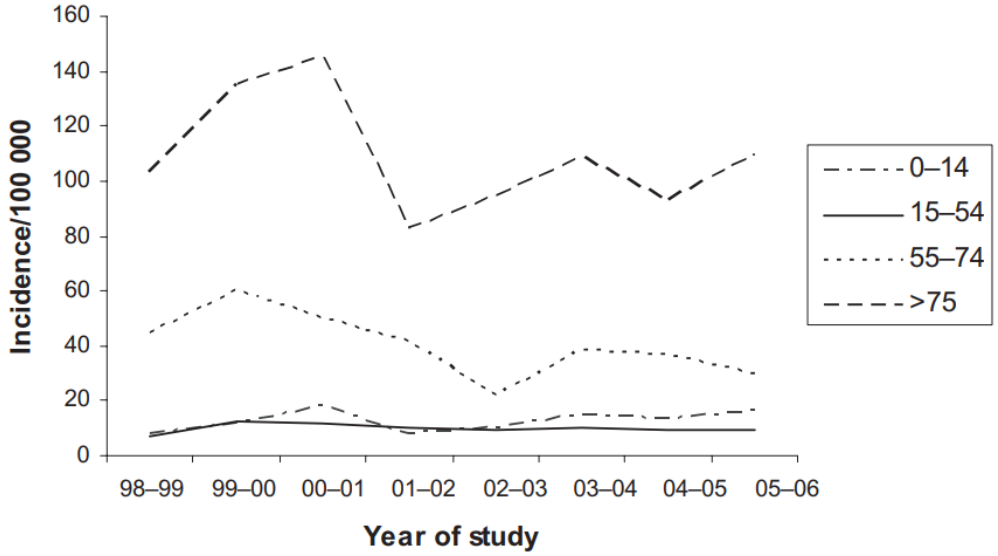


Figure 4.2. Incidence of *Staphylococcus aureus* bacteraemia in Canterbury by age and year of study.

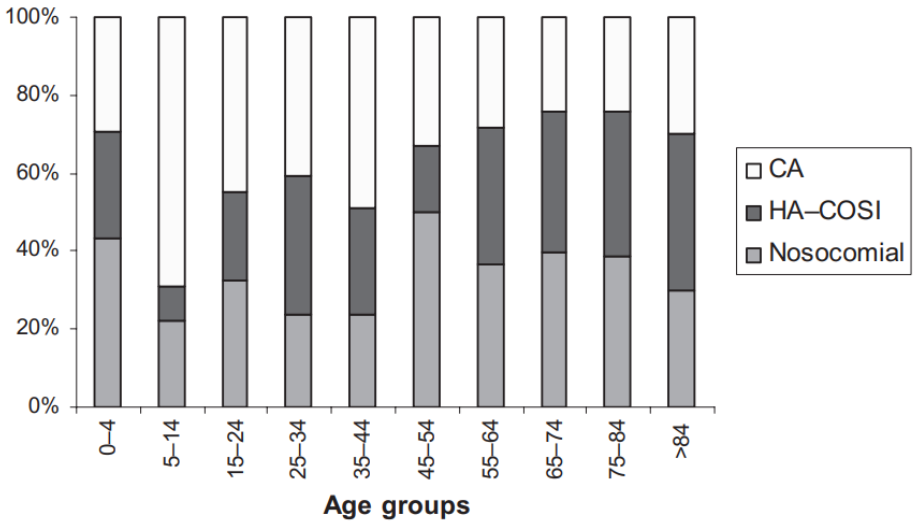


Figure 4.3. Proportion of *Staphylococcus aureus* bacteraemia cases by age and mode of acquisition.

Abbreviations: CA, community-acquired; HA-COSI, health care-associated community onset staphylococcal infection; Nosocomial, hospital-acquired bloodstream infection.

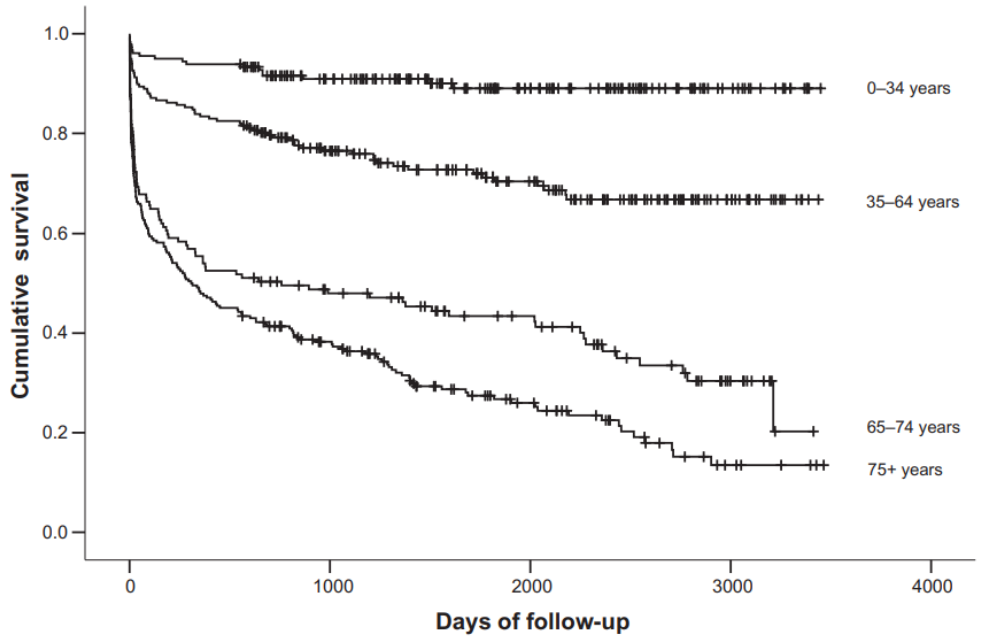


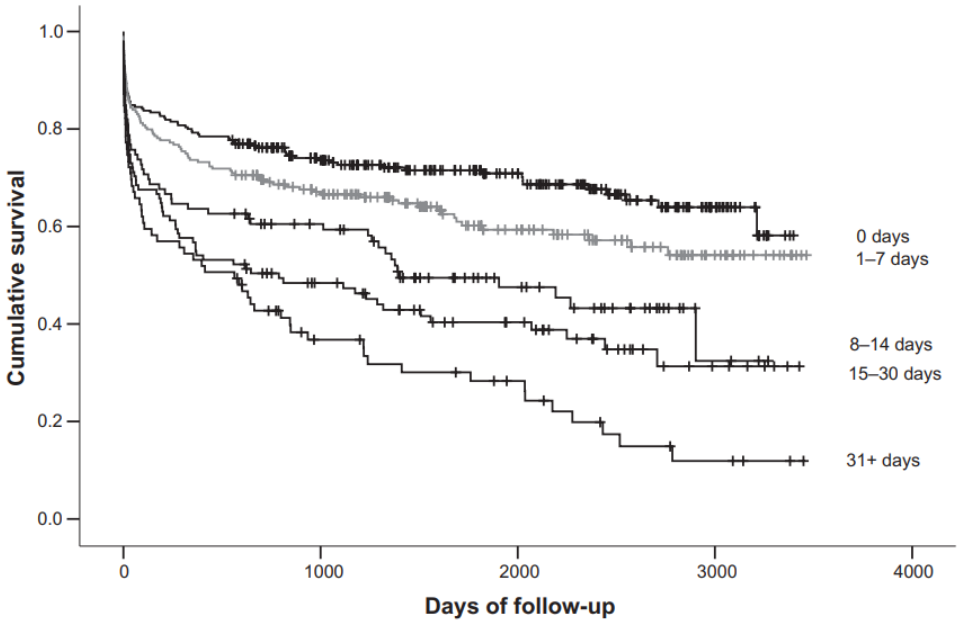
Figure 4.4. Survival following *Staphylococcus aureus* bacteraemia by age.

Vertical lines indicate censored data.

Table 4.2. Rate of nosocomial *Staphylococcus aureus* bloodstream infection per 1000 bed-days in Canterbury hospitals between 1998 and 2006.

Department	Bed-days	SABSI (hospital-acquired†)/1000 bed-days
Intensive care	23170	30.2
Haematology	31260	9.66
Cardiothoracic surgery	23018	7.99
Paediatric surgery	13018	7.6
Gastroenterology	13440	5.65
Neurosurgery	48020	4.56
Neurology	27351	4.53
Nephrology	16128	3.53
Neonatology	93558	3.47
Long term care (rural)	23658	3.39

†Hospital-acquired= S.aureus growing in blood culture more than 48 h after initial admission to hospital



Vertical lines indicate censored data.

Figure 4.5. Survival following *Staphylococcus aureus* bacteraemia by days of hospitalization in the year prior to index culture.

Table 4.3. Incidence of *Staphylococcus aureus* bloodstream infection by New Zealand Deprivation Index Quintiles.

New Zealand Deprivation Index Deciles†	Rate per 100,000‡	Unadjusted rate ratio (95% CI)	Adjusted rate ratio§ (95% CI)
1 & 2 (least deprived)	16.0	0.75 (0.57-1.0)	0.74 (0.56-0.98)
3 & 4	20.8	0.98 (0.75-1.28)	0.88 (0.67-1.15)
5 & 6	27.7	1.3 (1.0-1.7)	1.13 (0.86-1.47)
7 & 8	25.6	1.2 (0.92-1.57)	1.08 (0.82-1.41)
9 & 10 (most deprived)	21.3	1.0	1.0
Overall test (χ^2, d.f., p)		29.90, 4, <0.0001	19.2, 4, 0.0007

†Small area index based on Census Area Units (CAU). Patient allocated to decile by domicile. ‡n=773. Four gave overseas addresses, one came from a CAU without a deprivation value and one gave no domicile.
§Adjusted for age (18 5-year age categories) and sex. 95%CI, 95% confidence interval

Discussion

This study provided useful insights into the contemporary effects of demography, deprivation and hospitalization on the epidemiology of SABSI in a population in which MRSA bacteraemia is infrequent. Our main findings are as follows: (i) CDHB rates of SABSI were comparable with internationally reported rates, (ii) hospital- and health care acquired SABSI were major contributors to SABSI incidence, (iii) SABSI was shown to be a condition of high short-term and 1-year mortality which, to the limit of our ability to control for confounding variables, was higher with increasing age and more than 14 days of prior hospitalization and (iv) relating our results to other studies showed significant regional variation in SABSI which, we believe related primarily to differences in population structure.

The incidence of SABSI in this population averaged 21.6 per 100 000. (P. Collignon et al., 2005; Hill PC, 2001; Lyytikäinen et al., 2005; Morin & Hadler, 2001) National estimates of SABSI incidence in the contemporary literature ranged from 17 to 41 per 100 000. National studies in countries of low MRSA prevalence report increases in SABSI incidence into the present decade. (Lyytikäinen et al., 2005) In contrast, rates of SABSI fell in the CDHB over the period studied from a peak of 27.3 to 21.1 at study end. Monitoring SABSI incidence at a regional level therefore revealed fluctuating rates and a fall in incidence not mirrored in the international literature.

HA-SABSI accounted for 36% of cases recorded over the study period. The average hospital-only costs of intravascular catheter-associated SABSI were calculated to $US36 300 by Chu et al. in 2005.(Chu et al., 2005; Thomas & Morris, 2005) Extrapolating from this, we estimate that 79 cases of HA-SABSI occur each year in the South Island of New Zealand (population 1 million), incurring at least 4.8 million NZ dollars in direct costs alone. Efforts to reduce HA-SABSI, particularly as a result of intravascular catheter-associated infection, must remain paramount in the activities of researchers, clinicians and infection control practitioners.(Thomas & Morris, 2005)

The association we found between individual mortality following SABSI and bed-days occupied in the preceding year has not previously been reported. Compared with patients without documented hospital admission prior to presentation, the HR for death increased from 1.8 to 2.6 in patients with 15–30 and 31 days of hospitalization respectively. It is well known that age and comorbidity are significantly associated with hospitalization and poor outcome following SABSI.(Laupland & Church, 2014; Lesens et al., 2003) This alone might adequately explain our observations but for the results of two other studies. Wyllie et al. reported a risk of HA-SABSI due to MRSA in proportion to duration of hospital admission.(Wyllie et al., 2006) In a study from the Netherlands (in which MRSA occurred in only 0·03% of isolates tested), 24% of patients were colonized with *S.aureus* at admission to hospital.(Wertheim et al., 2004) These patients were three times more likely than non-colonized patients to develop HA-SABSI and were bacteraemic with colonizing strains 80% of the time. However, all-cause and SABSI-specific mortality was significantly higher in the non-colonized group, in which the time from hospital admission to bacteraemia was also longer. In summary, prolonged hospitalization seems to increase the chance of *de novo* colonization and infection with hospital-associated strains of *S.aureus*. This is likely to contribute to detrimental outcomes in vulnerable populations.

We showed an association between high socioeconomic advantage and lower adjusted rates of SABSI. Although the effect of deprivation on SABSI could only be demonstrated between the highest and lowest socioeconomic quintiles in our region (Table 4.3), these findings are of significance. An earlier study of SABSI combining the populations of Auckland and Christchurch reported an incidence of 41 per 100 000, almost double that observed here. Age-adjusted incidence rates per 100 000 were 22, 32 and 91 in NZ European, Māori and Pacific Island populations respectively.(Hill PC, 2001) No separate incidence was quoted for the CDHB area. However, the fact that the average yearly incidence of SABSI in the CDHB (21.6 per 100 000) almost exactly matches that for people of NZ European ethnicity in two distinct population centres suggests that SABSI incidence is significantly driven by population structure.

The Māori and Pacific Island population of the CDHB averaged 8% across the period of this study. In Auckland, 25% of the population are of Māori or Pacific Island descent, the majority living in conditions of hardship.(Hutchinson A et al., 2006; Jensen J et al., 2006; Robson &

Harris, 2007) New Zealand's serogroup B meningitis epidemic preferentially affected these communities, in which household overcrowding and smoking were clearly associated with increased risk of disease.(M. Baker et al., 2001) We believe that socioeconomic deprivation plays a significant part in generating similar differences in SABSI incidence.(M. Baker et al., 2001; Hill et al., 2001; Hill PC, 2001; Hutchinson A et al., 2006; Jensen J et al., 2006; Robson & Harris, 2007)

There are clear links between socioeconomic deprivation and adverse health outcomes.(Berkman & Epstein, 2008) Deprivation leads to health inequalities through differences in exposure to environmental risks (such as smoking), in access to health care and often in the quality of health care received.(Robson & Harris, 2007) By these pathways, deprivation is typically associated with higher rates of cancer, poorly controlled diabetes, renal failure and alcohol abuse.(Einsiedel et al., 2008; Robson & Harris, 2007) These conditions (among others) are in turn associated with elevated risk of SABSI, often in association with necessary hospitalization and/or vascular catheter insertion.(Laupland & Church, 2014) It should not, therefore, be unexpected for deprivation to be reflected in SABSI incidence data. The Aboriginal population of central Australia provides a stark example of this. Sixty per cent of all in-hospital deaths reported in this group are infection related, and SABSI incidence approaches 200 cases per 100 000 population.(Einsiedel et al., 2008) In this context, bacteraemia rates become directly relevant to issues of public health and social policy reform. Furthermore, unless it is specifically controlled for, regional variation in population at risk (by virtue of age, ethnicity and/or low socioeconomic status) may confound efforts to use SABSI incidence as an indicator of health-care quality.

This study had several limitations. We relied on retrospectively collected data and on information from historical reports to describe regional and ethnic differences in the epidemiology of SABSI. To provide a direct comparison with an earlier study from New Zealand, we used a primary rather than a prioritised approach to the determination of indigeneity. This would have underestimated the number of people of Maori descent. It was also impossible from our data to estimate the number of blood cultures representing contamination, although this is a rare event.(A. G. Jensen et al., 2002) We did not collect data from community laboratories except where these provided services to our hospitals. This may have led to a small under-

representation of the true number of cases. An address-based measure of deprivation cannot adequately express the complex interplay of intrinsic and extrinsic determinants of health, which contribute to individual risk of SABSI. Our reliance on patient-defined ethnicity data on admission to hospital may have introduced numerator-denominator bias when combined with census-defined ethnicity, which is by multiple affiliation.(Ajwani et al., 2003) We had no clinical data from which to attribute means of acquisition of SABSI and had to use definitions of hospital and health care-associated infection that have since been superseded.(Horan et al., 2008)

Regardless of this, and in common with other studies, we demonstrated that hospital and health care-associated SABSI exact a significant toll on the community in terms of excess morbidity and mortality. Prevention of this condition should be a major priority, which attracts proportionate funding for primary research and infection control interventions. Population differences in age, ethnicity and deprivation are likely to underlie the interregional variation in SABSI incidence observed in NZ and elsewhere.(Lyytikäinen et al., 2005; Skogberg et al., 2008) Further research should focus on the effectiveness of public health interventions in reducing SABSI rates, and to what extent population factors affect schemes using mandatory SABSI reporting as a measure of health-care quality between hospitals.(P. J. Collignon et al., 2006; Skogberg et al., 2008)

In summary, *Staphylococcus aureus* is a highly pathogenic organism commonly associated with the sepsis syndrome. However, other organisms which cause invasive infection can conceptually cause severe outcomes. Fusobacteria are obligate gram-positive anaerobic bacteria which are universally sensitive to beta-lactam antibiotics. They are thought to be opportunistic pathogens, causing disease only in the setting of compromised innate immune defences. In the following chapter, the clinical features and outcomes associated with these infections are investigated as a counterpoint to the outcomes associated with SABSI.

Chapter 5: Fusobacterial infections: clinical spectrum and incidence of invasive disease

Abstract

Objectives: Clinically significant infections caused by members of the genus *Fusobacterium* are rare. We sought to describe the spectrum of clinical disease and epidemiology of these conditions presenting to an acute hospital over a five year period.

Methods: Clinical records relating to consecutive laboratory isolates of *Fusobacterium* species were reviewed and cases classified according to pre-specified definitions of primary site and invasive infection.

Results: 78 *Fusobacterium* isolates were identified, 25 of which were associated with invasive disease, most commonly in men (76% of cases). Invasive *Fusobacterium necrophorum* infection of the head and neck was not observed in patients over 50. Invasive intra-abdominal disease was not observed amongst those under 60. 2 cases of *Fusobacterium nucleatum* bacteraemia were identified in neutropenic children. One retroperitoneal abscess may have represented secondary infection due to periodontitis. Obstetric infections were the most common clinical syndromes associated with isolates from the female genital tract. The incidence of invasive head and neck disease in the population aged 15-50 was 6.7 per million/year. There was one in-hospital death recorded.

Conclusions: Invasive fusobacterial infections are rare, affect distinct patient groups and are associated with good clinical outcomes in the majority of cases.

Introduction

The genus *Fusobacterium* comprises a heterogenous group of strictly anaerobic, non-spore forming gram-negative bacilli the modern taxonomy of which includes 13 species.(Brazier, 2006; Citron, 2002; Hagelskjaer Kristensen & Prag, 2000; Lemierre A, 1936) *Fusobacterium necrophorum subspecies funduliforme* and *Fusobacterium nucleatum* (a major component of dental plaque) cause the majority of invasive infections in humans.(Bolstad et al., 1996; Brazier, 2006; Citron, 2002; Hagelskjær Kristensen & Prag, 2008b; A. Jensen et al., 2007) The most dramatic presentations of disease due to *F. necrophorum* were coherently described by Lemierre in 1936, in a dissertation dealing with clinical presentations of anaerobic septicaemias.(Lemierre A, 1936) These were typically, but not uniformly, associated with a primary focus of *F. necrophorum* infection in the head and neck accompanied some days later by ipsilateral internal jugular vein thrombosis and metastatic necrotic abscess formation. Other primary foci included the abdomino-pelvic viscera and female genital tract, with cases originating from soft tissue infections later reported by Alston.(Alston, 1955) Left untreated, these infections were almost uniformly fatal. Dramatic reductions in incidence and mortality coincided with the introduction of effective antimicrobial therapy.(Brazier et al., 2002; Hagelskjær Kristensen & Prag, 2008b)

Whilst most reports focus on severe presentations, recent clinical and laboratory studies point to a wider spectrum of human disease.(Aliyu et al., 2004; Amess et al., 2007; Batty et al., 2005; Brook, 1994; Candoni et al., 2003; Easterling T & Garite T, 1985; Ewald et al., 2006; Hagelskjær Kristensen & Prag, 2008a; A. Jensen et al., 2007; Landsaat et al., 1995) In particular, *F. necrophorum* has been identified as a frequent primary cause of infection in the head and neck, implicated in the pathogenesis of tonsillitis, paratonsillar abscess, post-anginal cervical lymphadenitis, otitis media in children and sinusitis in adults.(Hagelskjær Kristensen & Prag, 2008a) *F. nucleatum* is an unusual cause of these infections, being associated more with periodontitis, obstetric infections, brain abscess complicating periodontal disease and with bacteraemia during prolonged neutropenia. (Bearfield et al., 2002; Bolstad et al., 1996; Brook, 1994; Candoni et al., 2003; Ewald et al., 2006; Han et al., 2004; Landsaat et al., 1995; H. Liu et al., 2007; Offenbacher et al., 1996)Estimates of the incidence of these conditions have been complicated by their rarity, difficulties in recovery of anaerobic organisms, lack of consistent

case definitions and reliance on case reporting to reference laboratories.(Brazier, 2006; Brazier et al., 2002; Hagelskjaer Kristensen & Prag, 2000; Hagelskjær Kristensen & Prag, 2008b)

The principle aim of this study, having already studied the local epidemiology and clinical outcomes of SABSI, was to describe the clinical spectrum of fusobacterial infection presenting to a single tertiary level hospital. Secondary objectives were to document the regional epidemiology of invasive disease and associated in-hospital mortality.

Methods

Christchurch Hospital is the only acute tertiary hospital serving a population of approximately 480,000 living in the catchment of the Canterbury District Health Board (CDHB). The population is described in detail by a five yearly national census, and record linkage occurs to national mortality records. Consecutive isolates of Fusobacteria from any site were identified from the hospital laboratory database from 1 June 2002 to 31 May 2007. Hospital and laboratory policy throughout the period of the study was to recommend aerobic and anaerobic blood cultures for all adult patients (patients aged 15 or over). For paediatric patients anaerobic cultures were submitted at the discretion of the treating clinician. Blood cultures were incubated using the Bac-T Alert system (bioMerieux Australia PTY Ltd, Baulkham Hills, New South Wales, Australia).

Except for swabs, all clinical specimens were submitted for aerobic and anaerobic cultures after immediate transfer in sterile containers to the hospital laboratory, which is on-site and staffed 24 hours a day. Anaerobic cultures were prepared from swabs at the discretion of reception staff on the basis of anatomical site and clinical history. Anaerobic cultures were first examined after 48 h incubation. Blood cultures were incubated for up to 5 days before being reported as negative (unless prolonged incubation was specifically requested by a clinician).

Identification of Fusobacteria was based on typical gram stain and colonial morphologies, susceptibility pat-terns to selected antibiotics (erythromycin, rifampicin, colistin, penicillin,

kanamycin and vancomycin) using the An-ident Disc Identification System (Oxoid, Basingstoke,UK) and degradation of specific substrates using the RapID^{TM} ANA II System (Remel, Lenexa, KS, USA). Some isolates were further identified using 16S rRNA sequencing. Antibiotic susceptibility testing was not carried out and so beta-lactamase production in clinical isolates could not be assessed.

Local ethics committee approval was given for review of all patient case notes in the hospital medical records department. A single reviewer (P.J.H.) classified primary site and invasive infection in each case. Demographic details and microbiological findings were recorded as well as clinical information relating to the context in which samples were taken. Survival to 30 days from the date of the first positive microbiological specimen was determined from the clinical record or by record-linkage to a national mortality database.

Infections were classified by primary site into four clinical groups. These were 1) head and neck, 2) abdomino-pelvic, 3) skin and soft tissue, and 4) pleuro-pulmonary. Invasive fusobacterial infection (IFI) was defined by i) growth of a fusobacterium species in blood culture and/or ii) clinical or radiologic demonstration of thrombosis within the major venous drainage relating to the primary site of infection and/or iii) abscess formation in a structure non-contiguous with the site of primary infection or crossing tissue planes. Draining lymph nodes were considered to be a contiguous anatomical structure. Any evidence of abscess formation below the head and neck was defined as metastatic disease. Thus, a dental infection with abscess formation within a single submandibular node would be localized disease whereas pharyngitis with evidence either of internal jugular vein thrombosis or liver abscess would be classed as invasive disease. All cases of disease primary to pleura, abdomen, and pelvis, were assumed to be invasive *a priori*.

Data were entered into a spreadsheet (Excel for Windows, Microsoft, Seattle, USA) and tables based on the 2001and 2006 New Zealand census used to estimate summary and category specific incidences of IFI. Descriptive statistics were used to describe summary data and Fisher's exact test used to compare categorical variables.

Results

Clinical presentation of invasive Fusobacterial infection

There were 78 cultures identified relating to 78 patients. The overall number of patients in each group was as follows: head and neck; 26 isolates (nine invasive): abdomino-pelvic; nine isolates (five invasive): skin and soft tissue;26 cases (two invasive): and pleuro-pulmonary; seven cases. Two cases of pure *F. nucleatum* bacteraemia were excluded from further study as they occurred in paediatric patients undergoing chemotherapy for haematologic malignancy. Eight isolates related to the female genital tract without evidence of invasion, and 5 of these were associated with cases of obstetric infection.

Male patients accounted for 24 of 53 (45%) cases but 19 (76%) of the 25 cases of invasive disease (p=0.015, two-tailed Fisher's exact test). 13 of 78 (17%) isolates were from blood culture, constituting 68% of isolates defining invasive disease. Fusobacterium isolates were grown in pure culture in 13 (24%) non-invasive cases and 14 (56%) invasive cases. Of 76 in-patients 75 (99%) survived to discharge from hospital.

Head and neck isolates related to tonsillitis, para-tonsillar abscess, dental sepsis, sinusitis, otitis media and wound infection following head and neck surgery. Features of patients with IFI of head and neck are shown in Table 5.1. Notably, only one patient with IFI of the head and neck was aged over 50 in whom *F. nucleatum* brain abscess occurred as a complication of dental sepsis. We separated this case from others given the association of dental sepsis rather than sore throat as the preceding event, reports describing F.nucleatum as a cause of brain abscess and the absence of key descriptors associated with Lemierre syndrome.(93) Correspondingly, we described the other cases as IFI 'of Lemierre's type' (IFILT). All except three patients were treated with metronidazole either singly or in combination with amoxicillin or a cephalosporin. One patient was treated with ciprofloxacin alone, one with cefuroxime alone, and one patient received no antimicrobial therapy.

No patient under 60 had invasive disease primary to the gastrointestinal tract (Table 5.2). An aspirate from a patient with a retroperitoneal abscess grew a *Fusobacterium* species and

Actinomyces naeslundii. This was not included as an invasive case due to uncertainty surrounding the nature of the primary focus of infection. The presence of *F. nucleatum* and A. naeslundii in gingival flora makes a primary periodontal focus the most likely explanation for this presentation, but cannot be proven retrospectively and was not considered at the time. All patients with invasive gastro-intestinal disease were treated with beta-lactam/metronidazole combinations.

Table 5.1. Invasive fusobacterial infection originating from sites in the head and neck

Patient	Age	Sex	Site	Metastatic involvement	Positive specimen	Species	Mono/ polymicrobial	Other organisms
1	33	M	Peritonsillar abscess	Nil	Blood	F.necrophorum	Monomicrobial	
2	42	F	Periodontal disease	Nil	Blood	F.necrophorum	Monomicrobial	
3	26	F	Pharyngo-tonsillitis	Lung	Blood	F.necrophorum	Monomicrobial	
4	72	M	Periodontitis/pharyngitis	Brain abscess	Aspirate	F.nucleatum	Polymicrobial	Microaerophilic streptococci. Haemophilus aphrophilus
5	45	M	Periodontitis/pharyngitis	Lung abscess/ empyema	Pleural fluid	Not specified	Polymicrobial	Anaerobic Gram-positive cocci
6	48	M	Periodontal disease	Liver abscess	Blood	Not specified	Monomicrobial	
7	18	M	Oropharyngeal trauma	Nil	Blood	Not specified	Monomicrobial	
8	32	M	Mastoiditis with extradural abscess and dural venous sinus thrombosis	Nil	Blood	F.necrophorum	Monomicrobial	

Table 5.2. Invasive fusobacterial infection originating from sites in the abdomen and pelvis

Patient	Age	Sex	Primary site	Secondary site	Positive specimen	Species	Mono/ polymicrobial	Other organisms
1.	82	M	Diverticulitis	Liver abscess	Blood	Not specified	Polymicrobial	B.fragilis
2.	77	M	Gastric angiodysplasia	Aortic graft	Blood	F.necrophorum	Monomicrobial†	
3.	74	M	Diverticulitis	Liver abscess	Aspirate	Not specified	Monomicrobial	
4.	60	F	Diverticulitis	Nil	Blood	Not specified	Polymicrobial	*Bacillus* species
5.	76	F	Diverticulitis	Liver abscess	Blood not specified	Not specified	Polymicrobial	Anaerobic Gram-positive cocci

†Patient 2. Multiple blood cultures over following months growing enteric pathogens. Fusobacterium species not repeatedly isolated.

From specimens relating to skin and soft tissue, two cases of invasive disease were identified. A 41-year-old male intravenous drug user with a large thigh abscess, associated septic thrombophlebitis and multiple lung abscesses had anaerobic gram-positive cocci and a *Fusobacterium* species isolated from a thigh aspirate. Although blood cultures were positive only for the former, an attending infectious disease specialist thought the metastatic phenomena reflected polymicrobial bacteraemia and recommended therapy directed specifically against both organisms in the form of amoxicillin and metronidazole. A 57-year-old male with syringomyelia and a chronic discharging buttock abscess developed necrotising fasciitis of the buttock, perineum and abdomen with *Fusobacterium mortiferum* and *Bacteroides fragilis* grown from blood. The patient survived following therapy with ceftriaxone and clindamycin.

The co-morbidities and clinical presentations associated with pleuro-pulmonary disease were heterogenous and 50% of isolates were polymicrobial (Table 5.3). Only two laboratory isolates clearly matched existing descriptions of pleuro-pulmonary FI (Patients 4 and 5, Table 5.3). Adequate details of antimicrobial therapy could be identified only in 6/7 cases. Of these, three received no antibiotic therapy at the point that specimens were obtained and the remain-der received metronidazole in combination with amoxicillin or ceftriaxone.

Features of infections in the eight patients with disease relating to the female genital tract are shown in Table 5.4.

Epidemiology of invasive Fusobacterial infection

The overall incidence of IFI during the study period was 9.9 per million population/year. The category-specific yearly incidence of IFI per million population was as follows: head and neck, 3.9; gastrointestinal tract, 2.2; skin and soft tissue, 0.8; and lung and pleura, 3.

Given the rarity of invasive disease primary to the head and neck in patients over 50, and invasive intra-abdominal and pelvic disease in those under 50, the incidence of disease for these conditions was calculated using the relevant population at risk. The incidence of IFILT in the population aged 15-50 years was 6.7 per million/year. For abdomino-pelvic IFI in the population over 50 years of age the incidence was 7.8 per million population/year. Given the small number of invasive cases identified in each category and the short period studied no attempt was made to identify trends in incidence over time.

Table 5.3. Clinical conditions associated with isolation of Fusobacterium species from respiratory/pleural specimens

Patient	Age	Sex	Associated condition	Specimen	Mono/ polymicrobial	Other organisms
1.	64	M	Obstructive pneumonitis 2^{o} lung cancer	Lung (post-resection)	Polymicrobial	Bacteroides species
2.	63	M	Obstructive pneumonitis 2^{o} foreign body	Broncheoalveolar lavage	Polymicrobial	Anaerobes (multiple)
3.	77†	M	Complex parapneumonic effusion, possible oesophageal perforation	Pleural fluid	Monomicrobial	
4.	83‡	M	Pneumonia/empyema	Pleural fluid	Monomicrobial	
5.	38	M	Lung abscess/empyema	Pleural fluid	Monomicrobial	
6.	57§	F	Progressive non-specific interstitial pneumonia	Lung biopsy	Monomicrobial	
7.	21	M	Pan bronchiolitis; treated Goodpasteurs syndrome	Bronchioalveolar lavage	Polymicrobial	H.influenzae, GpC streptococci, mixed anaerobic flora

†Patient died during admission.
‡Aspirate taken from chest wall abscess at site of chest drain previously inserted for management of empyema. Initial pleural aspirates delayed due to loculation, subsequently culture negative. Fusobacteria assumed to be component of original anaerobic infection.
§Patient discharged from hospital but died subsequently due to progressive respiratory failure.

Table 5.4. Clinical conditions associated with isolation of Fusobacterium species from the female genital tract.

Patient	Age	Sex	Condition	Sample	Other organisms
1.	85	F	Pyometria	Endometrial curretings	E.coli
2.	43	F	Chorioamnionitis (septic abortion)	Placental tissue	Gp B streptococcus
3.	1d†	F	Chorioamnionitis (premature delivery)	Placental swab	Nil
4.	38	F	Chorioamnionitis (premature delivery)	Placental swab	Nil
5.	1d†	M	Chorioamnionitis (premature delivery)	Gastric aspirate at delivery	*Ureaplasma urealyticum*‡
6.	46	F	Tubo-ovarian abscess associated with IUCD	Swab at laparoscopy	Nil
7.	39	F	Chorioamnionitis (septic abortion)	Placental tissue	Aerobic and anaerobic vaginal flora
8.	29	F	Chorioamnionitis (premature delivery)	Placental tissue	*Ureaplasma urealyticum*‡

Abbreviations: IUCD, intra-uterine contraceptive device. †Specimen registered under child's hospital identifier, mother diagnosed with chorioamnionitis. ‡Determined by urease activity measured by Mycoplasma Duo™ assay (Biorad, Marnes-la-Coquette, France).

