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Preface

In the acute hospital, infections in critically care patients are more common than in most other parts of the hospital and are often the most complicated. The complexity of underlying disease and the reasons requiring admission to the critical care unit, e.g. multiple trauma, make the diagnosis, management and prevention of infection challenging and the input of a range of healthcare professionals is required.

As developments and new technology push forward the boundaries of medicine to include the treatment of malignancies that were previously untreatable and the availability of a more complex menu of organ transplantation, these together with an increasing age profile in the developed world result in more patients being vulnerable to infection, In addition, many patients with a range of underlying diseases such as ischemic heart disease, diabetes mellitus and chronic obstructive pulmonary disease are now surviving into their 80s or beyond. All these groups of patients may present to the intensive care unit, requiring organ support, resuscitation and the rapid and effective treatment of one or more infections that may complicate their stay such as catheter-related bloodstream infection, ventilator-associated pneumonia, *Clostridium difficile* infection with or without the acquisition of a range of multi-antibiotic resistant bacteria. Also, some infections presenting in the community, such as meningococcal septicaemia, severe community-acquired pneumonia or generalised faecal peritonitis may require admission to the intensive care unit following resuscitation in the emergency department.

The effective management of severe infection, whether community-acquired or intensive care unit-acquired, requires the input of a multi-disciplinary team whose skills, experience and expertise can optimise patient care and do so in a cost-effective manner. This team includes the intensivist, clinical microbiologist and infectious diseases physician, critical care nurse, physician, surgeon, pharmacist and others. This book has been co-authored by a clinical microbiologist, intensivist and clinical infectious diseases physician to cover some of the major infections presenting in the adult critical care unit. While it is not written to provide detailed, step-by-step instructions of the management of individual patients, it provides broad principles to be used based on the latest evidence combined with common sense and the results of many years of combined experience.

The book should be helpful to the trainee in the three respective disciplines and also to physicians, surgeons and others managing the acutely ill patient either in the intensive care unit, before transfer there from the emergency department or on the hospital ward where effective management may mean the avoidance of admission to the intensive care unit. The case scenario at the start of each chapter serves to embed what follows in a clinical context and to highlight the purpose of the book, i.e. to improve the management of patients. The content of each chapter covers the main conditions under the various systems and the references that follow provide the evidence-base for what precedes it.

Some have predicted the end of the antibiotic era with the advent of carbapenem-resistant Enterobacteriaceae and the emergence of resistance to new agents recently developed and used to treat Gram-positive infections such as methicillin-resistant *Staphylococcus aureus*. However, many simple interventions can prevent infection or modify the course of infection such that the care of patients is not compromised and without the acquisition and spread of antibiotic resistance. The combination of a heightened awareness of infection, the appropriate use of diagnostic tests, the early and effective use of anti-infectives and best practice in terms of infection prevention can go a long way towards ensuring that patients requiring intensive care are treated effectively for infection and survive. Hopefully, this book will assist in the pursuit of that objective and also promote collaboration and co-operation between the many healthcare professionals that are required to effectively manage infection in the modern intensive care setting.

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Disclaimer

Every reasonable effort has been made to check and verify facts before the publication of this book. However, readers are advised to access local or other appropriate sources elsewhere for details of anti-infective dosing, side-affects and potential drug interactions.

Contents

Abbreviations

ACTH	Adenocorticotropic hormone
AGNB	Aerobic Gram-negative bacilli
AIDS	Acquired immunodeficiency syndrome
ALI	Acute lung injury
APACHE II	Acute physiological and chronic healthcare evaluation, version 2.
aPTT	Activated partial thromboplastin time
ARDS	Adult respiratory distress syndrome
ARF	Acute renal failure
BAL	Broncho-alveolar lavage
BCG	Bacille Calmette-Guérin (vaccine for TB)
BHSGA	β-Haemolytic streptococci group A
BISAP	Bedside index severity in acute pancreatitis score
BSI	Bloodstream infection
BTS	British Thoracic Society
BUN	Blood urea and nitrogen
CA-MRSA	Community-acquired methicillin resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CAPD	Chronic ambulatory peritoneal dialysis
CA-UTI	Catheter-associated urinary tract infection
CDAD	*Clostridium difficile*–associated diarrhoea
CDC	Centres for Disease Control and Prevention (USA)
CI	Confidence intervals
CIED	Cardiovascular implantable electronic device
CLABSI	Central line-associated bloodstream infection
CMV	Cytomegalovirus
C_{max}	Maximum concentration (of an antibiotic)
CNA	Cytotoxin neutralisation assay (for diagnosis of *C. difficile*)
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase

CRBSI	Cather-related bloodstream infection
CRE	Carbapenem-resistant Enterobacteriaceae
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerised tomography
CURB-65	Confusion, urea, respiratory rate and blood pressure (refers to assessment of severity of community-acquired pneumonia)
CVC	Central venous catheter
EBV	Epstein-Barr virus
ECMO	Extra-corporeal membrane oxygenation
EIA GDH	Enzyme-immunoassay for glutamine dehydrogenase (for diagnosis of *Clostridium difficile*)
EM	Electron microscopy
EMA	European Medicines Agency
EPCR	Endothelial protein receptor
ERCP	Endoscopic retrograde cholangio-pancreatography
ESBL	Extended spectrum b-lactamases
ESR	Erythrocyte sedimentation rate
EVD	External ventricular device
FDA	Food and Drugs Agency (US)
FESS	Functional Endoscopic Sinus Surgery
FiO_2	Inspired oxygen tension
FNA	Fine-needle aspiration
FPG-PET	18-Fluorodeoxyglucose positron emission tomography
GBS	Guillan-Barré syndrome
G-CSF	Granulocyte colony stimulating factor
GM	Galactomannan (for diagnosis of aspergillosis disease)
GVHD	Graft versus host disease
H1N1	Haemagglutinin 1 and neuramidase 1 (refers to strains of influenza)
HAART	Highly active anti-retroviral therapy
HAP	Hospital-acquired pneumonia
HCA	Healthcare-associated
HCAI	Healthcare-associated infection
HEPA	High efficiency particulate air (referring to air filtration systems)
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplantation
ICE-PCS	International Collaboration on Endocarditis–Prospective Cohort Study
ICNARC	Intensive Care National Audit & Research Centre (UK)
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IE	Infective endocarditis
IgM	Immunoglobulin, M fraction
INICC	International Nosocomial Infection Control Consortium

INR	International normalised ratio
IRIS	Immune reconstitution inflammatory response
IU	International units
IVIG	Intravenous immunoglobulin
LD	Loading dose
LDH	Lactic dehydrogenase
LP	Lumbar puncture
LPS	Lipopolysaccharide
MALDI-TOF MS	Matrix-assisted laser desorption and ionisation time-of-flight mass spectrometry
MAP	Mean arterial pressure
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration (refers to antibiotic susceptibility)
MIU	Million international units
MODS	Multi-organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NF	Necrotising fasciitis
NFk-B	Nuclear factor B
NHSN	National Healthcare Safety Network
NIV	Non-invasive ventilation
NK	Natural killer (cells, refers to lymphocytes)
NO	Nitric oxide
NOS	Nitric oxide synthase
NVE	Native valve endocarditis
OPA	Ortho-phthaldehyde
PAE	Post-antibiotic effect
PaO_2	Arterial oxygen tension
PBP	Penicillin binding protein
PBS	Protected brush specimen
pCO_2	Carbon-dioxide partial pressure
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction (for rapid diagnostic testing)
PD	Pharmacodynamic
PEEP	Positive end expiratory pressure
PICC	Peripherally inserted central catheter
PID	Pelvic inflammatory disease
PK	Pharmacokinetic
POC	Point of care (refers to laboratory testing)
PPI	Protein pump inhibitors
PTLD	Post transplantation lymphoproliferative disease
PVE	Prosthetic valve endocarditis

