Related titles

*Biocompatibility and performance of medical devices*  

*Cellular response to biomaterials*  

*Sterilisation of biomaterials and medical devices*  
(ISBN 978-1-84569-932-1)
List of contributors

Y. Achermann  University of Maryland, Baltimore, MD, USA
M. Al-Mayahi  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
K. Bazaka  James Cook University, Townsville, QLD, Australia
O. Bazaka  James Cook University, Townsville, QLD, Australia
A. Bistol  Adelaide Hospital, Turin, Italy
S. Bose  Pravara Institute of Medical Sciences, Rahata, India
L. Carson  Queen’s University of Belfast, Belfast, UK
I. R. Cooper  University of Brighton, Brighton, UK
D. G. Cvitkovitch  University of Toronto, Toronto, ON, Canada
L. Deabate  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
Y. Delaviz  University of Toronto, Toronto, ON, Canada
A. K. Ghosh  Pravara Institute of Medical Sciences, Rahata, India
B. F. Gilmore  Queen’s University of Belfast, Belfast, UK
S. P. Gorman  Queen’s University of Belfast, Belfast, UK
E. T. Kang  National University of Singapore, Singapore
P. Kerns  University of Maryland, Baltimore, MD, USA
G. Laverty  Queen’s University of Belfast, Belfast, UK
A. Lomessy  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
G. Massazza  University of the Studies of Turin, Turin, Italy
I. M. Mehdawi  Benghazi University, Benghazi, Libya
M. Miola  Polytechnic of Turin, Turin, Italy
K. G. Neoh  National University of Singapore, Singapore
L. Ravera  University of the Studies of Turin, Turin, Italy
F. Rosso  University of the Studies of Turin, Turin, Italy
J. P. Santerre  University of Toronto, Toronto, ON, Canada
M. E. Shirtliff  University of Maryland, Baltimore, MD, USA
D. Suvà  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
I. Uçkay  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
P. Vaudaux  Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
E. Verné  Polytechnic of Turin, Turin, Italy
R. Wang  National University of Singapore, Singapore
A. Young  UCL Eastman Dental Institute, London, UK
Woodhead Publishing Series in Biomaterials

