EDITORIAL

Guideline for the prevention and management of nosocomial infections in South Africa

This congress edition of the journal is a bumper issue and is particularly exciting for a number of reasons. This edition appears in association with the first combined congress of the various infectious disease societies of South Africa and with the impending launch of FIDSSA, the Federation of the Infectious Diseases Societies of South Africa. Mark Cotton, as the incumbent president of the Infectious Diseases Society of Southern Africa, has kindly written the editorial describing the background, purpose and benefits of a single umbrella organisation for the various societies with interest in infectious diseases. Ultimately it is intended that each of the individual societies will embrace the journal as their own and have considerable input into the journal from a number of points of view, including editorial comment, manuscript review, and article submission. In this way the journal will embrace the motto of the first congress, which is “Simunye”.

Secondly, the FIDSSA Congress will purposefully for the first time also overlap with COPICON, which is the combined congress of the South African Thoracic Society and the Critical Care Society of Southern Africa. Infectious diseases, particularly in the developing world, overlap throughout the activities of members of all these societies and it is hoped that the cross pollination between the societies will be both informative and interesting.

Lastly, all the articles contained in the current edition of the journal are manuscripts dealing with various nosocomial infections. These articles were written as background documents and templates for discussion by a working group tasked with developing a guideline for the management of nosocomial infections in South Africa. It is planned for this guideline, in a much shorter version than these background documents, to be completed and published in the near future. However, each of the background documents was written by an expert in the field, edited according to the comments of the members of the working group at that meeting, and then finally re-edited and re-formatted by the editorial group. They are presented in the journal as review articles and for interest and for educational purposes only.

Charles Feldman
Adrian Brink
Adriano Dusé

The Guideline Working Group of the South African Thoracic Society, Infectious Diseases Society of Southern Africa and the Critical Care Society of Southern Africa consisted of the following members:


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Infection control in developing countries with particular emphasis on South Africa

AG Dusé

Introduction

Guidelines for infection control in South Africa and developing countries have been formulated to assist healthcare professionals to deal with five important challenges that face healthcare workers: antimicrobial resistance, nosocomial pneumonia, bloodstream infections caused by intravascular catheters, nosocomial urinary tract infections, and nosocomial intra-abdominal infections. Intelligent infection control strategies are essential to minimise the impact of these challenges on patient outcomes. Nosocomial (healthcare-associated) infections are a cause of significant morbidity and mortality in patients receiving healthcare and the costs (direct and indirect) of these infections deplete the already limited financial resources allocated to healthcare delivery. Lower respiratory tract infections, urinary tract infections, bloodstream infections, and post-surgical (including intra-abdominal) infections collectively account for the majority of nosocomial infections. The burgeoning problems and challenges posed by antimicrobial resistance have far-reaching implications for treatment of these infections worldwide and it is therefore appropriate that the emphasis of this guideline document is on these five issues.

Concerns that we are entering the post-antibiotic era have been expressed globally by many experts in the fields of microbiology and infectious diseases. It is particularly relevant to note that the indiscriminate use of antibiotics in developing countries has serious implications and is making the containment and treatment of infections caused by multiply-resistant organisms a costly and formidable task. At first, the focus of multiply-resistant organisms was in hospitals, where antimicrobial agents are used most extensively. A causal relationship between antibiotic usage and resistance of nosocomial organisms has been established on the basis of evidence of consistent associations of the emergence of resistant strains with concurrent variations of use in populations over time. Organisms of current concern in developed countries - methicillin-resistant and glycopeptide intermediate Staphylococcus aureus (MRSA and GISA), vancomycin-resistant enterococci and S. aureus (VRE and VRSA) and multiple-drug-resistant (MDR) Gram-negative bacteria - are also important nosocomial pathogens in the developing world. However, over the last decade, nosocomial transmission of commonly encountered community-acquired, multiply drug-resistant organisms such as the pneumococcus,13,14 Mycobacterium tuberculosis,15 Salmonella species,16 Shigella species18 and Vibrio cholerae15,18 has been increasingly documented in developing countries. The flow of antimicrobial resistance is therefore bi-directional. MDR organisms are introduced from the community into hospitals, and vice versa.