PVL	Panton Valentine leucocidin (refers to toxin produced by some strains of *S. aureus*)
QID	Refers to four times a day dosing of a drug
RCT	Randomised controlled trial
RR	Relative risk
RSV	Respiratory syncytial virus
RTI	Reverse transcriptase inhibitors
RT-PCR	Reverse transcriptase–polymerase chain reaction
SBP	Systolic blood pressure
$ScvO_2$	Central venous oxygen saturation
SDD	Selective decontamination of the digestive tract
SHEA	The Society for Healthcare Epidemiology of America
SIRS	Sepsis inflammatory response syndrome
SOD	Selective oropharyngeal decontamination
SOT	Solid organ transplant
SSI	Surgical site infection
TB	Tuberculosis
TC	Toxigenic culture (for *C. difficile*)
TEE	Transesophageal echocardiography
Th 1 & 2	T-helper cell type 1 and 2, i.e. lymphocytes
TLR	Toll-like receptors
TMP-SMX	Trimethoprim-sulphamethoxazole (co-trimoxazole)
TPN	Total parenteral nutrition
UTI	Urinary tract infection
VAT	Ventilator-associated pneumonia
vCJD	Variant Creutzfeldt-Jakob disease
VRE	Vancomycin-resistant enterococci
WBC	White blood cell count
ZIG	Zoster immunoglobulin

Chapter 1
Basic Microbiology and Infection

Scenario
A 74 year old male patient is admitted to the intensive care unit following an emergency aortic aneurysm repair. He has a complicated post-operative course with systemic sepsis, and renal and respiratory failure. Five days after admission, he develops ventilator-associated pneumonia, which is treated empirically with vancomycin and piperacillin-tazobactam. As he is not responding, a BAL specimen is taken 3 days later and grows *Candida albicans*, 10^4 /ml.

1. *What is the likely source of the C. albicans?*
2. *Is it significant?*
3. *What are the options for the treatment of this microbe?*
4. *From what other samples may C. albicans be isolated?*

Introduction

Microbiology is strictly speaking the study of organisms visible under the microscope, i.e. bacteria, fungi and viruses (by electron microscope). However, some microbial pathogens are visible to the naked eye, such as helminths or worms and others such as hepatitis C have never been visualised [1]. Consequently the discipline is no longer confined to that specific definition but covers the study of microbial agents, and medical or clinical microbiology covers those that cause human infection or are relevant to human health.

When a pathogenic microbe such as a bacterium or a fungus invades or interacts with a host, i.e. the patient, there is usually an immune response, resulting in infection depending on amongst other things the virulence of the microbe [2]. The infection may be asymptomatic, i.e. the development of antibodies in the patient's serum but with no clinical illness (e.g. sub-clinical infection with herpes simplex), or there may be symptoms or signs of an illness together with an immune response such as antibody production.

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The microbial kingdom is traditionally subdivided into bacteriology, virology, mycology, parasitology, etc. This represents a somewhat dated categorisation, largely based upon phenotypic characterisation. Recent advances in molecular biology and related areas indicate that there is some overlap, and furthermore investigational and diagnostic techniques for virology and bacteriology have somewhat converged.

There is considerable interaction between microbiology and many other disciplines of science and medicine, such as biochemistry, e.g. diabetes mellitus, immunology, e.g. HIV disease, tropical medicine, e.g. malaria, neuropathology, e.g. prions and gastroenterology, e.g. hepatitis C. Furthermore, there is increasing interest in the potential role of microbes as a pathogenic factor in the development of chronic diseases, e.g. *Helicobacter pylori* and duodenal ulcer, *Chlamydia pneumoniae* and coronary artery disease.

Microbes were present on the planet before man appeared and are likely to survive should man's viability become untenable due to global warming or some other ecological or military catastrophe. The survival of microbes is largely explained by their simplicity, adaptability and related to this their capacity to evolve according to changing circumstances, whether it is the development of resistant mechanisms following exposure to a new antibiotic or the capacity for genetic re-arrangement amongst viruses resulting in pandemic influenza. Consequently, man's struggle with that component of the microbial kingdom, which is capable of causing disease, is only ever likely to be partly or temporarily successful. Man is usually responding and reacting to rapid evolutionary change and is at best trying to anticipate the next microbial surprise that may be just around the corner, i.e. "playing catch up".

Microbial Normal Flora and Its Importance

The human body supports an impressive range and quantity of microbes in various body sites. This commensal flora, largely bacteria, is beneficial in preventing the colonisation or carriage of more virulent pathogens and assists the body in homeostasis and nutrition. The term, "colonisation resistance" is a concept particularly highlighted by Dutch intensivists and others during the mid 1980s to describe the capacity and importance of the normal flora (especially anaerobes) in preventing infection by crowding out potential pathogens that emerge and colonise due to medical interventions, trauma and ill health [3]. We are now much more aware of the adverse consequences of antibiotics on normal flora when they are prescribed to treat an organism in a specific body site, such as the blood, resulting in an adverse consequence elsewhere, e.g. oral thrush due to candida overgrowth.

On admission to hospital, and particularly to the intensive care unit, the patient's normal flora changes to that of the ambient environment (other patients, equipment, the physical environment, and the flora present on the hands of healthcare professionals). This explains the regular and frequent emergence and subsequent carriage of methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida* species and

Clostridium difficile as part of the normal flora in hospital patients and sometimes resulting subsequently in infection within days of critical care unit admission.

An important concept in the development of infection in the intensive care setting is the invasion by microbes of a part of the body that is normally sterile. The bloodstream, brain and cerebrospinal fluid, lower respiratory tract below the vocal cords, joint, pleural and cardiac fluid, are all normally sterile [4]. Therefore after excluding the possible contamination of a microbiology sample when it is being taken from a patient, the recovery or identification of a microbe from such sites is abnormal until proven otherwise. There may be predisposing often iatrogenic factors for sterile site infections, e.g. intubation, resulting in microbes in the lower respiratory tract and in the critically ill patient there may be translocation of commensal or normal flora to a normally sterile site from elsewhere, e.g. bloodstream infection due to intra-colonic aerobic or anaerobic bacteria. Other body organs or sites, e.g. skin, lower urinary tract have normal colonising flora (Fig. 1.1) and when attempting to make a diagnosis of infection at these sites, e.g. surgical site infection, the key challenge for the clinician and the diagnostic microbiology laboratory is to interpret this normal or colonising flora, which may include *S. aureus*, from the pathogens that are causing the infection.