1 Sterilisation of tissues using ionising radiations
   Edited by J. F. Kennedy, G. O. Phillips and P. A. Williams

2 Surfaces and interfaces for biomaterials
   Edited by P. Vadgama

3 Molecular interfacial phenomena of polymers and biopolymers
   Edited by C. Chen

4 Biomaterials, artificial organs and tissue engineering
   Edited by L. Hench and J. Jones

5 Medical modelling
   R. Bibb

6 Artificial cells, cell engineering and therapy
   Edited by S. Prakash

7 Biomedical polymers
   Edited by M. Jenkins

8 Tissue engineering using ceramics and polymers
   Edited by A. R. Boccaccini and J. Gough

9 Bioceramics and their clinical applications
   Edited by T. Kokubo

10 Dental biomaterials
    Edited by R. V. Curtis and T. F. Watson

11 Joint replacement technology
    Edited by P. A. Revell

12 Natural-based polymers for biomedical applications
    Edited by R. L. Reiss et al.,

13 Degradation rate of bioresorbable materials
    Edited by F. J. Buchanan

14 Orthopaedic bone cements
    Edited by S. Deb

15 Shape memory alloys for biomedical applications
    Edited by T. Yoneyama and S. Miyazaki

16 Cellular response to biomaterials
    Edited by L. Di Silvio

17 Biomaterials for treating skin loss
    Edited by D. P. Orgill and C. Blanco

18 Biomaterials and tissue engineering in urology
    Edited by J. Denstedt and A. Atala

19 Materials science for dentistry
    B. W. Darvell

20 Bone repair biomaterials
    Edited by J. A. Planell, S. M. Best, D. Lacroix and A. Merolli

21 Biomedical composites
    Edited by L. Ambrosio

22 Drug–device combination products
    Edited by A. Lewis

23 Biomaterials and regenerative medicine in ophthalmology
    Edited by T. V. Chirila

24 Regenerative medicine and biomaterials for the repair of connective tissues
    Edited by C. Archer and J. Ralphs
54 Joining and assembly of medical materials and devices
   Edited by Y. (Norman) Zhou and M. D. Breyen
55 Diamond-based materials for biomedical applications
   Edited by R. Narayan
56 Nanomaterials in tissue engineering: Fabrication and applications
   Edited by A. K. Gaharwar, S. Sant, M. J. Hancock and S. A. Hacking
57 Biomimetic biomaterials: Structure and applications
   Edited by A. J. Ruys
58 Standardisation in cell and tissue engineering: Methods and protocols
   Edited by V. Salih
59 Inhaler devices: Fundamentals, design and drug delivery
   Edited by P. Prokopovich
60 Bio-tribocorrosion in biomaterials and medical implants
   Edited by Y. Yan
61 Microfluidic devices for biomedical applications
   Edited by X-J. James Li and Y. Zhou
62 Decontamination in hospitals and healthcare
   Edited by J. T. Walker
63 Biomedical imaging: Applications and advances
   Edited by P. Morris
64 Characterization of biomaterials
   Edited by M. Jaffe, W. Hammond, P. Tolias and T. Arinzeh
65 Biomaterials and medical tribology
   Edited by J. Paolo Davim
66 Biomaterials for cancer therapeutics: Diagnosis, prevention and therapy
   Edited by K. Park
67 New functional biomaterials for medicine and healthcare
   E. P. Ivanova, K. Bazaka and R. J. Crawford
68 Porous silicon for biomedical applications
   Edited by H. A. Santos
69 A practical approach to spinal trauma
   Edited by H. N. Bajaj and S. Katoch
70 Rapid prototyping of biomaterials: Principles and applications
   Edited by R. Narayan
71 Cardiac regeneration and repair Volume 1: Pathology and therapies
   Edited by R-K. Li and R. D. Weisel
72 Cardiac regeneration and repair Volume 2: Biomaterials and tissue engineering
   Edited by R-K. Li and R. D. Weisel
73 Semiconducting silicon nanowires for biomedical applications
   Edited by J. L. Coffer
74 Silk biomaterials for tissue engineering and regenerative medicine
   Edited by S. Kundu
75 Biomaterials for bone regeneration: Novel techniques and applications
   Edited by P. Dubrueil and S. Van Vlierberghem
76 Biomedical foams for tissue engineering applications
   Edited by P. Netti
77 Precious metals for biomedical applications
   Edited by N. Baltzer and T. Copponnex
78 Bone substitute biomaterials
   Edited by K. Mallick
79 Regulatory affairs for biomaterials and medical devices
   Edited by S. F. Amato and R. Ezzell
80 Joint replacement technology Second edition
   Edited by P. A. Revell
81 Computational modelling of biomechanics and biotribology in the musculoskeletal system:
   Biomaterials and tissues
   Edited by Z. Jin
82 Biophotonics for medical applications
   Edited by I. Meglinski
83 Modelling degradation of bioresorbable polymeric medical devices
   Edited by J. Pan
84 Perspectives in total hip arthroplasty: Advances in biomaterials and their tribological interactions
   S. Affatato
85 Tissue engineering using ceramics and polymers Second edition
   Edited by A. R. Boccaccini and P. X. Ma
86 Biomaterials and medical device-associated infections
   Edited by L. Barnes and I. R. Cooper
87 Surgical techniques in total knee arthroplasty (TKA) and alternative procedures
   Edited by S. Affatato
88 Lanthanide oxide nanoparticles for molecular imaging and therapeutics
   G. H. Lee
89 Surface modification of magnesium and its alloys for biomedical applications Volume 1:
   Biological interactions, mechanical properties and testing
   Edited by T. S. N. Sankara Narayanan, I. S. Park and M. H. Lee
90 Surface modification of magnesium and its alloys for biomedical applications Volume 2:
   Modification and coating techniques
   Edited by T. S. N. Sankara Narayanan, I. S. Park and M. H. Lee
91 Medical modelling: The application of advanced design and rapid prototyping techniques in medicine Second Edition
   Edited by R. Bibb, D. Eggbeer and A. Paterson
92 Switchable and responsive surfaces for biomedical applications
   Edited by Z. Zhang
93 Biomedical textiles for orthopaedic and surgical applications: Fundamentals, applications and tissue engineering
   Edited by T. Blair
94 Surface coating and modification of metallic biomaterials
   Edited by C. Wen
Introduction to biomaterials and medical device-associated infections