Discussion

The Fusobacteria are notable amongst gram-negative anaerobic bacteria in their ability to invade the human host as primary pathogens. Numerous virulence determinants have been described including expression of leucotoxin, proteolytic enzymes, lipopolysaccharide and haemagglutinin.(Aliyu et al., 2004) Whilst *F.nucleatum* is clearly a significant component of the gingival flora there is a little evidence that *F. necrophorum* universally colonises the healthy oropharynx, as has previously been suggested.(Aliyu et al., 2004; Bolstad et al., 1996; Brazier, 2006) Supportive of its role as a primary pathogen, recent culture and PCR-based reports show that *F. necrophorum* is second only to the Group A *streptococci* amongst bacterial pathogens causing sore throat.(Aliyu et al., 2004; Amess et al., 2007; Batty et al., 2005) It has been postulated that tissue adhesion and invasion by *F. necrophorum* rely on viral co-

infection.(Aliyu et al., 2004; Brazier, 2006; Ramirez et al., 2003) Indeed, most invasive infections caused by this organism seem to require compromise of mucosal integrity.

It is unclear why invasive *F. necrophorum* infection is so uncommon in comparison with the frequency of sore throat in the community. Case reports and series point to a link between IFILT and genetic mutations linked to thrombophilia and abnormal innate immune response.(Constantin et al., 2006; Goldenberg et al., 2005; Schmid et al., 2005) Thrombophilia was identified in all nine patients with IFILT diagnosed at a children's hospital in Denver between 2001 and 2005, consisting mainly of antiphospholipid antibodies and elevated factor VIII activity.(Goldenberg et al., 2005) A three-year-old boy with IFILT was reported to have underlying hypercoagulability due to elevated lipoprotein a and a 20210G prothrombin gene mutation.(Schmid et al., 2005) A 17-year-old female developed IFILT in the presence of a single nucleotide polymorphism (SNP) of the Toll-like receptor five (TLR 5) gene and further SNPs within the promoters of genes encoding Tissue Factor and Plasminogen-Activator Inhibitor (PAI).(Constantin et al., 2006) PAI mutations are also associated with increased risk of septic shock with meningococcal meningitis.(Haralambous et al., 2003; Westendorp et al., 1999) The rarity of IFILT and its restriction in classic form to younger male patients likely represents a matrix of risk relating to rare predisposing genetic traits and in-creasing immunity with age to common viral pathogens, and to *F. necrophorum* itself following exposure throughout life.

Alternatively, several authors have pointed to reduced antibiotic prescribing in primary care as a potential extrinsic driver of IFILT.(Aliyu et al., 2004; Brazier et al., 2002; Ramirez et al., 2003) In a US children's hospital, isolation of *F. necrophorum* rose from one clinical specimen per year from 1996 to 1999 to five isolates per year in 2000-2001. Four cases of IFILT (each with evidence of a viral or bacterial co-infection) were diagnosed in the latter period where previously no cases had been recognised for many years. These authors noted a 20% reduction in antibiotic prescribing to children in their region in the late 1990s attributable to a multifaceted state-wide education programme, coupled with a shift towards macrolide prescribing to avoid multiple daily dosing regimens.(Belongia et al., 2001; Halasa et al., 2002) The authors also suggested that resistance to macrolides amongst Fusobacteria may have selected or perpetuated infection, so leading to more severe presentations. Whilst our findings may have been confounded by the lack

of routine anaerobic blood culture amongst children, it is reassuring that we only identified one case of IFILT in a patient under the age of 20 over the period studied. A nationwide antibiotic control programme has been in place in New Zealand since 1997.(Pharmaceutical Management Agency, 2007) Any increase in incidence of IFILT related to restricted antibiotic prescribing would presumably have manifested prior to the commencement of our study, which argues against this factor playing an important role in IFILT incidence.

We identified five cases of abdomino-pelvic IFI. In a 3-year prospective study in Denmark 42 cases of IFI with abdomino-pelvic foci were observed.(Hagelskjær Kristensen & Prag, 2008b) In keeping with our findings the majority occurred in elderly patients. Malignant disease of the infected organ system was apparent in 14 (33%) cases, and the in-hospital mortality was 25%. In Finland, whilst a 40% increase in annual incidence of bloodstream infection occurred amongst those over 75 between 1995 and 2002 the proportion of anaerobic organisms recovered remained stable at 5%.(Skogberg et al., 2008) In common with developed nations, the proportion of the population aged over 65 in New Zealand is expected to exceed 25% by the middle of this century.(*Population Ageing in New Zealand*, 2000) Therefore, in the case of abdomino-pelvic IFI we expect the incidence to increase as the elderly population at risk grows.

Fusobacteria may have an important role in the pathogenesis of chorioamnionitis and pre-term delivery. Micro-organisms can be recovered from the chorioamnion in 21% of women delivering at term and 61% of women delivering before 37 weeks of gestation.(Hillier et al., 1988) In one case series where isolates were only identified to genus level, *Fusobacterium* species were grown in 50% of febrile cases of chorioamnionitis.(Easterling T & Garite T, 1985) *F. nucleatum* is frequently found in the amniotic fluid of women with preterm labour both with and without premature membrane rupture, this despite being an infrequent component of the vaginal flora.(Han et al., 2004) Epidemiological and laboratory studies have linked periodontal disease with premature delivery.(Bearfield et al., 2002; Offenbacher et al., 1996) *F. nucleatum* septicaemia causes premature delivery and stillbirth in pregnant mice. Interestingly, bacterial invasion of the placental endothelium can occur without prominent infiltration of inflammatory cells, an effect potentially mediated by Toll-like receptor 4 (TLR-4).(Han et al., 2004; H. Liu et al., 2007) Without speciation we offer insufficient information to judge the potential contribution

of *F. nucleatum* to obstetric infections in our region. Laboratory identification of obstetric isolates to species level would seem worthwhile, if only to promote further interest and research on the potential link between premature delivery, foetal loss and periodontal disease.

The clinical presentations associated with pleuro-pulmonary disease were heterogeneous. This may relate to the assumption that all isolates reflected invasive disease. Presentations of primary pleuro-pulmonary IFI as classically described were rare. However, we suggest that isolates from sites including bronchoalveolar lavage fluid merit close clinical attention, particularly as the place of *F. necrophorum* as a normal component of the oropharyngeal flora has been questioned.(Aliyu et al., 2004; Brazier, 2006) Atypical presentations of *F. necrophorum*-associated pulmonary disease may yet be described in larger series, and targeted antimicrobial therapy should be considered where this organism is isolated in a setting suggestive of infection.

This study has several weaknesses. A number of cases of IFI were probably missed due to either inappropriate clinical sampling or difficulties in the recovery and identification of isolates in the laboratory. Significant disparities have been noted between differing anaerobic transport and culture methods for recovery of anaerobic organisms.(A. Jensen et al., 2008) Some cases meeting the study definition of invasive disease received no antibiotic therapy and survived. Presumably, some anaerobic bacteraemia are now appreciated where routine blood culturing is available but where progressive clinical disease does not occur. The observation of uniformly favourable outcomes in such a small number of cases may misrepresent true mortality rates, particularly in abdomino-pelvic infection. Finally, a significant proportion of isolates was identified only to genus level raising questions about the relative importance of various species in the causation of disease. For all these reasons, though, it is unlikely that our calculations overestimate the incidence of invasive disease due to Fusobacteria, and our active case finding strategy has provided estimates of incidence close to those reported in a national study of similar design.(Hagelskjær Kristensen & Prag, 2008b)

Despite being rare isolates in routine laboratory practice, *Fusobacterium* species are associated with important infectious syndromes that can present to a variety of services. The true spectrum of associated disease is therefore unlikely to be appreciated by clinicians. The microbiologist

therefore stands key to re-evaluating procedures and processes required for optimal identification of the Fusobacteria, and in attributing pathogenicity appropriately where they are identified. Increasing awareness of beta-lactamase production (particularly amongst *F. nucleatum* isolates) should be used to guide empiric therapy of invasive disease and promote formal antibiotic susceptibility testing where indicated.(Nyfors et al., 2003)

Close to 100% in-hospital survival in frequent association with serious morbidity confirms that Fusobacteria are not potent causes of the *dysregulated* immune response to infection characteristic of the sepsis syndrome. In Lemierre's original description of disease in the pre-antibiotic era, the time from presentation to death without effective therapy was measured in weeks in many cases. This confirms that acute sepsis outcomes are pathogen-driven, and that study of specific pathogen-associated factors may better define individual patient risks. In the following chapter, this is explored by examining the association of S.aureus bacteriuria in patients presenting with SABSI.

Chapter 6: Concomitant *Staphylococcus aureus* bacteriuria is associated with poor clinical outcome in adults with S.aureus bacteraemia

Abstract

Objectives: A retrospective cohort study was undertaken to determine the prognostic significance of *Staphylococcus aureus* bacteriuria in patients presenting to our hospital with *S.aureus* bacteraemia between January 2000 and December 2003.

Methods: A total of 378 patients had at least one positive blood culture for *S.aureus*, of whom 221 had urine cultured within 24 h of presentation. For this group, 206 case records could be retrieved for review. Of these patients, all had methicillin-susceptible *S.aureus* bacteraemia and 35 (17%) had *S.aureus* cultured in urine. Logistic regression analysis was used to control for age, genitourinary tract status and comorbidity.

Results: Concomitant *S.aureus* bacteriuria persisted as a significant risk factor for ICU admission [risk ratio (RR): 2.5; 95% confidence interval (CI): 1.06-4.36; p = 0.04] and in-hospital mortality (RR: 2.18; 95% CI: 1.05e 3.57; p = 0.04). Other findings were that cerebrovascular disease in males and increasing age in both sexes were associated with in-hospital and one year mortality.

Conclusions: Prospective studies are warranted exploring the link between *S.aureus* bacteriuria and clinical outcome in patients with *S.aureus* bacteraemia.

Introduction

Staphylococcus aureus bacteriuria in association with *S.aureus* bacteraemia is well-documented.(151,152) (Kunin CM, 1997; B. K. Lee et al., 1978)*S.aureus* is a recognised cause of urinary tract infection or colonisation in patients with indwelling catheters or recent urinary tract instrumentation, and occasionally this leads to secondary bacteraemia. (Arpi & Renneberg, 1984; Demuth PJ et al., 1979; Ekkelenkamp et al., 2007; B. K. Lee et al., 1978; Muder et al., 2006; Mylotte et al., 2002)Alternatively, *S.aureus* bacteriuria can be secondary to *S.aureus* bacteraemia, although this may be a relatively uncommon event. (Ekkelenkamp et al., 2007; B. K. Lee et al., 1978) A separate issue is whether or not the finding of bacteriuria is a poor prognostic factor in patients with *S.aureus* bacteraemia. To investigate this, we undertook a retrospective cohort study of patients presenting to our institution with *S.aureus* bacteraemia whose urine had been submitted for culture.

Methods

From 1 January 2000 to 31 December 2003, all blood cultures growing *S.aureus* were identified from the microbiology database at Christchurch Hospital, a 644-bed tertiary level hospital in New Zealand. Cases were patients aged 18 years at the time of the first positive blood culture for *S.aureus* and from whom a sample of urine had been submitted within 24 hours. Patients were only enrolled once within the study period. Patients were excluded if the bacteraemia was deemed by attending clinical staff to represent contamination.

Microbiology records and clinical notes were reviewed and data collected regarding patient age, residence, need for ICU admission, major comorbidities, genitourinary tract abnormality, mortality during index hospitalisation and at one year. One-year mortality was determined from national archives held by the New Zealand Health Information Service.

Endocarditis was deemed present if entered as a clinical, echocardiographic, or post-mortem diagnosis in the clinical record. Genitourinary tract abnormalities were defined as: (i) insertion, removal or permanent presence of an indwelling vesical catheter in the two weeks before the

index positive culture; (ii) genitourinary tract instrumentation or surgery in the two weeks before the index positive culture; (iii) documentation of a structural genitourinary tract lesion or a functional lesion causing urinary incontinence.

Healthcare-associated infection was defined as: (i) infection occurring 48 h after admission or (ii) occurring within seven days of prior hospital discharge or (iii) relating to intravenous catheter associated-infection. In-hospital mortality was defined as death occurring during initial hospital admission. One year mortality was defined as death occurring within 365 days of the index positive culture.

Blood cultures were processed using the Bac-T Alert system (bioMe´rieux Australia PTY Ltd, Baulkham Hills, NSW, Australia). Urine was processed using quantitative culture of 0.001 mL of sample plated onto sheep blood agar. *S.aureus* isolates were identified using standard methods and were not typed. Antibiotic effect in urine was not routinely assessed.

Statistical analysis was performed using STATA version 8.2 (StataCorp., College Station, TX, USA). Dichotomous variables were analysed with the Chi-squared test and continuous variables with the Wilcoxon rank sum test. Logistic regression analysis was used to investigate which potential risk factors were associated with outcomes, adjusting for possible confounding by other potential risk factors. Separate models were used to assess each of the following binary outcome variables: ICU admission, in-hospital mortality, and one-year mortality. Each model included the following potential risk factors as explanatory variables: age groups (18-49 years, 50-64 years, 65-79 years, 80 years), sex, *S.aureus* bacteriuria, indwelling urethral catheter, urinary tract structural abnormality, recent genitourinary surgery or instrumentation, current smoking status, diabetes mellitus, congestive heart failure, cerebrovascular disease, and cancer. With the exception of age groups, all variables were binary. Likelihood ratio tests were used to compare models with and without interaction terms and to test for linear trend for variables with more than two categories. Because the outcomes in the study population were not rare events (i.e. >10% in each group), the odds ratios derived from our logistic models were converted to relative risks to more clearly convey the strength of the associations with potential risk factors.(Zhang &

Yu, 1998) Only data from subjects with complete data for all outcome and explanatory variables were analysed in the multivariate models.

Results

During the study period 378 patients were identified with positive blood cultures for *S.aureus* on at least one occasion, 221 of whom had concomitant urine cultures. Clinical records could be retrieved for 206 cases, 35 of whom had *S.aureus* bacteriuria. None of the *S.aureus* isolates was MRSA (which is consistent with local epidemiology), and in all cases the bacteraemia was deemed genuine rather than contamination. Of the 15 patients whose records were unavailable two were bacteriuric. Therefore at least 9% (35/378) of patients with *S.aureus* bacteraemia during the study period had *S.aureus* concurrently isolated from urine. Table 6.1 compares baseline variables and outcome for the 206 cases studied.

Eight of the 35 bacteriuric patients had normal genitourinary tracts. Seven of these met the study definition of community-acquired infection, four were admitted to the ICU, endocarditis was identified in three and half died in-hospital. None was thought by attending clinicians to have urinary tract infection as a primary source of *S.aureus* infection. Five of these patients submitted midstream specimens of urine (MSU), one a catheter specimen of urine (CSU), and in two cases the mode of sampling was not clear. Only one of these eight samples showed $>10^9$ white blood cells/L of urine, and the mean white cell count in the remaining seven was 187 x 10^6 /L. Seven urine samples grew *S.aureus* in pure culture: six of these were present at >108 cfu/L ($>10^5$ cfu/mL).

Twenty-seven of the 35 bacteriuric patients had abnormal genitourinary tracts. Of these, 22 (81%) showed $>10^8$ cfu/L ($>10^5$ cfu/mL) of *S.aureus*. In nine cases *S.aureus* was recovered from mixed culture. Fourteen (52%) had urinary white cell counts $>10^9$ /L. The mean white cell count in the 13 remaining specimens was 300 10^6 /L.

Crude risk ratios were 1.78 (95% CI: 0.86-3.66) for the effect of *S.aureus* bacteriuria on the risk of ICU admission, 2.12 (95% CI: 1.23-3.63) for the effect of *S.aureus* bacteriuria on the risk of

in-hospital mortality, and 1.39 (95% CI: 0.93-2.07) for the effect of *S.aureus* bacteriuria on the risk of one-year mortality.

Logistic regression analysis was performed on the 194 subjects (32 with *S.aureus* bacteriuria) with complete datasets. Table 6.2 shows the corrected risk ratios for the effect of *S.aureus* bacteriuria on the risk of ICU admission, in-hospital mortality and one-year mortality together with other independent associations after adjusting for all other potential risk factors of interest. The models for in-hospital mortality and one-year mortality were both significantly improved by the inclusion of interaction terms between sex and cerebrovascular disease. Including separate effects for each age group did not significantly improve any of the three models, therefore linear trend was assumed for this variable. *S.aureus* bacteriuria was independently associated with both ICU admission and in-hospital mortality. Other findings were that cerebrovascular disease in males and (in both sexes) increasing age were associated with in-hospital and one-year mortality. Increasing age and cancer were associated with a reduced risk of ICU admission.

Discussion

The main findings of this study are that concomitant *S.aureus* bacteriuria is associated with a two-fold increased risk of both ICU admission and in-hospital mortality in patients with *S.aureus* bacteraemia, even after adjusting for potential confounders. Consequently *S.aureus* bacteriuria may be a clinically important finding, alerting clinicians to the increased risk of morbidity and mortality in such patients. Since concomitant bacteriuria is found in 7-10% of patients with *S.aureus* bacteraemia, this may be a useful addition to the assessment of severity in patients with bacteraemia.(Ekkelenkamp et al., 2007; B. K. Lee et al., 1978)

In a proportion of patients with *S.aureus* bacteraemia, *S.aureus* bacteriuria has been thought to reflect haematogenous seeding of the kidneys with abscess formation.(B. K. Lee et al., 1978) The clinicopathological evidence that this can occur is well established and an association with poor outcome is plausible. *S.aureus* was a common cause of renal abscess in the pre-antibiotic era.(Kunin CM, 1997; B. K. Lee et al., 1978) Renal cortical micro-abscesses were a frequent finding in autopsied cases of *S.aureus* bacteraemia in the first half of the twentieth century, and

animal models of *S.aureus* bacteraemia demonstrate a frequency of renal abscess formation proportional to the number of organisms inoculated into the bloodstream. It is likely that haematogenous renal metastasis was manifest in the eight bacteriuric patients in this study with normal genitourinary tracts.

The relationship between bacteriuria and adverse outcome in patients with structurally abnormal genitourinary tracts may be more complex. *S.aureus* infection of the genitourinary tract in this group of patients is not infrequent and progression to bacteraemia occurs in a significant proportion.(Arpi & Renneberg, 1984; Muder et al., 2006; Mylotte et al., 2002) Twenty-seven (78%) of the 35 patients in this study with concomitant *S.aureus* bacteriuria had identifiable genitourinary tract abnormalities. The poor short-term clinical outcomes demonstrated in this group persisted after controlling for comorbidity, age and genitourinary tract status. Kim et al. reported an increased risk of mortality in patients with *S.aureus* bacteraemia who had non-eradicable sites of *S.aureus* sepsis.(Kim et al., 2003) The genitourinary tract may be one such site in patients with obstructing lesions or unrecognised infectious complications of vesical catheterisation.

Alternatively, *S.aureus* bacteriuria may be a surrogate marker of underlying comorbid conditions. Though we used multivariable analysis to control for composite comorbidity, we did not weight comorbidities based on their actuarial association with mortality in the manner of Lesens et al. or include an estimate of illness severity.(Lesens et al., 2003) This may, for example, explain the association between bacteriuria and mortality if this was associated with a greater degree of physiological compromise. Furthermore this may also have confounded reporting of mortality amongst males with cerebrovascular disease.

We acknowledge the weakness and potential for bias inherent in this study's retrospective design. In particular, our acceptance of *S.aureus* in urine at any concentration, occasionally in mixed culture and without typing results to link blood and urine isolates, casts some doubt over the true significance of bacteriuria in every case.

We conclude, however, that the presence of concomitant *S.aureus* bacteraemia and bacteriuria may be a clinically useful marker of illness severity. Prospective studies are required both to confirm and explore our findings, to clarify interpretive criteria for S.aureus in cultures of urine and to determine the value of infection control and eradication measures for patients with *S.aureus* bacteriuria.

Summary: in the work reported thus far, the focus has been on the clinical outcomes associated with microbiologic findings. In routine clinical practice, however, the initial phase of sepsis is managed without this information. To make good decisions in an acute setting, clinicians must combine history and examination findings with an understanding of health and disease in the local (resident) population. In Chapter 7, the utility of morbidity, frailty and acute physiology are described with respect to the prediction of acute organ failure (reflected in mortality and/or ICU admission) and clinical complexity (reflected in measure related to hospital length of stay). In Chapter 8, a discharge coding method is used to study the epidemiology of sepsis in the Waikato region. This work was used to inform the design and execution of the whole-of-system sepsis quality improvement project reported in Chapter 9.

Table 6.1. Baseline demographics, clinical features, and outcome for 206 patients with *S.aureus* bacteraemia with and without *S.aureus* bacteriuria

Variables	Patient without bacteriuria N=171 (%)	Patients with bacteriuria N=35 (%)	P-value
Median Age	70	67	0.75
Male Sex	93 (54)	27 (77)	0.01
Comorbidities			
Smoker	24/167[†](14)	8/33[†] (24)	0.16
Prednisone > 7.5mg	15/170[†] (9)	2 (6)	0.54
Haemodialysis	6 (4)	0	0.26
Diabetes	32 (19)	8 (23)	0.57
Ischaemic heart disease	61 (36)	9 (26)	0.26
Heart failure	51 (30)	4(11)	0.06
Peripheral vascular disease	17 (9)	1 (3)	0.18
Cerebrovascular disease	26 (15)	4 (11)	0.56
Chronic liver disease	26 (15)	4 (11)	0.56
IVDU	6 (4)	1 (3)	0.85
Burns	4 (2)	0	0.36
Renal transplant	2 (1)	0	0.52
Bone marrow transplant	2 (1)	0	0.52
Malignant neoplasm	34 (20)	8 (23)	0.69
Chemotherapy <4 weeks	12 (7)	0	0.11
Neutropaenia <1week	10 (6)	0	0.14
Non-GU surgery <4 weeks preceding BSI	32 (19)	3 (9)	0.15
Genitourinary tract data			
Any abnormality	74 (43)	27 (77)	0.0003
IDUC <2weeks	37 (22)	11 (31)	0.21
Surgery/instrumentation	6 (4)	8 (23)	0.0001
History of TURP	6 (4)	2 (6)	0.54
Other GU abnormalities	33 (19)	18 (51)	0.0001
Acquisition			
Nosocomial	77 (45)	14 (40)	0.59
Outcomes			
ICU following first positive culture	20 (12)	8 (23)	0.08
Endocarditis	20 (12)	4 (11)	0.96
Mortality in-hospital	30 (18)	13 (37)	0.009
Mortality at 1 year	59 (35)	17 (49)	0.12

Abbreviations: IVDU, intravenous drug use; BSI, bloodstream infection; IDUC, indwelling urinary catheter; TURP, transurethral resection of prostate; GU, genitourinary; ICU, intensive care unit.
-†Denotes denominator where some clinical information was unavailable.

Table 6.2 Association of *S.aureus* bacteriuria and other significant independent associations with in-hospital mortality, one-year mortality and intensive care unit (ICU) admission in patients with *S.aureus* bacteraemia

Outcome variable	Explanatory variable	Corrected RR	95% CI	P-value
ICU admission	S.aureus bacteriuria	2.50	1.06-4.36	0.04
	Age group†	0.62	0.38-0.98	0.04
	Cancer	0.13	0.01-0.87	0.04
In-hospital mortality	S.aureus bacteriuria	2.18	1.05-3.57	0.04
	Age group†	1.48	1.02-2.04	0.04
	Cerebrovascular disease			
	Males	3.53	1.78-4.81	0.02
	Females	0.42	0.02-2.38	0.32
One-year mortality	S.aureus bacteriuria	1.40	0.74-2.07	0.26
	Age group†	1.61	1.3-1.9	<0.0001
	Cerebrovascular disease			
	Males	2.27	1.4-2.69	0.005
	Females	0.67	0.06-1.46	0.2

Abbreviations: RR, risk ratio; CI, confidence interval.
†For each increase in age group category.

Chapter 7: Measures of acute physiology, co-morbidity and functional status to differentiate illness severity and length of stay amongst acute general medical admissions – a prospective cohort study

Abstract

Background: Simple measures of acute physiologic compromise, functional status and comorbidity may help clinicians to make decisions relating to clinical care and resource utilisation.

Aims: To explore the usefulness of common assessment tools in predicting outcomes of (i) death or intensive care unit (ICU) admission and (ii) length of hospital stay at a busy tertiary hospital in Singapore.

Methods: Three hundred and ninety-eight consecutive admissions to two general medicine teams were prospectively assessed during 2 months in 2011. Patients were followed until discharge or transfer to ICU/high dependency unit (HDU). Data collected included routine demographic data, final diagnosis, comorbid conditions including a weighted prognostic comorbidity index (the updated Charlson index) and the modified Early Warning Score (MEWS) at presentation to the emergency department. The admission modified Barthel Index was recorded for patients aged 65 and over. Death and total length of hospital stay were recorded in all cases.

Results: Of 398 patients, 16 (4 %) died or were transferred to ICU and 99 (25%) stayed for more than 7 days. Medical early warning (MEW) scores of≥5 were significantly associated with death or ICU admission (hazard ratio 5.50, 95% confidence interval 1.77–17.07, P=0.003). There was no independent association between this outcome and the Charlson score or admission Barthel Index. Excess length of stay was associated with a modified Barthel Index≤17 and altered mental status at presentation.

Conclusion: Among unselected general medical patients, MEW scores of≥5 were significantly associated with death or ICU admissions and only functional status and altered mental status were independent predictors of excess length of stay.

Introduction

Disease-specific mortality prediction tools have multiplied over the past several decades to serve the needs of patients with a secure clinical diagnosis. However, triage and initial medical assessments are undertaken when a range of diagnostic possibilities co-exist, rendering these tools less useful to front-line clinicians.(Glare et al., 2003) 'Downstream 'in-patient care in internal medicine is supervised by a senior internal medicine specialist, but the first few hours of the patient journey usually belong to emergency medicine physicians and their junior medical staff in training.(Black, 2004; Scott et al., 2009) Faced with a new cohort of patients each day, staff face the complex task of recognising the potential for clinical deterioration in individual patients while planning their disposition. Few tools have been developed to help with this process.

Prognostic scores are ubiquitous in medicine, having been developed for a wide range of diseases, patient populations and outcome.(Glare et al., 2003) Available scores are usually disease specific, such as the CURB65 score in pneumonia, while those that are not have undergone limited validation.(Aujesky et al., 2005; Robertson-Steel, 2006) Although the potential for acute deterioration and mortality are universally important considerations in acute care, early identification of patients likely to require prolonged hospitalisation is of great importance to in-patient clinicians and managers. A small number of patients often account for a large proportion of hospital bed-days, a key determinant of total in-patient cost and efficiency.(Lim et al., 2006; Schwartz & Mendelson, 1991) Ideally, therefore, prognostic scores for undifferentiated adult medical in-patients should identify (i) the sickest patients and (ii) those patients likely to generate the highest burden on in-patient resources, for which length of hospital stay is a surrogate.

With these issues in mind, we undertook to investigate how scores that are already in widespread clinical use (the modified Early Warning Score (MEWS), modified Barthel Index (MBI) and updated Charlson comorbidity index) interacted with routine administrative and demographic data to influence the following outcomes in a cohort of adult medical admissions in a busy

tertiary hospital environment: (i) in-hospital death or intensive care unit (ICU) admission and (ii) length of in-hospital stay.(Collin et al., 1988; Quan et al., 2011; Subbe et al., 2001)

Methods

Design and Setting

We undertook a prospective, observational cohort study at the National University Hospital, a 1024-bed tertiary academic medical centre situated in the west of Singapore. In the year of the study, 26368 patients were admitted to internal medicine specialties of which 6308 were categorised as general internal medicine (GIM) by emergency department staff. The study took place in two acute medicine wards, totalling 92 available beds, to which GIM patients were preferentially admitted. Each of these wards was continuously covered by consultant physicians with higher training in general/acute internal medicine supported by a multi-disciplinary team of junior medical and allied health staff. GIM patients admitted to other wards were cared for by internal medicine subspecialty teams and are not included in this study. The hospital did not operate a separate acute admitting service for elderly patients nor did any GIM team maintain a formal presence in the emergency department.

Study Population

Data were prospectively collected for 398 GIM patients admitted directly to the two study wards from the emergency department between May 25 and June 28 2011. This represents a 6% sample of GIM patients admitted to the hospital during 2011 and a 57% sample of the 693 GIM patients admitted to study wards in May and June.

The following differentiated patients are typically admitted directly to subspecialty care and are therefore largely excluded: (i) patients with acute hemiparetic stroke; (ii) patients with acute myocardial infarction or decompensated heart failure; (iii) patients with lobar pneumonia or exacerbations of chronic obstructive airways disease; (iv) patients known to be infected with human immunodeficiency virus (HIV); (v) patients with frank gastrointestinal bleeding or

jaundice; (vi) patients requiring immediate admission to an ICU; (vii) patients with an exacerbation of a condition under the active management of a medical subspecialty team, that is dialysis and transplant patients; and (viii) patients requiring isolation for droplet or airborne precautions (there being only four isolation rooms in the study wards).

Data Capture

Study wards were visited daily by investigators to ensure patient record review within 24 hours of admission. The following data were obtained: demographic details (including age, sex, spoken and preferred language), number of comorbid conditions, smoking status (smoker or non-smoker), hospital admissions in the preceding 12 months, social set-up (home dwelling; supported care; other hospital), antibiotic prescription on admission (a surrogate for suspected infection), a weighted comorbidity index (the updated Charlson comorbidity index) and the MEWS at presentation to the emergency department. For patients aged 65 or over, the 20-point MBI was calculated at admission and at a point 2 weeks prior to admission on the basis of interview with the patient or caregiver. Patients were followed for the duration of their admission if they remained under the GIM team or to the point of death, ICU transfer or transfer of care to another specialty. For all patients, the length of stay, final disposition (own home, nursing home or other hospital) and final discharge diagnosis were recorded using the hospital discharge summary. Ethical approval was granted by the National Healthcare Group domain-specific review board.

Statistical analysis

Demographic and clinical characteristics of patients involving categorical variables were summarised using frequencies and percentages. For continuous variables, means and standard deviations were used to describe the data distribution. We dichotomised component medical early warning (MEW) scores into normal (zero)and elevated (≥1) except for respiratory rate which we divided into scores of≥2 (i.e.>20 breaths per minute) and<2. Total MEW was dichotomised into scores of <5 and ≥5 based on the work of Subbe *et al* (Subbe et al., 2001). We classified patients as independent at admission (Barthel score>17) or needing assistance (Barthelscore≤17) at admission. In the analysis of the primary composite outcome of ICU

admission or in-hospital mortality, survival times were calculated from the time of hospital admission to time of ICU/high dependency unit (HDU) admission or death, whichever was earlier, or 30-days post-hospital discharge in the case of censored observations. The Cox proportional hazards model was then used to determine the predictors of the composite outcome and the effect estimates were quantified using hazards ratios (HR). Excess length of stay (ELOS) was defined as a length of stay above the upper end of the interquartile range for the cohort. Its associations with categorical risk factors were tested using the Chi-squared test. The corresponding effect estimates were calculated as odds ratios (OR) and multivariable analysis performed using logistic regression. Covariates associated with the outcome in univariable analysis were excluded in a stepwise manner using a two-sided test at the 5% level of significance to obtain the final multivariable model. All statistical analyses were generated using STATA version 11 (StataCorp LP, College Station, TX, USA).

For ELOS, we conducted two separate analyses, one including only data available to clinicians at presentation to hospital and a second including the following explanatory variables for length of hospital stay: (i) the number of interdisciplinary consultations requested during admission (a surrogate for complexity of medical care) and (ii) need for alternative discharge domicile (a surrogate for complexity in discharge planning).

Results

Data were captured for 398 patients. Information for some of the variables was missing for less than 1% of the total dataset.

The breakdown of conditions managed, and patient morbidity is shown in Table 7.1. Two hundred and twenty-nine (56%) patients were aged 65 and over and the racial profile reflected the local population (Chinese 65%, Malay 17.5%, Indian 10.3%, other 6.8%). Three hundred and sixty patients were admitted from their own or a relative's home, including 206 of 229 patients (90%) aged 65 or over. Of this group of home-dwelling elderly, 146 (71%) required minimal or no care and 32 (16%) were completely dependent as indicated by a MBI of ≥12 or ≤4

respectively 2 weeks prior to admission. Two hundred and seven patients (52%) had been hospitalized in the preceding year, including 137 (60%) patients aged 65 or older. One hundred and fifty-three (38.4%) patients had at least one comorbid condition of prognostic significance as defined by the Charlson index.