The skin, by virtue of its dryness and high salt content, is relatively hostile to many bacteria, including aerobic Gram negative bacilli such as *Escherichia coli* and fungi. Hence, the normal skin flora largely consists of coagulase negative staphylococci such as *Staphylococcus epidermidis*, diphtheroids, micrococci and propionibacteria, the latter being anaerobic Gram negative bacilli. The upper gastro-intestinal tract is relatively microbial free, largely due to the innate defences that include gastric acidity. The small and large intestines are colonised by aerobic Gram negative bacilli such as *Escherichia coli* (coliforms) and anaerobes, e.g. *Bacteroides fragilis*. Anaerobic bacteria substantially outnumber all other bacteria in the lower gastro-intestinal tract such as the colon and rectum. The lower genito-urinary tract compromises a mixture of skin flora, e.g. coagulase negative staphylococci and peri-anal or gastro-intestinal flora, e.g. *E. coli* but during the reproductive years the upper vagina is sterile. Throughout life, the bladder is relatively bacteria free, if not sterile much of the time, except when associated with instrumentation such as urinary catheterisation.

The upper respiratory tract has a rich natural flora that includes skin microbes as well as *Candida* spp, viridans streptococci, commensal neisseria and potential lower respiratory tract pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. These last three bacteria intermittently colonise the upper respiratory tract, e.g. pharynx and tonsils, may result in upper, e.g. sinusitis, or lower respiratory tract infection, e.g. pneumonia, sometimes preceded by a viral illness such as influenza or aspiration or intubation. This explains the occurrence of pneumococcus and haemophilus as a cause of early onset ventilator-associated pneumonia (VAP) in the intensive care unit.

In the intensive care unit, every effort should be made to minimise disruption of the normal flora through the careful and responsible use of anti-infective agents and avoidance of unnecessary devices. Healthcare personnel also need to be aware of the consequences of the translocation of normal flora to sites where microbes are

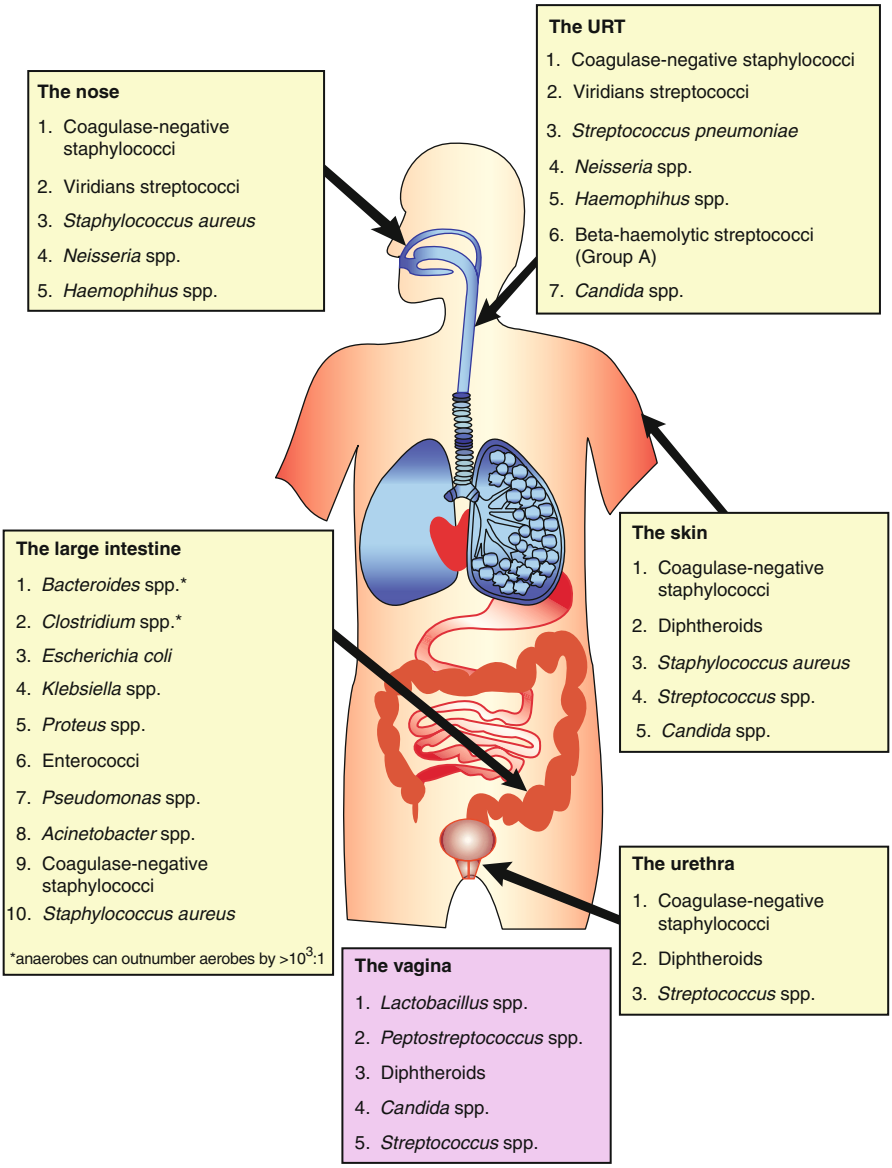

Fig. 1.1 Body sites with the commensal flora during normal health

not normally present, e.g. upper airway or upper gastro-intestinal flora gaining access to the lung parenchyma, causing VAP. While most microbiology laboratories will attempt to interpret the results from diagnostic specimens, intensivists and others should be aware of what constitutes normal flora when deciding whether or not to treat a microbe isolated from a specimen taken in a critical care patient. For example,

Candida spp. may be isolated from lower respiratory tract specimens such as endotracheal aspirates or broncho-alveolar lavage (BAL), but *Candida* spp. are rarely a cause of pneumonia and most often represent overgrowth and migration of upper respiratory tract flora [5]. Close collaboration between the critical care team and clinical microbiology/infectious diseases can assist in diagnosis and in the appropriate use of anti-infective agents.

Microbial Pathogenesis

While for some microbial pathogens, e.g. group A streptococci (*Streptococcus pyogenes*), there are well recognised virulent determinants such as haemolysins and erythrogenic toxin that have recognised physiological effects *in vitro* and *in vivo* resulting in invasive infection, for many other microbes there are no obvious virulence factors associated with the pathogen. For example *Acinetobacter* spp, although a Gram negative bacillus with endotoxin (see below) is relatively avirulent, its success as a pathogen is often confined to very debilitated patients [6]. The complex interaction between the attachment of the pathogen to the host and the immune response may also explain the clinical presentation arising from damage to the host tissue where infection is caused by a microbe not renowned for its virulence. Recent years have seen a welcome emphasis in research and in clinical care on the importance of the inflammatory response in explaining the full pathogenic and clinical consequences of infection.