I. R. Cooper,
University of Brighton, Brighton, UK

1.1 History of biomaterials

The use of artificial medical devices has increased dramatically over the previous decades. Devices ranging from catheters to artificial hearts, stents and replacement joints are widely used in modern medicine to reduce patient morbidity and increase quality of life. Evidence suggests that biomaterials have been used for many thousands of years in an attempt to ameliorate patient suffering. Early devices include a leather toe (Finch et al., 2012), which was entirely external to the body and used to provide ambulatory stability to the patient after physical trauma. Modern devices include entirely internal structures, such as drug-eluting stents, which are sited in the body through surgical procedures. They are usually made of metal (Merkely et al., 2009), and are used to treat biochemical conditions. Focus has now shifted towards not only making devices clean and sterile at the manufacturing stage, but to make them chemically resistant to colonisation by microbial cells, whilst not evoking an immune response by the human host.

Modern technology has given medical and related scientists access to a wide range of materials able to be used in treatment regimes. These now include plastics, ceramics, metals, and bioactive polymers. As our understanding of the human immune response to the implantation of devices improves, alongside our understanding of microbial pathogenicity cycles, it has become clear that the precise chemical composition of the device is critical for several reasons. Firstly, the ability of the pathogen to adhere and survive on a surface must be minimalised in order to prevent post-operative infections developing. Secondly, the need for the device to prevent human immune responses from developing in order to avoid the device being rejected, must be prioritised. Also, the device must be able to either maintain its properties if it is a permanent implant, or it must be able to biodegrade if it is temporary device, without causing physical harm to the patient as it reduces.

1.1.1 The birth of biomaterials: early materials used

One of the earliest biomedical devices discovered is an artificial toe discovered in Egypt, and currently housed in the British museum. It is made from leather, and appears to have been sewn to another material to facilitate walking by the wearer,
dating from the first millennium BC (Reeves, 1999). Another Egyptian biomedical device was the use of wooden splints to treat fractured arm bones (Smith and Dawson, 1924). Both of these early examples of biomaterial are externally applied. This is important to note, as a large proportion of modern devices are now used as implantations, or pushing through the intact skin or mucous membranes, such as catheters. It is also important to note that both of these devices were constructed from naturally occurring materials: leather and wood. As technology has advanced we are now able to employ a wide range of materials, sometimes combined together, to facilitate a more comprehensive approach to treatment. There is evidence that amputation was employed to treat severe injury in Ancient Egypt (Nerlich et al., 2000; Williams, 2010). It is likely that, as today, amputation was considered as an option for the treatment of severe infection as well as injury from physical trauma. This is usually an option of last resort, used only in an attempt to save the patients’ life. However, it is also considered in relation to the use of artificial prostheses, where evidence suggests that this practice is centuries old; analysis indicating that the wearer of the artificial toe lost the original toe due to amputation (Nerlich et al., 2000). This data inextricably links the science of biomaterial prostheses design to medicine in an attempt to ameliorate suffering and improve patients’ lives.

1.1.2 Types of early medical device

Moving in to the modern era, biomedical devices can now be constructed using machines, and can come from a range of materials. Examples include metals, such as stainless steel (Torricelli et al., 2003), ceramics (Ngai et al., 2014), plastic (Lim et al., 2013), and bio-responsive polymers in recent years (Keegan et al., 2007). Depending on the body location, the physical and biological pressures of that location will vary. For example, a prosthetic knee will face greater shear during walking than a dental implant. However, a dental implant will be subject to both shear associated with mastication and greater degrees of chemical stress in relation to nutritional intake, as well as microbial metabolism and acid production in response to nutrient availability. A full assessment of the biological and physical needs of each device must be made if successful utilisation and application is to be achieved.

According to broad consensus, a biomaterial is defined as a nonviable material used in a medical device, intended to interact with biological systems (Williams, 1987). Within this scope, biomaterials can be largely divided in to one of three types, or generations of device:

1. bioinert;
2. biologically active and biologically degradable; and
3. location-specific response-inducing materials.

The original devices were usually made of one solid material, an example of which would be the wrought iron false tooth found in a Roman cadaver from approximately the year 200 AD (Crubezy et al., 1998). These first generation devices were designed to allow functionality, with no proper understanding of the biological processes underpinning the structures. That being said, Crubezy et al., did note that the iron tooth
implant had achieved a degree of osteointegration, suggesting at least partial success of the implantation procedure (Crubezy et al., 1998). Being constructed of such materials, there was a much reduced chance of unwanted leakage or particle release that has been associated with some of contemporary materials. They were also largely biologically inert, which satisfies the criterion for inducing as little host response to a foreign body as possible. Another example would be polymethylmethacrylate (PMMA), which shows good adhesive property, and an example of these would be to act as cement to solidify prostheses to damaged bones (Charnley, 1960). However, some biochemical problems have been noted post-implantation of PMMA, leading on to further research in to its use.