ICU/HDU admission and in-hospital death

Table 7.2 shows the clinical and demographic features of patients with respect to the composite outcome of ICU admission or in-hospital death. Sixteen patients (4%) reached this endpoint. Eight were transferred to ICU/HDU of whom three died while a further eight patients died in general wards. All but one of these events occurred within 7 days of hospital admission. Patients who were prescribed antibiotics within 24 h of admission had a higher risk of death or ICU admission (HR 3.04,95% confidence interval (CI) 1.05–8.74, P=0.039) on univariable analysis, with no association found between older age (≥65), gender, race, supported living, smoking status, prior hospitalisation or use of alternative medicines (traditional herbal medicine). No independent association was found between the primary outcome and the Charlson score or admission Barthel Index. MEW scores of ≥ 5 were significantly associated with death or ICU admission (HR 5.50, 95% CI 1.77–17.07, P=0.003). Table 7.3 shows the results of multivariable analysis that has suggested that patients with MEW scores ≥1 for systolic blood pressure had an approximately 3.6 times higher risk of ICU/HDU admission or death (95% CI 1.26–10.11, P=0.017). Patients with MEW scores >1 for respiratory rate had an approximately six times higher risk of ICU/HDU admission or death (95% CI 2.11–16.91, P=0.001).

Length of Stay

Table 7.4 shows the demographic and clinical characteristics of patients with respect to ELOS in hospital. The median length of stay was 5 days (interquartile range 3–7) with 99 (25%) in the ELOS group, that is staying more than 7 days in hospital. For every unit increase in age, the odds of ELOS increased by 3% (95% CI 1–4, P<0.001). Univariable analyses suggested statistically significant association between length of stay and age, race (Chinese vs non-Chinese/non-Malay), prior hospitalisation, antibiotic prescription on admission, Charlson score, Barthel Index and altered mental state (MEW consciousness score≥1). Table 7.5 shows the results of

multivariable analysis using only data available to clinicians at presentation to hospital. In this analysis, ELOS was predicted by an MBI ≤17 (OR 1.93, 95% CI 1.01–3.7, P=0.048) and an AVPU score ≥1 (OR 4.39, 95%CI 1.09–17.71, P=0.038). Table 7.5 shows the results of multivariable analysis using post-admission explanatory variables for increased length of stay. ELOS was more than twice as likely among patients referred from GIM to a medical subspecialty (OR 2.26, 95% CI 1.21–4.22, P=0.01). ELOS was almost four times as likely (OR 3.73, 95% CI 1.28–10.84, P=0.016) among patients unable to return to their original domicile. The MEW AVPU score was replaced as a prognostic variable by the inclusion of these additional variables in logistic regression (Table 7.6).

Table 7.1. Discharge diagnosis and comorbidity of patients admitted under general internal medicine at the National University Hospital, Singapore

Discharge diagnosis† (n=385)	**n (%)**	**Comorbidities (n=398)**	**n (%)**
Infectious diseases	164 (42.6)	Hypertension‡	240 (60.3)
Urinary tract	48 (12.5)	Diabetes mellitus	161 (40.4)
Soft tissue	34 (8.8)	Hyperlipidaemia‡	151 (37.9)
Respiratory tract	23 (6.0	Cerebrovascular disease	96 (24.1)
Gastro-enteritis	19 (4.9)	Ischaemic heart disease	74 (18.6)
Sepsis syndrome	19 (4.9)	Asthma/COPD	45 (11.3)
Tropical infection	7 (1.8)	Psychiatric conditions	39 (9.8)
Other	14 (3.6)	Rheumatologic conditions	39 (9.5)
Undifferentiated, atypical presentation§	48 (12.5)	Renal disease	35 (8.8)
Cardiovascular disease	32 (8.3)	Gastrointestinal disease	34 (8.5)
Hypertension	3 (0.8)	Cardiac arrhythmia‡	25 (6.3)
Cardiac ischaemia	7 (1.8)		
Syncope	9 (2.3)		
Other	9 (2.3)		
Geriatric syndromes	19 (4.9)		
Toxicology	17 (4.4)		
Haematological	14 (3.6)		
Gastrointestinal	12 (3.1)		
Rheumatological	11 (2.8(		
Urological	9 (2.3)		
Renal and electrolyte disorders	7 (1.8)		
Others (conditions each accounting for <2% of admissions)	52 (13.5)		

Abbreviations: COPD, chronic obstructive pulmonary disease.
†Determined by review of clinician discharge summaries (discharge diagnosis for 14 patients transferred to other wards was not available). ‡Comorbid conditions not included in the Charlson Comorbidity Index. §Patients discharged after presenting with non-specific and atypical symptoms without clear attribution of cause.

Table 7.2. Demographic and clinical characteristics of study subjects with respect to composite outcome of death or admission to the intensive care or high dependence unit. (reproduced with permission)

Risk factor	Total (*n* = 398)	With event (*n* = 16)	Crude HR (95% CI)	*P* value
Age (SD)	64.6 (20.2)	73.5 (17.0)	1.03 (1.00, 1.06)	0.083
Gender				
Male	191 (48.0)	10 (5.2)	1.00	0.239
Female	207 (52.0)	6 (2.9)	0.54 (0.20, 1.50)	
Race				
Chinese	260 (65.3)	12 (4.6)	1.00	0.527
Malay	70 (17.6)	2 (2.9)	0.62 (0.14, 2.76)	0.554
Indian and others	68 (17.1)	2 (2.9)	0.64 (0.14, 2.84)	
Smoking status†				
Non-smoker	280 (70.7)	11 (3.9)	1.00	0.862
Smoker	116 (29.3)	5 (4.3)	1.10 (0.38, 3.16)	
Social set-up				
Home	361 (90.7)	13 (3.6)	1.00	0.188
Others	37 (9.3)	3 (8.1)	2.32 (0.66, 8.15)	
Number of hospitalisations in the past year				
0	191 (48.0)	7 (3.7)	1.00	
≥1	207 (52.0)	9 (4.4)	1.19 (0.44, 3.19)	0.734
Antibiotics prescribed				
No	229 (57.5)	5 (2.2)	1.00	0.039
Yes	169 (42.5)	11 (6.5)	3.04 (1.05, 8.74)	
Updated Charlson Index				
0 (Disease-free)	245 (61.6)	9 (3.7)	1.00	0.677
≥1 (Diseased)	153 (38.4)	7 (4.6)	1.23 (0.46, 3.31)	
Modified Barthel Index†				
>17 (Independence)	74 (32.5)	4 (5.4)	1.00	0.935
≤17 (Dependence)	154 (67.5)	8 (5.2)	0.95 (0.29, 3.16)	
Modified Early Warning Score (MEWS)				
<5	374 (94.0)	12 (3.2)	1.00	
≥5	24 (6.0)	4 (16.7)	5.50 (1.77, 17.07)	0.003
MEWS SBP†				
0	351 (88.4)	10 (2.9)	1.00	0.002
≥1	46 (11.6)	6 (13.0)	4.78 (1.74, 13.15)	
MEWS PR†				
0	317 (79.9)	11 (3.5)	1.00	0.267
≥1	80 (20.2)	5 (6.3)	1.82 (0.63, 5.24)	
MEWS RR†				
0–1	365 (91.9)	10 (2.7)	1.00	<0.001
≥2	32 (8.1)	6 (18.8)	7.54 (2.74, 20.77)	
MEWS Temperature†				
0	362 (91.2)	14 (3.9)	1.00	0.584
2	35 (8.8)	2 (5.7)	1.51 (0.34, 6.65)	
MEWS AVPU†				
0	385 (97.0)	15 (3.9)	1.00	0.440
≥1	12 (3.0)	1 (8.3)	2.22 (0.29, 16.81)	
Resuscitation status				
Yes	378 (95.0)	11 (2.9)	1.00	<0.001
No	20 (5.0)	5 (25.0)	9.46 (3.28, 27.25)	
Number of interdisciplinary consultations†				
0	175 (45.7)	3 (1.7)	1.00	
≥1	208 (54.3)	5 (2.4)	1.41 (0.34, 5.89)	0.640
Return to domicile†				
Yes	372 (93.7)	5 (1.3)	1.00	<0.001
No	25 (6.3)	10 (40.0)	36.69 (12.50, 107.68)	

†Contains missing information. AVPU, conscious level score (Alert, responds to voice (V) or pain (P), or unconscious (U)); HR, hazards ratio; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure.

Table 7.3. Covariates associated with the (HDU/ICU + death) composite outcome in multivariable analysis

Risk factor	Total (n=397)	With event (n=16)	Adjusted HR (95% CI)	P value
MEWS BP				
0	351 (88.4)	10 (2.9)	1.00	0.017
≥1	46 (11.6)	6 (13.0)	3.57 (1.26-10.11)	
MEWS RR				
0-1	365 (91.9)	10 (2.7)	1.00	0.001
≥2	32 (8.1)	6 (18.8)	5.97 (2/11-16.91)	

Abbreviations: CI, confidence interval; HDU, high dependency unit; HR, hazards ratio; ICU, intensive care unit; MEWS, Modified Early Warning Score; RR, respiratory rate.

Table 7.4. Demographic and clinical characteristics of study subjects with respect to length of stay (reproduced with permission)

Risk factor	Length of stay		OR (95% CI)	*P* value
	≤7 days (*n* = 299)	>7 days (*n* = 99)		
Mean age (SD)	62.2 (21.1)	72.1 (15.4)	1.03 (1.01, 1.04)	<0.001
Gender				
Male	140 (46.8)	51 (51.5)	1.00	0.418
Female	159 (53.2)	48 (48.5)	0.83 (0.53, 1.31)	
Race				0.040
Chinese	194 (64.9)	66 (66.7)	1.00	0.213
Malay	47 (15.7)	23 (23.2)	1.44 (0.81, 2.55)	0.067
Indian and others	58 (19.4)	10 (10.1)	0.51 (0.24, 1.05)	
Smoking status†				
Non-smoker	211 (71.0)	69 (69.7)	1.00	0.800
Smoker	86 (29.0)	30 (30.3)	1.07 (0.65, 1.75)	
Social set-up				
Home	274 (91.6)	87 (87.9)	1.00	0.267
Others	25 (8.4)	12 (12.1)	1.51 (0.73, 3.13)	
Number of hospitalisations in the past year				
0	153 (51.2)	38 (38.4)	1.00	
≥1	146 (48.8)	61 (61.6)	1.68 (1.06, 2.68)	0.028
Use of alternative medicine†				
No	238 (83.5)	83 (87.4)	1.00	0.370
Yes	47 (16.5)	12 (12.6)	0.73 (0.37, 1.45)	
Antibiotics prescribed				
No	183 (61.2)	46 (46.5)	1.00	0.011
Yes	116 (38.8)	53 (53.5)	1.82 (1.15, 2.87)	
Updated Charlson Index				
0 (Disease-free)	193 (64.6)	52 (52.5)	1.00	0.034
≥1 (Diseased)	106 (35.5)	47 (47.5)	1.65 (1.04, 2.61)	
Modified Barthel Index†				
>17 (Independence)	58 (37.4)	16 (21.9)	1.00	0.021
≤17 (Dependence)	97 (62.6)	57 (78.1)	2.13 (1.12, 4.05)	
Modified Early Warning Score (MEWS)				
<5	282 (94.3)	92 (92.9)	1.00	
≥5	17 (5.7)	7 (7.1)	1.26 (0.51, 3.14)	0.616
MEWS SBP†				
0	265 (88.6)	86 (87.8)	1.00	0.815
≥1	34 (11.4)	12 (12.2)	1.09 (0.54, 2.19)	
MEWS PR†				
0	241 (80.6)	76 (77.6)	1.00	0.514
≥1	58 (19.4)	22 (22.5)	1.20 (0.69, 2.09)	
MEWS RR†				
0–1	273 (91.3)	92 (93.9)	1.00	0.419
≥2	26 (8.7)	6 (6.1)	0.68 (0.27, 1.72)	
MEWS Temperature†				
0	274 (91.6)	88 (89.8)	1.00	0.577
2	25 (8.4)	10 (10.2)	1.25 (0.58, 2.69)	
MEWS AVPU†				
0	295 (98.7)	90 (91.8)	1.00	0.003
≥1	4 (1.3)	8 (8.2)	6.56 (1.93, 22.28)	
Resuscitation status				
Yes	290 (97.0)	88 (88.9)	1.00	0.003
No	9 (3.0)	11 (11.1)	4.03 (1.62, 10.03)	
Number of interdisciplinary consultations†				
0	149 (51.0)	26 (28.6)	1.00	
≥1	143 (49.0)	65 (71.4)	2.60 (1.57, 4.34)	<0.001
Return to domicile†				
Yes	287 (96.0)	85 (86.7)	1.00	0.002
No	12 (4.0)	13 (13.3)	3.66 (1.61, 8.31)	

†Contains missing information. AVPU, conscious level score (Alert, responds to voice (V) or pain (P), or unconscious (U)); CI, confidence interval; OR, odds ratio; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure.

Table 7.5. Covariates associated with the length of stay outcome in multivariable analysis†

Risk factor	Length of stay		Adjusted OR (95% CI)	P-value
	<7 days (n=155)	≥7days (n=73)		
Modified Barthel Index				
>17 (Independence)	58 (37.4)	16 (21.9)	1.00	0.048
≤17 (Dependence)	97 (2.6)	57 (78.1)	1.93 (1.01-3.70)	
MEWS AVPU				
0	152 (98.1)	66 (90.4)	1.00	0.038
≥1	3 (1.9)	7 (9.6)	4.39 (1.09-17.71)	

Abbreviations: AVPU, conscious level score (Alert, responds to Voice or Pain, or Unconscious); CI, confidence interval; MEWS, Modified Early Warning Score; OR, odds ratio.
†Excluding number of interdisciplinary consultations and return to domicile from the analysis as post-admission explanatory variables for increased length of stay.

Table 7.6. Covariates associated with the length of stay outcome in multivariable analysis†

Risk factor	Length of stay		Adjusted OR (95% CI)	P-value
	<7 days (n=155)	≥7days (n=73)		
Modified Barthel Index				
>17 (Independence)	56 (36.8)	11 (16.4)	1.00	0.010
≤17 (Dependence)	96 (63.2)	56 (83.6)	2.67 (1.26-5.63)	
Number of interdisciplinary consultations				
0	83 (54.6)	22 (32.8)	1.00	0.010
≥1	69 (45.4)	45 (67.2)	2.26 (1.21-4.22)	

Abbreviations: CI, confidence interval; OR, odds ratio.
†Included the number of interdisciplinary consultations and return to domicile in the analysis.

Discussion

Over the past half-century, Singapore and other countries in Southeast Asia have transited rapidly from low to high per-capita gross domestic product with attendant advances in life expectancy and other health-related outcomes.(Meng-Kin, 1998) Our study is consistent with others in developed countries in painting a picture of an ageing population maintaining functional independence despite increasing ill health.(Arai et al., 2012; Chongsuvivatwong et al., 2011) Fifty-six percent of our cohort were over 65 of whom most were living independently with no or minimal additional care 2 weeks prior to hospital admission. Independent living is taken as a marker of relative health in an ageing population but 60% of patients over 65 had been admitted to hospital in the preceding year and the vast majority had at least one significant comorbid illness. The burden on the healthcare system of comorbidity and impaired functional status can only rise with population growth and population ageing.(Arai et al., 2012) Therefore, as in all developed countries facing these challenges, healthcare providers need to develop innovative systems of assessment and management to optimise utilisation of relatively static resource, namely hospital bed-days.(Schwartz & Mendelson, 1991)

The effects of organisational efficiency and workload (reflected by emergency department overcrowding) exert a well-documented effect on hospital length of stay.(McCarthy et al., 2009) Emergency department overcrowding could not be controlled for in our study but its persistence as a problem in many healthcare systems reinforces the need to help staff make high-quality decisions with minimal information. To this end, significant efforts have been made to prognosticate patient outcomes using measures available at the point of presentation with acute illness. (Alam et al., 2015; Badriyah et al., 2014; Cameron et al., 2015; Corfield et al., 2014) Early warning scores of various design have been used singly or as part of multi-faceted early warning systems to guide early identification and treatment of deteriorating patients in emergency departments and hospital wards.(Alam et al., 2015; McGaughey et al., 2007) While heterogenous study designs and interventions have made the absolute effect of these scores on patient outcomes difficult to assess, they do appear to be useful in guiding prioritisation of assessment, predicting need for hospital admission and predicting adverse out-comes among

patients with the sepsis syndrome, regardless of source.(Badriyah et al., 2014; Cameron et al., 2015; Corfield et al., 2014; McGaughey et al., 2007)

Of the physiologic scoring systems that are not specific to a clinical syndrome, the composite MEW score is one of the best known and was a predecessor of the National Early Warning Score now in use in the UK National Health Service.(Burch et al., 2008; Subbe et al., 2001) The MEW score has been studied in a limited number of patient populations and none in South East Asia. In the original validation study conducted in a district general hospital in the UK, a MEW score of ≤2 among acute adult medical in-patients equated to a risk of ICU/HDU admission or death of 7.9% and a score of>4 was suggested as an indication for rapid escalation in care.(Subbe et al., 2001) In our study, a presentation MEW score of >4 would only have identified four of the 16 patients with subsequent critical deterioration. Burch et al. used the MEW score in a study of patients presenting to an emergency department in urban South Africa, where 43% of medical admissions were reported to be HIV positive.(Burch et al., 2008) In this study, a MEW score of 1 or more was associated with in-hospital mortality of at least 20%. We found that only elevated MEW abnormalities of blood pressure (score≥1, in most cases relating to a systolic blood pressure of 100 mmHg or less) and respiratory rate (score>1, meaning a respiratory rate above 20 breaths per minute) were independently associated with ICU admission or death using logistic regression. This suggests that a clinical focus on patients with these abnormalities would be a quick and effective way of flagging patients for enhanced assessment and monitoring without the need to calculate the MEW score in full.

In 43% of our cases, admissions were primarily for management of infection. We note the association in univariate analysis of antibiotic use (OR 0.55, 95% CI0.34, 0.89, P=0.014), age≥65 (OR 2.75, 95% CI 1.62,4.77, P<0.001) and altered level of consciousness (MEW AVPU≥1, OR 4.39, 95% CI 1.09–17.71) with excess length hospital stay. Infection is the most common cause of delirium among older hospitalised patients.(George et al., 1997) We hypothesise that much of the ELOS observed could be accounted for by the frail elderly presenting with infection and delirium. Delirium is associated with higher measures of functional impairment and both impact prognosis and risk of nursing home placement. (Luppa et al., 2010)The median survival of frail patients with delirium was 88 days in one recent study. (Eeles

et al., 2012)In a seminal article by Iwashyna and colleagues, older survivors of sepsis were more likely than matched controls to develop persistent new cognitive and functional deficits. (Langa & Iwashyna, 2012)The role of sepsis in accelerating dependence among the elderly deserves ongoing study.

In our explanatory model for excess length of hospital stay, a Barthel Index ≤17 remained significantly associated with this outcome, together with need for inter-disciplinary consultation and alternative placement at discharge. This illustrates that the needs of those with the shortest hospital admissions are dramatically different to those who remain in hospital for 7 days or more. (Ben-Tovim et al., 2008) At one end of the spectrum of medical assessment, the principal aim is to provide timely resuscitation, diagnosis and prompt discharge while at the other end the aim is to address complex, multi-faceted and multi-system presentations requiring comprehensive multi-disciplinary assessment over several days. Geriatric consultation liaison is an attractive model to deal with an increasing number of older patients in hospital but has not been associated with consistent reductions in length of hospital stay.(Deschodt et al., 2013) However, in studies of this approach, the time from admission to assessment by the liaison team and mean overall length of hospital stay varied significantly, suggesting considerable heterogeneity in patient populations and referral processes. To our knowledge, no studies have taken simple measures of morbidity and physical function at initial presentation and used them to target early geriatric assessment to those who might benefit most (i.e. those facing a long in-hospital stay). Further efforts are required to generate a generalisable model predicting increased length of hospital stay that could be used for this purpose.

This study has several weaknesses. Although we report prospectively collected data, our patient sample remains small and potentially underpowered to detect statistically significant associations with the outcomes of interest. Predicting length of stay using only the variables apparent at first presentation to hospital was exploratory and we are not surprised to find that the models produced using our data are poorly sensitive and specific. Although we believe our practice of general medicine to be broadly comparable with other centres in Singapore and overseas, the concurrent admission of general and ‘specialty-specific’ patients to other clinical areas may have produced a study population unique to general medicine at our hospital. Furthermore, we were

only able to study a small part of the hospitalised population and bias may have been generated in the systematic selection of patients to our unit by emergency department staff and bed managers.

Conclusion

Despite the limitations of this study, we provide important pointers to relevant future work. First, early identification of patients at high risk of in-patient deterioration or death appears feasible using simple physiological measures and may be combined with other strategies to monitor admitted patients for signs of clinical deterioration. Studies assessing the clinical impact of a uniform, evidence-based clinical pathway prioritising care of patients with high acute physiology 'scores' across the continuum of the hospital admission process are lacking. Second, targeting additional resources to patients at increased risk of prolonged hospital stay may have potential to reduce overall hospital bed utilisation. We believe in the relevance of this approach, but further work is required both to define a tool that can identify such patients accurately and to define the optimal prevention and management strategy for sepsis-induced delirium among elderly patients.

Chapter 8: Evidence of high mortality and increasing burden of sepsis in a regional sample of the New Zealand population

Abstract

Background. Sepsis is a life-threatening complication of infection. The incidence of sepsis is thought to be on the increase but estimates making use of administrative data in the United States may be affected by administrative bias.

Methods. We studied the population-based incidence of sepsis in the Waikato region of New Zealand from 2007 to 2012 using International Classification of Diseases, Tenth Revision, Australian Modification.

Results. Between 2007 and 2012, 1643 patients met coding criteria for sepsis in our hospitals. Sixty-three percent of patients were 65 or over, 17% of cases were admitted to an intensive care unit, and the in-hospital and 1-year mortality with sepsis were 19% and 38%, respectively. Age-standardized rate ratios (ASRRs) demonstrated that sepsis was associated with male sex (ASRR 1.4; 95% confidence interval [CI], 1.23–1.59), Māori ethnicity (ASRR 3.22 compared with non-Māori; 95% CI, 2.85–3.65), study year (ASRR 1.62 comparing 2012 with 2008; 95% CI, 1.18–2.24), and socioeconomic deprivation (ASRR 1.72 comparing the highest with the lowest quintile of socioeconomic deprivation; 95% CI, 1.5–1.97). Multiorgan failure was present in approximately 20% of cases in all age groups. Intensive care unit admission rate fell from 30% amongst 25- to 34-year-olds to less than 10% amongst those aged 75 and over.

Conclusions. In a 9% sample of the New Zealand population, the incidence of sepsis increased by 62% over a 5-year period. Māori, elderly, and disadvantaged populations were most affected.

Introduction

It is generally accepted that the incidence of sepsis is rising, but this assertion is based almost entirely on studies of temporal trends in the United States.(Fleischmann et al., 2016a) These have made use of coding datasets to suggest that this increase may have been as much as 13% annually from 2004 to 2009. Although the light that these headline figures shines on a major public health problem is clearly welcome, it has been asserted that coding artifact and improved documentation may be driving these observations.(Gaieski et al., 2013) Rhee et al showed stable or falling incidence of hospitalization with bacteraemia and objective clinical markers of organ failure at 2 US hospitals.(Rhee et al., 2015a, 2015b) This was accompanied by an increase in the incidence of sepsis detected using International Classification of Diseases, Ninth Revision (ICD-9) codes and a fall in the threshold for coding organ failure. Gohil et al showed that the introduction of specific sepsis codes to the ICD and changes to the diagnosis-related group reimbursement system (in 2002 and 2007, respectively) were independently associated with increases in sepsis diagnosis in California's state-wide Mandatory Hospital Discharge Set, an administrative bias described as "up-capture".(Gohil et al., 2016) The true extent of changes in sepsis incidence are therefore unknown internationally and difficult to assess even in the United States. The assertion that sepsis incidence may even be stable rather than increasing could damage high-profile efforts to improve recognition and treatment.(Rhee et al., 2014)

New Zealand has a single-payer public healthcare system that collects administrative data using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM). Coding practices in New Zealand may be less prone to the administrative and clinical bias reported in the United States. The ICD10-AM does not have a coding series for the sepsis syndrome, and data are universally extracted by trained administrators under robust systems of quality control to allow submission to a National Minimum Data Set. This is in contrast to the United States where clinicians are often involved in submitting coded data linked to reimbursement.("Physician Coding and Reimbursement," n.d.) We conducted an investigation to determine the incidence of sepsis in the Waikato region of New Zealand, to describe the demographic and clinical features of the condition and (given

ethnic disparities in sepsis reported elsewhere) to compare incidence specifically between Māori and non-Māori populations.

Methods

Ethical approval for this study was obtained through the Ministry of Health Northern B ethics committee.

Population and Data Sources

The Waikato District Health Board (DHB) provides comprehensive, publicly funded healthcare to a population of 403 368 people, representing 9.5% of the New Zealand population at the 2013 national census. A total of 20.7% of the population are Māori. A 600-bed, tertiary-level hospital operates in the regional centre, and 4 other regional and community hospitals have emergency and in-patient departments. No acute in-patient care is provided in private hospitals.

We used an administrative database containing demographic and coded data to identify patients admitted to our facilities with sepsis. The Waikato DHB clinical coding service makes use of ICD-10-AM and the Australian Classification of Healthcare Interventions systems (New Zealand Ministry of Health). Coding is regularly audited and is in adherence with the Australian Coding Standards and New Zealand Conventions. Coded data are submitted to the New Zealand National Minimum Dataset (NMDS), which has been used extensively for population health research.(M. G. Baker et al., 2012a) Population denominators and patient survival were determined using census, and mortality data were distributed by Statistics New Zealand and the New Zealand Health Information Office, respectively.

Case Definition and Data Collection

Patients admitted with sepsis admitted between the July 1, 2007 and the June 30, 2012 were identified. A case of sepsis was defined in this study as a primary diagnosis of infection accompanied by 1 or more secondary codes indicating organ failure. Primary and secondary

ICD-10-AM codes were based on the ICD-9 algorithm published by Angus et al, and translated by Sundararajan et al.(Angus et al., 2001; Sundararajan et al., 2005b) Excluded from study were elective admissions and non-overnight admissions that did not end in death. For estimates of sepsis incidence, we excluded patients not domiciled in the region, and, because the outcomes of sepsis are time and treatment dependent, we excluded sepsis cases from analysis if the patient had been admitted and discharged with the same primary diagnosis in the preceding 30 days. For all cases, we recorded age, sex, date of death (up to July 2013), domicile, ethnicity, New Zealand residency status, admitting hospital, length of hospital stay, and need for intensive care unit (ICU) admission. The Charlson comorbidity index was calculated using additional diagnosis codes according to the method of Quan et al.(Quan et al., 2005) Multiorgan failure was defined by the presence of >1 organ failure code.

Ethnicity and Socioeconomic Status

The NMDS allows for the recording of multiple ethnicities per patient. We classified ethnicity using a total response system for "European/Other", "Māori", "Pacific", and "Asian", whereby patients recording multiple ethnicities were counted in each of those groups. A further comparison (previously used by Baker et al) was made between patients identifying as Māori and those belonging exclusively to the "European/ Other" group, which was non-Māori, non-Pacific, and non-Asian.(M. G. Baker et al., 2012b) Patient domiciles were assigned to a New Zealand Index for Socioeconomic Deprivation (NZDep). This is a method for determining socioeconomic status that has been extensively used in health outcomes research and is validated elsewhere.(Salmond et al., 2007) Scores are assigned based on national deciles of socioeconomic status with 1 indicating least deprived and 10 most deprived.

Statistical Analysis

Data were analysed using STATA 13 (Stata Corp, College Station, TX) and Microsoft Excel (Microsoft Corporation, Seattle, WA) supported by an add-in provided by Public Health England (http://www.wmpho.org.uk/tools/). Crude annual incidence of sepsis was calculated using Waikato regional mid-year population estimates provided by Statistics New Zealand. Age standardized rate ratios and confidence intervals (Cis) were calculated to allow comparisons

based on age and ethnic group. Five-year age, gender, and ethnicity-specific incidence was calculated using 2013 Waikato census data. Annualized and age-standardized incidence rates were calculated using Waikato mid-year population estimates. In each case, the 2013 New Zealand census population was taken as the direct standard.

Results

Clinical Characteristics of Infection and Sepsis

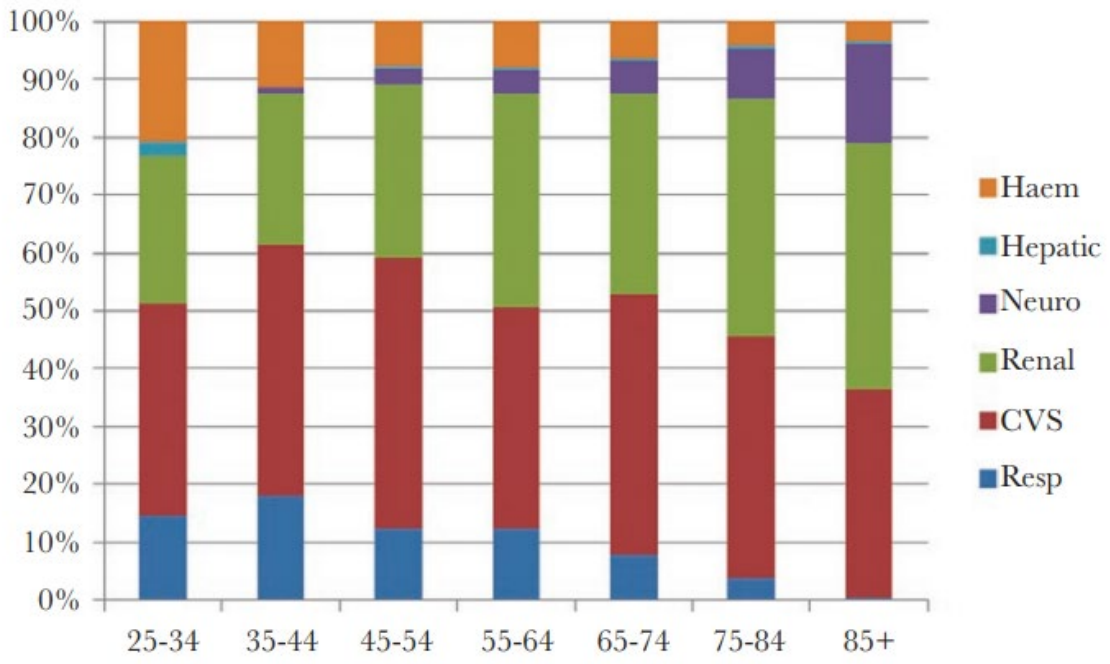
Over the 5-year study period, there were 209,730 acute overnight admissions to Waikato DHB facilities. Of these 8% (16,624) were assigned a primary diagnosis consistent with severe infection or sepsis. Secondary organ failure codes were recorded for 1701 (10.2%) of these cases. After excluding non-residents and 30-day readmissions, we identified 1643 individual sepsis episodes, the general characteristics of which are shown Table 8.1. The median length of stay (LOS) for sepsis was 6 days (range 0–203; interquartile range [IQR], 3–11) with in-hospital and 1-year mortality of 18.7% (308 of 1643) and 37.7% (620 of 1643), respectively. A total of 16.9% (278 of 1643) of sepsis episodes led to an ICU admission with a median ICU LOS of 1.75 days (range 0.25–49.75 days; IQR, 0.75–4). The respective in-hospital and 1-year mortality of sepsis for patients admitted to ICU was 33.8% (94 of 278) and 42.4% (118 of 278).

Infections of the bloodstream, heart, lower respiratory tract, and nervous system were classified as severe in >10% of cases so identified. The total organ failures taken to indicate sepsis in each age group are shown in Figure 8.1. With increasing age, the proportion of sepsis cases identified by respiratory and hematologic dysfunction fell whereas rates of neurologic, cardiovascular, and renal dysfunction increased. Proportionate multiorgan failure, comorbidity, ICU admission, and 1-year mortality are shown by age group in Figure 8.2. The proportion of patients admitted to ICU fell steadily with increasing age, from 30% of 25- to 34-year-olds to 3% amongst those 85 or older, despite the proportion of patients with multiorgan failure remaining constant.

Table 8.1. Basic descriptive characteristics for cases admitted with severe sepsis: number, proportions, and specific rates (per 100,000 population), July 2007 to June 2012, Waikato DHB resident population

Variable	N	%	Specific rate/100,000	95% CI
Female	779	47.4	450.5	419.4-483.3
Male	864	52.6	519.8	466.9-534.1
Ethnicity				
European	1161	70.7	467.8	441.3-495.5
Māori	418	25.4	617.9	560.1-680.1
Pacific	36	2.2	489.3	342.7-677.3
Asian	28	1.7	175.4	116.6-253.5
Age				
0-14	32	3.2	50.2	37.5-65.8
15-24	36	2.2	84.5	59.2-117.0
25-64	137	31.7	346.1	317.0-377.1
65+	384	62.9	2437.9	2291.5-2591.1
Median age (years) (IQR)	38 (13-67). Range 0-102			
Mortality				
In-hospital mortality	308	18.7		
One-year mortality	620	37.7		
ICU				
Admit to ICU	279	17.0		
Median days in ICU (IQR)	1.75 (0.75-4), Range 0.25-49.75			
NZ Dep Quintiles				
1-2	152	9.3	329.4	279.1-386.2
3-4	102	6.2	322.9	279.1-386.2
5-6	295	18.0	366.5	325.8-410.8
7-8	494	30.2	465.5	425.4-508.5
9-10	595	36.3	631.3	581.6-684.2
Year (July to June)				
2007/2008			66.9	58.6-75.9
			74.0	65.4-83.4
			86.7	77.4-96.8
			104.0	93.8-114.9
			115.3	104.6-126.7

Abbreviations: CI, confidence interval; Dep, deprivation; DHB, District Health Board; ICU, intensive care unit; IQR, interquartile range; NZ, New Zealand



Data are shown as proportions of all recorded organ failures in all episodes (n=1643).
Abbreviations: CVS, cardiovascular system; Haem, hematologic; Neuro, neurologic; Resp, respiratory

Figure 8.1. Organ failures identifying sepsis by age group.