For bacterial infections, the classical sequence of events is bacterial adherence, followed either by invasion or the production of a toxin/enzyme, leading to an inflammatory response. Well recognised and described virulent features of bacteria include toxins, e.g. endotoxin (as occurs with Gram negative bacilli, Fig. 1.2) of which lipopolysaccharide is an important component and which can precipitate septic shock, and exotoxin (as typically occur with Gram positive bacteria), e.g. tetanospasm produced by *Clostridium tetani*. Also, flagellae which allow for bacterial movement, the presence of a capsule, and pili or fibriae, which facilitate the exchange of genetic material between bacteria including that capable of coding for toxins, are also important. While phagocytes, such as polymorph neutrophils, present in the bloodstream, often greatly assist in the removal of many bacterial pathogens, some microbes interfere with phagocytic chemotaxis or movement, e.g. *Staphylococcus aureus*, or possess surface components that inhibit the process of phagocytosis, e.g. the capsule of the pneumococcus.

Viruses, like chlamydia and rickettsiae are intracellular parasites and consequently without gaining access and taking over the reproductive nucleic acid synthesis mechanism of the host cell, cannot replicate. However, as part of viral replication, many host cells will lyse resulting in subsequent tissue damage through inflammation with symptoms, e.g. nasal discharge due to the effects of rhinovirus, a cause of the common cold. Typically, the interaction between viruses and the host may result in viremia, i.e. viruses in the bloodstream, damaged cells, an immune response, both humoral (antibody response) and cellular (T-lymphocytes), and an inflammatory cascade involving an array of cytokines. The occasional adverse consequences in otherwise

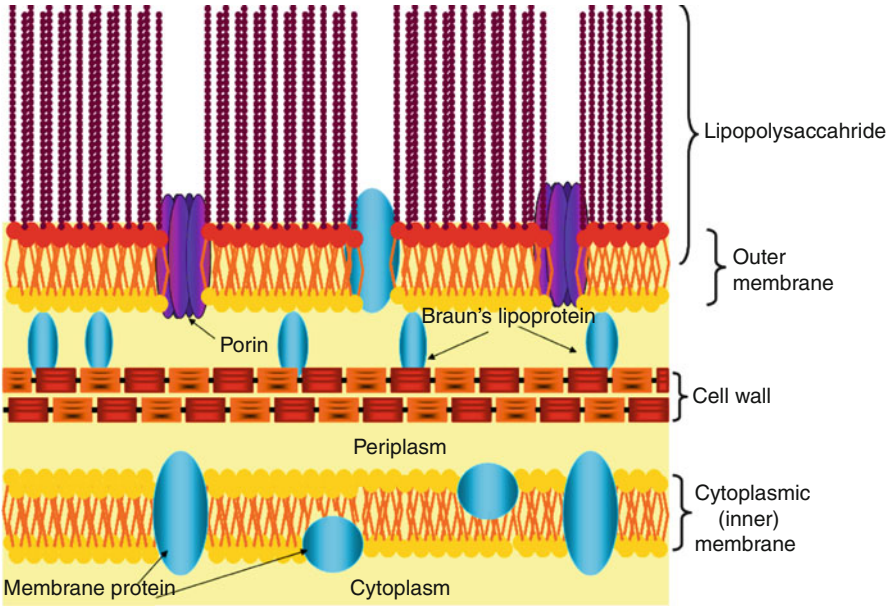

Fig. 1.2 Schematic diagram of the Gram negative cell wall

healthy patients from H1N1 infection seen in intensive care units during 2009/10 [7], for example, is probably partly explained by an excessive pro-inflammatory response, leading to acute lung and adult respiratory distress syndrome (ARDS) as in most of these patients, there was no secondary pathogen causing infection. If the inflammatory cascade in response to any microbe is pro-inflammatory, this can partly explain the apparent paradox of the continuingly septic patient unresponsive to a range of anti-infective agents in the presence of negative microbiology, but remaining critically ill with evidence of organ damage and failure (see also Chap. 2).

Certain interventions in the intensive care unit, such as the use of corticosteroids as part of the treatment of ARDS, may modulate the host response resulting in more prolonged infection, where present. Furthermore, the continued evolution of microbes ensures that new variants may emerge that present differently or result in complications, not hitherto seen. Pandemic H1N1 and VAP, PVL-producing MRSA [8] and pneumonia or complicated skin and soft tissue infection, and O27-hypervirulent *Clostridium difficile* [9] resulting in toxic megacolon are all recent examples of this.

Acquisition and Spread of Infection

Infection may be acquired by ingestion (fecal-oral route), inhalation, contact or penetration (e.g. needle stick injury resulting in hepatitis B), sexual and transplacental or vertical, i.e. from the mother to the fetus/neonate. In the intensive care unit, the three

likely portals of entry are ingestion but more importantly, inhalation and contact. Where the patient is intubated and ventilated with a nasogastric tube *in-situ*, physical contact with the patient or with the patient's devices, are often the main portal of entry.

Spread of infection may arise from contact with a contaminated environment, from other patients, from healthcare workers or from medical devices or equipment. For example, the capacity of *C. difficile* to form spores, enables it to survive in the environment for prolonged periods and inadequate hygiene, may contribute to outbreaks. The failure of critical care personnel to comply with standard precautions (see Chap. 3), including hand hygiene, may result in pathogens acquired from contact with the environment being transmitted to patients.

While measures are taken to minimise the risk of cross-infection (Chap. 3) in intensive care areas and elsewhere, this is largely to prevent exogenous infection, i.e. bacteria acquired by the patient from outside their own body, i.e. from other patients, healthcare staff, equipment or the environment. However, in intensive care patients, many infections are endogenous, i.e. the microbe causing infection is or was part of the colonising flora of that patient. For example, patients admitted to intensive care units, rapidly become colonised in the upper respiratory tract and stomach with aerobic Gram negative bacilli such as *E. coli* and *Klebsiella pneumoniae*. These bacteria may migrate to the lower respiratory tract thus resulting in VAP. Such endogenous infections are best prevented by preserving the normal flora for as long as possible, using best professional practice, e.g. maintenance of the airway, closed suctioning, etc. Selective decontamination of the digestive tract, which reduces the load of endogenous bacteria and fungi, is discussed in Chap. 3 [5].

Answers to Scenario Questions

1. *Candida* spp., are present in small numbers as part of the normal flora of the upper respiratory tract and gastrointestinal tract. During normal health, bacteria greatly outnumber yeasts but in the intensive care patient, especially if the patient is on broad-spectrum antibacterial agents, yeast numbers increase and may be the predominant growth in diagnostic specimens from non-sterile sites.
2. *Candida* spp. recovered from a BAL are rarely significant except in a severely immunosuppressed patient where Candida pneumonia is possible. More likely, these yeasts have been translocated to the lower respiratory tract via the process of intubation and suctioning and may have been greatly facilitated by the use of anti-bacterial agents, which reduce overall bacterial numbers and therefore preferentially select fungi. Similarly, patients may also develop oral or vaginal thrush, due to *Candida* overgrowth. This is referred to as a superinfection, i.e. an infection arising from the treatment of another infection. To definitively confirm *Candida* as a cause of pneumonia requires histological evidence of invasion with yeasts and yeast-like hyphae on lung sections.
3. An azole such as fluconazole, is appropriate initial therapy for suspected *Candida* infection in the intensive care patient (although not in this case for the reasons outlined in 2 above) unless the patient is likely to have a species of *Candida* not-susceptible to fluconazole such as *C. kruzei.* However, fluconazole is not active against moulds such as *Aspergillus* and if a broader spectrum anti-fungal cover is required, then an echinocandin, or alternatively amphothericin B may be indicated.