1.1.3 Problems associated with early biomaterials and the need for further development

The two key problems associated with the use of biomaterials is the ability of microbes to colonise a surface, and the elucidation of a host response. Research into understanding these concepts led to the development of the definition of biocompatibility: the ability of a material to perform with an appropriate host response in a specific application (Williams, 1987). Recent advances in ceramic technology have led to the use of Si$_3$N$_4$, a non-oxide material, which possesses the needed strength and toughness to allow device functionality, whilst allowing resurfacing if needed (Pezzotti and Yamamoto, 2014). The inclusion of magnesium and magnesium alloys in orthopaedic biomaterials is also noted as a potential improvement, due to their biodegradability, along with desirable mechanical properties (Farraro et al., 2013). This means that older materials might be able to be adapted for future use, if the host-material chemistry can be researched further, and new properties are given to these devices without the loss of existing function. For example, the inclusion of titanium in to existing bone implants in the early 1990s showed an improved rate of implant success (Jensen and Sindet-Pedersen, 1991).

1.2 Overview of current medical devices and applications

Second generation devices are often referred to as demonstrating biological activity, and or biodegradability. This can refer to the induction of a specific host response, or that the device can successfully degrade without causing the patient harm. Degradation is often accompanied by the promotion of tissue repair, as these materials are often coated to prevent host cell death or to promote cell proliferation. One such example would be biodegradable stents used to treat restenosis. Whilst pure metal stents can reduce the rate of tissue revascularisation, studies have suggested that biodegradable materials have shown a decrease in later stage thrombosis and myocardial infarction (Stefanini et al., 2012), which is of notable importance. Other examples include bioactive glasses and ceramics.
Finally, third generation devices can be so-called location-specific response-inducing materials that encompass elements from human tissue engineering, which encourage cell invasion of the device itself. Examples include biodegradable organic scaffolds which encourage cell infiltration within the device (Agrawal and Ray, 2001) and pre-developed tissues produced in the laboratory (Temenoff and Mikos, 2000). These later approaches might offer significant advantages by overcoming the potential for tissue rejection by the host, if the material to be implanted can be assured to be free of harmful chemicals used in the manufacturing process.

Other types of third generation device include bioactive polymers, which are designed to respond to localised changes in pH, and sometimes to encourage tissue infiltration. Hydrogels have been widely researched as vehicles for the delivery of biological compounds. By manipulation of the polymer chemistry, it has been possible to produce materials that can uptake drugs in the laboratory, but then to release them once physiological conditions adjust the local environmental conditions, and thus influence the polymer. Examples of materials used to construct hydrogels include heparin, alginate and polyester compounds (Khanh Nguyen and Alsberg, 2014). The key is the adaptation of cross-linking technologies (Goddard and Hotchkiss, 2007), with the intention of allowing polymers to release a compound upon exposure to one physiological stress, and then to stop release once the stress has been removed. One example would be the use of carbopol compounds to deliver zinc ions in to the oral cavity to function as an antibacterial active. Here the polymer releases zinc ions upon exposure to decreasing pH associated with bacterial metabolism of sugars, whilst reducing their release in response to increasing pH as salivary flow returns to pre-prandial conditions (Keegan et al., 2007). Such advances in understanding the fundamental chemistry of the materials used in relation to the biological processes to be encountered at the location of the device is an area of intense research at present, and new smart materials are currently being produced across the world to treat a wide range of infectious and non-infectious disease. This could be one area of significant advancement in future years.