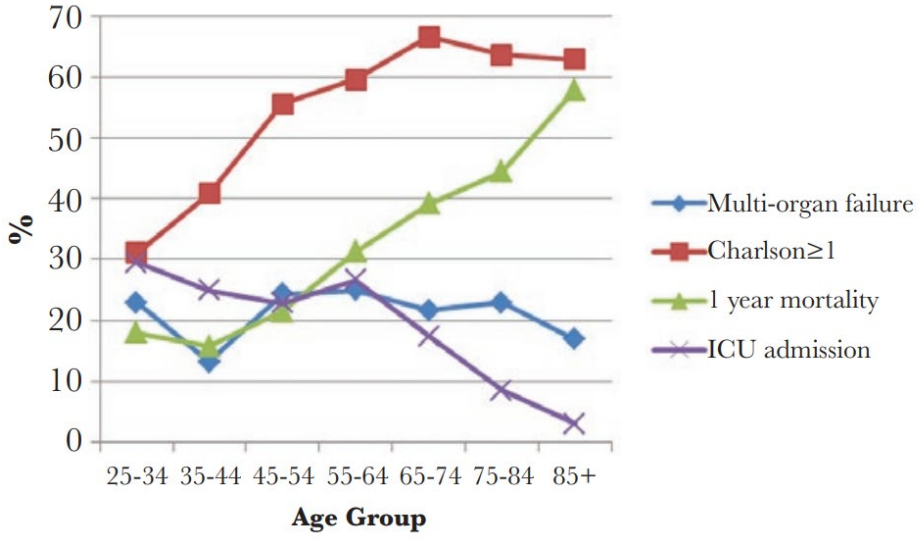


Figure 8.2. Proportions by age-group with multi-organ failure, comorbidity (Charlson score >1), 1-year mortality, and intensive care unit (ICU) admission.

Epidemiology of Sepsis

Sepsis was a disease of older patients, with approximately two thirds (63%) aged 65 or over (Table 8.2). Table 8.2 shows 5-year, age-standardized incidence and age-standardized rate ratios of sepsis by age, gender, and ethnicity. From 2007 to 2012, the age-standardized incidence of sepsis rose from 65.5 to 106.7 per 100000 population (rate ratio 1.62; 95% CI, 1.18–2.24) with two thirds (66.6%) of patients whose NZDep score could be assigned residing in the 2 highest quintiles of deprivation. Corresponding to this, the incidence of sepsis was highest in the most deprived NZDep quintile (age-standardized rate ratio 1.72 [95% CI, 1.5–1.97] compared with the least deprived quintile). Compared with non-Māori, Māori were more than 3 times as likely to suffer an episode of sepsis (age-standardized rate ratio 3.22; 95% CI, 2.85–3.65). This corresponded to an increased risk of in-hospital death with sepsis amongst Māori in all age groups. By age 0–19, 20–59, and ≥60, the annual rates (per 100000 population) of in-hospital death with sepsis were 0.77, 4.23, and 91 in the general population and 1.87, 12.58, and 188 amongst Māori.

Table 8.2. Five-year age standardized sepsis rates and rate ratios in the Waikato region

Variable	ASR	95% CI	ASRR	95% CI
Gender				
Female	419.9	390.5-449.2	1.0	--
Male	586.2	547.3-625.2	1.40	1.23-1.59
NZ Dep Quintiles				
1	341.5	286.9-396.1	1.00	--
2	364.5	292.8-436.1	1.07	0.92-1.24
3	364.2	322.8-405.6	1.07	0.92-1.24
4	376.5	342.7-410.3	1.11	0.95-1.28
5	578.8	532.2-625.4	1.72	1.50-1.97
Ethnicity				
Non-Māori	341.5	322.3-361.5	1.00	--
Māori	1100.5	966.8-1244.2	3.22	2.85-3.65
Study Year				
2007-08	65.5	57.5-74.4	1.00	--
2008-09	71.8	63.4-80.9	1.09	0.77-1.55
2009-10	83.0	74.1-92.6	1.26	0.90-1.76
2010-11	98.3	88.7-108.7	1.48	1.08-2.06
2011-12	106.7	96.8-117.3	1.62	1.18-2.24

Abbreviations: ASR, age-standardized rate; ASRR, ASR ratio; CI, confidence interval; Dep, deprivation; NZ, New Zealand.

Discussion

To our knowledge, this was the only non-US study in the decade prior to publication that estimated multiyear, population-based incidence of sepsis.(Fleischmann et al., 2016c) Findings parallel those of others from resource rich countries by showing a significant increase in the burden of sepsis borne disproportionately by aged, ethnic minority, and socioeconomically deprived populations.

New Zealand is an ideal country in which to study the epidemiology of infection. All acute in-patient care is provided by networks of publicly funded hospitals; all hospital discharges are coded using robust systems of quality control; detailed census-based population data are available; and extensive research has validated the local use of ICD-10-AM and the NZDep score in relation to the population burden of disease and a range of clinical and nonclinical outcomes.(M. G. Baker et al., 2012b; Pearson et al., 2013; Salmond et al., 2007) The clinical coding rules in use during this study did not include specific codes for sepsis, and we are not aware of any changes in the prevailing mechanism of healthcare funding that might have changed coding practices specifically to optimize hospital reimbursement. Against this background, the age-standardized incidence of sepsis rose by 63% over the 5-year period studied.

It has been suggested that the increase in incidence and falling mortality of sepsis seen in some studies can be explained by administrative "up-capture" and falling thresholds for defining organ failure.(Rhee et al., 2015b) We are confident that we have reported on a population of critically ill patients. The observed in-hospital and 1-year mortality for sepsis was 19% and 38%, respectively. In a system that carefully rations bed-days and ICU resources, the median length of hospital stay was 6 days, and 17% of our sepsis cases required ICU admission.(Streat S & Judson JA, 1994) The in-hospital mortality of the cohort as a whole (19%) was the same as that reported for 2012 in a large prospective study of sepsis in Australian and New Zealand ICUs.(K. M. Kaukonen et al., 2014) Of the 17% of patients admitted to ICU, the in-hospital mortality was 34%. All patients in our cohort had an infectious disease as a primary diagnosis. This strategy would have excluded cases in which infection was coded as a complicating rather than primary

illness. Our inclusion criteria were designed to detect community-onset sepsis cases. Nosocomial sepsis accounts for approximately 10% of total cases and carries a higher mortality than community-onset disease.(Tsertsvadze et al., 2016) Therefore, we are likely to have underreported nosocomial cases of sepsis and consequently the true sepsis-associated mortality in our population.

Sepsis as the primary cause of ICU admission in Australia and New Zealand rose from 7.2% to 11.1% between 1997 and 2012.(K. M. Kaukonen et al., 2014) By reporting population-based data, we provide support for the argument that this reflects an increase in sepsis in the populations that these units serve, something that was by no means clear based on ICU observations alone. The decision to admit to an ICU depends on such parameters as bed availability, the need for intubation, local precedent, and the skill mix of non-ICU wards. Varying proportions of sepsis cases are managed outside the ICU; therefore, the ICU incidence of sepsis represents the treated rather than the true incidence of disease.(Linde-Zwirble & Angus, 2004) The sequelae of sepsis exert major burdens of physical and cognitive impairment on survivors for years after the event, independently of ICU admission.(Iwashyna, 2010) That 83% of the episodes we report in this study were managed in general wards suggests that in New Zealand, sepsis is a common condition that is not primarily managed in the ICU, an important consideration when implementing interventions to improve sepsis outcomes.

It is relevant to consider why the incidence of sepsis would be on the increase while disproportionately affecting Māori and those of lower socioeconomic status. Life-course studies provide strong evidence that experience of ill health, risk behaviours, and social stress contribute to morbid events later in life.(Danese, 2013; Poulton et al., 2002) Chronic medical conditions, lower education and income, alcohol and tobacco use, elevated baseline high-sensitivity C-reactive protein, household overcrowding, and obesity are all linked to incident infectious disease, whereas lower socioeconomic status and (in the United States) lack of insurance contribute to mortality.(Koch et al., 2013; G. Kumar et al., 2014; H. E. Wang et al., 2012; H. E. Wang, Griffin, et al., 2013; H. E. Wang, Shapiro, Safford, et al., 2013b; Zhang & Howden-chapman, 2013) Baker et al used the need for hospital admission to define “serious” infection in a landmark study, making use of the New Zealand National Minimum Data Set.(M. G. Baker et

al., 2012a) Between 2 time periods, 1989–1993 and 2004–2008, there was a 51.3% relative increase in admission for infection-related illness against a 16.3% relative increase in total hospital admissions. In keeping with our findings, the rate of hospitalization for infection was more than double i) amongst Māori compared with non-Māori and ii) amongst the most socioeconomically deprived compared with the least. It is intriguing that hospital admission for infection has been rising in New Zealand since the early 1990s, a time of widening socioeconomic disparity and growing obesity, for example, amongst Māori and non-Māori alike.(M. G. Baker et al., 2012a; M. Ng et al., 2014) Exposures to risks of environment (ie, household overcrowding, social dislocation and socioeconomic deprivation), host (ie, smoking, diabetes, obesity, chronic disease, malnutrition), and organism (ie, colonization with *Staphylococcus aureus*, *Streptococcus pneumoniae* and other pathogens) are concentrated amongst deprived and marginalized populations and are likely to account for higher rates of sepsis. It would follow that the individual, societal, and financial burdens of sepsis will not be attenuated until entrenched health and socioeconomic disparities are addressed.

We acknowledge that our study has several limitations. An apparent increase in sepsis incidence could still be explained by a trend toward more complete capture of organ failure by clinical coding staff. However, we have pointed to the quality-control efforts in place to prevent this, and we have referenced published studies that would have been vulnerable to the same bias if present. We were unable to validate the coding definition of sepsis against a prospective sample of patients meeting confirmatory clinical criteria. This may have been valuable, for example, to explain the low proportion of cases amongst children less than 1 year old. In the report by Sundararajan et al, 8% of patients admitted with sepsis to hospitals in the state of Victoria from 1999 to 2003 were less than 1 year of age.(Sundararajan et al., 2005a) In our study, using the same coding algorithm, only 0.7% of cases were in this age group. It is possible that natural or epidemic variation in the incidence of important infectious illnesses contributed to the reported incidence of sepsis. Finally, the findings in one region of New Zealand may not extrapolate to all others or indeed to any other jurisdiction. Therefore, ongoing research is needed to describe the incidence of sepsis at a national and international level. Existing methods seem to be sufficient to document significant disparities in sepsis incidence based on age, socioeconomic status, and ethnicity. Given the paucity of data describing sepsis morbidity and mortality, their use should be

prioritized to generate accurate comparisons between different healthcare settings and populations.(Fleischmann et al., 2016b)

Chapter 9: A whole-of-system quality improvement approach to improving sepsis outcomes

Abstract

Background: Mortality, length of stay and quality measures were studied before and after implementing a programme of quality improvement at Waikato Hospital, a tertiary academic medical centre in the upper North Island of New Zealand.

Methods: The "Raise the Flag" programme was a multi-dimensional quality improvement initiative focussed on the use of the "Red Flag Sepsis" concept developed by the UK Sepsis Trust and the UK National Institute of Clinical Excellence (NICE). The programme was launched in August 2018. Evaluation included assessment of outcomes in administrative data, supplemented by a clinical record audit to document changes in resuscitation practice. The primary outcome of all analyses was mortality, measured in-hospital and at 30 and 90 days. Completion of the 3-hour sepsis resuscitation bundle was measured as an intermediate outcome.

Results: The post-implementation period was associated with reduced adjusted odds of acute in-hospital death (OR 0.83, 95% CI 0.7-0.98, $p<0.05$) and a trend toward lower 30-day mortality (OR 0.86, 95% CI 0.74-1.00). Age, co-morbidity, and socioeconomic deprivation were independently associated with mortality at 30 and 90 days. An audit of 266 clinical records spanning programme launch showed significant improvement in completion of the sepsis resuscitation bundle within 3 hours (from 60% to 75%, $p=0.008$). Crude mortality was lower at 90 days amongst those who received the 3-hour bundle (25.8% vs 38.1%, $p=0.042$) but this difference did not persist after adjustment for confounding variables (OR 0.59, 95% CI 0.29-1.16, $p>0.05$). The incidence rate ratio was 2.2 comparing Māori with non-Māori. The adjusted odds ratio of death was significantly lower in cases where a gram-negative pathogen was identified in blood culture (OR 0.20, 95% CI 0.08-0.55, $p<0.01$).

Conclusion: A whole-of-system approach to improving sepsis care led to early improvements in the delivery of sepsis resuscitation and reduction in hospital mortality.

Introduction

Considerable evidence has accumulated to show that programmes of quality improvement can improve sepsis outcomes. (J. Marshall et al., 2010; M.M. Levy et al., 2015) World Health Assembly Resolution 70.7 encourages member-states to invest in these programmes to reduce sepsis morbidity and mortality.(Reinhart et al., 2017) To justify these investments, local evidence must accumulate to demonstrate that practice improvements are effective in diverse health systems and settings.

In New Zealand, a quarter of hospital admissions are associated with infectious diseases known to cause sepsis.(P. Huggan et al., 2021) In Chapter 8 it was shown that 17% of patients admitted with sepsis presenting to Waikato Hospital were admitted to an intensive care unit (ICU), and 19% died in-hospital. It was also demonstrated that the incidence of hospital admission with sepsis is significantly higher amongst Māori, the indigenous people of New Zealand. Concern for these findings led to design and implementation of a whole-of-system quality improvement programme, called "Raise the Flag". Outcomes before and after introduction of this programme are reported here.

Methods

Setting and Context

10% of the resident New Zealand population (485,202 people) live in the Waikato region, 24% of whom identify as Māori.(Statistics New Zealand, n.d.) Waikato Hospital is a 600-bed facility situated in the regional centre, which provides tertiary referral services to the upper North Island and acute services to four other hospitals in the Waikato district. In 2015, 10% of New Zealand's emergency department presentations are managed across our acute hospital network, and two thirds of these (68%) are managed at Waikato Hospital.(Ministry of Health, 2016)

From October 2017, Waikato District Health Board introduced the New Zealand Early Warning System (NZ-EWS) into practice in its adult medical and surgical facilities. The NZEWS is based on the UK National Early Warning Score. Contemporaneously, a national sepsis management

guideline was published by the New Zealand Best Practice Advocacy Centre.(Bpacnz Guidelines : Sepsis: Recognition, Diagnosis and Early Management, 2021) This was based on guidance published in 2016 by NICE. These are all aligned, in that the NZEWS, BPAC and NICE guidance all reference early warning score response variables developed and validated in the United Kingdom. (Badriyah et al., 2014)Where infection is suspected as their underlying cause, these are termed "Red Flags". Red Flag findings have been incorporated into a "Red Flag Sepsis Screening and Action Tool" (RFSSAT) by the United Kingdom Sepsis Trust.(Kopczynska, Sharif, Cleaver, Spencer, Kurani, et al., 2018) For high-risk, treatment-eligible patients, the RFSSAT recommends delivery of a streamlined version of the Surviving Sepsis Campaign (SSC) resuscitation bundle. This is popularly known as the "Sepsis Six".(Daniels et al., 2011) Our operational aim was to deliver the bundle within one hour, in line with prevailing SSC recommendations at the time of programme development.(Rhodes et al., 2017) However, we judged that 3-hour bundle completion represented acceptable care for the purposes of programme evaluation.(Pruinelli et al., 2018)

Intervention

With executive support for improvements in sepsis care, we were able to develop and implement a quality-improvement programme focused on recognition and resuscitation of Red Flag Sepsis. Development of the programme was led by a multi-disciplinary Sepsis Action Group (SAG), which included quality improvement experts, rural health specialists, data analysts and consumer representatives, including a Māori consumer representative. External advisors included the UK Sepsis Trust (UKST) and the New South Wales-based Clinical Excellence Commission (CEC). The SAG adapted the RFSSAT to practice in New Zealand by population (adult, paediatric and maternal) and setting (primary or acute care). These are available in Appendix 3. An accompanying guideline was published outlining appropriate steps in the management of persistent hypoperfusion and shock states (Appendix 3). This hypoperfusion pathway and the versions of the RFSSAT developed by the SAG can be found at www.sepsis.org.nz. Prior to implementation, the programme was endorsed by the hospital's Māori health team, and the Iwi Māori Council, an advisory group made up of iwi (tribal) stakeholders and Māori health advocates.

The RFSSAT was launched to all frontline services and facilities in August 2018 with a planned one year implementation period (to August 2019). Interventions to support its uptake included: recruitment of a nurse coordinator for sepsis quality improvement; an e-Learning package for all frontline staff; in-person orientation to sepsis care standards for all new clinical staff; departmental and institutional grand rounds; small group teaching for nurses and junior doctors; internet and social media posts elevating the topic of sepsis and introducing the RFSSAT; publication of a sepsis-specific antimicrobial guideline; site visits by clinical leads to all frontline clinical areas; an in-person visit of the SAG clinical lead to centres of excellence in the UK; local modification of the NZEWS chart to include a sepsis screening prompt for scores of ≥3 in the setting of suspected infection; distribution of quarterly newsletters for the year following launch; publication of routine data demonstrating sepsis admission rates; prospective audit of intensive care unit (ICU) and high-dependency unit (HDU) sepsis cases with feedback to treating staff; engagement with national and regional print media; publication of a progress report on World Sepsis Day 2019. The SAG reviewed and reported on programme delivery throughout the post-implementation period. Due to New Zealand's elimination approach to SARS CoV-2, normal hospital services were preserved through all periods of implementation and data collection.

Programme Evaluation

The evaluation framework we established is shown in Table 9.1. Study planning and execution was informed by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance.(Elm et al., 2007) Based on the results of the New South Wales "Sepsis Kills" programme, our *a priori* programme goals were to reduce sepsis-associated mortality and length of stay.(Burrell et al., 2016) These were therefore selected as primary and secondary evaluation endpoints, with mortality measured at acute hospital discharge, at 30 days and at 90 days. We postulated that as a system-wide effort to improve care, changes would accrue across the acute in-patient journey and over time that could not be measured simply by time-based measures of acute resuscitation. Completion of the resuscitation bundle within 3 hours was therefore assessed as an intermediate outcome.

Table 9.1. Evaluation framework for the "Raise the Flag" sepsis quality improvement programme at Waikato Hospital.

Case definition and data source	Cohort	Primary outcome	Secondary outcomes
ICD-10-AM discharge diagnosis codes in adults (aged ³15) Primary diagnosis code consistent with infection AND one or more secondary codes consistent with sepsis-associated organ failure	Extended baseline cohort (May 2015-July 2019) Post-implementation cohort (August 2019-June 2021) n=4268	Mortality	Hospital, ICU and acute in-patient length of stay Association between mortality and age, co-morbidity, ethnicity and socio-economic deprivation
As above plus review of clinical records	Pre-launch baseline cohort (December 2017-July 2018) Post-launch cohort (August 2018-December 2019) n=266	Completion of 3 hour resuscitation bundle	Association of mortality with 1 hour and 3 hour bundle completion

Abbreviations: ICD-10-AM, International Classification of Disease, 10th edition, Australian Modification

Outcomes in administrative data

As shown in Figure 9.1, sepsis cases were identified from May 2015 to July 2021 using a method developed to allow reporting of sepsis numbers in routine data.(P. Huggan et al., 2021). For this work, we chose to use the more restrictive primary code set used by Martin *et al* as translated from ICD9 to ICD10 by Sundararajan *et al.*(Sundararajan et al., 2005b) This change was made to more accurately reflect disease caused by invasive bacterial infection and to expand the number of qualifying organ failures (see Appendix 1). Otherwise, case selection was similar to earlier work using discharge coding to estimate local sepsis incidence. Cases were adult (aged 15 or over) overnight admissions direct to our facility that were associated with i) a primary diagnosis code consistent with sepsis, and ii) a secondary code consistent with major organ failure. For each case we recorded age, prioritized ethnicity, the Charlson co-morbidity index (according to the method of Quan *et al*), ICU admission, ICU length of stay, in-patient length of stay (excluding admissions to rehabilitation facilities), and mortality measured at discharge, at 30 days and at 90 days.(Quan et al., 2005) Noting evidence of delays of up to two years between the introduction of quality interventions and their associated outcomes, cases were divided into an

extended-baseline cohort and a post-implementation cohort (Table 9.1 and Figure 9.1).(Burrell et al., 2016) A final record extract was undertaken on the 16th October 2021. This included an address-based measure of socioeconomic deprivation and complete mortality records through to the 30th September 2021 (n=4268).

Clinical record audit

3-hour bundle implementation and changes in clinical management were studied using individual clinical records (see Table 9.1). Except during a planned reporting period (June-August 2019) a random sample of at least 15 records was reviewed monthly from December 2017 to December 2019. A screening step excluded those who did not have documented evidence of infection or high-risk (Red Flag) findings at presentation. Also excluded were cases deemed ineligible for resuscitation by a senior clinician at "Time Zero". Time Zero (T0) was further defined as the first point at which patients became eligible for initiation of the sepsis resuscitation bundle, determined by i) documented symptoms or signs of infection and ii) concurrent high-risk findings.

In this sample we documented final clinical diagnosis, hospital length of stay and delivery of initial bundle elements. These are: delivery of antibiotics; fluid bolus if indicated; oxygen therapy if indicated; sampling for blood culture and serum lactate. Oxygen was deemed necessary at T0 only if oxygen saturations were <92%, and a fluid bolus only if systolic blood pressure <90mmHg or lactate ≥ 2 mmol/l. Patients who did not require these interventions were recorded as having received appropriate resuscitation in these categories. We used a strict definition to define a subset of patients with shock and a high risk of a poor short-term outcome. Patients were defined as having shock if presenting with i) hypotension (systolic blood pressure <90mmHg or a fall of >40mmHg against normal findings) and ii) a first serum lactate ≥4. (JAMA. 2016 Feb 23; 315(8): 775–787, J Thorac Dis. 2016 Jul; 8(7): 1388–1390). Based on eligibility criteria used in studies of Early Goal Directed Therapy trials, a larger group of patients with haemodynamic instability was identified with either i) a first serum lactate ≥4 *or* ii) hypotension.(Gaieski et al., 2010)

The results of all blood cultures taken within 24 hours of T0 were identified in our Laboratory Information System (LIS). Other than coagulase negative staphylococci, Micrococci and Corynebacteria, all positive blood cultures were assumed to be pathogenic, and were further grouped into the following categories: aerobic gram-positive, aerobic gram-positive and anaerobic. This hierarchy was also used to classify patients with polymicrobial bacteraemia (ie patients with *E.coli* and *E.faecalis* or *E.coli* and *B.fragilis* in blood would be allocated to the aerobic gram-positive group).

Statistical analysis

Well described methods were used to determine rates, odds ratios and 95% confidence intervals. Planned analyses are shown in Table 9.1. Regional population estimates derived from the 2018 New Zealand Census were used to estimate age-standardised sepsis incidence. Differences were examined by chi-square test for categorical variables and results considered significant at a p-value of less than 0.05. Mean, median and interquartile ranges were reported for time to antibiotic and fluid delivery, and differences examined using the Mann–Whitney U test and Median test. Logistic regression was used to calculate adjusted odds ratios for individual variables against outcomes of interest. All data analyses were performed in IBM SPSS statistics 27 (New York, United States).

Ethics

As a low-risk observational study, this work was deemed out-of-scope by the Health and Disability ethics Committee. The study was registered prospectively with the local audit committee.

Results

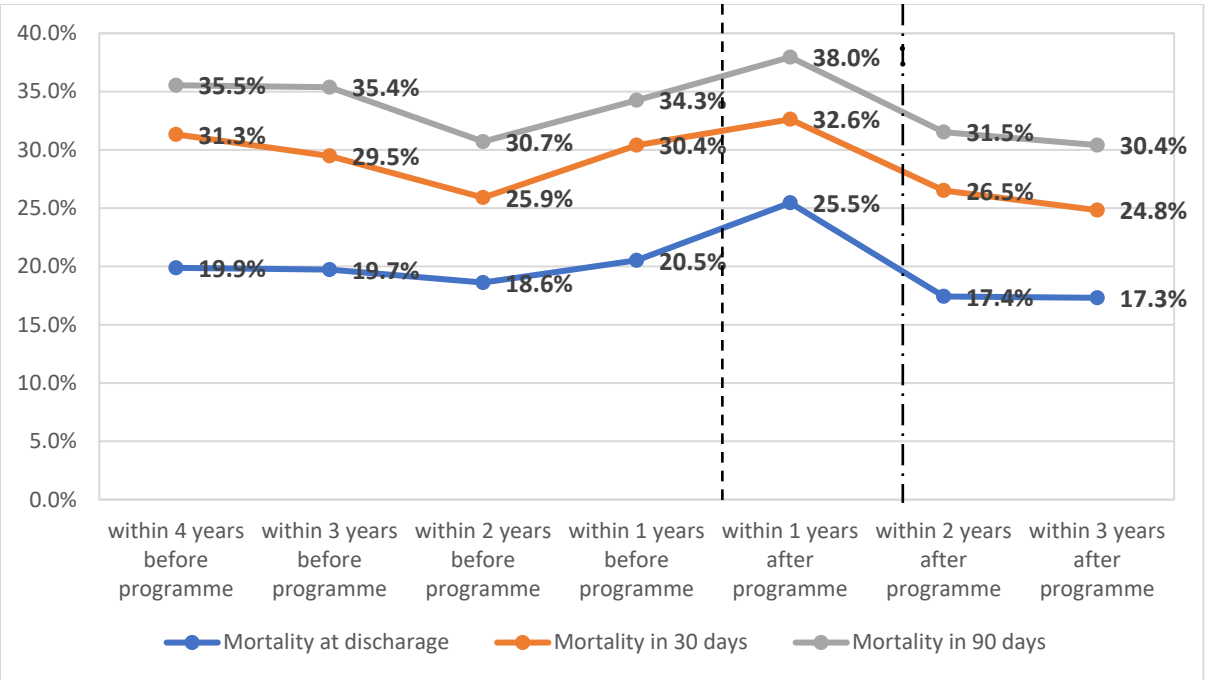


Figure 9.1 Annual in-hospital, 30-day and 90-day mortality in extended-baseline and post-implementation periods.

The first dashed line marks launch of the programme in August 2018, and the second marks the end of the implementation period in August 2019.

Table 9.2 Characteristics of adult sepsis cases identified in administrative data from February 2015 to June 2021, Waikato Hospital.

Characteristic	Before Aug 2019		From Aug 2019		Total		P-value
Gender							
Female	1041	42.8%	738	40.2%	1779	41.7%	0.23
Male	1391	57.2%	1098	59.8%	2489	58.3%	
Ethnicity							
Māori/Pacific	827	34.0%	621	33.8%	1448	33.9%	0.98
Non-Māori and non-Pacific	1605	66.0%	1215	66.2%	2820	66.1%	
Age group (years)							
15-54	449	19.2%	315	17.8%	764	18.6%	0.69
55-74	956	40.8%	709	40.1%	1665	40.5%	
75+	936	40.0%	744	42.1%	1680	40.9%	
Unknown	91		68		159		
NZ deprivation (quintile)							
1	199	8.2%	168	9.2%	367	8.6%	0.38
2	168	6.9%	138	7.5%	306	7.2%	
3	419	17.3%	285	15.6%	704	16.5%	
4	726	30.0%	569	31.1%	1295	30.4%	
5	912	37.6%	672	36.7%	1584	37.2%	
Unknown	8		4		12		
Charlson Score							
0	878	36.1%	770	41.9%	1648	38.6%	0.001
1	372	15.3%	274	14.9%	646	15.1%	
2	494	20.3%	356	19.4%	850	19.9%	
3+	688	28.3%	436	23.7%	1124	26.3%	
Overall LOS (days)							
Median (IQR)	7.3 (3.8-14.9)		7.1 (3.5-14.3)		7.3 (3.7-14.6)		0.74
Mean	13.9		13.3		13.7		0.14
In ICU							
No	1981	81.5%	1502	81.8%	3483	81.6%	0.77
Yes	451	18.5%	334	18.2%	785	18.4%	
ICU LOS (days)							
Median (IQR)	2.4 (1.3-5.7)		2.2 (1.3-4.6)		2.3 (1.3-5.4)		0.47
Mean	5.3		4.3		4.9		0.64
Mortality at discharge	517	21.3%	319	17.4%	836	19.6%	0.002
Mortality in 30 days	728	29.9%	472	25.7%	1200	28.1%	0.002
Mortality in 90 days	846	34.8%	569	31.0%	1415	33.2%	0.009
Total	**2432**		**1836**		**4268**		

Abbreviations: LOS, length of stay; IQR, inter-quartile range; ICU, intensive care unit

Sepsis in administrative data, 2015-2021

6312 episodes with primary infection codes were identified between May 2015 and June 2021. Mortality at 30 days was 28% (1200/4268) and 11% (229/2044) respectively amongst those with and without secondary organ failure codes. 4268 cases meeting criteria for selection are described in Table 9.2 and Figure 9.1. 2432 were included in the extended-baseline period and 1836 in the post-implementation period. The highest (33%) and lowest (25%) annual 30-day mortality rates were reported in the three years following launch of the programme in August 2018 (Figure 9.1). Sepsis was more common amongst men (58% vs 42%), amongst those aged 55 and over (81% of cases), and amongst those with significant co-morbidities based on a Charlson score ≥1 (61% of cases). Multi-morbidity (>1 co-morbidity) was identified in 46% of cases and over a quarter (26%) had 3 or more Charlson co-morbidities. Over two thirds (68%) of all cases were recorded as living in the 2 highest quintiles of socioeconomic deprivation. One third (34%) of all patients were of Māori or Pacific ethnicity (Table 9.2). Crude mortality was lower in the post-implementation group (for example 26% vs 30% 30-day mortality, p=0.002, Table 10.2). However, the proportion of patients with no significant co-morbidity was also higher in the post-implementation period (proportion of patients with a Charlson score of zero, 42% vs 36%, p=0.001). There was no change in ICU or in-patient length of stay (LOS).

The results of multivariable logistic regression in are shown in Table 9.3. Admission during the post-implementation period was associated with reduced odds of acute in-hospital death (OR 0.83 (95% CI 0.7-0.98, p <0.05) and a non-significant trend towards lower odds of 30-day mortality (OR 0.86, 95% CI 0.74-1.00). There was a significant association with mortality and socioeconomic deprivation. This was present at all time points amongst those in NZDep quintile 5 (for example, odds of 30-day mortality 1.37, 95%CI 1.02-1.83, p<0.05). Age was strongly associated with mortality (OR of 30-day mortality 1.04 for every additional year of age (95% CI 1.03-1.05, p<0.001)). The odds ratio (OR) for 30-day mortality was 2.55 (95% CI 2.04-3.17, p<0.001) for those with a Charlson score of 1, rising to an OR of 6.37 for those with a Charlson score of 3 or more (95% CI 5.22-7.78, p<0.001).

Clinical Record Audit

Of 338 clinical records screened during the clinical audit period, we excluded 16 cases who were for palliation alone, 12 for whom no infection was suspected, and 44 who did not manifest high-risk findings. Table 9.4 and Table 9.5 show the general characteristics and blood culture findings for 266 treatment and audit-eligible cases. 117 baseline cases were compared with 149 managed after programme launch in August 2018. Most (n=197, 74%), arrived by ambulance, most (178, 67%) had high-risk criteria on arrival at hospital and the majority (230, 87%) developed high-risk findings during their Emergency Department stay. 186 (69.9%) had two or more high-risk criteria at T0. 27 (10%) met a strict definition of septic shock and almost half (123, 46%) were haemodynamically unstable. A third of patients were transferred to the ICU or high dependency unit after T0, although 154 (57.9%) patients were eligible for ICU referral based on *a priori* recommendations (Appendix 3). Of this group, only 57 (37%) were actually referred to an ICU team and 25 (16%) were ultimately managed in the ICU. Of the 32 patients for whom ICU admission was declined, only 14 were clearly documented to have co-morbidities limiting ICU eligibility.