4. Where a patient has been in a intensive care unit, particularly for some days, and especially if the patient is or has been on broad-spectrum anti-bacterial agents (e.g. vancomycin and piperacillin-tazobactam), in this case *Candida* overgrowth may occur in the upper and lower respiratory tract, and in the gastrointestinal and genitourinary tracts. Therefore sputa/endotracheal aspirates, catheter specimens of urine and surgical site samples are often positive for *Candida* sp. but their presence may not be of clinical significance if the patient is stable. However, colonisation in several sites can sometimes predict subsequent invasive infection. Occasionally, *Candida* spp. is isolated from normally sterile sites such as the blood, pleural fluid and CSF. In such situations, aggressive anti-fungal therapy is warranted.

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Chapter 2
The Physiology of Sepsis and Its Implications

Scenario
A 27 year old student in his first year at university is admitted via the emergency department. He is profoundly shocked with a systolic blood pressure of 75 mmHg and has a Glasgow Coma Score of 12.

1. What factors are important in the early management of this patient.
2. What features of shock might predict outcome early in the presentation

Introduction

Severe sepsis is a major clinical challenge in the intensive care unit (ICU). In 1997, it was estimated that 10,016 deaths occurred amongst ICU admissions in England and Wales, representing 24 deaths per 100,000 population per year or about 6 % of all UK deaths [1]. Also, 46 % of patients who met the criteria for severe sepsis on admission to ICU died. In the United States, an estimated 700,000 cases of sepsis occur each year, resulting in more than 210,000 deaths, i.e. 10 % of all deaths annually and this exceeds the number of deaths due to myocardial infarction [2]. This has recently been reported as an incidence of severe sepsis of 286 (CI 253–319) per 100,000 from a prospective evaluation of an urban population in the USA [3]. Hence, a greater understanding of sepsis in the critical care setting, and improvements in diagnosis and management have the capacity to significantly impact on the overall population mortality as well as mortality in the ICU population.
"Sepsis" is defined as a documented or suspected infection with one or more of the following variables as outlined in Table 2.1.

"Severe sepsis" is defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension. The criteria or variables are outlined in Table 2.2.

"Septic shock" is defined as acute circulatory failure unexplained by other causes. Acute circulatory failure is defined as persistent arterial hypotension, systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <60, or a reduction in SBP >40 mmHg from the baseline despite adequate volume resuscitation.

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Table 2.1 Variables used in the definition of sepsis

Variable	Value
General variables	
Fever	Core temperature >38.3 °C
Hypothermia	Core temperature <36 °C
Heart rate	>90/min or >2 SD Above the normal value for age
Tachypnea	
Altered mental status	
Significant edema or positive fluid balance	>20 ml/kg over 24 h
Hyperglycemia in the absence of diabetes mellitus	Plasma glucose >120 mg/dL
Inflammatory variables	
Leukocytosis	WBC count >12,000/μL
Leukopenia	WBC count <4,000/μL
Normal WBC count with immature forms	>10 %
Plasma C-reactive protein	>2 SD above the normal value
Plasma procalcitonin	>2 SD above the normal value
Other	
Saturated venous O_2	>70 %
Cardiac index	>3.5 L/min/m^2

SD standard deviations, *WBC* white blood cell count

Pathophysiology

The mediator response to infection and sepsis is extremely complex. Initially there is a pro-inflammatory response which later becomes immunosuppressive. Immune cells such as neutrophils and macrophages are activated via Toll-like receptors (TLR) and severe infection with Gram-negative organisms leads to the appearance of lipopolysaccharide (LPS) endotoxin in the blood. This interacts with lipopolysaccharide-binding protein and binds to CD14 receptors, and via TLR activates Nuclear Factor k B (NFk B). NFk B activation leads to increased gene expression of several mediators, including chemokines, cytokines, adhesion molecules, tissue factor, metalloenzymes and nitric oxide synthase (NOS). Although endothelial cells do not themselves express CD14, LPS can activate these cells via interaction with soluble CD14 and lipopolysaccharide binding protein present in the circulation. Similar mechanisms are believed to occur with Gram positive bacteria (e.g. peptidoglycan in the staphylococcal cell wall) and fungi, when they cause acute sepsis. The lack of endotoxin in the outer cell wall is compensated for by the presence of exposed peptidoglycan and a range of other toxic secreted products. It appears that cell wall components of Gram-positive bacteria may signal via similar receptors as Gram-negative endotoxin, although the type of signal and coreceptor may differ.

Table 2.2 Criteria or variables used to define severe sepsis

Variable	Value
Organ dysfunction	
Arterial hypoxemia	PaO_2/FiO_2 <300 mmHg
Acute oliguria	Urine output <0.5 ml/kg/h for at least 2 h
Creatinine	>2.0 mg/dL (175 mmol/l)
Coagulation abnormalities	INR >1.5 or aPTT >60 s
Thrombocytopenia	Platelet count <100,000/μl
Hyperbilirubinemia	Plasma total bilirubin >2.0 mg/dl or 35 mmol/l
Tissue perfusion	
Arterial hypoxemia	PaO_2/FiO_2 <300 mmHg
Acute oliguria	Urine output <0.5 ml/kg/h-for at least 2 h
Creatinine	>2.0 mg/dL (175 mmol/l)
Coagulation abnormalities	INR >1.5 or aPTT >60 s
Thrombocytopenia	Platelet count <100,000/μl
Hyperbilirubinemia	Plasma total bilirubin >2.0 mg/dL or 35 mmol/l
Hyperlactatemia	>2 mmol/L
Hemodynamic	
Arterial hypotension	Systolic blood pressure <90 mmHg, or Mean arterial pressure <70 mmHg, or Systolic blood pressure decrease >40 mmHg

FiO_2 inspired oxygen tension, *INR* international normalised ratio, *aPTT* activated partial thromboplastin time

Nitric Oxide

It has long been recognised that myocardial dysfunction is commonly present in septic patients despite the increased cardiac output observed in many patients once adequately volume resuscitated. However, the ejection fraction is reduced compared with non-septic control patients [4]. The increased cardiac output is a reflex response to the reduction in systemic vascular resistance and subsequent hypotension, all of which is thought to be contributed to by increased levels of nitric oxide (NO). Nitric oxide is produced from L-arginine by NOS of which there are three main isoforms: neuronal which synthesizes NO as a neurotransmitter, constitutive (endothelial) which is responsible for basal NO production, and an inducible form, expressed after cytokine stimulation and sepsis. In the normal physiological state, low levels of NO are produced by constitutive NOS which is concerned with homeostasis of blood flow, possibly, controlled by negative feedback [5]. Inducible NOS is not present in significant quantities in

health but is expressed following stimulation by inflammatory cytokines such as TNFa, IL-1, IL-2, IL-6 and interferon-gamma, all components of the inflammatory cascade triggered by LPS endotoxin from the Gram negative bacterial cell wall. Inducible NOS produces large quantities of NO, and is insensitive to feedback control. However, blockade of all NO production using synthetic analogues of arginine, such as monomethylarginine, does not improve, and may in fact lead to increased mortality [6].