1.2.1 Nosocomial and primary healthcare facilities

Within the healthcare environment, medical devices are utilised daily. Despite them being supplied as sterile, the moment the device packages are opened, handled and inserted in to a patient, they become exposed to the plethora of micro-organisms that colonise the human body and the hospital environment itself. Given that care facilities are known to be reservoirs of micro-organisms (Weinstein and Hota, 2004), and sometimes multi-drug resistant micro-organisms, the use of devices must be driven by prudent healthcare policy. Handling by untrained personnel would present a risk for the device to become colonised by micro-organisms, and thus it should be best practice to only utilise them when needed. It has been observed that changes in antibiotic stewardship policy can influence the presence of antibiotic resistant micro-organisms (Khan and Cheesbrough, 2003; Huerta et al., 2013), suggesting that healthcare workers can indeed alter the type of micro-organism that might cause infections. Therefore device governance and risk management strategies must be at the heart of infection control policy and enforced in practice.
1.2.2 Morbidity and mortality rates

Implementation of prudent antimicrobial stewardship and infection control guidelines has been shown to decrease levels of both patient mortality and morbidity. Rosenthal et al., (2006) reported that the inclusion of surveillance programmes on infectious disease and antimicrobial prescription could reduce infection rates by up to 30%, as well as a reduction in associated costs. It is logical to note that proper antimicrobial stewardship can reduce the need to prescribe more than one course of treatment, and also have a positive effect to reduce the rate of antimicrobial resistance amongst nosocomial pathogens.

Between 2004 and 2008, the UK Health Protection Agency reported that a total of 3360 patients were diagnosed with a nosocomial infection in England and Wales (Anon., 2012); and that the prevalence of these infections dropped to 6.4% in 2011, from 8.2% in 2006. They report that the most common types of infection were respiratory tract infections, urinary tract infections, surgical site infections, clinical sepsis, gastrointestinal tract infections, and bloodstream infections; accounting for 80% of all nosocomial infections. During the same period, the prevalence of antimicrobial usage was reported to be 34.7% within care facilities, with respiratory tract infections accounting for approximately 31%, followed by soft tissue and skin infections at 19%, and 13% of patients being prescribed antimicrobials for the prevention of postsurgical infections. An interesting point from the report highlights that where certain biomedical devices were utilised, infections associated with device insertion occurred between 1–3 days post-implantation (Anon., 2012). This highlights the importance of correct stewardship associated with device insertion, and also indicates the level of burden placed upon individuals in terms of morbidity and mortality, and the healthcare system in terms of costs. Such devices included intubation, urinary and vascular catheters, which devices accounted for the majority of the infections, with surgical site infections also noted as a significant source of infection. In 2009, it was reported that over 1.3 million cardiovascular devices were implanted (Mind and Proclemer, 2011). Within the same period, the infection rate for cardiovascular defibrillator usage ranged from 0 to 0.8%, and approximately 0.1% to 19.9% for pacemakers. It was also reported that of these patients, 23% developed device-related endocarditis (Sohail et al., 2007).

1.3 Overview of problems associated with medical devices

One of the greatest problems associated with nosocomial and biomedical device infections is identifying the source of the infectious agent. Numerous studies have been conducted to identify the source of these organisms, and the results indicate that prior infection, current or long-term antibiotic therapy is of key importance to contracting a nosocomial or medical device-associated infection. For example, in 2011, Harinstein et al., reported that key factors leading to the patient contracting hospital-acquired Methicillin Resistant Staphylococcus aureus infection (HA-MRSA) were
the presence of peripheral vascular disease, use of a central venous catheter, a Foley catheter, or the patient suffering from three or more comorbidities.

### 1.3.1 Host response to material

Upon insertion, medical devices rapidly become coated with a layer of host-derived materials, including proteins and polysaccharides, often referred to as a conditioning layer or film. This layer facilitates the attachment of host fluids and cells to the material, and promotes integration of the material with the host body. However, it can also allow microbial cells to attach to the device, and once attached, the cells can replicate to form a monolayer, eventually developing into a biofilm. Evidence suggests that the presence of microbial cells, and perhaps their waste products, attracts immune cells to migrate to the area and express pro-inflammatory cytokines into the vicinity of the device. There is evidence to suggest that an exaggerated release of cytokines and bactericidal agents into a localised area might be responsible for tissue degradation on a small scale (Arciola et al., 2012). Indeed, several authors have stated that in *Staphylococcus aureus* infections, the presence of activated polymorphonuclear neutrophils (PMNs) secreting Interleukin–8 (IL–8) and monocytes secreting inflammatory proteins MIP–1α and MIP–1β were not able to eradicate all of the infectious bacteria as they were unable to remove the biofilm architecture, thus providing the bacterial cells with a means of recalcitrance.