Table 9.3. Adjusted odds ratios for mortality using logistic regression in 4268 adult sepsis cases admitted to Waikato Hospital, 2015-2021

Characteristic	Mortality at discharge	Mortality at 30 days	Mortality at 90 days
Gender			
Female	Reference	Reference	Reference
Male	0.86 (0.73-1.01)	0.87 (0.75-1.01)	0.89 (0.77-1.03)
Ethnicity			
Māori/Pacific	Reference	Reference	Reference
Non-Māori and non-Pacific	1.16 (0.95-1.41)	1.04 (0.87-1.24)	0.97 (0.82-1.15)
Age (years, continuous)	1.03 (1.02-1.03)***	1.04 (1.03-1.05)***	1.04 (1.03-1.04)***
NZ deprivation (quintile)			
1	Reference	Reference	Reference
2	1.36 (0.90-2.06)	1.21 (0.83-1.77)	1.36 (0.95-1.96)
3	1.45 (1.02-2.07)*	1.43 (1.04-1.96)*	1.44 (1.06-1.95)*
4	1.30 (0.93-1.81)	1.30 (0.97-1.74)	1.44 (1.09-1.91)*
5	1.47 (1.06-2.04)*	1.37 (1.02-1.83)*	1.39 (1.05-1.85)*
Unknown			
Charlson Score			
0	Reference	Reference	Reference
1	2.72 (2.10-3.52)***	2.53 (2.00-3.19)***	2.55 (2.04-3.17)***
2	1.98 (1.53-2.57)***	2.36 (1.89-2.95)***	2.66 (2.16-3.28)***
3+	4.76 (3.81-5.95)***	6.37 (5.22-7.78)***	7.24 (5.98-8.77)***
Sepsis group based on time			
Before Aug 2019	Reference	Reference	Reference
From Aug 2019	0.83 (0.70-0.98)*	0.86 (0.74-1.00)	0.90 (0.78-1.04)

All variables in the table were included in the regression and all odds ratios were adjusted for other variables.
* p-value <0.05, ** p-value <0.01, ***p-value <0.001

Table 9.4 Characteristics of 266 high-risk, treatment-eligible patients with sepsis at Waikato Hospital

Characteristic		**N (%)**
Gender	Female	104 (39.1)
	Male	162 (60.9)
Ethnicity	Māori or Pacific	77 (28.9)
	Non-Māori/non-Pacific	196 (73.7)
	(Missing)	2 (0.8)
Mean age	Māori or Pacific	58.80
	Non-Māori/non-Pacific	70.30
	Overall	67.40
Charlson Score	0	112 (42.1)
	1	42 15.7)
	2	40 (15)
	≥3	66 (24.8)
	Missing	6 (2.2)
Number of Red Flags	1	79 (29.7)
	2	72 (27.1)
	3	49 (18.4)
	4	41 (15.4)
	5	14 (5.3)
	6	9 (3.4)
	7	1 (0.4)
Haemodynamic status	Septic shock* Haemodynamic instability**	27 (10.2) 123 (46.2)
Mode of arrival	Ambulance	197 (74.1)
	GP referral, own transport	12 (4.5)
	Self-presentation	22 (8.3)
	Not known	35 (13.2)
Location at T0	Emergency Department	230 (86.5)
	General Ward	35 (13.2)
	HDU	1 (0.4)
Disposition After T0	General Ward	177 (66.5)
	HDU	60 (22.6)
	ICU	25 (9.4)
	Mortuary	4 (1.5)
Source of Infection (per hospital discharge summary)	Pneumonia	70 (26.4)
	Urinary tract	58 (21.8)
	Skin/soft tissue	40 (15.0)
	No source identified	34 (12.8)
	Abdominal viscera	30 (11.3)
	Endovascular	10 (3.8)
	Bone/joint	7 (2.6)
	Device relate infection	4 (1.5)
	Meningitis/CNS infection	1 0.4)
	Other	12 (4.5)

Abbreviations: GP, general practitioner; HDU, high dependency unit; ICU, intensive care unit; CNS, central nervous system

The most common (clinical) discharge diagnosis was pneumonia (25% of cases), even with the exclusion of relevant ICD-10-AM codes from our abstraction method. This was followed by urinary tract and soft tissue infection. 236 (89%) patients had at least one set of cultures taken, yielding 111 individual bacterial isolates from 103 patients (Table 9.5). Blood cultures were categorised as gram-positive in 56% of these cases, 40% were gram-positive, and 4% were anaerobic. As shown in Table 9.5, in blood culture, *Escherichia coli* was isolated in over a third of positive samples. Together, beta-haemolytic streptococci and *Staphylococcus aureus* accounted for over a quarter (28%).

Table 9.5 111 bacterial isolates in blood culture from 104 patients with infection and high-risk clinical findings

Organism	Number of Isolates
*Escherichia coli**	39 (35.1)
Beta-haemolytic streptococci Group A Group B Group G	 11 (9.9) 4 (3.6) 6 (5.4)
*Staphylococcus aureus***	10 (9.0)
Streptococcus pneumoniae	7 (6.3)
Klebsiella pneumoniae	6 (5.4)
Pseudomonas aeruginosa	4 (3.6)
Proteus mirabilis	3 (2.7)
Serratia marcescens	3 (2.7)
Enterococcus faecalis	3 (2.7)
Other	15 (13.5)
Total	111 (100)

*4(10%) identified with *extended-spectrum beta-lactamase* activity.

**1 (10%) *methicillin resistant Staphylococcus aureus*

Comparison of management before and after programme launch, and the adjusted odds for bundle completion following logistic regression are shown in Table 9.6 and 8.7 respectively. The resuscitation bundle was delivered within one hour in 32% of cases overall, with no change observed in the post-launch period (p=0.53). However, delivery of the resuscitation bundle at 3 hours improved from a baseline of 59.8% to 75.2% (p=0.008). As shown in Table 9.7, this

association remained statistically significant after adjustment, with post-implementation odds of 3-hour bundle completion increasing to 1.93 (95% CI 1.11-3.35, p<0.05). Table 9.7 also demonstrates that those aged 75 and over were less likely to receive the resuscitation bundle within 3 hours (adjust OR 0.38, 95% CI 0.16-0.88, p<0.05). The odds of bundle delivery within one hour were highest for patients subsequently found to have gram-positive organisms in blood culture (adjusted OR 3.09, 95% CI 1.44-6.64, p<0.01) and lowest in patients with significant co-morbidity (adjusted OR of 0.41 for Charlson scores of ≥3, 95% CI 0.19-0.87, p<0.05).

Relationship between bundle completion and mortality

The characteristics of patients receiving (and not receiving) the resuscitation bundle within 3 hours are shown in Table 9.8. The adjusted odds for mortality in the clinical audit cohort are shown in Table 9.9. Crude mortality was lower at all time points in the group who received the 3-hour bundle (Table 9.8). After adjusting for confounding variables, receipt of the 3-hour bundle was not associated with improved mortality (for example, adjusted OR for 30-day mortality 0.64, 95% CI 0.31-1.30). Higher adjusted odds of death were seen in the elderly (30-day odds of death in those aged 75 and over 10.36, 95% CI 2.8-38.8, p<0.001) and in those with significant co-morbidity (OR 6.04 for 30 day mortality if Charlson Score ³3, 95% CI 2.52-14.46, p<0.001). Gram-positive infections were associated with lower odds of death (for example, adjusted odds ratio for 30-day mortality 0.20, 95% CI 0.08-0.55).

Table 9.10 shows crude comparisons in the 123 patients with haemodynamic instability based on receipt of the sepsis resuscitation bundle with three hours. Logistic regression was not undertaken in this group due to sample size. Receiving the bundle within 3 hours was associated with a crude 3.5 day reduction in median hospital stay (7.5 to 4 days, p=0.003), together with a trend toward lower mortality at 90 days (from 43.8% to 26.4% (p=0.067)). Patients with no pathogen identified in blood culture appeared to be more likely to receive the 3-hour bundle (p=0.021).

Table 9.6 Comparison of 266 patients with high-risk findings admitted to Waikato Hospital from December 2017 to December 2019

Characteristic	Before Aug 2018		From Aug 2018		Total		P-value
Gender							
Female	46	39.3%	58	38.9%	104	39.1%	0.948
Male	71	60.7%	91	61.1%	162	60.9%	
Ethnicity							
Māori/Pacific	29	24.8%	46	31.3%	75	28.4%	0.230
Non-Māori and non-Pacific	88	75.2%	101	68.7%	189	71.6%	
Unknown			2		2		
Age group (years)							
15-54	25	22.5%	34	24.6%	59	23.7%	0.597
55-74	33	29.7%	48	34.8%	81	32.5%	
75+	53	47.7%	56	40.6%	109	43.8%	
Unknown	6		11		17		
Pathogen							
No pathogen identified	66	56.4%	97	65.1%	163	61.3%	0.364
Obligate anaerobe	1	0.9%	3	2.0%	4	1.5%	
Gram-positive	20	17.1%	21	14.1%	41	15.4%	
Gram-positive	30	25.6%	28	18.8%	58	21.8%	
Charlson Score							
0	49	43.0%	63	43.2%	112	43.1%	0.962
1	18	15.8%	24	16.4%	42	16.2%	
2	16	14.0%	24	16.4%	40	15.4%	
3+	31	27.2%	35	24.0%	66	25.4%	
Unknown	3		3		6		
Resuscitation bundle ≤1 hour							
No	82	70.1%	99	66.4%	181	68.0%	0.527
Yes	35	29.9%	50	33.6%	85	32.0%	
Resuscitation bundle ≤3 hours							
No	47	40.2%	37	24.8%	84	31.6%	0.008
Yes	70	59.8%	112	75.2%	182	68.4%	
Time to antibiotic delivery from Time Zero (minutes)							
Median (IQR)	51 (22-121)		62 (33-109)		60 (27-115)		0.585
Mean	133		146		140		0.675
Time to fluid delivery from Time Zero (minutes)							
Median (IQR)	32 (10-74)		39 (15-71)		36 (14-73)		0.584
Mean	62		69		66		0.059
Total	**117**		**149**		**266**		

Table 9.7 Adjusted odds ratios for resuscitation bundle completion at 1 and 3 hours using logistic regression in 266 adult sepsis cases admitted to Waikato Hospital, 2017-2019

Characteristic	Resuscitation bundle completed in 1 hour	Resuscitation bundle completed in 3 hours
Gender		
Female	-	-
Male	1.65 (0.91-3.01)	1.33 (0.75-2.36)
Ethnicity		
Māori/Pacific	-	-
Non-Māori and non-Pacific	1.87 (0.93-3.75)	1.72 (0.89-3.34)
Age group (years)		
15-54	-	
55-74	0.61 (0.29-1.30)	0.74 (0.32-1.70)
75+	0.49 (0.22-1.06)	0.38 (0.16-0.88)*
Pathogen		
No pathogen identified	-	-
Obligate anaerobe	2.37 (0.21-26.32)	1.28 (0.12-13.92)
Gram-positive	3.09 (1.44-6.64)**	1.10 (0.49-2.47)
Gram-positive	1.40 (0.70-2.81)	0.55 (0.28-1.07)
Charlson Score		
0	-	-
1	0.89 (0.40-2.01)	0.60 (0.26-1.36)
2	0.42 (0.16-1.08)	0.96 (0.41-2.28)
3+	0.41 (0.19-0.87)*	0.83 (0.41-1.71)
Unknown	0.93 (0.08-10.57)	0.45 (0.05-3.94)
Before or after Aug 2018		
Before Aug 2018	-	-
After Aug 2018	1.34 (0.76-2.35)	1.93 (1.11-3.35)*

All variables in the table were included in the regression and all odds ratios were adjusted for other variables.

* p-value <0.05, ** p-value <0.01, ***p-value <0.001

Table 9.8. Patient characteristics based on completion of the sepsis resuscitation bundle within 3 hours, Waikato Hospital December 2017- December 2019

Characteristic	Resuscitation bundle incomplete at 3 hours		Resuscitation bundle complete at 3 hours		P-value
Gender					
Female	36	42.9%	68	37.4%	0.393
Male	48	57.1%	114	62.6%	
Ethnicity					
Māori/Pacific	25	29.8%	50	27.8%	0.594
Non-Māori and non-Pacific	59	70.2%	130	72.2%	
Unknown			2		
Age group (years)					
15-54	12	15.2%	47	27.6%	0.030*
55-74	22	27.8%	59	34.7%	
75+	45	57.0%	64	37.6%	
Unknown	5		12		
Pathogen					
No pathogen identified	47	56.0%	116	63.7%	0.200
Obligate anaerobe	1	1.2%	3	1.6%	
Gram-positive	11	13.1%	30	16.5%	
Gram-positive	25	29.8%	33	18.1%	
Charlson Score					
0	29	35.4%	83	46.6%	0.371
1	18	22.0%	24	13.5%	
2	13	15.9%	27	15.2%	
3+	22	26.8%	44	24.7%	
Unknown	2		4		
Overall LOS (days)					
Median (IQR)	7.0 (4.0-10.8)		5.0 (3.0-11.0)		0.095
Mean	8.3		8.6		0.118
Mortality at discharge	16	19.0%	24	13.2%	0.214
Mortality in 30 days	25	29.8%	37	20.3%	0.091
Mortality in 90 days	32	38.1%	47	25.8%	0.042*
Total	**84**		**182**		

Table 9.9 Adjusted odds ratios for mortality using logistic regression in 266 adult sepsis cases admitted to Waikato Hospital, 2017-2019

Characteristic	Mortality at discharge	Mortality in 30 days	Mortality in 90 days
Gender			
Female			
Male	1.19 (0.55-2.56)	1.50 (0.74-3.05)	1.36 (0.69-2.66)
Ethnicity			
Māori/Pacific			
Non-Māori and non-Pacific	1.14 (0.44-2.94)	1.86 (0.79-4.40)	1.97 (0.86-4.51)
Age group (years)			
15-54			
55-74	2.14 (0.53-8.67)	4.58 (1.17-17.94)	2.76 (0.85-8.93)
75+	5.63 (1.49-21.31)*	10.36 (2.77-38.84)***	8.41 (2.72-26.01)***
Unknown	-	2.42 (0.33-17.72)	3.38 (0.68-16.73)
Pathogen			
No pathogen identified			
Obligate anaerobe	-	2.44 (0.28-21.30)	-
Gram-positive	0.43 (0.14-1.37)	0.60 (0.21-1.67)	0.40 (0.14-1.13)
Gram-positive	0.17 (0.05-0.60)**	0.20 (0.08-0.55)**	0.30 (0.13-0.71)**
Charlson Score			
0			
1	2.38 (0.80-7.05)	1.93 (0.70-5.34)	1.89 (0.72-4.99)
2	1.96 (0.60-6.44)	1.72 (0.58-5.10)	2.61 (0.95-7.18)
3+	2.39 (0.88-6.47)	6.04 (2.52-14.46)***	8.60 (3.70-19.96)***
Unknown	-	1.78 (0.14-22.90)	1.14 (0.09-13.88)
Bundle completed in 3 hours			
No			
Yes	0.81 (0.37-1.79)	0.64 (0.31-1.30)	0.59 (0.29-1.16)

All variables in the table were included in the regression and all odds ratios were adjusted for other variables.
* p-value <0.05, ** p-value <0.01, ***p-value <0.001

Table 9.10 Characteristics of 123 patients with haemodynamic instability based on completion of the sepsis resuscitation bundle within 3 hours

Factors	Bundle incomplete by 3 hours		Bundle complete by 3 hours		Total		P-value
Gender							
Female	10	31.3%	31	34.1%	41	33.3%	0.771
Male	22	68.8%	60	65.9%	82	66.7%	
Ethnicity							
Māori/Pacific	11	34.4%	21	23.3%	32	26.2%	0.397
Non-Māori and non-Pacific	21	65.6%	69	76.7%	90	73.8%	
Unknown			1		1		
Age group (years)							
15-54	4	13.8%	27	31.8%	31	27.2%	0.157
55-74	7	24.1%	24	28.2%	31	27.2%	
75+	18	62.1%	34	40.0%	52	45.6%	
Unknown	3		6		9		
Pathogen							
No pathogen identified	12	37.5%	59	64.8%	71	57.7%	0.021*
Obligate anaerobe	1	3.1%		0.0%	1	0.8%	
Gram-positive	6	18.8%	13	14.3%	19	15.4%	
Gram-positive	13	40.6%	19	20.9%	32	26.0%	
Charlson Score							
0	8	25.0%	44	50.0%	52	43.3%	0.124
1	9	28.1%	16	18.2%	25	20.8%	
2	7	21.9%	12	13.6%	19	15.8%	
3+	8	25.0%	16	18.2%	24	20.0%	
Unknown			3		3		
Overall LOS (days)							
Median (IQR)	7.5 (4.3-14.5)		4.0 (2.0-7.8)		5.0 (2.0-9.0)		0.003*
Mean	9.5		7.3		7.9		0.004
Mortality at discharge	7	21.9%	14	15.4%	21	17.1%	0.401
Mortality in 30 days	10	31.3%	20	22.0%	30	24.4%	0.293
Mortality in 90 days	14	43.8%	24	26.4%	38	30.9%	0.067
Total	**32**		**91**		**123**		

Discussion

We have shown that gains can be made in adherence to sepsis management guidelines in a New Zealand healthcare setting, and that these are associated with improved outcomes. Specifically, a programme of continuous quality improvement focussed on response to high-risk findings improved delivery of a sepsis resuscitation bundle. Trends in the effect of early resuscitation appeared most pronounced in patients with haemodynamic instability, supporting guidelines recommending urgent recognition and management of shock states.(Evans et al., 2021) Practice improvements were durable over a year of follow-up and were associated with a time-dependent, post-implementation reduction in risk of in-hospital death. Differences in the incidence of sepsis were noted in relation to ethnicity, and with mortality in relation to socio-economic deprivation. Important variations in care were observed based on age and co-morbidity, and a significant proportion of patients did not receive timely resuscitation even after our programme launched, implying that further gains can be made.

The time-dependence of interventions which require behaviour change is reflected in the quality improvement literature generally and in sepsis quality improvement specifically.(Burrell et al., 2016; M. M. Levy et al., 2010; Varkey et al., 2007) Changes arising from the Sepsis Kills program in New South Wales were evaluated over four years, and the international validation of the Surviving Sepsis Campaign reported over three.(Burrell et al., 2016; M. M. Levy et al., 2010) Both demonstrated a post-implementation reduction in mortality of 5%, with the greatest effects seen at the end of their evaluation periods. Our short post-implementation evaluation (August 2019-June 2021) may explain why the trends visualised and observed in post-implementation mortality data (Figure 9.1, Table 9.2) were not statistically significant in logistic regression (Table 9.3). This may also go some way to explaining the lack of reduced ICU and hospital length of stay, as the benefits of sequential improvements across the system tend to accrue over time.(Braithwaite, 2018) An extended analysis of mortality and ICU admission data may prove this point in future.

That age and co-morbidity are both common and strongly associated with mortality in sepsis does not invalidate efforts to improve care, and we were very concerned to find that older age and co-morbidity were associated with reduced odds of receiving prompt resuscitation. In what

appears to be a local example of the inverse care law, those who may have the most to gain from early resuscitation are the least likely to receive this intervention. This accords with known difficulties in the management of older and sicker patients in acute care environments and should be the focus of further research and intervention.(Salvi et al., 2007; Samaras et al., 2010; The Lancet, 2021) We are similarly concerned that the incidence of sepsis amongst Māori people is twice as high as non-Māori people living in our region. Reports on health inequities between Māori and non-Māori describe differences in risk exposure and health outcome throughout life, as well as multiple failings across a(Gurney et al., 2020; Hikaka et al., 2021; Hobbs et al., 2019; Huria et al., 2018; Mazengarb et al., 2020; Robson B & Harris R, 2007; Steyn et al., 2021)ris R, 2007; Steyn et al., 2021) We were reassured in this study to find no difference in the delivery of care based on ethnicity, and that ethnicity itself is not an independent risk factor for mortality. However, it seems unlikely that sepsis care is uniquely unaffected by clinician bias and institutional racism, both of which are well reported across New Zealand's acute healthcare system.(Hobbs et al., 2019)

Socio-economic status is known to increase mortality following hospital admission from a range of underlying causes, and this association was clear in our study.(Kempker et al., 2018) Kempker *et al* compared sepsis outcomes with data submitted to the US National Health Interview Survey. Self-reported health status, self-reported disability and markers of socio-economic status exerted a greater influence on mortality than non-sepsis conditions. In our study, almost three quarters (74%) of cases attributed to invasive group A beta-haemolytic streptococcal infection (iGAS) were observed in the two highest quintiles of socioeconomic deprivation. We are relatively fortunate, then, that these organisms remain susceptible to antimicrobial therapy. However, recent evidence from the UK and Europe has shown that the re-emergence of pathogenic strains of group A, beta-haemolytic streptococci has driven increases in both scarlet fever and iGAS.(Watts et al., 2019) Increasing deprivation has the potential to increase the number and severity of infection-related hospitalisations, and clearly increases short and medium-term mortality. In essence, the burden of sepsis falls to deprived and vulnerable populations already experiencing high burdens of invasive infection, who are then more likely to die following a sepsis admission.

We were surprised to observe a strong association between survival and gram-negative bacteraemia. This was associated with an 80% reduction in the odds of 30-day mortality (adjusted OR 0.20, 95% CI 0.08-0.55, p<0.01), with similar strength of association observed at 90 days. Over more than two decades of sepsis data analysed by Martin *et al,* gram-positive organisms accounted for 38% of cases attributed to a specific organism. In this group, mortality decreased by 3% per year from 1979 to 2001 despite increasing age and co-morbidity. Improvements in sepsis outcomes have repeatedly been attributed to what these authors describe as "non-specific improvements intensive care", including in more recent study of ICU sepsis outcomes in Australia and New Zealand.(K. M. Kaukonen et al., 2014; Martin et al., 2003) Arguing against this, most patients reported here did not receive ICU-based care, and in ICU populations, gram-positive bacteraemia is more commonly associated with septic shock.(Abe et al., 2010) In our cohort, 55% of patients with gram-positive bacteraemia received a clinical diagnosis of urinary tract infection, which is associated with better outcomes in patients who initially present with severe sepsis and shock.(Hsiao et al., 2015; Leligdowicz et al., 2018) Whether the underlying source of infection fully explains the observed differences in mortality reported here needs further investigation.

The high rate of ICU and HDU admission and early mortality amongst cases confirms that our code-based definition selects a critically ill patient population. In earlier work, we demonstrated that these cases equate to about 0.5% of acute hospitalisations. However, Rhee and others have reported that 6% of the hospitalised population in the United States meet an electronic health record (EHR) definition of sepsis during admission.(Rhee & Klompas, 2020a) In this study, we have shown that removing the requirement for a secondary organ failure code increases the population of patients with primary sepsis diagnosis codes by 44%, and that mortality in this group is 23% (1429/6312 cases). Building on this, we have now demonstrated that many patients who would be admitted to an ICU in other jurisdictions are diverted to non-ICU care. 58% of patients met criteria for ICU review which were agreed to prospectively by our intensive care team. Just a third of this group were referred and only a small proportion accepted. This practice appears to accommodate constrained ICU capacity. Avoidance of admission to ICU fails to acknowledge a high-needs population who require intensive therapy, as well as the adverse outcomes associated with delayed ICU admission. In a recent prospective study of 401 ICU

admissions in Brazil, 57% of whom had sepsis, delay in ICU admission was shown to account for 30% of attributable ICU mortality.(Cardoso et al., 2011) ICU deferral also masks the cost and severity of sepsis by diverting high-dependency patients to low-dependency areas, which in epidemiologic terms creates a "treated" and a "true" population of patients.(Linde-Zwirble & Angus, 2004) Given that ICU bed availability was historically low and falling prior to the SARS-CoV2 pandemic, it appears safe to assume that sepsis-related demand for critical care resources exceeded supply, even in a pre-pandemic context.(Betteridge T & Henderson, 2020)

Foundational studies of sepsis resuscitation bundles report mortality as an outcome, and we have replicated this approach here. Singer *et al* have raised concerns that much of the reported mortality in sepsis may be more related to frailty and comorbidity than an intermediate sepsis event.(Singer et al., 2019) Daviaud et al have shown that in the setting of septic shock, 80% of deaths within 3 days of admission to ICU are indeed the result of sepsis-associated multiorgan failure.(Daviaud et al., 2015) Outside the ICU, the fraction of mortality attributable to sepsis may be as low as 25%, with death commonly attributed to chronic morbidities and cancer.(Kopczynska, Sharif, Cleaver, Spencer, Banerjee, et al., 2018; Rhee et al., 2019) The high proportion of cases in this study with both haemodynamic instability *and* significant co-morbidity plausibly explains why improvements in early mortality, attributed to early resuscitation, were not sustained at 90 days.

This points to one of this study's principle weaknesses, which is that we have not reported outcomes amongst survivors, including early survivors who succumbed by 90 days. Quality can be measured in multiple dimensions, and Iwashyna has argued powerfully that a focus on mortality fails to recognise the person-centric priorities such as time out of hospital, control of pain, and clear communication about the cause of critical illness and likely outcome. (Iwashyna, 2010) Additionally, our period of observation may have been too short to document significant improvements in ICU length of stay and may also under-report the improvements in mortality seen over longer periods in other studies. This underlines the importance of efforts to generate a minimum set of short and long outcomes in studies reporting on sepsis quality improvement interventions.(Schinkel et al., 2021)

Conclusion

This is the first study from New Zealand to show that a whole-of-system sepsis quality improvement intervention reduces in-hospital mortality. Sepsis is associated with high mortality, and we confirm the association between mortality, patient age and co-morbidity. The incidence of sepsis in our region is higher amongst Māori than non-Māori. Outcomes are worsened by exposure to socio-economic deprivation and improved in association with gram-negative bacteraemia.

Funding

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Contribution statement

PH led the study conception and KW led clinical audit design and collection of data with OP and RM. PH led the statistical analysis. PH drafted the manuscript with input from KW. RD also provided critical revision of drafts. KW and PH share responsibility for the integrity of the work as a whole.

Chapter 10: The cost of major infection and sepsis in New Zealand

Abstract

Background: the aim of this study was to explore the population-at-risk and potential cost of a sepsis episode in New Zealand.

Methods: Retrospective analysis of the National Minimum Data Set using two code-based algorithms selecting (i) an inclusive cohort of hospitalised patients diagnosed with a 'major infection' with the potential to cause sepsis and (ii) a restricted subset of these patients with a high likelihood of clinical sepsis based on the presence of both a primary admission diagnosis of infection and at least one sepsis-associated organ failure.

Results: In 2016, 24% of all inpatient episodes were associated with diagnosis of a major infection. The sepsis coding algorithm identified a subset of 1,868 discharges. The median (IQR) reimbursement associated with these episodes was $10,381 ($6,093–$10,964). In both groups, 30-day readmission was common (26.7% and 11% respectively).

Conclusion: Infectious diseases with the potential to cause sepsis are common among hospital inpatients. Direct treatment costs are high for those who present with or progress to sepsis due to these infections.

Introduction

Sepsis is defined as "life-threatening organ dysfunction due to a dysregulated immune response to infection."(Singer et al., 2016) Sepsis is a major health challenge globally, with incidence stratified by geography and national income.(Rudd et al., 2020b) In high-income countries, sepsis-associated mortality remains high, with a wide variation based on the age and underlying health status of the individual.(Angus et al., 2001) A proportion of patients with sepsis require treatment in an intensive care unit (ICU), survivors often require long stays in hospital and hospital readmission is common.(Chang et al., 2015; P. J. Huggan et al., 2017) Unsurprisingly perhaps, sepsis is a leading cause of healthcare spending. In the US in 2018, USD$22,000,000,000 was charged to the Medicare and Medicaid budgets for inpatient sepsis management.(Buchman et al., 2020)

Sepsis is a complication of infection. In New Zealand, infection-related public-hospital admissions have increased significantly over time, particularly among Māori and Pacific people and those facing high levels of socioeconomic deprivation.(M. G. Baker et al., 2012a; P. J. Huggan et al., 2010; Milne & vander Hoorn, 2010; Safar et al., 2011) Presentations with infectious diseases and sepsis are therefore a major barrier to population health equity, and their prevention, mitigation and treatment are deserving of investment. Investment requires an understanding of the scale of the underlying problem and its associated cost. There are no studies reporting the cost of infection and sepsis to the New Zealand public health system. We used routine data to estimate (i) the number of inpatients with infections that can cause sepsis and (ii) the potential cost of a sepsis episode.

Methods

This study was registered as a quality improvement activity with the Clinical Audit Support Unit at Waikato District Health Board (WDHB). It was considered a low-risk observational study and therefore out of scope for New Zealand Health and Disability Ethics Committee review. Funding

for an independent health-economist (IS) was provided by the Accident Compensation Corporation (ACC).

Defining infection and sepsis using routine data

This was a retrospective analysis of the National Minimum Data Set (NMDS). The analysis made use of codes derived from the International Classification of Disease, Tenth Edition, Australian Modification (ICD-10-AM). The *a priori* design of this explorative study addressed several problems known to impact studies of sepsis epidemiology and cost.

Firstly, we had to identify a source of data from which to derive estimates of prevalence and cost. Although prospective databases are maintained to identify sepsis within intensive care unit admissions, limiting studies to ICU-treated populations is highly problematic.(P. J. Huggan et al., 2017) The NMDS is the only resource available to judge the total number of infectious disease and sepsis-associated hospital admissions in New Zealand. It has been the preferred data source for national reporting of infection-related hospital admissions and is linked to hospital reimbursement data. The NMDS was therefore chosen as the data source for this study.

Secondly, we needed a method to identify sepsis within the NMDS. Significant controversy and debate surround the contemporary clinical definition of sepsis, and the limitations associated with defining it within routine data are well described.(P. J. Huggan et al., 2017; Inada-Kim et al., 2017; Wilhelms et al., 2010) Briefly, the clinical definition of sepsis has changed over time, as have the International Classification of Disease versions from which sepsis coding algorithms are constructed.(Shankar-Hari et al., 2016; Wilhelms et al., 2010) Multiple code-based definitions of sepsis exist, and their accuracy has been reported against different populations in different health systems.(Angus et al., 2001; Wilhelms et al., 2010) We chose to use a coding algorithm that made use of explicit sepsis codes in the International Classification of Disease. The codes used in this algorithm are shown in Appendix 1, and henceforth this method is referred to as the New Zealand Sepsis Indicator (NZSI).

Due to the syndromic nature of sepsis (as opposed to the binary presence or absence of infections with specific ICD-10-AM codes), clinical validation of the NZSI was undertaken by reviewing a sample of clinical records at WDHB. We retrospectively identified 100 NZSI discharges from WDHB facilities in each of two one-year time periods (July to June 2008/09 and 2012/13). These adult patients were found to have confirmed sepsis if their presentations were both consistent with infection and associated with a new increase of two or more in the modified-Sequential Organ Failure Assessment (mSOFA).(Raymond et al., 2019) Use of the original SOFA score is required to satisfy the current clinical definition of sepsis.(Singer et al., 2016) mSOFA replaces the cardiovascular and respiratory requirements of the original score to make use of information typically entered into the clinical record.

Thirdly, we recognised the limited sensitivity of the NZSI and, therefore, our inability to identify all patients with sepsis from the NMDS. We therefore sought to identify the hospitalised population-at-risk of sepsis. This approach is in routine use in the UK and is used to identify trends in the presentation and outcome of specific infectious diseases in NHS hospitals. The so-called 'suspicion of sepsis' approach was first developed by Inada-Kim et al.(Inada-Kim et al., 2017) These authors conducted a consensus review of the International Classification of Disease to extract all infectious disease diagnoses commonly complicated by sepsis. To these codes we added 14 that were part of a sepsis coding strategy developed by Huggan et al.(P. J. Huggan et al., 2017) From then on, we labelled this algorithm as the 'New Zealand Major Infection' indicator (NZMI).

Hospital discharge episodes in 2016 (e.g., from 1 January 2016 to 31 December 2016) were identified using the NZSI and NZMI, applied to the National Minimum Data Set (NMDS). The resulting cohorts were analysed separately. For each episode, further hospitalisation within 30 days was identified as a readmission and assumed to be linked to the index admission. In both cohorts, admission more than 30 days after the index discharge was counted as a separate episode of care.

To estimate total in-patient discharges in calendar year 2016, we subtracted day-case admissions from total reported hospital episodes provided by the New Zealand Ministry of Health (tables

available at https://www.health.govt.nz/nz-health-statistics/health-statistics-and-data-sets/publicly-funded-hospital-discharges-series/publicly-fund-ed-hospital-discharges-series/publicly-funded-hospital-discharges-series. [Accessed October 2020]). We then calculated an average based on numbers derived for the period July–June 2016/2017 and 2015/2016.

In summary, to estimate the population-at-risk of sepsis, we identified all patients admitted to New Zealand hospitals with infections known to cause this condition (NZMI). From within this cohort, we identified a subpopulation with a high likelihood of sepsis (NZSI) and validated this assumption by conducting a clinical record review to .

Data extraction and hospital reimbursement

The National Minimum Data Set (NMDS) was used to identify discharges meeting NZSI and NZMI criteria for the 2016 calendar year (see Appendix). We extracted 30-day readmissions for any reason through to 31 January 2017. The NMDS was accessed under a pre-existing memorandum of understanding between the Ministry of Health and ACC. This limited the information provided to the patient's age, district health board and discharge diagnosis codes. Mortality and ethnicity data were not available.

Data were entered into Microsoft Excel (2016) and further analysed in SAS Enterprise Guide (version 7.1). Public-hospital reimbursement for each case was derived from the New Zealand Case mix System for Publicly Funded Hospitals (WEISNZ16v1.0, NCCP Casemix—Cost Weights Project Group, 2016).(*The New Zealand Casemix System – An Overview | Ministry of Health NZ*, n.d.) This system uses case-weights to estimate average costs for cases of varying complexity, as determined by Diagnosis Related Groups (DRGs) linked to ICD-10-AM codes. For cases not covered by the Case mix System (namely those paid by Crown agencies such as ACC), we used the average inlier costs for relevant DRGs. We had no data relating to reimbursements for private hospitals or facilities run by community trusts. To compare case-weighted reimbursement with true inpatient costs at Waikato District Health Board, we used I. Patient Manager (DXC Technology, Tysons Corner, US) to describe the actual costs of care for patients included in the NZS clinical validation cohort.

Results

Regarding validation of the NZS algorithm, 192 sets of clinical records were available for review. Clinical sepsis was identified in 165 (86%); 125 (76%) of these satisfied the clinical sepsis definition (mSOFA score of two or more) at first presentation to hospital, 43 (26%) identified as Māori, 36 (22%) were admitted to ICU and 30 (18%) died in hospital.