Vasopressin

In septic shock, after an initial peak, vasopressin levels fall very low compared with other causes of hypotension [7]. These low plasma levels are partly due to a depletion of vasopressin stores in the neurohypophysis. As vasopressin levels are high in early sepsis when vascular resistance is already low, it is unlikely that depletion of vasopressin is the main cause of vasodilation in sepsis. However, it probably contributes in the later stages of the disease.

Endothelial Cells

The vascular system is not a passive conducting system for blood. Endothelial cells are physiologically active and have a role in maintaining a non-thrombogenic blood-tissue interface and also regulate coagulation, vascular tone and hence blood flow. An uncontrolled endothelial cell response is involved in many disease processes, including sepsis and inflammatory syndromes. Both inducible and constitutive NO synthase have been found in endothelial cells and endothelin, a potent vasoconstrictor, is produced by endothelial cells. There is considerable interaction between endothelin, NO and prostacyclin in the regulation of vascular tone [8]. Also the "tight junctions" between endothelial cells act as a barrier to molecules from the circulation preventing leakage into the interstitium.

Endothelial cells also regulate the movement of neutrophils into the intersitium via adhesion molecules. These do so by binding to specific ligands. Intercellular adhesion molecule-1 and vascular cell adhesion molecule are only minimally expressed by resting endothelial cells but their expression is increased by cytokines and endotoxin.

Coagulation-related receptors on the surface of endothelial cells and circulating coagulation factors regulate and initiate coagulation in response to vascular injury. Endothelial cells can express a variety of proteins that directly participate in coagulation.

Tissue Factor

Tissue factor, the receptor for factor VII, is procoagulant, is inhibited by tissue factor pathway inhibitor, which is bound to the endothelial cell surface and its expression leads to activation of factor X, which combines with factor Va to convert prothrombin to thrombin. Thrombin binds to thrombomodulin, expressed on the endothelial cell surface, which is the major physiological buffer against the procoagulant effects of thrombin. The thrombin-thrombomodulin complex activates protein C resulting in initiation of the activated protein C pathway. This process is augmented by the endothelial protein C receptor (EPCR). Activated protein C must dissociate from EPCR before it can bind to protein S and function as an effective anticoagulant, through the inactivation of factor Va.

Lactate

Hyperlactaemia is a frequent accompaniment of sepsis and is not due to hypoperfusion and anaerobic metabolism. Catecholamine-mediated increases in aerobic metabolism enhance the production of pyruvate, which exceeds the mitochondrial oxidative capacity. This leads to lactate production with NO contributing to mitochondrial dysfunction. Hyperlactaemia is an important indicator of a poor prognosis and is therefore a useful clinical marker for the severity of sepsis.

Organ Specific Effects

The Heart

Adequately resuscitated patients with severe sepsis characteristically have a hyperdynamic circulation with low systemic vascular resistance and a high cardiac output. However, despite this increased cardiac output, most patients have intrinsic myocardial dysfunction. Stroke volume is maintained by a dilated ventricle with a reduced ejection fraction [9].

Septic shock may also be associated with diastolic dysfunction [10]. Nitric oxide is markedly elevated in severe sepsis and has been shown to depress myocardial energy production [11]. In addition, there are alterations in intracellular calcium trafficking, with a reduction in intracellular calcium concentration with resultant cardiac contraction, compounded by down-regulation of the b-adrenergic response to catecholamines [12, 13].

The Lung

In the ALIVE study of 78 ICUs in 10 European countries, sepsis was responsible for >50 % of cases of acute lung injury (ALI) or adult respiratory distress syndrome (ARDS) [14]. Pathological changes in the lung include an early, exudative phase followed by proliferative and fibrotic phases. Persistent ARDS is characterized by ongoing inflammation, parenchymal-cell proliferation, and disordered deposition of collagen. Since atelectasis and oedema reduce the aerated lung volume in patients with acute lung injury, the inspiratory airway pressures used to generate "adequate" tidal volumes are often high, leading to the possibility of excessive distention, or "stretch," of the aerated lung [15].

In a rat model of ARDS, large tidal volume ventilation disrupted the pulmonary epithelium and endothelium, and caused lung inflammation, atelectasis, hypoxemia, and the release of inflammatory mediators. These inflammatory mediators potentially increase lung inflammation and cause injury to other organs [16]. Disruption of the alveolar-capillary membrane can permit the passage of cytokines from the lung into the systemic circulation and contribute to the development of multi-organ failure.

The ARDSNet study explored this hypothesis and demonstrated a reduction in mortality and cytokine release in a group ventilated with 6 ml/kg tidal volume rather than 12 ml/kg [17]. However, the pathophysiology of sepsis-induced ALI/ARDS is complicated. As well as direct effects on the lung from cytokines, oxygen free radical damage from inflammatory cells may also contribute to lung injury in sepsis. Sepsis-induced ALI is characterized by activation of neutrophils and macrophages, and increased levels of inflammatory mediators. Upregulation of attractant molecules (chemokines) establishes a concentration gradient that attracts the neutrophils into the lung. Adhesion molecules are also involved in this process [18]. Neutrophil infiltrates occur in the lungs of humans and animals with sepsis. The number of neutrophils in broncho-alveolar lavage (BAL) fluids from patients with ARDS is significantly increased and associated with reduced survival [19], hence supporting the important role of inflammation in ALI/ARDS.

The Kidney

Acute renal failure (ARF) is the most common renal manifestation of sepsis and sepsis accounts for more than 50 % of cases of ARF. Renal failure in this setting usually occurs as a component of multiple organ dysfunction syndrome (MODS), indicating that similar mechanisms are operative in inducing dysfunction in other organ systems. A prospective study involving 345 patients who had acute renal failure with or without sepsis showed an increased requirement for mechanical ventilation with higher mortality in patients with sepsis [20].

Activation of the sympathetic nervous and the renin–angiotensin–aldosterone systems, increase levels of vasopressin, and an increase in cardiac output are essential in maintaining the arterial circulation in patients with severe sepsis. Consequently, septic shock may lead to ARF. Although the activation of the neurohumoral axis

during septic arterial vasodilatation is essential in maintaining arterial circulatory integrity, it is associated with renal vasoconstriction, due at least in part, to the ability of tumor necrosis factor alpha to release endothelin, a potent vasoconstrictor [21].

The choice of pressor agent may also theoretically influence the development of ARF. Norepinephrine constricts the afferent arteriole in the glomerulus, dropping filtration pressure, whilst arginine vasopressin has been shown to constrict the efferent arteriole, increasing the filtration pressure and consequently, the glomerular filtration rate.

Sepsis affects the expression of complement, coagulation, and the fibrinolytic cascade and can lead to disseminated intravascular coagulation which has been associated with glomerular microthrombi and acute renal failure.

The choice and "dose" of renal replacement therapy has also been suggested as being important in outcome from ARF associated with sepsis. However, in the RENAL Study, 1,464 patients with ARF who required intensive care were randomised to receive continuous venovenous hemodiafiltration at a total effluent flow rate of 25 ml/kg/h or 40 ml/kg/h until kidney function recovered or the patient was discharged from intensive care. In both treatment groups, 44.7 % of patients died in the first 90 days after randomization. Overall, 94.4 % of patients who were alive after 90 days no longer required dialysis, with similar rates of recovery of kidney function in both treatment groups [22]. Consequently, it is difficult to be dogmatic on this aspect of renal management in the patient with acute sepsis.