Complement activation has also been demonstrated to be of prime importance when considering biomaterial-associated infection. Upon introduction of the material, contact occurs with the host cells and the fluid proteins. The complement cascade is estimated to involve at least thirty proteins, and is initiated either by the formation of antibody–antigen complexes or the binding of polysaccharides to mannan-binding lectins or ficolins (Andersson et al., 2005; Engberg et al., 2009). Bacterial species have been noted to overcome such contact binding by expressing human factors on their cell surface which disguises these cells to the immune system. One example is the production of plasminogen binding receptors by *Staph. aureus*. These can be converted into cell surface-bound plasmin, which has the ability to cleave IgG immunoglobulins and the C3b convertase enzyme of the complement cascade (Rooijakkers and van Strijp, 2007), thus interrupting the sequence. These proteins have also demonstrated potential to decrease the ability of neutrophils to phagocytose the bacterial cell, thus presenting another advantage to the invading pathogen (Rooijakkers et al., 2005). Understanding this use of biomarkers has led to their innovative adaptation where biomaterials coated with human complement activation factors, such as the streptococcal M-protein, are able to modulate the cascade to a point where activity is reported to be negligible (Engberg et al., 2009). This technology could represent a platform for modulating cell–host and host–microbe interaction in the future.

### 1.3.2 Colonisation and infection

Colonisation is the definitive prerequisite for infection to arise. The normal flora of the human body is diverse, and the majority of medical device-associated infections
arise from these species, and thus the infection site itself is of prime importance when considering long-term effects with, for example, the use of a central venous catheter (Maki et al., 1997). Usually, colonisation of the device arises from skin flora, such as *Staph. aureus* or *Staphylococcus epidermidis*, through improper cleansing of the skin prior to device insertion, or from microbes migrating across the newly vacant areas to occupy new niches. Using an animal model, Cooper et al., (1988) demonstrated that device colonisation can arise just one hour after insertion, suggesting a rapid expansion of the skin flora and also that the micro-organisms can switch from colonisers to infectious agents rapidly once the immune barrier of the skin is compromised.

Harinstein et al., (2011) reported that the conversion of colonising MRSA bacteria to HA-MRSA infection was exacerbated by the use of a central venous catheter or the patient receiving two or more hospitalisations. One possible way to reduce the rate of conversion to infection might be to reduce key antibiotic therapy to those patients in Intensive Care Units (ICU), surgical patients, or other priority areas (Harinstein et al., 2011). However, clinical trials have met with limited success, mainly due to the different methodologies employed being incomparable at the statistical level, or level of implementation (Cooper et al., 2004). A reduction in the empirical use of antibiotics has long been promulgated as a method to reduce the evolution of microbial resistance. However, since different countries and regions produce divergent guidelines, a cohesive strategy remains elusive.

### 1.3.2.1 Costs to economies, patients and the NHS

In the UK, the National Audit Office (NAO) reports that between 2006 and 2008, a reduction in the rate of *Clostridium difficile* infection reduced healthcare costs by between £94 and £207 million (Anon., 2010), suggesting that improved awareness and implantation of updated treatment and patient care strategies can indeed impact both patient quality of life and economic burden. Indeed, the NAO published that healthcare-associated infections cost the NHS approximately £1 billion per annum, including approximately £56 million associated with costs incurred from patients discharged from hospital (Anon., 2009).

Also, in 2009, the US Center for Disease Control and Prevention published that the direct cost of healthcare-associated infections to US hospitals ranged from $28.4 to $45 billion, including all inpatient and other services (Scott, 2009). This accounted for 1,737,125 total healthcare-associated infections, divided into 290,485 surgical site infections, 92,011 central line associated bloodstream infections, 5,243 ventilator-associated infections, 449,334 catheter-associated urinary tract infections, and 178,000 *C. difficile*-associated infections. The report stated that the enactment of preventative measures could reduce the number of hospital-associated infections by 20%, leading to a potential saving of $5.7 to $6.8 billion, using 2007 figures. These figures underline the importance of correct procedures in the effective management of hospitals, treatment and patient care.

In agreement with this research, in the US in 2009 it was reported that the mean total charges for the treatment of nosocomial bloodstream infections increased from
$32,474 to $85,508, when associated with a mean hospital stay of 7.5 days. This research supports data published in Canada in 2008 where the incidents of ventilator-associated pneumonia were found to be associated with a 4.3 day length of hospital stay, resulting in a mean number of 230 deaths per annum (Muscedere et al., 2008). The authors reported that the cost to the Canadian health system was CAN$46 million, with items ranging between $10 and $82, and accounted for 2% of all patients visiting ICU wards.