Table 10.1 shows the number of cases identified using the NZMI and NZSI in 2016, stratified by age group. In the 2016 calendar year, we estimated that there were 725,294 non-day-stay discharges from New Zealand public hospitals. 174,619 discharges (24%) were associated with a NZMI code. 47% of patients were male, 40% were over 70 years of age and 16% were under 20. NZMI admissions absorbed 949,026 hospital bed days, for which $1,191,279,897 was reimbursed. The average length of stay (ALOS) for these admissions was 5.5 days (range 1–225 days, median 3.0 days, inter-quartile ration (IQR) 1–6 days) and the average reimbursement per discharge was $6,822 (range $147–$410,599, median $3,995, IQR $2,231–$6,865). 46,627 NZMI discharges (26.7%) were associated with readmission within 30 days, accounting for 341,606 additional bed days and reimbursement of $373,700,000 (mean $8,014, median $5,167, IQR $2,807–$8,446). We found 3,904 (2.2%) NZMI cases that were not reimbursed using the Case mix System. Assigning the case mix average to these admissions added $26,300,000 to the total.

1,868 hospital discharges were identified using NZSI codes. Of these patients, 54% were male and 60% were aged 70 or over. NZSI admissions absorbed 15,137 hospital bed days, for which $21,500,000 was reimbursed. The ALOS was 8.1 (range 1–86, median 6, IQR 3–10) and the average reimbursement per discharge was $11,552 (range $717–$181,988, median $10,381, IQR $6,177–$10,964). There were 203 NZSI discharges (11%) that were associated with readmission within 30 days. This accounted for an additional 2,418 bed days and a further reimbursement of $2,800,000 (average $13,682, range $717–$179,231, median $10,381, IQR $6,093–$10,964).

We found 26 (1.4%) NZSI cases that were not reimbursed using the Case mix System. Assigning the case mix average to these admissions added $355,732 to the total reimbursement.

Table 10.1: Hospital discharges identified by the New Zealand Major Infection (NZMI) and New Zealand Sepsis (NZS) indicators, 2016.

Age group (years)	N	%	N	%
	NZMI		NZS	
0-2	13255	8	18	1
3-19	14136	8	35	2
20-29	15053	9	28	2
30-39	11449	6	41	2
40-49	11950	7	86	5
50-59	16337	9	202	11
60-69	22832	13	330	18
70-79	29471	17	472	25
80 and over	40136	23	656	35
Total	174619	100	1868	100

Abbreviations: NZMI, New Zealand Major Infection; NZS, New Zealand Sepsis Indicator

For the 192 patients in the clinical validation cohort at Waikato District Health Board, 79% of the actual costs of care were identified using national case mix methodology ($2,150,209 costs incurred, against reimbursement of $1,699,155).

Discussion

To our knowledge, this is the first effort to report hospital resource utilisation associated with episodes of infection and sepsis in New Zealand. Codes for ‘major infection’ were associated with 24% of all hospital discharges, almost 1,000,000 hospital bed days and over $1,000,000,000 in reimbursement. A high proportion of patients were readmitted to hospital within 30 days (27% and 11% of the NZMI and NZSI cohorts, respectively). Sepsis episodes were high-cost events, and the actual costs of care for a sepsis cohort identified at a large district health board were 26% higher than reimbursement derived using the case-weight system.

As an exploratory analysis, our aim was to estimate the population-at-risk of sepsis and the likely cost of a sepsis episode while recognising the limitations placed on studies using routine data. We did this by applying two entirely different algorithms to a single database: one which identified patients with the infections that cause sepsis (NZMI), the other which identifies patients with a high likelihood of true clinical sepsis (NZSI). Comparison of these cohorts provides two important observations. Firstly, NZMI codes more completely represent the bimodal distribution of infection-related hospital admissions, a pattern observed in the Global Burden of Disease study but not by the NZS algorithm.(P. J. Huggan et al., 2010; Rudd et al., 2020b) Secondly, both methods demonstrate a steep increase in the proportion of cases with age. This is a universal observation in studies of infection and sepsis incidence, including those reported from New Zealand.(M. G. Baker et al., 2012b; P. J. Huggan et al., 2010)

The NZS algorithm was designed to report sepsis incidence from hospital coding data. Due to concerns about the reliability of coding strategies to identify true clinical sepsis, it aims to maintain specificity for the sepsis syndrome at the expense of sensitivity. This is achieved by requiring an explicit organ failure code while also excluding infection codes other than in the primary position (see Appendix). Merely by including cases with infection codes in primary *or* secondary positions in our database, we would have increased the number of NZS cases by 64% to 3,073, and a further 2,615 cases would have been identified by combining infection and organ failure codes in any position. With 86% of cases satisfying contemporary sepsis definitions in our validation work, we conclude that NZS codes can be used to estimate the cost of sepsis episodes, although they will underestimate sepsis incidence and prevalence.

This brings earlier findings into question. In the Waikato region, the NZS algorithm led to an estimate of 107 cases of sepsis per 100,000 in the year to June 2012.(P. J. Huggan et al., 2017) This is at the lower limit of sepsis incidence estimated in high-income economies by the Global Burden of Disease study, which employed code-based methods to estimate 120 to 200 cases per 100,000 population in high-income countries including New Zealand and Sweden.(Rudd et al., 2020b) Swedish studies identifying the presence of sepsis in patients receiving intravenous antibiotics report annual sepsis rates of 800 per 100,000 population.(Ljungström et al., 2019; Mellhammar et al., 2016) By implication, rates of sepsis are much higher in New Zealand than

previously reported. Better estimates of sepsis incidence are needed, particularly given the severity of the associated outcomes and the high cost presented to public hospitals.

We also note that critical illnesses requiring complex multidisciplinary care are associated with deficits in hospital reimbursement. For example, the average case-weighted inpatient reimbursement for major trauma at Whangārei Hospital from 2015 to 2017 was $17,042, but the actual costs of care were 36% higher.(Helena Lee et al., 2018) For both trauma and sepsis, additional costs will extend well beyond hospital care, with non-inpatient ('indirect') costs adding substantially to total spending following critical illness.(Ministry of Health, 2009) Sepsis has recently been shown to cause a durable increase in health spending over at least five years of follow-up.19 Further work is required to establish a better estimate of short- and long-term costs, but a clue to the true extent of resource utilisation associated with infectious disease and sepsis diagnosis is provided by the high readmission rate found in this study.

The 30-day readmissions in the NZMI and NZS cohorts respectively added 31% ($373,700,000 added to $1,200,000,000) and 13% ($2,800,000 added to $21,500,000) to the reimbursement associated with index hospitalisation. Large studies in the US have shown that readmission rates after sepsis are similar for heart failure and myocardial infarction.(Chang et al., 2015) Reasons for hospital readmission are likely to be heterogenous. Possibly for this reason, interventions focused solely on supporting sepsis survivors at discharge have shown little impact on rates of readmission.(Cuthbertson et al., 2009; Goodwin & Ford, 2018; Schmidt et al., 2016) Intriguingly, though, total healthcare utilisation does appear to be reduced by efforts to identify and treat patients at risk of sepsis in hospital. A machine-learning algorithm designed to identify sepsis using electronic medical records reduced 30-day readmission rates from a baseline of 46% to 23% in one single-centre study.(Burrell et al., 2016) Evaluation of a state-wide sepsis quality improvement programme in New South Wales, Australia, pointed to a reduction in intensive care utilisation and the total length of stay.(Burrell et al., 2016) The hypothesis proposed by these authors and others is that early sepsis identification and treatment improves clinical recovery by preventing the accumulation of sepsis-associated tissue injury. We can't support this conclusion from the data provided here, but we have shown that quality improvement programmes aimed at

preventing, mitigating and treating infection and sepsis would be relevant to a high proportion of our inpatient population.

A major weakness of our study is the omission of data relating to mortality and ethnicity. The dynamic impacts of infection are most marked among populations suffering high rates of chronic morbidity and socioeconomic disadvantage, which unfortunately includes a significant proportion of Māori and Pacific people. For example, compared with non-Māori living in the Waikato, Māori are 3.2 times more likely to suffer sepsis and at a much younger age.(P. J. Huggan et al., 2017) Under-reporting rates of infection and sepsis at a national level risks obscuring the important contribution of these conditions to health inequity.

In summary, infection and sepsis are costly and previously under-appreciated sources of direct healthcare spending in New Zealand. Total healthcare spending on sepsis will be significantly higher than reported here, due to under-reporting, the ongoing costs of care in the community and, potentially, the significant gap between reimbursement and actual spending. The NZMI and NZS approaches have their strengths and weaknesses. The first can estimate the size of the inpatient population at risk of sepsis, and the second can provide a representative sample of patients with a high probability of sepsis, which can be used to study clinical outcomes and costs. Both groups would benefit from investments in infection control, antimicrobial stewardship and sepsis care aimed at preventing or reducing long lengths of stay and readmission.

Chapter 11: Discussion

Sepsis is now a global health priority, with the World Health Organisation urging member states to take concerted action to reduce sepsis-associated harm (K Reinhart, 2017). To inform that work, the data presented in this thesis provide important insights into the epidemiology, clinical characteristics, and cost of sepsis in New Zealand, as well as evidence that quality improvement efforts improve outcomes.

General observations on approach to the study of infectious disease and sepsis

This thesis demonstrates two approaches to the study of infectious disease. In the first, individual infectious diseases are identified which have the potential to cause sepsis. In the second, the study of "sepsis", however defined, provides a single lens through which to view the most serious harms caused by a range of bacterial infections.

In Chapters 4 and 5, the population burdens of two separate "serious" infectious diseases revealed very different outcomes based on infecting organism. Although critical illness, age and co-morbidity were present in both patient cohorts, invasive infections caused by Fusobacteria were associated with only one death, compared with the 18% 30-day mortality seen in a cohort of patients with *Staphylococcus aureus* bloodstream infection. Amongst all bloodstream isolates described in Chapter 9 (Table 9.5), 75% of cases were caused by just 5 major groups of bacteria. Also, in Chapter 9, we demonstrated that outcomes in sepsis were improved in association with gram-negative bacteraemia.

As described in Chapter 2, changes in the prevailing discourse dealing with sepsis changed over the 20th Century. With the availability of anti-microbial agents allowing early survival in the face of invasive bacterial infection, the concept of sepsis as a "final common pathway" of immune dysfunction demoted the pathogen from the centre of paradigms driving sepsis research, to be replaced with a focus on inflammatory and counter-inflammatory responses. The finding here,

that clinical outcomes vary substantially by infecting organism, suggests that treatment of sepsis needs to be much more attentive to the pathogen involved.

The benefits of viewing infectious diseases through a "sepsis lens" are demonstrated in Chapters 8 to 10. Prior to the publication of work associated with this thesis there were no studies in a New Zealand context which attempted to cohort the incidence, clinical characteristics and outcomes associated with the sepsis syndrome. Although rates of admission with infectious diseases were known to be rising, the information in Chapter 8 confirms that this has been associated with an increase in their severe clinical manifestations. Similar trends toward increasing sepsis admission are reported in Chapter 9, and Chapter 10 provides an estimate of the average cost of these admissions (including in a broad cohort of 'major infections' in children).

Table 11.1 summarises the clinical validation of the administrative method used to select sepsis cases. Without this, there is no 'clinical face' to general statistics and trends. The requirement for a secondary organ failure code in our case definition increased 30-day mortality from 11% (in the population with a primary code alone) to 28%. A significant majority of these patients (86%) satisfied a contemporary clinical definition of sepsis, which cannot itself be regarded as a gold standard. Our method can therefore be used in large routine datasets to study trends in sepsis admission and outcome in New Zealand. Table 11.2 demonstrates how the use of this method has already contributed to the research priorities for sepsis.

Beyond these observations, the findings which will be further explored in this discussion are i) the association of ethnicity and socio-economic deprivation with incident sepsis, ii) the role of the endothelium in determining the expression of the sepsis syndrome and iii) the long term burdens of sepsis survivorship.

Table 11.1. Validation of the New Zealand Sepsis Indicator (NZSI)

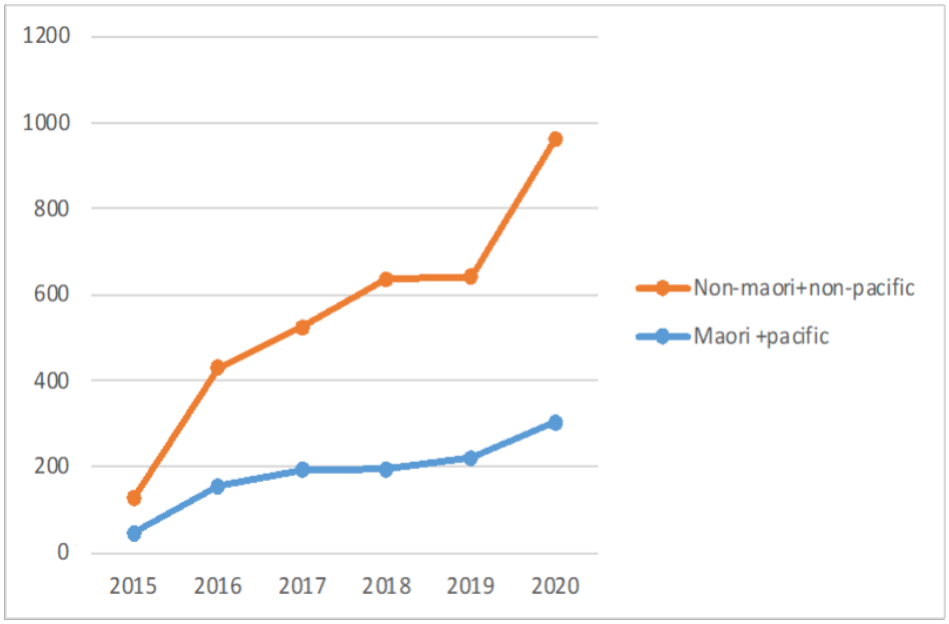
Key Points Under Evaluation	**Evidence**
Is the consensus clinical definition of sepsis in clinical records satisfied in cases selected using the NZSI?	Clinical sepsis identified in 86% (165/192 records identified, Chapter 10)
Are patients identified using the NZSI likely to benefit from enhanced recognition and resuscitation?	In-hospital mortality: 18% ICU admitted: 22%
Do patients identified using the NZSI have infections that are likely to benefit from urgent antimicrobial therapy?	Blood cultures positive at presentation in 38% (103/266) cases (Chapter 9)
Are patients identified using the NZSI eligible for urgent resuscitation and escalation of care?	Overall admission rate to an ICU or HDU: 32% (75 of 266 cases (Chapter 9) Only 16 of 338 cases (5%) ineligible for sepsis resuscitation bundle at presentation due to co-morbidity, illness severity or advanced care plan

Table 11.2 Thesis contributions to national research priorities in sepsis

Research recommendation	Contribution
What is the incidence, presentation, and management of sepsis in New Zealand?	• Estimates derived from routine data demonstrate patterns that are consistent with known risks relating to age, sex, morbidity, and socio-economic status • The ASRR for men is 1.4 (95%CI 1.23-1.59) • The ASRR for Māori compared with non-Māori is 3.22 (95%CI 2.85-3.65) • The ASRR for the highest quintile of deprivation is 1.72 (95% CI 1.5-1.97) • Incidence is increasing – the population ASRR comparing 2012 with 2008 was 1.62 (95%CI 1.18-2.24). There were twice the number of presentations with sepsis at Waikato Hospital in 2020 compared with 2016
What effect will the BPACNZ contextualised sepsis guideline have on patient care processes and outcomes in New Zealand over the next 5 years?	When implemented as part of a system-wide quality improvement initiative, use of the guideline is associated with a reduction in in-hospital mortality and a trend toward lower 30-day mortality. The wider benefits of the guideline have not been studied (for example on quality of life). Outcomes may be affected by deficits in ICU availability
Can early warning scores be used to improve the detection of sepsis and facilitate prompt and appropriate clinical response in pre-hospital settings and in emergency departments?	Introduction of the Raise the Flag programme followed closely on the introduction of the NZEWS to Waikato Hospital. The possibility remains open that use of the NZEWS led to the above outcome.
Is it possible to derive and validate a set of clinical decision rules or a predictive tool to rule out sepsis which can be applied to patients presenting to hospital; with suspected sepsis?	The Red Flag Sepsis Screening and Action Tool offers a low risk and intermediate risk (amber flag) pathway to guide decision making. Further work would be required to determine sepsis risk in these categories.

These priorities were identified by the Guideline Review and Contextualisation Group, Best Practice Advocacy Centre (BPAC), Dunedin. Full guideline and review group summary available at www.bpac.org.nz/guidelines/4/#other. ASRR, age-standardised rate ratio; OR, odds ratio.

A



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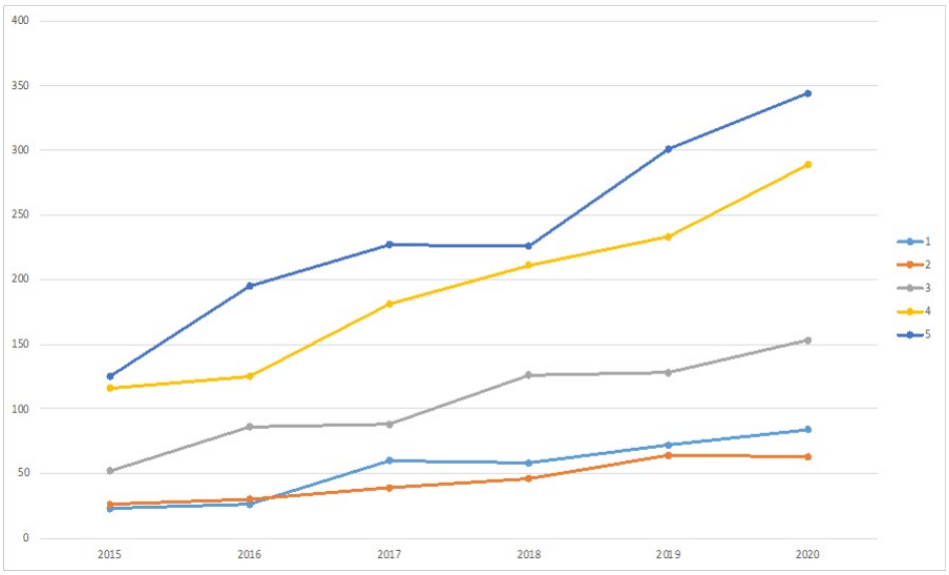

Figure 11.1 Growth in presentations meeting administrative coding definition of sepsis at Waikato Hospital, 2015-2020.

A. Number of presentations with sepsis comparing Māori and Pacific with non-Māori non-Pacific people B. Growth in sepsis presentations based on NZDep quintile over the same period. Data taken from 4628 sepsis admissions to Waikato Hospital, May 2021-December 2020.

In our data, two thirds of patients with sepsis had at least one co-morbidity of prognostic significance (calculated using the Charlson score) and a strong impression emerges that people with sepsis will almost always have some sort of underlying *vulnerability,* be it increasing age, pathogen virulence, socio-economic deprivation, or morbidity. The review of contemporary sepsis pathobiology provided in Chapter 1 places the vascular endothelium at the centre of events leading to expression of the clinical sepsis syndrome, and each of the *vulnerabilities* listed are linked to disturbed endothelial function.

The endothelial frailty/failure hypothesis

In Chapter 2, evidence was presented of a link between traditional vascular risk factors and incident sepsis. This has led some to the hypothesis that sepsis represents a state of immune-mediated, acute-on-chronic dysfunction of the vascular endothelium (Figure 11.2). This would provide a unifying theory explaining risk, severity, and the long-term non-infectious morbidity observed following a septic event. To develop the hypothesis of sepsis as a manifestation of "endothelial frailty" and failure, it is necessary to examine the overlapping pathways to endothelial dysfunction (ED) created by long term exposure to deprivation, co-morbidity and both modifiable and non-modifiable risk factors.

In Chapter 1, describing the septic endothelium, it was assumed that the dysregulated immune response which currently defines sepsis affects a *normal* vascular endothelium (conceptualized in Figure 1.4). Considering the pathogenesis of vascular disease, and the morbid characteristics of the cohorts described in this thesis, it seems very unlikely that patients with sepsis had normal pre-sepsis endothelial function. Many of the processes affecting the vascular endothelium in atherosclerosis are mirrored in sepsis.(Libby & Lüscher, 2020) These are, respectively, chronic and acute states of endothelial dysfunction mediated by inflammatory injury. The mechanisms underpinning chronic endothelial dysfunction in atherosclerosis have been elegantly reviewed by Deanfield *et al*, and the biological commonalities between sepsis and chronic endothelial dysfunction summarised by Bermejo-Martin *et al*.(J. F. Bermejo-Martin et al., 2018; Deanfield et

al., 2007) These commonalities are increased oxidative stress, glycocalyx shedding, loss of barrier function, enhanced leukocyte-adhesion, transition to a pro-coagulant/anti-fibrinolytic state, and impairment of endothelial repair. Infection and the associated immune and haemostatic injuries described in Chapter 1 are thought to precipitate acute endothelial failure on a background of chronic endothelial activation. The degree of endothelial dysfunction can also be determined by pathogen-derived virulence factors and the extent of tissue damage caused by resuscitation efforts (ie surgery, high volume fluid infusion).

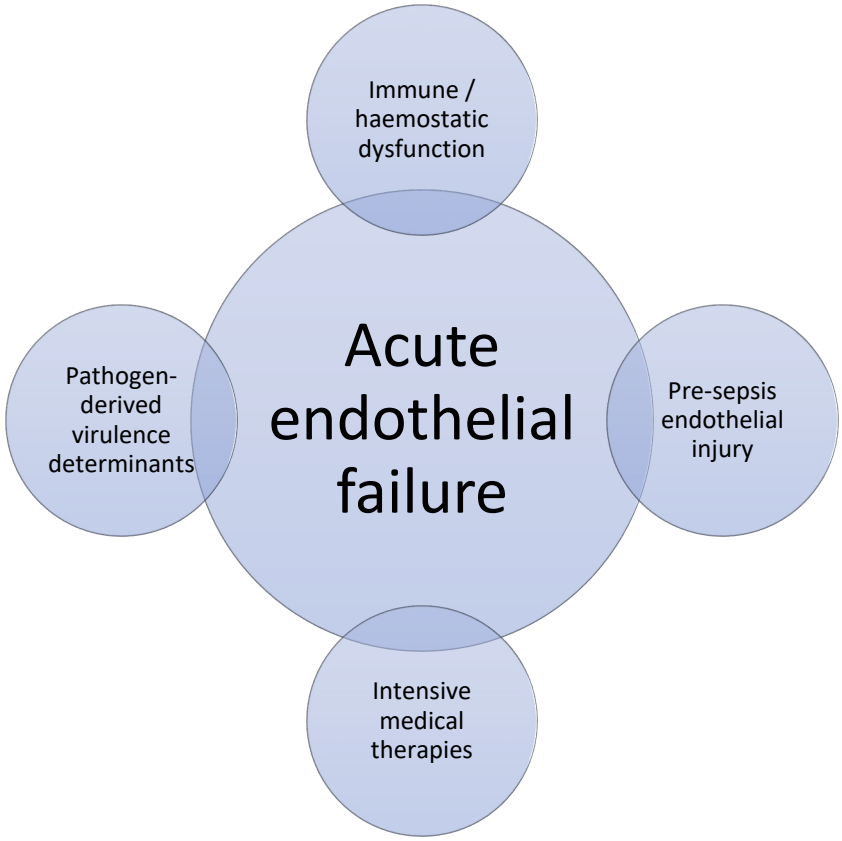

Figure 11.2. The sepsis syndrome represented as acute infection-associated endothelial failure

This leads to a new model of the sepsis syndrome, visualised in Figure 11.2. This proposes that acute inflammatory and pathogen-mediated injury overlap with chronic endothelial dysfunction and the effects of medical treatment. In addition to explaining the heterogeneity of sepsis

presentations, Table 11.3 shows how this model accommodates diverse phenomena and unites patients with sepsis based on i) vulnerability to an infection-related trigger and ii) disturbance in the function of a *single organ* – namely the vascular endothelium.

The value of the endothelial frailty/failure model in understanding sepsis pathogenesis is perhaps best illustrated at extremes. At one extreme, a patient with advanced age, pre-existing vascular (endothelial) morbidity and diabetes manifests acute endothelial dysfunction despite a clinically "trivial" infectious injury, with no positive microbiologic findings. This may explain why over 10% of patients who underwent clinical record audit in our quality improvement study (Chapter 9) were discharged without a clearly defined source of infection, this despite attending clinicians being confident of an infection-related cause for severe physiologic disturbance. Age-related decline in renal endothelial function may also explain why acute kidney injury dominates secondary organ failure codes in the elderly (Figure 8.1). At the other extreme, a young adult with no pre-existing morbidity might fall prey with frightening rapidity to sepsis caused by *Neisseria meningitidis*, whose predilection for endothelial adhesion and invasion was summarised in detail in Chapter 1. Both of the patients described in these examples have sepsis, and both may very well have high a 30-day mortality. However, the immune-inflammatory model of sepsis would not unite these cases in the mind of a treating clinician. In the first, a poor outcome would be explained and presaged by age and morbidity-associated chronic endothelial dysfunction. In the second, all organ failures would be attributed to the infecting organism, and intensive care unit admission would be assured if necessary on the basis that quality of life in recovery would be restored based on normal 'pre-morbid' endothelial function.

The endothelial frailty/failure model continues to operate under more complex conditions. Patients receiving anti-cancer chemotherapy are at risk of infection by virtue of treatment and disease-related immunosuppression. Separately, anti-cancer agents can induce vascular endothelial damage, endothelial cell apoptosis and increased vascular permeability.(Guipaud et al., 2018; Romanov et al., 2007) The interplay of both predisposes patients to acute, infection-related endothelial dysfunction and tissue injury (ie sepsis). Underlying risks for infection and endothelial dysfunction would also explain high rates of sepsis in diverse geographical settings. For example, sepsis is common in sub-Saharan Africa, where advanced medical and age-related

frailty are less apparent, and the profile of pathogens causing sepsis is very different. However, HIV infection is much more prevalent, which increases the risk of invasive infection and causes chronic endothelial dysfunction (Bermejo-Martin et al., 2018a; Lewis et al., 2019). The causes of endothelial dysfunction are different, but 'sepsis' is the product.

Table 11.3. Component risks for sepsis in the endothelial frailty/failure model

Risk factors for infection	Risk for endothelial dysfunction
Impaired innate and adaptive immunity -age -co-morbidity -medical therapy -nosocomial infection (e.g. central venous catheter infection) Vaccination status Prior infection (e.g. sepsis events, measles) Nutritional status Cancer chemotherapy Social factors -overcrowding -injecting drug use HIV infection Colonisation with virulent organisms (i.e. *N.meningitids*)	*Chronic* Co-morbidities associated with elevated cardiovascular risk -Diabetes -HIV infection -Chronic renal disease -Hypertension -Chronic liver disease Tobacco use Nutritional status Socio-economic deprivation *Acute* Bacterial toxins NFκB accumulation Vitamin deficiency (i.e. Vitamin C)

The association of sepsis with ethnicity and socio-economic deprivation

The severe sequelae of infection exert a disproportionate burden on those living in the highest quintiles of deprivation in New Zealand, as measured using various iterations of the New Zealand Deprivation Index (NZDep). The NZDep was developed to measure deprivation in routine data using a census-based tool which allocates a score to one or more household in a census mesh block (Salmond et al., 2007). The NZDep has been revised over time but remains one of the principal methods through which measurement of deprivation informs government planning, purchasing and policy development. We used the NZDep to study the association between i) deprivation and risk of *Staphylococcus aureus* bacteraemia, ii) deprivation and mortality following sepsis events in the Waikato population and iii) the effect of deprivation as an explanatory variable for mortality in a population admitted to Waikato Hospital with sepsis.

In Canterbury, the incidence of *Staphylococcus aureus* bacteraemia was lower amongst people living in the lowest quintile of deprivation (adjusted rate ratio 0.74, 95% confidence interval: 0.56–0.98, p=0.007 after adjustment for age and sex). This was found in a population in which only 8% were of Māori or Pacific ethnicity. In unadjusted data collected in the Waikato region, where 24% are Māori, the age-standardised rate ratio of sepsis was 1.72 (95% CI 1.50-1.97), comparing NZDep quintile 5 with quintile 1.

Socio-economic deprivation is more commonly experienced by Māori and Pacific people living in New Zealand, and these populations experience sepsis at least twice as often as the non-Māori, non-Pacific population, and many times more than this in specific areas and communities.(M. Baker et al., 2000; Campbell et al., 2021) Studies from the US and Australia demonstrate the link between indigenous and African-American ethnicity and increased sepsis risk.(Kempker et al., 2018) Davis et al reported a 4% annual population incidence of admission with sepsis amongst Aboriginal Australians living in the Northern Territory, a rate times just under four times higher than non-Indigenous people.(Davis et al., 2011) The synchrony of modifiable vascular risk, co-morbidity and life-long exposure to inequality and deprivation represent a constant threat to the health of marginalised communities, which in New Zealand includes many whānau Māori.(Robson & Harris, 2007) However, this risk synchronisation is likely to affect Māori disproportionately but not singularly. For example, amongst sepsis cases we linked to NZDep quintiles 3 to 5 (Chapter 9), the adjusted odds ratio for 90-day mortality was independent of ethnicity. Supporting the contention that socio-economic risks are contributing to sepsis presentations across the population, we observed that growth in sepsis volumes at our hospital occurred most prominently amongst non-Māori and non-Pacific people living in NZDep quintiles 3 to 5 (Figure 11.1).

Based on the data presented in this thesis, an endothelial frailty/failure model would also need to explain the association of socio-economic deprivation with increased sepsis incidence. With respect to the known association between socio-economic deprivation and accelerated atherosclerosis, changes are complex, multi-factorial, cumulative and discrete to the specific medical, genetic and social history of the individual (Table 11.4).(Celermajer et al., 1992;

Deanfield et al., 2007) Long-term exposure to pro-inflammatory stimuli is thought to transition the vascular endothelium from a quiescent to an activated phenotype.(Deanfield et al., 2007) New Zealand-based life-course studies have demonstrated that various hardships in childhood are associated with increases in circulating inflammatory mediators.(Danese et al., 2009; Poulton et al., 2002) Periodontitis, infections associated with overcrowding, rheumatic fever, vaccine-preventable diseases, malnutrition, tobacco nicotine exposure, obesity and diabetes are all more common in deprived communities in New Zealand.(M. Baker et al., n.d.; Chepulis et al., 2021; "Global, Regional, and National Prevalence of Overweight and Obesity in Children and Adults during 1980–2013: A Systematic Analysis for the Global Burden of Disease Study 2013," n.d.; Shackleton et al., 2018) Each causes endothelial dysfunction and increases risks of infection through effects on innate and adaptive immune function.(Hansen et al., 2017) Chronic endothelial injury would also be predicted by the status anxiety hypothesis, which provides that perceived socio-economic position causes long-term psychosocial stress and chronic activation of the 'acute' stress response.(Layte et al., 2019) Baker *et al* have pointed to increasing infectious disease admissions in New Zealand following reforms to employment, healthcare and social spending which increased socioeconomic inequality.(M. G. Baker et al., 2012a) Rising sepsis admissions three decades later could be a signal that the biologic correlates of long-term, rising inequality are a combination of pro-inflammatory endothelial damage and predisposition to organ failure in the face of infection.

Table 11.4. Potential links between socio-economic deprivation, morbidity and chronic endothelial dysfunction in New Zealand

Hypothesis	Supporting Data from New Zealand
Endothelial dysfunction (leading to atherosclerosis) begins in childhood in association with oxidative stress and systemic inflammation (Deanfield et al., 2007)	Increased circulation of inflammatory mediators observed in children facing adversity/deprivation(Danese et al., 2009)
The status anxiety hypothesis: systemic inflammation is caused by chronic psychosocial stress and socioeconomic position.(Layte et al., 2019)	Concentrations of CRP are higher in countries with a high socio-economic gradient, even after adjusting for risks relating to lifestyle and co-morbidity. (R. S. Liu et al., 2017)
Chronic endothelial dysfunction manifests in middle age(Deanfield et al., 2007)	Sepsis incidence (together with myocardial infarction and stroke incidence) increases earlier in Māori and Pacific people (Chapter 8)
Atherosclerosis accelerates in association with pro-inflammatory conditions including periodontitis(D'Aiuto et al., 2013)	Increased risk of periodontitis and dental extraction in children experiencing deprivation(Shackleton et al., 2018)
Mild episodes of infection in childhood causes loss of vasomotor function (Deanfield et al., 2007)	Increased risk of respiratory illness and infectious disease hospitalisation in areas of high deprivation(M. Baker et al., 2001, 2010; O'Sullivan et al., 2011)
Exposure to tobacco nicotine causes vasoconstriction and endothelial damage (J. Bermejo-Martin et al., 2018)	Higher rates of smoking and second-hand smoke exposure amongst Maori children† (Mason & Borman, 2016)

Abbreviations: ICAM, inter-cellular adhesion molecule; CRP, C-reactive protein

The potential links between chronic and acute (septic) endothelial injury are summarised in Table 11.4. Chronic endothelial injury is initiated in childhood in response to both adversity and childhood infection.(Danese et al., 2009; Deanfield et al., 2007). Broad societal factors leading to increased circulating inflammatory markers may include status anxiety, which increases in unequal societies. (Layte et al., 2019) Risk factors for chronic endothelial damage cluster in areas of socio-economic deprivation. (Mason & Borman, 2016) Detection of circulating markers of endothelial inflammation are associated with an increased risk of sepsis independently of known co-morbidity.(H. E. Wang, Shapiro, Griffin, et al., 2013) Once sepsis is established, the failing endothelium may distort normal responses to pro-inflammatory cytokines, and over-produce chemokines which antagonise nitric oxide. (Wiewel et al., 2016) The hypothesis that

sepsis itself causes long term damage to endothelial function is provided by the long-term risk of cardiovascular events in post-sepsis populations. (Kosyakovsky et al., 2021)

The discussion presented above does not readily explain the association between socio-economic status and poor sepsis *outcomes,* which persisted in Chapter 9 even after using logistic regression adjusting for age, sex, ethnicity, and co-morbidity. One potential explanation for this finding would be that the care provided to patients in NZDep 3-5 is systematically inferior to that provided to those in NZDep quintile 1 and 2. This is mentioned simply because implicit and explicit bias towards Māori has been demonstrated at every level of the New Zealand healthcare system, in the academic peer review process and in the individual care processes employed to manage complex chronic conditions such as diabetes and cancer.(Chepulis et al., 2021; Lawrenson et al., 2017; Selak et al., 2020) Further work would be required to document whether these factors are at play in the care processes deployed to manage sepsis patients based on socio-economic stratum. For example, reduced access and distance to care could plausibly lead to poor outcomes if this was associated with delayed illness recognition and administration of appropriate antimicrobial therapy.