Splanchnic Organs

Splanchnic tissue oxygenation is at risk in septic shock, even though total hepatosplanchnic blood flow may be normal or elevated. This is due to a major increase in metabolic demand, reflected by increased tissue oxygen consumption and impaired oxygen extraction [23].

Hypoxia of the gut wall is associated with increased permeability, endotoxaemia, the presence of bacteria in abdominal lymph nodes and possibly bloodstream infection [24]. Low gastric mucosal pH, as determined by gastric tonometry has been associated with an increase in morbidity and mortality in the critically ill [25, 26]. Using microlightguide reflectance spectrophotometry to assess the microvasculature, differences between healthy individuals and patients with septic shock have been recorded. Septic patients have lowered levels of mucosal oxygenation, with heterogeneity of regional oxyhaemoglobin, and small discrete areas of severe hypoxia. This suggests that during septic shock abnormal microcirculatory oxygenation occurs in the gastrointestinal tract, despite an apparent adequate systemic oxygen supply [27].

Under normal conditions of low splanchnic blood flow, the liver is relatively protected due to the hepatic arterial buffer response, which increases hepatic arterial blood flow as portal flow falls. This response is abolished early during endotoxaemia and only partially recovers later [28]. Fluid-resuscitated clinical sepsis is characterized by ongoing liver ischaemia due to a defective oxygen extraction despite enhanced perfusion. How and whether standard resuscitation therapy influences the hepatic microvascular response to sepsis is unknown.

Central Nervous System

Patients surviving sepsis often display impaired neurocognitive function but it can be difficult to distinguish between the direct effects of sepsis resulting from mediator actions and indirect effects, such as those from hypotension, pyrexia, or altered intracranial pressure. After an infusion of endotoxin, the plasma concentration of S-100B, thought to be a marker of glial damage, increases. This may be derived from glial or Schwann cell damage, accompanied by an opening of the blood–brain barrier [29].

These observations raise the possibility that diffuse brain injury is due to local hypoxia, hypoperfusion, cytokine-mediated inflammation and microvascular thrombosis, all components of MODS [30].

Management of Sepsis

General Measures

The cardiovascular management of the septic patient continues to rely on conventional approaches such as fluids, vasopressors and source control (including antibiotics and surgical drainage, which are specifically addressed in the relevant sections). One recent study from the USA [31] has suggested that "goal directed therapy", using protocols, can improve outcome when there is a central venous oxygen saturation target of 70 %. However, this study can be criticised as senior staff were involved in the management of the treatment but not the control arm, and furthermore, the results appear to be in conflict with earlier similar studies. However, the difference may lie in the timing of the intervention in the patient's illness. This therapeutic strategy formed part of the Surviving Sepsis Campaign's approach to the management of severe sepsis (www.survivingsepsis.org/).

In general, the source of sepsis needs to be removed, drained, or otherwise eradicated. For source control to be effective, cultures need to be taken from all likely sites including blood as soon as possible and ideally before starting antimicrobials. Once cultures have been taken and in conjunction with drainage of obvious collections, broad-spectrum antimicrobials should be started according to local protocols. There is some evidence that in sicker patients, combination antibiotic therapy may confer a survival advantage (Chap. 5).

Respiratory Management

Supplemental oxygen should be given to any patient with sepsis who is hypoxaemic or in respiratory distress and titrated against arterial saturation or arterial blood gases. If the patient's airway is not secure, gas exchange or acid–base balance is

abnormal or there is evidence of respiratory muscle fatigue or distress, the patient should be intubated. In general patients require intubation and ventilation because respiratory failure exists at presentation or develops during the course of the illness. If ventilation is required then lung protective strategies (6 ml per kilo tidal volumes and peak pressures below 30 cm water) should be employed as described in the ARDSNet study [17].

Cardiovascular Management

The haemodynamics of septic shock are influenced by multiple physiological changes characterized by components of hypovolemic, obstructive, cardiogenic, distributive, and cytotoxic shock. The haemodynamic profile is modified by any fluid resuscitation. After adequate restoration of left ventricular filling, the severity of hypotension is dependent on contractility (both sepsis-induced and baseline) and the amount that the systemic vascular resistance is lowered. Persistent hypotension, despite adequate fluid resuscitation is an indication for vasopressors and is the hallmark of septic shock.

Distributive shock may represent some maldistribution of blood flow at organ and micro-vascular level and in addition may be associated with a cytotoxic component. It has become apparent that the correction of macro-hemodynamic variables is unable to prevent multiple organ dysfunction in sepsis and that persistent microvascular dysfunction is associated with the development of organ dysfunction and death [32]. The endothelium plays a central role in microvascular dysfunction and the physiopathology of sepsis, regulating vasomotor tone, inter cellular signaling, coagulation, and the balance between pro- inflammatory and anti-inflammatory mediators [33].

Elevation of the blood lactate level on serial measurements of lactate can indicate inadequate tissue perfusion. Mixed venous oxygen saturation may give some indication of the balance between oxygen delivery and consumption. A decrease in mixed venous oxygen can indicate a decrease in cardiac output or inadequate oxygen supply; however, maldistribution of blood flow or failure of oxygen utilisation may artificially elevate mixed venous oxygen saturation. A mixed venous saturation 65 % or less is generally felt to represent inadequate tissue perfusion. The significance of normal or elevated mixed venous saturation is less clear. The adequacy of regional perfusion in patients with septic shock is best evaluated by effects on end organ function.

Despite agreement that aggressive fluid resuscitation is the appropriate initial intervention in septic shock, the choice of fluid resuscitation is not clear. Meta-analyses of clinical studies comparing crystalloid and colloid resuscitation in general populations of primarily surgical non septic shock patients indicate no clinical outcome difference between colloids and crystalloids at least as far as albumin is concerned [34]. Establishing a narrow range for filling pressures to guide fluid therapy is difficult because the left ventricular filling pressure required for adequate pre-load may vary based on features such as such as ventricular wall compliance, intra-thoracic

pressure, and in the case of right-sided filling pressure, pulmonary vascular resistance. Also, the potential negative effects of increasing pulmonary capillary leak in the presence of acute lung injury must also be considered as filling pressures increase.

Arbitrary values of systolic blood pressure (90 mmHg) or mean arterial blood pressure (60–65 mmHg) have traditionally been chosen to guide vasopressor therapy. However, a rise in blood pressure in isolation may or may not be of clinical benefit, a large placebo-controlled clinical trial of NG-methyl-L-arginine (a non-selective nitric oxide inhibitor) in septic shock produced significant increases in blood pressure but also a significant increase in mortality [35]. This may be because of inhibition of endogenous as well as inducible nitric oxide synthase but in addition a trade-off may exist between raising blood pressure and decreasing cardiac index that varies depending on the choice of vasopressor or combined inotrope/vasopressor made. Dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin have been demonstrated to be effective in raising blood pressure in patients with septic shock [36]. Data to date suggest that it is the timing of vasopressor (and other) therapy, rather than the specific agents, that are important. The effects of vasopressor choice on regional perfusion, e.g. renal blood flow, glomerular filtration pressure, splanchnic blood flow, hypothalamic-pituitary axis, and cerebral perfusion pressure, may also be important.