1.3.2.2 Principle pathogens

1.3.2.2.1 Enterobacteriaceae
During 2009–10, the Health Protection Agency (HPA, UK) published data revealing an increase in carbapenem resistance amongst Enterobacteriaceae isolates, and during 2008–9, the HPA reported a worrying trend of reference laboratories that characterised an increasing number of carbapenemase-producing Escherichia coli and Klebsiella pneumoniae strains (Anon., 2009). Alongside E. coli, K. pneumoniae is becoming recognised as a principle pathogen for nosocomial infections, with ICUs being a particular focus (Jacoby, 1997; Kim et al., 2002). Patients on ICU wards can require aggressive and invasive medical treatments, such as catheterisation, which can lead to an opportunity for pathogens to circumvent the skin and immune defences of the body. The nutrient rich environment and the bacterium’s ability to protect against host-mediated immune response can create an intractable colonisation, which is difficult to treat with standard antibiotic chemotherapy. In 2003, a study recommended the inclusion of a cleaning regime for ICU and sinks and drains with 1% sodium hypochlorite alongside the wearing and changing of gloves between patient examinations in an effort to combat the colonisation and persistence of bacterial human pathogens, including K. pneumoniae (Pessoa-Silva et al., 2003). Analysis revealed the persistence of K. pneumoniae in the ICU wards, despite the environmental samples, staff and patients stools testing negative for Extended Spectrum Beta-Lactamase (ESBL) producing-K. pneumoniae. These data suggest that bacteria are capable of persisting despite a rigorous cleaning regime in a primary healthcare facility.

1.3.2.2.2 Staphylococcus species
Methicillin resistant and sensitive strains of Staphylococcus aureus (MRSA and MSSA, respectively) are perhaps the most easily identifiable nosocomial pathogens. The first MRSA isolate was identified in 1961, only one year after the introduction of the antibiotic (Jevons, 1961), and has presented a problem for healthcare scientists ever since. Evidence suggests that the MRSA bacteria can modulate their genome through the acquisition of exogenous genes and mutation of existing genes to augment their already formidable resistance profiles (Kuroda et al., 2001). The SCCmec fragment of DNA most closely associated with the bacterium inserts clone the origin of replication, and contains two important genes, ccrA and ccrB, coding for recombinase genes capable of binding penicillin class antibiotics (Ito et al., 1999; 2001). It is important to note that not all MRSA or MSSA infection results from
patient stay in healthcare facilities. Research has shown that distinct strains of MRSA and MSSA exist in the environment, with community-acquired infections more likely to be susceptible to a greater range of antibiotics than those associated with healthcare facilities (Naimi et al., 2003). This suggests a diverse ecological cycle outside of the hospital setting. In 2005, Arciola et al., reported that amongst *Staphylococcus epidermidis* isolates recovered from orthopaedic implant infections, 40–80% of the strains tested were resistant to beta-lactam antibiotics, depending on the antibiotics tested, as well as 26% being resistant to ciprofloxacin and 41% resistant to erythromycin.

*Staph. epidermidis*, a coagulase negative species of staphylococci and member of the human normal flora. Alongside *Staph. aureus*, *Staph. epidermidis* has become a leading cause of indwelling medical device-associated infections (Rupp and Archer, 1994; Vuong and Otto, 2002). Several important virulence factors have been identified in their association with the ability of *Staph. epidermidis* to develop into biofilms, notably icaADBC-encoded proteins which mediate expression of the polysaccharide intercellular adhesion (PIA) factor (Rohde et al., 2001). The PIA factor has been reported in frequent association with patients with nosocomial *S. epidermidis* infections. However, further research has suggested that the pathogenesis mechanism is more complex, with the accumulation of protein at the site of infection representing an important factor for disease progression. Rodhe et al., (2007) reported that *Staph. epidermidis* isolates could produce biofilms in the absence of PIA involvement, and indeed that the presence of protein was not the only major contributing factor for the development of biofilms. Curiously, they also reported that for *Staph. aureus*, PIA and proteins work synergistically to aid biofilm development. This suggests differences in the exact mechanisms of pathogenesis between the *Staph. aureus* and *Staph. epidermidis*, and that biofilm and indeed gene expression potentially leading to new disease states warrants greater research.