Separately, and perhaps more likely, deprivation may be associated with unmeasured confounders. These could include tobacco use, obesity, and co-morbidities not included in the Charlson score, such as hypertension. The possibility also exists that vulnerability to post-sepsis vascular morbidity is highest in those with the greatest quantum of pre-sepsis endothelial dysfunction. This highlights how the endothelial frailty/failure model opens new avenues for research. For example, although the outcome of randomised trials of vitamin C in sepsis have led to conflicting results, their premise is based on solid *in vitro* findings pointing to a beneficial effect on endothelial function.(Assouline et al., 2021) There may also be benefit to re-interpreting the assumptions underlying corticosteroid use in septic shock. These have failed to influence mortality, but consistently demonstrate reduced requirement for vasoactive agents and shorter stays in intensive care. Glucocorticoids have significant effects on endothelial function, downregulating NO release, increasing vasomotor responses to catecholamines, and reducing inflammatory endothelial damage in pulmonary vessels by inducing macrophage sphingosine kinase 1 (*SphK1*).(Vandewalle & Libert, 2020; Vettorazzi et al., 2015) Restriction of their use to

patients with sepsis in an intensive care environment misses the point that the vast majority of patients with sepsis are managed on the general ward, where endothelial protective strategies may still be important, and may yet be investigated.

Finally, the endothelial frailty/failure model highlights serious underlying vulnerability in most patients admitted with sepsis and could act as a novel paradigm for interventions aimed at reducing post-sepsis morbidity. For example, whilst there have been limited efforts to aggressively manage cardiovascular morbidity in patients recovering from sepsis, a "go hard, go early" approach to intervention has yielded significant benefits in the post-event follow-up of minor strokes. In fact, the acute stroke management model became the *de facto* standard of care based on one influential randomised controlled trial (Rothwell et al., 2007). The premise for this study (of acute bundled intervention to reduce cardiovascular risk) was that minor stroke provides warning of unstable, inflammatory atheromatous disease. Lipophilic HMGCoA reductase inhibitors appear to reduce post-sepsis mortality, and as mentioned earlier, anti-platelet therapy reduces risk of the systemic inflammatory response in critical illness but has not yet been assessed as a *post-sepsis* intervention.(Hu et al., 2019) Patients with sepsis and stroke have similar underlying risk factors, yet clinical resources flow to the latter. This again illustrates the benefit of considering *evidence of endothelial dysfunction* as a distinct component of short and long-term risk management following admission with infection. It also illustrates how unifying clinical processes across the spectrum of acute care, whilst difficult in practice, is essential to improve clinical outcomes (P. J. Huggan, 2011).

Post-sepsis survivorship

A focus on post-sepsis morbidity and survivorship is yielding significant results in primary epidemiologic research. Patients who survive to hospital discharge are a highly vulnerable group, suffering excess cognitive and physical disability and excess mortality. This will be discussed here with specific reference to implications for the burden of survivorship to the New Zealand healthcare system.

Excess mortality in sepsis survivors

It has been known for some time that whilst acute mortality in sepsis has been falling, late mortality (beyond 30 days) amongst sepsis survivors exceeds that of the general population for up to 5 years following a sepsis event.(Prescott et al., 2016; H. E. Wang et al., 2014) It has been argued that the finding could be explained by the underlying morbidity and frailty of sepsis cohorts.(Prescott et al., 2016) However, by carefully matching sepsis survivors with non-admitted community-dwelling adults and those admitted for infection without organ failure, Prescott *et al* have demonstrated that sepsis is associated with a 22% absolute increase in excess late mortality (30 days to two years) amongst sepsis cases compared with community-based controls, equating to an adjusted odds ratio for late mortality of 1.6 (95% CI 1.1-2.4).(Prescott et al., 2016) Late mortality was consistent regardless of infection source (i.e. pneumonia versus genitourinary tract infection). Additional observations in this study were consistent with the assumption that the presence and extent of organ failure defines poor health trajectories. For example, comparing sepsis and non-sepsis admissions with infection, sepsis was associated with higher rates of readmission, and late mortality correlated positively with the number of acute sepsis-associated organ failures. These authors and others concluded that health-status prior to sepsis does not explain the extent of late post-sepsis mortality.(Prescott et al., 2016; Quartin et al., 1997)

In our work on the direct costs of hospitalisation due to sepsis, we reported an 11% 30-day readmission rate in the 1868 patients identified with sepsis in the National Minimum Data Set (NMDS). This rises to 14% if it is assumed that 20% of the admitted population did not survive to discharge. In the State of California, 30-day all-cause readmission rates vary from 11% to

40% depending on the institution and population served.(Chang et al., 2015) The causes and contributors of readmission and late mortality are not well delineated, but to conclude that sepsis increases vulnerability to further morbidity is at least biologically plausible. Endothelial injury leading to late accelerated atherosclerosis, post-sepsis immunosuppression predisposing to infection, and post-sepsis loss of tumour surveillance have been described in mice.(Prescott & Iwashyna, 2019; Yende et al., 2008, 2014) The exact correlates in humans are unclear, but increased rates of cardiovascular, infectious and cancer deaths have been documented in adult sepsis survivors.(Wilhelms et al., 2020; Yende et al., 2014) The association of mortality with inflammatory burden has been noted in at least one study, with Yende et al finding that patients discharged from hospital following pneumonia have high circulating levels of pro-inflammatory cytokines, levels of which correlated with post-discharge all-cause mortality. (Yende et al., 2008)

Specific causes of disability

In high-income economies, the rising incidence and volume of sepsis admission coupled with improvements in early survival have increased the number of people surviving following a sepsis event.(Iwashyna, Cooke, et al., 2012a) For example, Iwashyna *et al* showed that in the US between 1996 and 2008, in association with rising sepsis incidence and stable case fatality rates, the number of 3 year post-sepsis survivors increased by 119%.(Iwashyna, Cooke, et al., 2012b) A high proportion of survivors live with significant disability. Based on crude observation, and in comparison with a range of other acute in-patient conditions, sepsis is associated with loss of independent living status, high rates of readmission and a significant increase in post-discharge healthcare utilisation.(Prescott et al., 2014) Recovery following a sepsis event is often challenging, encompassing infection-specific outcomes, sepsis-associated morbidity and new morbidity linked to critical illness and hospitalisation. These challenges have been summarised in detail by Prescott et al., are conceptualised in Figure 11.3 (Prescott & Angus, 2018a), and have led to the development of a series of research questions addressing long-term survival, healthcare utilisation and quality of life post-sepsis.(Govindan et al., 2014; Prescott et al., 2014)

Whilst patients recovering from critical illness will exhibit a wide range of frailty and morbidity-associated disabilities, the specific biologic correlates of disability in sepsis (and those most

relevant to understanding what has recently been termed the *post-sepsis syndrome)* relate to effects on the central nervous system and muscle strength.

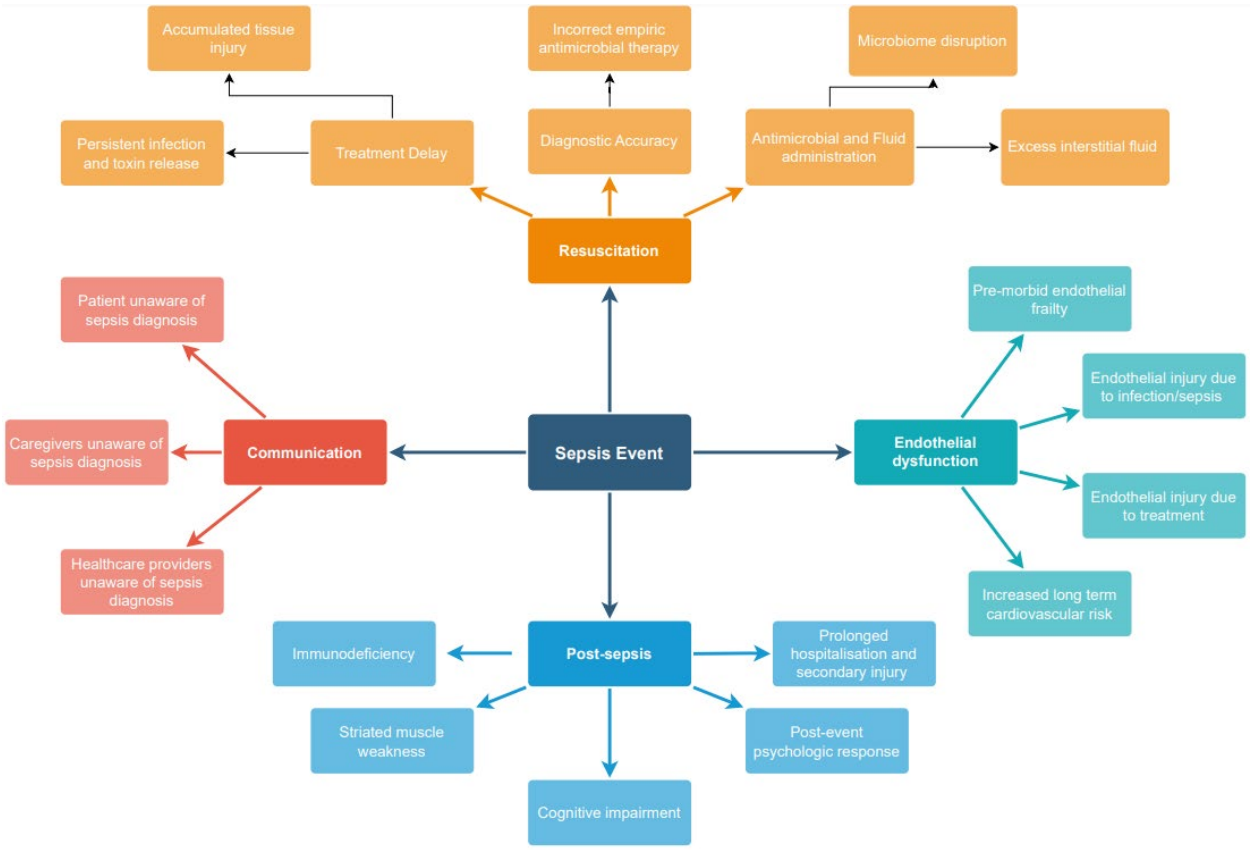

Figure 11.3. Recovery from sepsis. Multiple potential trajectories are available, depending on resuscitation, extent of endothelial dysfunction, post-sepsis symptoms, and communication with patient, caregivers, and healthcare providers.

Brain-muscle dysfunction and long-term sepsis recovery

Sepsis-specific abnormalities of the central nervous system have been summarised in detail by Sonneville *et al*.(Sonneville et al., 2013) Endothelial activation in the central nervous system leads to disturbance of the blood brain barrier and microglial activation. Microglial activation is also triggered following activation of axonal cytokine receptors on the vagal nerve, and by activation of circumventricular organs (CVOs), which have a role in sensing innate and adaptive

immune outputs. As with other pathways to an activated, "septic" state, microglial activation leads to the production of pro and anti-inflammatory cytokines, release of NO and reactive oxygen species into the brain parenchyma, accumulation of NFκB and HMGB1, and upregulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl D-aspartate receptors (NMDARs).(Sonneville et al., 2013) Overlapping interaction with sepsis-associated hypoperfusion, treatment, and disease-associated metabolic disturbance leads frequently to an encephalopathic state that is independent of microbial invasion into the central nervous system.(Prescott & Angus, 2018b; Sonneville et al., 2013) Sepsis encephalopathy is associated with a range of electroencephalographic abnormalities indicating generalised disturbance of normal brain function. Patients with sepsis who undergo MRI brain scanning also have distinct structural correlates which might explain short- and long-term cognitive difficulties described below. Acute changes include cytotoxic and vasogenic oedema affecting the hippocampus and cerebral cortex, with subsequent chronic atrophy focussed on the hippocampus and frontal lobes.(Sonneville et al., 2013)

Sepsis-associated myopathy has recently been reviewed by Callahan *et al*.(Callahan LA & Supinski GS, 2009) A summary of the evidence describing the link between sepsis-associated cytokine signalling, bioenergetic disturbance, proteolysis, apoptosis, reduced muscle strength and long-term muscle atrophy is complete and compelling. Importantly, sepsis-associated muscle weakness and wasting are *selective and additive* to muscle weakness and atrophy associated with hospital admission and bed-rest. This selective effect on striated muscle mass and strength can be identified, for example, in the increased risk of swallowing difficulty in sepsis versus non-sepsis survivors of ICU admission.(Prescott & Angus, 2018a) Also, whilst measures of muscle strength and function do improve in recovery, physical function may not recover to levels expected for age.(Iwashyna, Netzer, et al., 2012)

Persistent muscle weakness is also reflected in the pattern of functional disturbance identified in a series of studies conducted using the Health in Retirement Study (HRS). This is a large inception cohort representative of US adults over 50 years of age.(Iwashyna et al., 2010) By comparing pre and post-sepsis event data in the HRS, Iwashyna and colleagues first showed that when controlling for pre-sepsis function and illness-trajectory, sepsis was associated with

reduced post-sepsis body mass index, a proxy for muscle mass.(Langa & Iwashyna, 2012) These authors then went on to compare levels of cognitive and physical disability following sepsis and non-sepsis hospitalisation using individual pre-sepsis function as a control.(Iwashyna et al., 2010) This approach revealed that sepsis (as opposed to non-sepsis hospitalisation) was associated with increased odds of new, moderate to severe cognitive disability (OR 3.33, 95% CI 1.53 to 7.25), and new physical limitation affecting function (mean 1.57 new limitations, 95% CI 0.99 to 2.15). Importantly, these new disabilities were more prominent amongst those with no pre-morbid limitations and persisted for up to 8 years of follow-up. The emerging picture is of a post-sepsis brain-muscle syndrome, where sepsis-associated changes to cognitive function and muscle mass are reflected in prolonged functional deficits. The relative burden of this syndrome would be expected to manifest most prominently in those who have not previously adapted to ill health or disability.

At the start of this work (specifically in the publication reporting sepsis epidemiology in the Waikato region, Chapter 8), we lacked confidence in the ability of our coding algorithm to identify patients with 'true' clinical sepsis. The potential importance of rising sepsis incidence was therefore under emphasised. However, based on clinical validation efforts (summarised in Table 11.3), we can now recapitulate evidence of rising case numbers and draw preliminary conclusions about the additional burdens relating to survivorship. In Chapter 8, comparing 2011-2012 with the period 2007-2008, the age standardised sepsis rate ratio was 1.62 (95% CI 1.18-2.24). In 2020, 891 cases of sepsis were admitted compared with 442 in 2016 (Figure 11.1). This figure excludes those admitted to the four facilities that operate in our region other than Waikato Hospital. This represents a significant, unanticipated, previously unmeasured increase in infection-related morbidity and long-term harm, which accumulated in the pre-COVID era. In addition to the impact on individuals, families and whānau, the morbidity burden posed by these admissions must have exerted significant cost pressures on the local healthcare system and, if replicated nationally, on the New Zealand health budget.

Table 11.5. COVID-19 responses and their implications for sepsis research, care, and investment

	Findings related to COVID-19	**Relevance to sepsis research**
Public health	Socio-economic status determines incidence Respiratory viral illnesses drive admissions with pneumonia	Poverty reduction and investments to reduce household overcrowding are needed to reduce rates of hospitalisation with sepsis
Immunisation	Successful vaccination programmes attenuate hospitalisation and severe disease	Fund research into pathogen-specific vaccines which lower risk of severe disease
Age and co-morbidity	Determine risk of severe outcomes	Public and primary health interventions to reduce morbidity associated with *endothelial frailty*
Early recognition and treatment	Delayed presentations associated with increased risk of death and ICU admission	Invest in programmes of public awareness and healthcare quality improvement
Clinical features	Pathogenesis, clinical features, natural history, and outcome are pathogen-dependent	Report research outcomes and deliver care based on infection (i.e. *S.pneumoniae*) or clinical syndrome (i.e. pneumonia)
Early symptoms	Relate to pathogen replication in tissue and activation of the innate immune response	Direct early therapy towards control of pathogen and minimisation of tissue damage
Endothelial damage	Clinical features mediated by endothelial damage and dysfunction	Investigate endothelial 'protective and preventive' strategies to attenuate infection and cytokine-mediated endothelial damage
Pro-inflammatory cytokine signalling	IL-6 production correlates with outcome and anti-IL-6 therapy in COVID-19 improves outcomes	Target anti-inflammatory and anti-cytokine therapies to patients with evidence of cytokine-mediated disease
Recovery in severe disease	Characterised in many cases by prolonged symptomatology, principally weakness and impaired cognitive function	Implement programmes of recovery focussed on rehabilitation and return to normal function

Abbreviations: IL, interleukin

Strengths and Weaknesses

Strengths

This thesis demonstrates how practice-based research and audit can generate novel findings, and insights relevant to real-world clinical challenges and with the interests of patients and patient outcomes to the fore. It also demonstrates how the conduct of research over long periods allows for the integration of new information, resources and clinical discourse. For example, a quality improvement programme designed and implemented in 2008 (when this work began), would look very different to that implemented successfully in 2018. Another strength lay in our ready access to high quality discharge coding data, which is rigorously quality controlled and constitutes an important contribution to national health statistics. The application of coding algorithms to this data allowed selection of a cohort of patients that would be recognised as 'septic' by clinicians working in acute care environments. Finally, although similar work and similar findings have been produced in other countries, this is the first body of work which aims to describe sepsis epidemiology, clinical features and outcome in Aotearoa New Zealand. As such, we have answered key questions posed by the BPAC writing group, in their 2018 publication of a national sepsis care guideline (Table 11.2)

Weaknesses

Where weaknesses are inherent to the design of individual studies, we have pointed this out in the relevant chapter. Apart from the work on national cost estimates reported in Chapter 10, this work was conducted in specific geographic areas (ie Canterbury, Western Singapore and Waikato), leaving the generalisability of our observations in question. That said, we can think of no reason why the findings observed in Canterbury and Waikato would not be mirrored over New Zealand as a whole, and work in Singapore produced findings relevant to the thesis. We used different coding algorithms for sepsis – one to study population epidemiology according to the method of Angus, and a second method to examine quality improvement outcomes that best

represented primary invasive bacterial infection (Chapter 9).(Sundararajan et al., 2005a) The patterns in the data are similar, but this has created two cohorts which are not directly comparable, recapitulating the difficulties created when different methods are used to define sepsis in administrative data, referred to in detail in Chapter 2. Finally, whilst the time over which this work was undertaken allowed changes in the literature to be assessed and incorporated, and whilst the goals of the individual investigations reported were consistent over time (as outlined in Chapter 3), the thesis was not planned from end to end, conducted in a single location, or under consistent academic supervision. As such, we did not consider larger research goals, such as the establishment of a central repository of patient and laboratory information. These may arise, however, based on experience gained in the conduct of the research reported in this thesis.

Putting it all together using the example of COVID-19

The body of this thesis deliberately omits new data relating to the management of SARS-CoV-2 infection/COVID-19 for the following reasons:

i) the research reported here was conceived and executed before the COVID-19 epidemic
ii) debate is ongoing as to whether severe COVID-19 is an exemplar of the *dysregulated* host response to infection caused by bacterial infections.
iii) research into COVID-19 is evolving at an astonishing rate and much has been pre-published without peer review.

The rapid pace and early success of COVID-19 research can instead provide an example of how lessons learned during the pandemic might inform a new approach to sepsis therapy.

The results of this thesis point to the following conclusions:

- Age, co-morbidity, and socio-economic status underlie variability, inequity, and predisposition to sepsis admission in New Zealand
- These determine a state of endothelial vulnerability during infection, such that a failing endothelium results from pathogen-derived toxins and immune/haemostatic dysregulation
- The number and cost of sepsis-related hospitalization are largely hidden within general hospital statistics. Specific approaches are needed to isolate sepsis-related outcomes within routine data
- Education, prevention, and interventions to improve long term outcomes should focus on reducing pre-sepsis endothelial frailty and post-sepsis endothelial dysfunction.

These conclusions rest on data collected in a pre-COVID context and relate selectively to the features of *bacterial* sepsis. However, whilst anti-viral immune responses differ somewhat to the general processes described here in relation to bacterial infection, the ultimate outcomes are very similar in relation to cytokine release and endothelial dysfunction.(Libby & Lüscher, 2020).

These similarities, combined with the rapid clinical successes achieved when the world's attention focussed on a single pathogen, perhaps shine a light on what needs to change in the world of sepsis research and clinical care, in pursuit of better patient outcomes.

The principal similarities between the sepsis syndrome and COVID-19 disease are summarised in Table 11.5. COVID-19 has highlighted stark inequities in health which are known to persist at global, national, and regional levels. In New Zealand, indigenous and non-indigenous populations are partitioned by health system access and economic opportunity.(Keene & Dalton, 2021) High incidence and poor outcomes have been observed amongst ethnic minorities with COVID-19 in high-incidence countries.(Bassett et al., 2020; Buikema et al., 2021) Steyn and colleagues have reported that the infection fatality rate for Māori is likely to be 50% higher than non-Māori, after adjusting for age, co-morbidity, life-expectancy and unmet healthcare need.(Steyn et al., 2020) Against these known risks, the adult vaccination roll-out against COVID-19 has been less effective in reaching Māori compared with non-Māori communities. At the time of writing, this has been attributed by some to reliance on systems of commissioning and governance which have presided over inequities in indigenous health for decades.(Steyn et al., 2021) The same inequities are visible in data presented here, showing a disproportionate burden of infectious disease and sepsis falling on Māori and Pacific communities, largely attributable to socioeconomic deprivation and co-morbidity. Calls to prioritise health through changes in housing, health and social policy are highly relevant to any effort aimed at reducing the imbalance of sepsis incidence caused by the social determinants of health.

At the level of research and therapeutics for sepsis, the COVID-19 pandemic has provided some proof of many of the concepts explored in this thesis. Firstly, research into COVID-19 has focussed on a single pathogen. The homogeneity sought by definitions of the clinical 'sepsis syndrome' belie the complexity of the immune, endothelial and haemostatic responses to infection. Whilst using large cohorts to study general outcomes and trends provide valuable insights into the severe outcomes of infectious disease, the 'final common pathway' implied by current sepsis definitions may not even exist.(Schinkel et al., 2021) New models are needed to guide research. These may rely on integrating transcriptomic, biomarker and clinical data to create a sub-classification system for sepsis and applying this to the study of single pathogens or

groups of pathogens which share pathogenicity determinants. Alternatively, recapitulation of the PIRO classification in clinical research may delineate groups for whom intensive (or palliative) care is the most appropriate clinical strategy (Seymour et al., 2019; Stanski & Wong, 2019)al., 2019; Stanski & Wong, 2019).

Secondly, trials using novel therapeutics in sepsis have aimed to report short-term outcomes such as length of intensive care unit stay and 30-day mortality.(Iwashyna, 2010) These ignore the potential for some therapies to improve health system measures (such as overall length of stay and healthcare utilisation) or avoidance of morbidity. For example, therapeutic administration of recombinant bactericidal/permeability-increasing protein was shown to reduce the rate of multiple limb amputation and improve functional outcomes in children with meningococcal disease but has not been introduced into clinical practice due partly to lack of effect on mortality.(Levin et al., 2000) In the face of COVID-19, a core set of outcome measures was developed by the World Health Organisation, leading ultimately to a unified reporting framework for clinical trials using new agents.(J. C. Marshall et al., 2020) The same is needed to guide the design and reporting of sepsis trials.

Thirdly, the basic science in both COVID-19 and sepsis demonstrates the centrality of the endothelium in the pathogenesis of severe clinical outcomes.(Ince et al., 2016; Libby & Lüscher, 2020) The endothelium has not previously been considered as a single organ, yet it provides a continuous blood/tissue barrier, interacts with immune and coagulation cascades, mediates the normal function of major organs, and is chronically injured by aging and by the co-morbidities which have been shown to predispose to poor COVID-19 and sepsis outcomes. Study of a single disease allows decision making based on a relatively uniform set of clinical decision points. In the management of COVID-19, anti-microbial therapy appears to be effective early in the course of disease, or even before symptoms emerge.(Fischer et al., 2021) Once endothelial failure is established, however, anti-virals are much less effective and the introduction of well-timed anti-inflammatory therapy improves outcomes.(Abani et al., 2021; The RECOVERY Collaborative Group, 2021) The findings in this thesis hint that a unifying sepsis definition focussed on evidence of “endothelial failure” may drive the changes in clinical approach needed to prevent or mitigate poor outcomes.

Fourthly, uniting research, clinical and public health responses around the threat of a single pathogen or syndrome can galvanise professional, public, and political awareness of infectious disease threats. As an intermediate event (lying between an infection and its ultimate sequelae), the sepsis syndrome has not been well understood or communicated to the public, or even to the health professions.(Rudd et al., 2020b) Using Google Trends data, Jabaley *et al* have demonstrated that global average internet search volumes for sepsis are less than for influenza, myocardial infarction, and stroke.(Jabaley et al., 2018). Amongst more than 1000 medical professionals interviewed by Poeze *et al*, agreement surrounding sepsis definitions was very low, but most agreed that the lack of effective definitions impacted patient care.(Poeze et al., 2004) Pre-COVID, at least, the sepsis syndrome could not be regarded as a topic of major public concern, and this was reflected in prioritisation within systems of health funding and investment. A pandemic viral infection may represent unreasonable competition in terms of public priorities and "name recognition", but it is telling that the World Health Organisation did not establish a sepsis programme until 2017.(Reinhart et al., 2017)

Finally, recognition of poor quality of life and prolonged symptomatology in the post-COVID setting correlates with prolonged disability following hospitalisation with sepsis. Persistent organ failure, fatiguability and cognitive disturbance are common to both "Long-COVID" and the "Post-Sepsis Syndrome".(Lopez-Leon et al., 2021; Slikke et al., 2020) Whilst not necessarily proving a link between the two, the needs of both groups should attract programmes of research, support and enhanced recovery.

Conclusion

Sepsis is an under-recognised, severe consequence of common infectious disease in New Zealand. Increasing incidence and predilection for age, co-morbidity and deprivation reveal inequity and frailty within the population as well as within hospitalised individuals. Quality improvement efforts can lead to improvement in clinical outcomes, but cost-containment ultimately lies on prevention and recognising the complex needs of survivors. Further research is needed to determine the best approach to reducing sepsis-associated harm in New Zealand. This could easily include the reorganization of acute services to prioritise management of the highest risk sepsis cases (those associated with haemodynamic instability and shock). Waikato Hospital is well placed to investigate the utility of metabolic resuscitation strategies (for example, Vitamin C and hydrocortisone) in a population of patients who do not receive intensive care (typically the elderly and haemodynamically unstable patients who do not need intubation).

Physicians and other healthcare providers have an important part to play in community engagement and advocacy. Recognising the lack of an advocacy group to forward the interests of patients, family and whānau, the author helped to establish a Trust (the New Zealand Sepsis Trust) to externalise resources and to promote the public and political discussions necessary to create change and deliver appropriate investment. The Trust has organised several multi-disciplinary workshops and consultations with the aim of delivering a National Sepsis Action Plan, as advocated for by World Health Assembly Resolution 70.7.(Reinhart et al., 2017) The draft plan and supporting documents can be found at www.sepsis.org.nz/action. Much work lies ahead, but if the following steps can be taken, supported by high quality data and research, much can be achieved to increase awareness, improve care, and support survivors of sepsis in Aotearoa New Zealand.

1. Create a National Sepsis Network: clinical networks promote the importance of continuous quality improvement, develop best-practice guidance, and ensure that these are delivered in real-world settings
2. Increase Public Awareness: improved outcomes rely on early recognition, but community awareness of sepsis is low and presentations are often delayed

3. Improve recognition and treatment in all healthcare settings: recognition and early treatment rely on a confident, educated and empowered workforce
4. Collect data to drive quality improvement: information gathering can reveal the nature, location and extent of harms caused by infectious disease and sepsis
5. Support Sepsis Survivors: recovery from sepsis is often prolonged and difficult. Better resources are needed to support community and primary care teams working with sepsis survivors.

Nāu to raurau, nāku te rourou ka ora ai te iwi
"With your contribution and my contribution there lies wellbeing for the people".

Appendices

Appendix 1: Development of International Classification of Disease version 10, Australian Modification (ICD10-AM) administrative definitions of major infection and sepsis

New Zealand Major Infection indicator

The 'New Zealand Major Infection' (NZMI) indicator is comprised of the ICD-10-AM codes identified by UK Inada-Kim et al, with the addition of 14 ICD-10-AM codes used in a Waikato-based study conducted by Huggan et al (P. J. Huggan et al., 2017). These ICD-10 codes are applied to the first 30 diagnosis codes entered to the National Minimum Data Set (NMDS). Codes are listed under ICD-10-AM chapter headings.