Norepinephrine does have the advantage of being less prone to produce tachycardia than other catecholamine agents but does carry the risk that the increase in systemic vascular resistance will reduce cardiac index. Vasopressin can reduce the requirement for norepinephrine but has not been shown to alter mortality [37]. Dopamine is said to carry a risk of disturbing the hypothalamic-pituitary axis.

Early goal directed therapy (EGDT) [31] has been said to offer benefit although the study was single centre and the main difference between the groups was in the level of blood transfusion which does not fit with other studies in the area. Opponents point to the unreliability of central venous pressure in the assessment of ventricular filling pressures and that of $ScvO_2$ in assessing oxygen delivery. There is also a concern about general applicability due to the very high mortality in the control group (46.5 %) in Rivers' patients, who were from a hospital in a deprived area of Detroit. Van Beest [38] in the Netherlands found a low incidence of low $ScvO_2$ in their population and mortality in the absence of EGDT to be substantially less than in Rivers' intervention group. A number of studies attempting to replicate Rivers' work are ongoing.

There is evidence that the administration of arginine vasopressin in patients with sepsis-related vasodilatory shock may help maintain blood pressure despite the relative ineffectiveness of other vasopressor hormones such as norepinephrine and angiotensin. However, a randomised trial of vasopressin as a norepinephrine-sparing agent showed no difference in outcome [39]. Arginine vasopressin also decreases the synthesis of NO as a result of a decrease in the expression of inducible NOS and arginine also decreases cyclic guanosine monophosphate (cGMP) signaling by NO, thus attenuating the arterial vasodilatation and pressor resistance during sepsis [40]. Unlike norepinephrine and angiotensin II, arginine vasopressin does not have any inotropic effects. The increase in afterload during an arginine vasopressin infusion can decrease cardiac output.

Protein C

There have been many attempts to modulate the cytokine and immune response to sepsis which to date have proved unsuccessful in phase III clinical trials. In particular, trials using monoclonal antibodies against TNF have all being unsuccessful [41]. However, a phase III randomized, international, multicentre, fully blinded clinical trial of drotrecogin alfa (recombinant human activated protein C or ACP) in severe sepsis, the PROtein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial [42], showed a 6.1 % absolute and a 19.8 % relative increase in survival in the treatment group, compared with controls. The primary end-point was death from any cause and was assessed 28 days after entry into the study (and later at 90 days). The National Institute for Clinical Excellence (NICE) in the UK have published guidelines restricting the use of the drug due to its expense and it is currently the subject of a further trial, the PROWESS-shock RCT which has not confirmed the benefits seen in PROWESS. Lilly have withdrawn aPC from the market following these negative results in the PROWESS-SHOCK study where the mortality in the APC treated patients was 26.4 % compared with 24.2 % in the control arm (www.lilly.co.uk). The suggestion is that sepsis care has improved in the intervening period since the PROWESS trial such that the treatment effect of APC is lost.

The exact pathway by which the actions of activated protein C might have led to a survival advantage is unclear. Activated protein C is known to have several mechanisms that might limit the microvascular injury seen in severe sepsis. By inhibiting Factors Va and VIIIa, activated protein C has an antithrombotic effect. It also inhibits plasminogen activator inhibitor-1 and limits the production of thrombin fibrinolysis inhibitor (increasing thrombolysis).

Steroids

Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation, and whose plasma cortisol levels did not rise appropriately, after the administration of corticotrophin [43]. A more recent study failed to confirm these findings; hydrocortisone did not improve survival or reverse shock, even in patients who did not have a response to corticotrophin. However, hydrocortisone hastened the reversal of shock in patients in whom shock was reversible [44].

Differences between both studies may explain the apparent contradiction. The patients in the Annane [43] study had higher SAPS II scores at baseline, and the entry requirement for systolic blood pressure was less than 90 mmHg for more than 1 h, despite fluid and vasopressor therapy, and there was a much higher death rate at 28 days in the placebo group (61 % vs. 32 % in Corticus) [44]. Enrolment in the Annane study occurred within 8 h after fulfilling the entry criteria, as compared with a 72-h window for the Sprung and colleagues study. Also, fludrocortisone was

not given to patients in the Corticus Study on the grounds that 200 mg of hydrocortisone should provide adequate mineralocorticoid activity. Therefore, corticosteroids cannot currently be recommended in sepsis generally, but may be beneficial for patients poorly responsive to fluid resuscitation.

Glycaemic Control

Tight glycaemic control also formed part of the Surviving Sepsis guidelines and this was based on several studies especially that of Van den Berghe and colleagues [45] in post-operative critical care patients. A large multi-centre randomised control trial (NICE-SUGAR) performed more recently comparing tight control, i.e. maintaining glucose concentrations between 4.5 and 6.0 mmol/l compared with wider blood glucose levels maintained at 10.0 mmol or less per liter showed an excess of death in the tight control group [46]. Thus tight glycaemic control can also not be recommended.

Healthcare Bundles

Levy et al. have been shown that when analysing data on compliance with bundle targets and association with hospital mortality in 15,022 subjects at 165 sites, reductions in hospital mortality rates were sustained and associated with continuous quality improvement in sepsis care as measured by the bundles [47]. Compliance with the entire resuscitation bundle increased linearly from 10.9 % in the first site quarter to 31.3 % by the end of 2 years ($P<0.0001$). Compliance with the entire management bundle started at 18.4 % in the first quarter and increased to 36.1 % by the end of 2 years ($P=0.008$). Unadjusted hospital mortality decreased from 37 to 30.8 % over 2 years ($P=0.001$). The adjusted odds ratio for mortality improved the longer a site was in the campaign, resulting in an adjusted absolute drop of 0.8 % per quarter and 5.4 % over 2 years (95 % CI, 2.5–8.4 %), which is difficult to explain as more elements of the bundles fall by the wayside.

Autopsy studies have not shown the mechanism of death in the majority of patients with severe sepsis [48]. Occasionally, a patient with sepsis may die of pressor unresponsive shock, but this is unusual. Although patients with sepsis have profound myocardial depression, cardiac output is usually maintained because of cardiac dilatation and tachycardia [49]. Although the acute respiratory distress syndrome is relatively common in patients with sepsis, death from pure hypoxemia or hypercarbia is not. Renal failure is common, but treatable with either haemofiltration or dialysis. Liver dysfunction rarely progresses to hepatic encephalopathy and disseminated intravascular coagulation, whilst troublesome, rarely produces catastrophic haemorrhage. Thus the exact cause of death in patients with sepsis remains

elusive. Many patients die when care is withdrawn or not escalated when families, in consultation with physicians, decide that continued treatment is futile

Answers to Case Scenario

1. The evidence presented above suggests that early aggressive resuscitation possible guided by central venous oxygen saturation is the most important contributor to outcome. Once a patient is ventilated, then adherence to lung predictive ventilation strategies and adherence to care bundles, also improves outcome.
2. Reversibility of shock, measurement of serum lactate and its response to treatment as well as predictive scores such as APACHE II can all predict outcome.

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