1.3.2.2.3 *Candida* species

*Candida albicans* is the most prevalent cause of fungal infection in humans, with incidents of candidiasis being reported globally. Over recent years, other species, such as *Candida glabrata*, have come to prominence, and now account for a significant number of human fungal infections (Riera et al., 2012). Diseases of note include balanitis, thrush, mediastinitis, and mycotic aneurysm. *Candida* sp. are part of the normal flora, and disease usually occurs after physical trauma, including surgery, or biochemical imbalance altering the microenvironment in which the fungus resides. The morbidity and mortality rates for candidiasis are alarmingly high, and the progression of the disease has a fatal prognosis of up to 80%, even after the commencement of treatment. In 2011, the Health Protection Agency (London, UK) reported that of all the *C. albicans* isolates tested, 1% were resistant to amphotericin B, 9% to itraconazole, and 2% to fluconazole. For *C. glabrata*, resistance was noted as 0% to amphotericin B, 96% to itraconazole, 40% to fluconazole, and 5% to voriconazole. Finally, for *C. parasilooisis*, resistance was noted as being 4% against amphotericin B, and 6% against fluconazole (Anon., 2011a). These data could indicate the emergence of widespread azole drug
resistance, and should be monitored for future developments. Virulence factors associated with *Candida* sp. infections include a metalloprotease, which may play a role in the degradation of the subendothelial extracellular matrix components (Rodier *et al.*, 1999). This could facilitate the migration of the yeast in the tissues after crossing the endothelial layer, allowing fungal invasion of the body leading to systemic disease.

### 1.3.2.2.4 Other notable organisms

*Acinetobacter* sp. are fast becoming notorious amongst healthcare workers. They are part of the normal skin flora, and are often isolated from burn-associated infections, particularly in intensive care units (Karlowski *et al.*, 2003). Identification of species is a subject of controversy, and reports usually refer to the *A. baumannii–A. calcoaceticus* complex as being the most commonly associated with nosocomial infections (Henwood *et al.*, 2002). The bacterium has demonstrated the ability to persist on the skin of uninfected hospital patients and controls, with the rate of colonisation relative to the length of hospital stay (Seifert *et al.*, 1997). The organism is reported to be able to colonise and persist on common hospital equipment such as ventilators, indicating a reservoir and perhaps route of dissemination for the pathogen within a nosocomial environment (Allen and Green, 1987). Pan-resistance to the majority of available antibiotics appears to centre on their cell structure, and research has revealed that over 75% of *A. baumannii* isolates were resistant to cefotaxime and ceftazidine, as well as high resistance to ciprofloxacin and gentamicin, amongst others (Henwood *et al.*, 2002). In November 2011, the HPA (London, UK) reported a 32% decrease in isolations of *Acinetobacter* sp. bacteraemia in 2010 compared to 2006 (Anon., 2011b). However, as the agency suggests, this could be due to restructuring and merging of facilities leading to a skewing of reports. The actual number of isolations was 779 in 2010, compared with 1139 in 2006, with the most common causative bacterium being the *A. baumannii–A. calcoaceticus* complex. Alongside the empirical data, the HPA also reported a definite rise in resistance to imipenem to 27% in 2010, although the number of isolates tested was acknowledged to be relatively small. Curiously, the reported resistance to cefotaxime has reduced by 3% to 83% in the same time period, with resistance to gentamicin, amikacin, tobramycin, ciprofloxacin, meropenem and ceftazidime all remaining approximately constant.

In 2010, Dogru *et al.*, reported that *Acinetobacter* sp. and *Pseudomonas aeruginosa* accounted for the majority of device-associated infections in a Turkish hospital. The authors reported a 29% resistance rate to ciprofloxacin amongst *Ps. aeruginosa* isolates, and conjectured that duration of device use was a major factor for device-associated infections, which is in line with current thinking. *Acinetobacter baumannii* has been reported to exert resistance to carbapenems (Poirel and Nordmann, 2006), which is of clear concern to healthcare scientists given the restricted nature of available antibiotics. Further, the possession of metallo-beta-lactamases and the poorly understood ecology of *Acinetobacter* sp. make this organism an uncertain commodity in terms of its ability to disseminate within nosocomial, community and environmental spheres.