I. Certain infectious and parasitic diseases

1. A01 Typhoid and paratyphoid fevers (incl. A01.0, A01.1, A01.2, A01.3, A01.4)
2. A02 Other salmonella infections (incl. A02.0, A02.1, A02.2, A02.8, A02.9)
3. A03 Shigellosis (incl. A03.0, A03.1, A03.2, A03.3, A03.8, A03.9)
4. A04 Other bacterial intestinal infections (incl. A04.0, A04.1, A04.2, A04.3, A04.4, A04.5, A04.6, A04.7, A04.8, A04.9)
5. A06 Amoebiasis (incl. A06.0, A06.1, A06.2, A06.3, A06.4, A06.5, A06.6, A06.7, A06.8, A06.9)
6. A15 Respiratory tuberculosis (incl. A15.0, A15.2, A15.3, A15.4, A15.5, A15.6, A15.7, A15.8, A15.9)
7. A16 Respiratory tuberculosis, not confirmed bacteriologically or histologically (incl. A16.0, A16.1, A16.2, A16.3, A16.4, A16.5, A16.7, A16.8, A16.9)
8. A17 Tuberculosis of nervous system (incl. A17.0, A17.1, A17.8, A17.9)

9. A18 Tuberculosis of other organs (incl. A18.0, A18.1, A18.2, A18.3, A18.4, A18.5, A18.6, A18.7, A18.8)
10. A19 Miliary tuberculosis (incl. A19.0, A19.1, A19.2, A19.8, A19.9)
11. A27 Leptospirosis (incl. A27.0, A27.8, A27.9)
12. A32 Listerosis (incl. A32.0, A32.1, A32.7, A32.8, A32.9)
13. A37 Whopping cough (all subcategories)
14. A38 Scarlet fever
15. A39 Meningococcal infection (incl. A39.0, A39.1, A39.2, A39.4, A39.5, A39.8, A39.9)
16. A40 Streptococcal sepsis (incl. A40.0, A40.1, A40.2, A40.3, A40.8, A40.9)
17. A41 Other Sepsis (incl. A41.0, A41.1, A41.2, A41.3, A41.4, A41.5, A41.8, A41.9)
18. A42 Actinomycosis (all subcategories)
19. A43 Nocardiosis (all subcategories)
20. A44 Bartenollosis (all subcategories)
21. A46 Erysipelas
22. A48 Other Bacterial diseases, not elsewhere classified (incl. A48.0, A48.1, A48.2, A48.3, A48.4, A48.8)
23. A49 Bacterial infection of unspecified site (incl. A49.0, A49.1, A49.2, A49.3, A49.8, A49.9)
24. A51 Early syphilis (all subcategories)
25. A54 Gonococcal infection (incl. A54.1, A54.2, A54.3, A54.4, A54.5, A54.6, A54.8, A54.9)
26. A55 Chlamydial lymhogranuloma (venereum)
27. A56 Other sexually transmitted chlamydial diseases (incl. A56.0, A56.1, A56.2, A56.3, A56.4, A56.8)
28. A68 Relapsing fevers (all subcategories)
29. A69.2 Lyme disease
30. A70 Chlamydia psittaci infection
31. A75 Typhus fever (all subcategories)
32. A77 Spotted fever (all subcategories)
33. A78 Q fever
34. A79 Other rickettsioses (all subcategories)
35. B59 Pneumocystosis

VI. Diseases of the nervous system

36. G00 Bacterial meningitis, not elsewhere classified (incl. G00.0, G00.1, G00.2, G00.3, G00.8, G00.9)
37. G01 Meningitis in bacterial diseases classified elsewhere
38. G04.2 Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
39. G06 Intracranial and intraspinal abscess and granuloma (incl. G06.0, G06.1, G06.2)

VIII. Diseases of the ear and mastoid process

40. H60 Otitis externa (incl. H60.0, H60.1, H60.2, H60.3)
41. H66 Suppurative and unspecified otitis media (incl. H66.0, H66.4, H66.9)
42. H67.0 Otitis media in bacterial diseases classified elsewhere
43. H68.0 Eustachian salpingitis
44. H70 Mastoiditis and related conditions (incl. H70.0, H70.9)
45. H73.0 Acute myringitis

IX. Diseases of the circulatory system

46. I00 Rheumatic fever without mention of heart involvement
47. I01 Rheumatic fever with heart involvement (incl. I01.0, I01.1, I01.2, I01.8, I01.9)
48. I02 Rheumatic chorea (incl. I02.0, I02.9)
49. I33 Acute and subacute endocarditis (incl. I33.0, I33.9)
50. I38 Endocarditis, valve unspecified

X. Diseases of the respiratory system

51. J01 Acute sinusitis (incl. J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9)
52. J02 Acute pharyngitis (incl. J02.0, J02.9)
53. J03 Acute tonsillitis (incl. J03.0, J03.9)
54. J05.1 Acute epiglottitis
55. J06.9 Acute upper respiratory infection, unspecified
56. J13 Pneumonia due to Streptococcus pneumoniae,
57. J14 Pneumonia due to Haemophilus influenza,

58. J15 Bacterial pneumonia, not elsewhere classified (J15.0, J15.1, J15.2, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9)
59. J16 Pneumonia due to other infectious organisms, not elsewhere classified (incl. J16.0, J16.8)]
60. J17.0 Pneumonia in bacterial diseases classified elsewhere (incl. J17.0, J17.8)
61. J18 Pneumonia, organism unspecified (including J18.0, J18.1, J18.2, J18.8 and J18.9)
62. J20 Acute bronchitis (incl. J20.0, J20.1, J20.2, J20.8, J20.9)
63. J22 Unspecified acute lower respiratory infection
64. J36 Peritonsillar abscess
65. J39 Other diseases of upper respiratory tract (incl. J39.0, J39.1)
66. J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection
67. J69 Pneumonitis due to solids and liquids (incl. J69.0, J69.8)
68. J84.9 Interstitial pulmonary disease unspecified (interstitial pneumonia NOS)
69. J85 Abscess of lung and mediastinum (incl. J85.1, J85.2, J85.3)
70. J86 Pyothorax (incl. J86.0, J86.9)
71. J95.0 Sepsis of tracheostomy stoma
72. J98.5 Diseases of mediastinum, not elsewhere classified- Mediastinitis
XI. Diseases of the digestives system (dental disorders omitted)

73. K22.3 Perforation of oesophagus
74. K35 Acute appendicitis (incl. K35.2, K35.3, K35.8)
75. K37 Unspecified appendicitis
76. K57 Diverticular disease of intestine (incl. K57.0, K57.2, K57.4, K57.8,)
77. K61 Abscess of anal and rectal regions (incl. K61.0, K61.1, K61.2, K61.3, 61.4)
78. K63.0 Abscess of intestine
79. K63.1 Perforation of intestine (nontraumatic)
80. K65.0 Acute peritonitis (incl. K65.0, K65.8, K65.9)
81. K67 Disorders of peritoneum in infectious diseases classified elsewhere (all subcategories)
82. K75.0 Abscess of liver
83. K80.0 Calculus of gallbladder with acute cholecystitis/cholangitis (incl. K80.0, K80.1, K80.3, K80.4)

84. K81 Cholecystitis (incl. K81.0, K81.1, K81.8, K81.9)

85. K82.2 Perforation of gallbladder

86. K83.0 Cholangitis

87. K83.2 Perforation of bile duct

XII. Diseases of skin and subcutaneous tissue

88. L00 Staphylococcal scalded skin syndrome

89. L01 Impetigo (L01.0, L01.1)

90. L02 Cutaneous abscess, furuncle and carbuncle (incl. L02.0, L02.1, L02.2, L02.3, L02.4, L02.8, L02.9)

91. L03 Cellulitis (including L03.0, L03.1, L03.2, L03.3, L03.8 and L03.9)

92. L05.0 Pilonidal cyst with abscess

93. L08 Other local infections of skin and subcutaneous tissue (incl. L08.0, L08.8, L08.9)

94. L30.3 Infective dermatitis

95. L53.3 Erythema marginatum

96. L98.0 Pyogenic granuloma

XIII. Diseases of the musculoskeletal system and connective tissue

97. M00 Pyogenic arthritis (incl. M00.0, M00.1, M00.2, M00.8, M00.9)

98. M01 Direct infections of joint in infectious and parasitic diseases classified elsewhere (incl. M01.0, M01.1, M01.2, M01.3)

99. M46.2 Osteomyelitis of vertebra

100. M46.4 Discitis, unspecified

101. M65 Synovitis and tenosynovitis (incl. M65.0, M65.1)

102. M71.0 Abscess of bursa

103. M72.6 Necrotizing fasciitis

104. M86 Osteomyelitis

XIV. Diseases of genitourinary system

105. N10 Acute tubulo-interstitial nephritis

106. N11 Chronic tubulo-interstitial nephritis (incl. N11.0, N11.1, N11.8, N11.9)

107. N12 Tubulo-intestitial nephritis, not specified as acute or chronic
108. N13.6 Pyonephrosis
109. N15.1 Renal and perinephric abscess
110. N15.9 Renal tubulo-interstitial disease, unspecified
111. N30 Cystitis, unspecified (including N30.0, N30.8, N30.9)
112. N34.0 Urethral abscess
113. N39.0 Urinary tract infection, site not specified
114. N41.0 Acute prostatitis
115. N43.1 Infected hydrocele
116. N45 Orchitis and epididymitis (incl. N45.0, N45.9)
117. N48.2 Other disorders of penis (incl. N48.1, N48.2)
118. N49.9 Inflammatory disorder of unspecified male genital organ
119. N61 Inflammatory disorders of breast
120. N70 Salpingitis and oophoritis (incl. N70.0, N70.9)
121. N71 Inflammatory disease of uterus, except cervix (incl. N71.0, N71.9)
122. N73 Other female pelvic inflammatory diseases (incl. N73.0, N73.1, N73.2, N73.4, N73.9)
123. N75.1 Abscess of Bartholin gland
124. N76 Other inflammation of vagina and vulva (incl. N76.0, N76.1, N76.3, N76.4, N76.8)

XV. Pregnancy, childbirth and the puerperium

125. O08.0 Genital tract and pelvic infection following abortion and ectopic and molar pregnancy
126. O23 Infections of genitourinary tract in pregnancy (incl. O23.0, O23.1, O23.2, O23.3, O23.4, O23.5, O23.9)
127. O41.1 Infection of amniotic sac and membranes
128. O85 Puerperal sepsis
129. O86 Other puerperal infections (incl. O86.0, O86.1, O86.2, O86.3, O86.4, O86.8)
130. O88.3 Obstetric pyaemic and septic embolism
131. O91 Infections of breast associated with childbirth (incl. O91.0, O91.1)

XVI. Certain conditions originating in the perinatal period

132. P36 Bacterial sepsis of newborn (incl. P36.0, P36.1, P36.2, P36.3, P36.4, P36.5, P36.8, P36.9)
133. P39 Other infections specific to the perinatal period (incl. P39.0, P39.2, P39.3, P39.4, P39.8, P39.9)
134. P78 Other perinatal digestives system disorders (P78.0, P78.1,)
135. T814 Infection following a procedure, not elsewhere classified
136. T845 Infection and inflammatory reaction due to internal joint prosthesis
XVIII. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

137. R57.2 Septic shock
138. R65 Systemic Inflammatory Response syndrome (incl. R65.0, R65.1, R65.9)
The following 14 ICD-10-AM codes were added to the NZMI indicator as they are included in the NZS indicator and part of the study conducted by Huggan et al4.

A241 Acute and fulminating melioidosis
B377 Candidal sepsis
B387 Disseminated coccidioidomycosis
B393 Disseminated histoplasmosis capsulati
B407 Disseminated blastomycosis
B417 Disseminated paracoccidioidomycosis
B427 Disseminated sporotrichosis
B447 Disseminated aspergillosis
B457 Disseminated cryptococcosis
B464 Disseminated mucormycosis
A4150 Sepsis due to unspecified Gram-negative organisms
A4151 Sepsis due to Escherichia coli [E Coli]
A4152 Sepsis due to Pseudomonas
A4158 Sepsis due to other Gram-negative organisms

New Zealand Sepsis indicator

The New Zealand Sepsis (NZS) indicator is based on the work of Sundarajan *et al,* and is present when an explicit 'Primary Sepsis' code is found together with an 'Organ Failure' code.(Sundararajan et al., 2005b)

Where a pre-specified ICD10 code defining sepsis was present in the first (primary) diagnosis position the indicator 'Primary_infection' was assigned. Where the primary position was occupied by an ICD10 Z-code and an indicator code (as defined below) was in the second position, the 'Primary_infection' indicator was also assigned.

1 A010 Typhoid fever
2 A021 Salmonella sepsis
3 A190 Acute miliary tuberculosis of a single specified site
4 A191 Acute miliary tuberculosis of multiple sites
5 A192 Acute miliary tuberculosis, unspecified
6 A198 Other miliary tuberculosis
7 A199 Miliary tuberculosis, unspecified
8 A241 Acute and fulminating melioidosis
9 A327 Listerial sepsis
10 A394 Meningococcaemia, unspecified
11 A400 Sepsis due to streptococcus, group A
12 A401 Sepsis due to streptococcus, group B
13 A402 Sepsis due to streptococcus, group D
14 A403 Sepsis due to Streptococcus pneumoniae
15 A408 Other streptococcal sepsis
16 A409 Streptococcal sepsis, unspecified
17 A410 Sepsis due to *Staphylococcus aureus*
18 A411 Sepsis due to other specified staphylococcus
19 A412 Sepsis due to unspecified staphylococcus

20 A413 Sepsis due to Haemophilus influenzae

21 A414 Sepsis due to anaerobes

22 A4150 Sepsis due to unspecified Gram-negative organisms

23 A4151 Sepsis due to Escherichia coli [E Coli]

24 A4152 Sepsis due to Pseudomonas

25 A4158 Sepsis due to other Gram-negative organisms

26 A418 Other specified sepsis

27 A419 Sepsis, unspecified

28 A427 Actinomycotic sepsis

29 A430 Pulmonary nocardiosis

30 A481 Legionnaires' disease

31 A483 Toxic shock syndrome

32 A499 Bacterial infection, unspecified

33 A548 Other gonococcal infections

34 B377 Candidal sepsis

35 A78 Q fever (coded in logic as A780)

36 B387 Disseminated coccidioidomycosis

37 B393 Disseminated histoplasmosis capsulati

38 B407 Disseminated blastomycosis

39 B417 Disseminated paracoccidioidomycosis

40 B427 Disseminated sporotrichosis

41 B447 Disseminated aspergillosis

42 B457 Disseminated cryptococcosis

43 B464 Disseminated mucormycosis

44 P360 Sepsis of newborn due to streptococcus, group B

45 P361 Sepsis of newborn due to other and unspecified streptococci

46 P362 Sepsis of newborn due to *Staphylococcus aureus*

47 P363 Sepsis of newborn due to other and unspecified staphylococci

48 P364 Sepsis of newborn due to Escherichia coli

49 P365 Sepsis of newborn due to anaerobes

50 P368 Other bacterial sepsis of newborn

51 P369 Bacterial sepsis of newborn, unspecified

Organ failure: These ICD-10 codes, applied to the first 30 diagnosis codes, were used to identify organ failure. In addition, the 'Organ_failure' indicator was also applied when one of the three operation/procedure codes appeared within the first 30 operation/procedure codes.

1 I950 Idiopathic hypotension
2 I951 Orthostatic hypotension
3 I959 Hypotension, unspecified
4 R031 Nonspecific low blood-pressure reading
5 R572 Septic shock
6 R570 Cardiogenic shock (missing)
7 R571 Hypovolaemic shock
8 R578 Other shock
9 R579 Shock, unspecified
10 D65 Disseminated intravascular coagulation [defibrination syndrome]
11 D688 Other specified coagulation defects
12 D689 Coagulation defect, unspecified
13 D695 Secondary thrombocytopenia
14 D696 Thrombocytopenia, unspecified
15 K720 Acute and subacute hepatic failure
16 E872 Acidosis
17 F050 Delirium not superimposed on dementia, so described
18 F051 Delirium superimposed on dementia
19 F058 Other delirium
20 F059 Delirium, unspecified
21 G934 Encephalopathy, unspecified
22 R400 Somnolence
23 R401 Stupor
24 R402 Coma, unspecified
25 N000 Acute nephritic syndrome, minor glomerular abnormality

26 N001 Acute nephritic syndrome, focal and segmental glomerular lesions

27 N002 Acute nephritic syndrome, diffuse membranous glomerulonephritis

28 N003 Acute nephritic syndrome, diffuse mesangial proliferative glomerulonephritis

29 N004 Acute nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis

30 N005 Acute nephritic syndrome, diffuse mesangiocapillary glomerulonephritis

31 N006 Acute nephritic syndrome, dense deposit disease

32 N007 Acute nephritic syndrome, diffuse crescentic glomerulonephritis

33 N008 Acute nephritic syndrome, other

34 N009 Acute nephritic syndrome, unspecified

35 N010 Rapidly progressive nephritic syndrome, minor glomerular abnormality

36 N011 Rapidly progressive nephritic syndrome, focal and segmental glomerular lesions

37 N012 Rapidly progressive nephritic syndrome, diffuse membranous glomerulonephritis

38 N013 Rapidly progressive nephritic syndrome, diffuse mesangial proliferative glomerulonephritis

39 N014 Rapidly progressive nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis

40 N015 Rapidly progressive nephritic syndrome, diffuse mesangiocapillary glomerulonephritis

41 N016 Rapidly progressive nephritic syndrome, dense deposit disease

42 N017 Rapidly progressive nephritic syndrome, diffuse crescentic glomerulonephritis

43 N018 Rapidly progressive nephritic syndrome, other

44 N019 Rapidly progressive nephritic syndrome, unspecified

45 N170 Acute kidney failure with tubular necrosis

46 N172 Acute kidney failure with medullary necrosis

47 N178 Other acute kidney failure

48 N179 Acute kidney failure, unspecified

49 N171 Acute kidney failure with acute cortical necrosis

50 J80 Adult respiratory distress syndrome

51 J951 Acute pulmonary insufficiency following thoracic surgery

52 J952 Acute pulmonary insufficiency following nonthoracic surgery53 J9600 Acute respiratory failure, type I

54 J9601 Acute respiratory failure, type II

55 J9609 Acute respiratory failure, type unspecified (J6909)

56 J9690 Respiratory failure unspecified, type I

57 J9691 Respiratory failure unspecified, type II

58 J9699 Respiratory failure unspecified, type unspecified

59 J960 Acute respiratory failure

60 J969 Respiratory failure, unspecified

61 R092 Respiratory arrest

Procedure codes:

66 1388200 Management of continuous ventilatory support, <= 24 hours

67 1388201 Management of continuous ventilatory support, more than 24 hours and less than 96 hours

68 1388202 Management of continuous ventilatory support, 96 hours or more

The Modified "Angus" method used to estimate sepsis incidence in the Waikato Region

This method detects a wide range of primary codes and includes both explicit 'sepsis' codes (ie A40*, streptococcal sepsis) and codes for infectious diseases commonly associated with sepsis (ie G00* Bacterial meningitis, not elsewhere classified).(Sundararajan et al., 2005b) In both cases, a secondary organ failure code was required to qualify an administrative definition of sepsis. In contrast to the work described in Chapter 10, Z-codes were not replaced if entered in a primary position.

Angus codes for serious infection

A00* A00 Cholera
A01* A01 Typhoid and paratyphoid fevers
A02* A02 Other salmonella infections
A03* A03 Shigellosis
A04* A04 Other bacterial intestinal infections
A05* A05 Other bacterial food-borne intoxications
A08* A08 Viral and other specified intestinal infections
A09* A09 Diarrhea and gastroenteritis, presumed infectious origin
A15* A15 Respiratory tuberculosis, bacteriologically and histologically confirmed
A16* A16 Respiratory tuberculosis, confirmed bacteriologically or histologically
A17* A17 Tuberculosis of nervous system
A18* A18 Tuberculosis of other organs
A19* A19 Miliary tuberculosis
A20* A20 Plague
A21* A21 Tularemia
A22* A22 Anthrax
A23* A23 Brucellosis
A24* A24 Glanders and melioidosis
A25* A25 Rat-bite fevers
A27* A27 Leptospirosis
A28* A28 Other zoonotic bacterial diseases, not elsewhere classified

A30* A30 Leprosy (Hansen's disease)

A31* A31 Infection due to other mycobacteria

A32* A32 Listeriosis

A33* A33 Tetanus neonatorum

A34* A34 Obstetrical tetanus

A35* A35 Other tetanus

A36* A36 Diphtheria

A37* A37 Whooping cough

A38* A38 Scarlet fever

A39* A39 Meningococcal infection

A40* A40 Streptococcal sepsis

A41* A41 Other sepsis

A42* A42 Actinomycosis

A43* A43 Nocardiosis

A44* A44 Bartonellosis

A46* A46 Erysipelas

A48* A48 Other bacterial diseases, elsewhere classified

A50* A50 Congenital syphilis

A49* A49 Bacterial infection of unspecified site

A51* A51 Early syphilis

A52* A52 Late syphilis

A53* A53 Other and unspecified syphilis

A54* A54 Gonococcal infection

A65* A65 Nonvenereal syphilis

A66* A66 Yaws

A67* A67 Pinta (carate)

A69* A69 Other spirochetal infections

B35* B35 Dermatophytosis

B36* B36 Other superficial mycoses

B37* B37 Candidiasis

B38* B38 Coccidioidomycosis

B39* B39 Histoplasmosis

B40* B40 Blastomycosis

B41* B41 Paracoccidioidomycosis

B42* B42 Sporotrichosis

B43* B43 Chromomycosis and phaeomycotic abscess

B44* B44 Aspergillosis

B45* B45 Cryptococcosis

B46* B46 Zygomycosis

B47* B47 Mycetoma

B48* B48 Other mycoses, not elsewhere classified

B49* B49 Unspecified mycosis

G00* G00 Bacterial meningitis, not elsewhere classified

G01* G01 Meningitis in bacterial diseases classified elsewhere

G02* G02 Meningitis in other infectious and parasitic diseases classified elsewhere

G03* G03 Meningitis due to other and unspecified causes

G04* G04 Encephalitis, myelitis and encephalomyelitis

G05* G05 Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere

G06* G06 Intracranial and intraspinal abscess and granuloma

G07* G07 Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere

G08* G08 Intracranial and intraspinal phlebitis and thrombophlebitis

G09* G09 Sequelae of inflammatory diseases of central nervous system

I30* I30 Acute pericarditis

I33* I33 Acute and subacute endocarditis

I80* I80 Phlebitis and thrombophlebitis

J01* J01 Acute sinusitis

J02* J02 Acute pharyngitis

J03* J03 Acute tonsillitis

J04* J04 Acute laryngitis and tracheitis

J05* J05 Acute obstructive laryngitis (croup) and epiglottitis

J06* J06 Acute upper respiratory infections of multiple and unspecified sites

J13* J13 Pneumonia due to Streptococcus pneumoniae

J14* J14 Pneumonia due to Haemophilus influenzae

J15* J15 Bacterial pneumonia, not elsewhere classified

J16* J16 Pneumonia due to other infectious organisms, not elsewhere classified

J17* J17 Pneumonia in diseases classified elsewhere

J18* J18 Pneumonia, organism unspecified

J44.0* J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection

J44.1* J44.1 Chronic obstructive pulmonary disease with acute exacerbation, unspecified

J47* J47 Bronchiectasis

J85* J85 Abscess of lung and mediastinum

J86* J86 Pyothorax

K35* K35 Acute appendicitis

K36* K36 Other appendicitis

K37* K37 Unspecified appendicitis

K57.0*K57.02 Diverticulitis of small intestine with perforation and abscess, no hemorrhage

K57.0*K57.03 Diverticulitis of small intestine with perforation and abscess, hemorrhage

K57.1*K57.12 Diverticulitis of small intestine without perforation and abscess, no hemorrhage

K57.1*K57.13 Diverticulitis of small intestine without perforation and abscess, hemorrhage

K57.2*K57.22 Diverticulitis of large intestine with perforation and abscess, no hemorrhage

K57.2*K57.23 Diverticulitis of large intestine with perforation and abscess, hemorrhage

K57.3*K57.32 Diverticulitis of large intestine without perforation and abscess, no hemorrhage

K57.3*K57.33 Diverticulitis of large intestine without perforation and abscess, hemorrhage

K57.4*K57.42 Diverticulitis of both small and large intestine with perforation and abscess, no hemorrhage

K57.4*K57.43 Diverticulitis of both small and large intestine with perforation and abscess, hemorrhage

K57.5*K57.52 Diverticulitis of both small and large intestine without perforation and abscess, no hemorrhage

K57.5*K57.53 Diverticulitis of both small and large intestine without perforation and abscess, hemorrhage

K57.8*K57.82 Diverticulitis of intestine, part unspecified, with perforation and abscess, no hemorrhage

K57.8*K57.83 Diverticulitis of intestine, part unspecified, with perforation and abscess, hemorrhage

K57.9*K57.92 Diverticulitis of intestine, part unspecified, without perforation or abscess, no hemorrhage

K57.9*K57.93 Diverticulitis of intestine, part unspecified, without perforation or abscess, hemorrhage

K61* K61 Abscess of anal and rectal regions

K65* K65 Peritonitis

K63.0*K63.0 Abscess of intestine

K63.1*K63.1 Perforation of intestine (nontraumatic)

K75.0*K75.0 Abscess of liver

K75.1*K75.1 Phlebitis of portal vein

K81.0*K81.0 Acute cholecystitis

N10* N10 Acute tubulointerstitial nephritis

N11* N11 Chronic tubulointerstitial nephritis

N12* N12 Tubulointerstitial nephritis, not specified as acute or chronic

N34* N34 Urethritis and urethral syndrome

N39.0*N39.0 Urinary tract infection, site not specified

N41* N41 Inflammatory diseases of prostate

N70* N70 Salpingitis and oophoritis

N71* N71 Inflammatory disease of uterus, except cervix

N72* N72 Inflammatory disease of cervix uteri

N73* N73 Other female pelvic inflammatory diseases

N74* N74 Female pelvic inflammatory disorders in diseases classified elsewhere

N75* N75 Diseases of Bartholin's gland

N76* N76 Other inflammation of vagina and vulva

N77* N77 Vulvovaginal ulceration and inflammation in diseases classified elsewhere

L03* L03 Cellulitis

L04* L04 Acute lymphadenitis

L08* L08 Other local infections of skin and subcutaneous tissue

L88* L88 Pyoderma gangrenosum

M00* M00 Pyogenic arthritis

M86* M86 Osteomyelitis

A49.9* A49.9 Bacterial infection, unspecified

T82.6* T82.6 Infection and inflammatory reaction due to cardiac valve prosthesis

T82.7* T82.7 Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts

T83.5* T83.5 Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system

T83.6* T83.6 Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract

T84.5* T84.5 Infection and inflammatory reaction due to internal joint prosthesis

T84.6* T84.6 Infection and inflammatory reaction due to internal fixation device

T84.7* T84.7 Infection and inflammatory reaction due to other internal orthopedic prosthetic devices, implants and grafts

T85.7* T85.7 Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts

T81.4* T81.4 Infection following a procedure, not elsewhere classified

T88.0* T88.0 Infection following immunization

Secondary "Angus" Organ Failure Codes

Respiratory

569 Continuous ventilatory support (procedure block)

Cardiovascular

R57 Shock, not elsewhere classified

I95 Hypotension

Renal

N17 Acute renal failure

Hepatic

K720 Hepatic failure, not elsewhere classified

K763 Infarction of liver

Haematologic

- D65 Disseminated intravascular coagulation (defibrination syndrome)
- D688 Other specified coagulation defects
- D689 Coagulation defect, unspecified
- D695 Secondary thrombocytopenia
- D696 Thrombocytopenia, unspecified

Neurologic

- F05 Delirium, not induced by alcohol and other psychoactive substances
- G934 Encephalopathy, unspecified
- G931 Anoxic brain damage

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Chapter 4: Population-based epidemiology of *Staphylococcus aureus* bloodstream infection in Canterbury, New Zealand (P. J. Huggan et al., 2010)

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Chapter 5: Fusobacterial infections: clinical spectrum and incidence of invasive disease(P. J. Huggan & Murdoch, 2008)

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Chapter 6: Concomitant *Staphylococcus aureus* bacteriuria is associated with poor clinical outcome in adults with S.aureus bacteremia (P. J. Huggan et al., 2008)

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Chapter 8: Evidence of high mortality and increasing burden of sepsis in a regional sample of the New Zealand population(P. J. Huggan et al., 2017)

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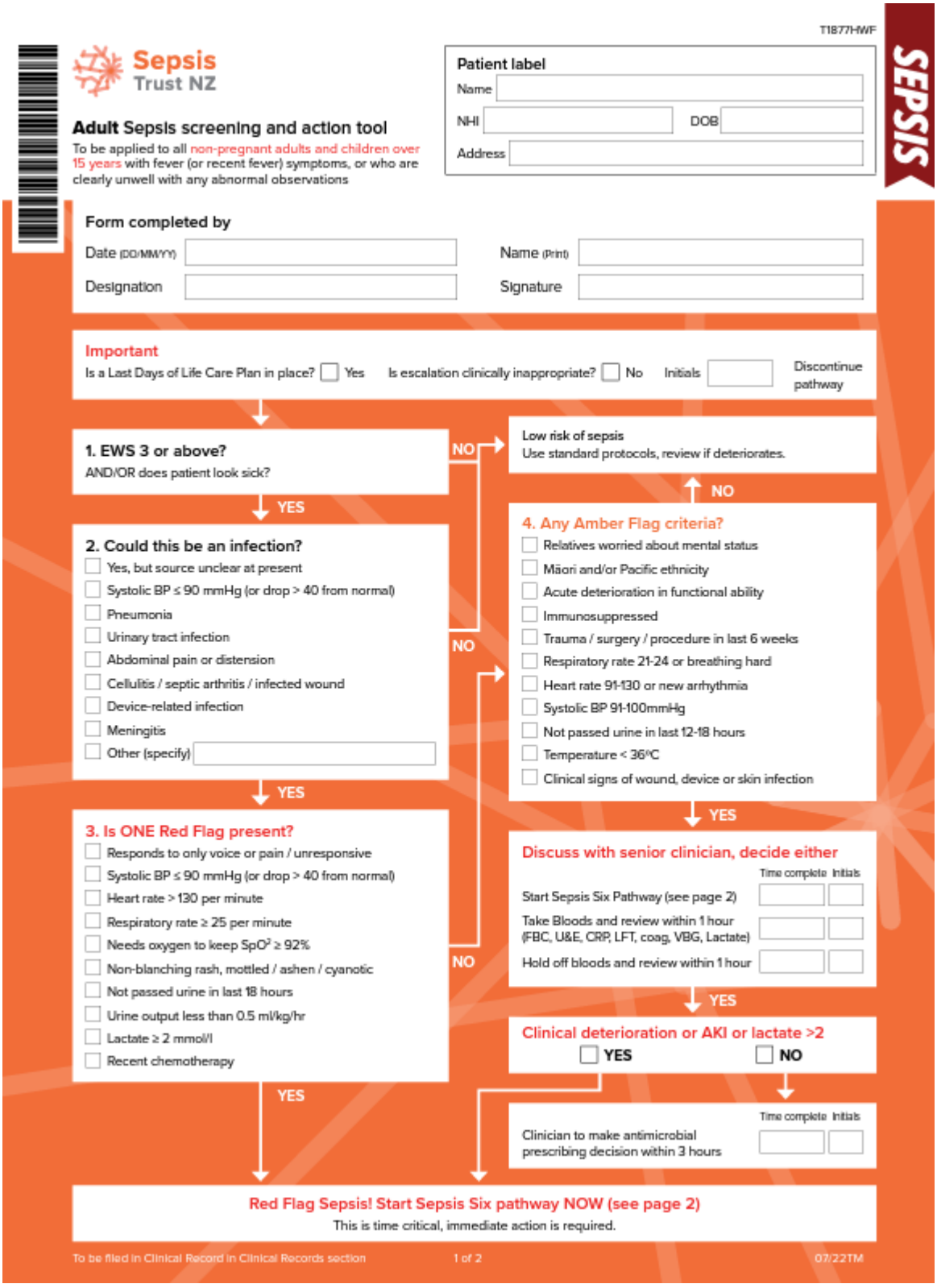
Appendix 3: Sepsis recognition and action tools used to implement the "Raise the Flag" program at Waikato Hospital



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SEPSIS

Sepsis Trust NZ

Maternal Sepsis screening and action tool

To be applied to all woman who are pregnant or up to six weeks postpartum (or after the end of pregnancy if pregnancy did not end in a birth) who have a suspected infection or have clinical observations outside normal limits.

Patient label

Name

NHI DOB

Address

Form completed by

Date (DD/MM/YY) Name (Print)

Designation Signature

1. Has MEWS triggered?

OR does woman look sick?

OR is fetus tachycardic (≥ 160bpm)?

OR more than 2 temperatures greater than 37.5°C

OR 1 temperature ≥ 38°C

NO → Low risk of sepsis. Use standard protocols, consider discharge with safety netting. Consider obstetric needs.

YES ↓

2. Could this be an infection?

- ☐ Yes, but source unclear at present
- ☐ Chorioamnionitis/ endometritis
- ☐ Urinary tract infection
- ☐ Infected caesarean or perineal wound
- ☐ Influenza, severe sore throat, or pneumonia
- ☐ Abdominal pain or distension
- ☐ Breast abscess / mastitis
- ☐ Other (specify)

NO → 4. Any Amber Flag criteria?

YES ↓

3. Is ONE maternal Red Flag present?

- ☐ Responds to only voice or pain / unresponsive
- ☐ Systolic BP ≤ 90 mmHg (or drop > 40 from normal)
- ☐ Heart rate > 130 per minute
- ☐ Respiratory rate ≥ 25 per minute
- ☐ Needs oxygen to keep SpO^2 ≥ 92%
- ☐ Non-blanching rash, mottled / ashen / cyanotic
- ☐ Not passed urine in last 18 hours
- ☐ Urine output less than 0.5 ml/kg/hr
- ☐ Lactate ≥ 2 mmol/l
  (Note – Lactate may be raised in and immediately after normal labour and delivery)

NO → 4. Any Amber Flag criteria?

YES ↓

4. Any Amber Flag criteria?

- ☐ Relatives worried about mental status
- ☐ Māori and/or Pacific ethnicity
- ☐ Acute deterioration in functional ability
- ☐ Respiratory rate 21-24 OR breathing hard
- ☐ Heart rate 100-130 or new arrhythmia
- ☐ Systolic BP 91-100mmHg
- ☐ Not passed urine in last 12-18 hours
- ☐ Temperature < 36°C
- ☐ Immunosuppressed / diabetes / gestational diabetes
- ☐ Has had invasive procedure in last 6 weeks (e.g. CS, forceps delivery, ERPC, cerclage, CVs miscarriage, termination)
- ☐ Prolonged rupture of membranes
- ☐ Close contact with Group A Strep
- ☐ Bleeding / wound infection / vaginal discharge
- ☐ Non-reassuring CTG / fetal tachycardia > 160

NO ↑

YES ↓

Discuss with senior clinician, decide either

	Time complete	Initials
Start Sepsis Six Pathway (see page 2)		
Take Bloods and review within 1 hour (FBC, U&E, CRP, LFT, coag, Lactate)		
Hold off bloods and review within 1 hour		

YES ↓

Clinical deterioration or AKI or lactate >2

☐ YES ☐ NO

	Time complete	Initials
Clinician to make antimicrobial prescribing decision within 3 hours		

Red Flag Sepsis! Start Sepsis Six pathway NOW (see page 2)

This is time critical, immediate action is required.

SEPSIS

Sepsis Trust NZ

Adult Sepsis screening and action tool

To be applied to all non-pregnant adults and children over 15 years with fever (or recent fever) symptoms, or who are clearly unwell with any abnormal observations

Patient label

Name

NHI DOB

Address

Action (complete ALL within 1 hour)

1. Administer oxygen

Aim to keep saturations >94%
(88-92% if at risk of CO_2 retention e.g. COPD)

Time complete

Initials

2. Take blood cultures

At least a peripheral set. Consider e.g. CSF, urine, sputum

Think source control! Call surgeon/radiologist if needed

Time complete

Initials

3. Give IV antibiotics

Refer to hospital antimicrobial guideline

Consider allergies prior to administration

Time complete

Initials

4. Give IV fluids

If hypotensive/lactate > 2mmol/l, 500ml stat

Repeat if clinically indicated – do not exceed 30ml/kg

Time complete

Initials

5. Check serial lactates

If lactate > 4mmol/l, call Critical Care and recheck VBG after each 10ml/kg IV fluid challenge

Time complete

Initials

6. Get senior help

Arrange urgent investigation and referrals

Document follow-up plan

Time complete

Initials

After delivering the Sepsis Six, does patient still have any of the following?

- systolic BP < 90 mmHg
- reduced level of consciousness despite resuscitation
- respiratory rate over 25 breaths per minute
- lactate not reducing or > 2mmol/l

If escalation remains clinically appropriate. Refer to hypoperfusion pathway

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