Microorganisms, with their diverse resistance mechanisms, have been extremely successful in outwitting the host, microbiologists and infectious disease physicians. The pharmaceutical industry is continuing in its quest to develop and exploit new antimicrobial agents or modify the chemical structure of older agents in order to circumvent bacterial resistance mechanisms. With the frightening increase in MDR organisms such as the pneumococci, MRSA, extended spectrum beta-lactamase-producing Gram-negatives, MDR M. tuberculosis, carbapenem-resistant Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae and Pseudomonas aeruginosa, as well as the emergence of VRE and GISA,17 it is true to say that the pharmaceutical industry is continuously challenged to develop new antimicrobial agents. To counter the emergence and spread of MDR pathogens, the only strategy that seems feasible is the implementation of an effective and integrated programme that involves antimicrobial resistance surveillance, a rational antimicrobial use programme, and infection control. Most importantly, such a programme must be realistic, adaptable, and take cognisance of the severe limitation of resources characteristic of many developing countries.14 It must be stressed that infection control activities on their own are primarily centered around the goal of decreasing or preventing the transmission of nosocomial pathogens to patients and staff, irrespective of whether these organisms are multiply drug-resistant or not. To further reduce and control the emergence of antimicrobial resistance, it is therefore essential that infection control activities are coupled with an optimised, effective and highly restrictive antimicrobial use programme.

Transmission and prevention of healthcare-associated infections

In order to develop simple, effective and sensible infection control interventions it is necessary to understand the sources of healthcare-associated infections and their modes of transmission.

Transmission of nosocomial pathogens basically occurs in three ways:

1. Contact spread. This involves skin-to-skin contact and the direct physical transfer of microorganisms from one patient to another or by a healthcare worker (HCW). Examples of direct contact include examination of patients with cross-infection occurring from contaminated hands of a HCW and patient bathing. Hand washing is singly the most important, evidence-supported, intervention for the prevention of transmission of organisms as a consequence of direct contact. Regrettably, most healthcare workers in high risk

AG Dusé, Division of Clinical Microbiology and Infectious Diseases, National Health Laboratory Service and School of Pathology of the University of the Witwatersrand, Johannesburg.
Correspondence to: Prof AG Dusé, PO Box 2115, Houghton 2041
E-mail: agduse@icon.co.za

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areas such as intensive care units (ICUs) do not wash their hands after each patient contact. On average, compliance with recommended hand washing is only 40% in ICUs. Indirect contact refers to contact with inanimate objects or surfaces such as bedpans, thermometers, etc that are contaminated with microbes. Organisms such as MRSA, VRE, ESBL-producing Gram-negatives, and _Clostridium difficile_ are typically spread by either direct and/or indirect contact routes.

2. Droplet spread. This involves spread of pathogens by respiratory droplets produced during coughing, sneezing, talking, and respiratory therapy procedures such as bronchoscope. Respiratory droplets larger than 5 microns do not remain suspended (airborne) in the air for long periods of time and fairly close contact with patients (within 1-2 meters) is required for transmission to occur. Organisms such as _Neisseria meningitidis_, _Streptococcus pneumoniae_, _Mycoplasma pneumoniae_, and the aetiological agents of pneumonic plague, streptococcal pharyngitis and viral infections caused by influenza viruses are among the many organisms that are spread via this route.

3. Airborne spread. This occurs when droplets that are less than 5 microns in size are produced by coughing, sneezing, or consequent to procedures such as bronchoscope and suctioning. These small droplets desiccate to form droplet nuclei that remain suspended in the air for long periods and travel long distances. The airborne nature of these contaminated droplet nuclei enables them to infect susceptible hosts several meters away from where they are produced. Organisms that are typically spread by this route include _M. tuberculosis_, measles virus and varicella-zoster virus.

Other modes of transmission of nosocomial pathogens include the contamination of the water supply, equipment, solutions, needles, multi-dose vials, or other articles used by more than one patient.

All patients presenting to healthcare facilities, irrespective of their diagnoses, must be treated using standard precautions. These precautions are designed to minimise the risk of transmission of microorganisms from patient to healthcare worker and vice versa. Standard precautions include: hand washing with either aqueous or non-aqueous hand decontamination agents, wearing of personal protective equipment as necessary (gloves, masks, gowns, and eye protection), safe disposal of waste, appropriate cleaning, disinfection, or sterilisation of equipment and patient-care items as well as appropriate decontamination of linen and the environment. Stringent attention to aseptic technique is crucial. The judicious use of preoperative prophylaxis to prevent post-surgical infections cannot be over emphasised. These principles are appropriately applied and emphasised in the ensuing articles. In addition to standard precautions, additional patient isolation procedures (contact isolation, droplet isolation and airborne isolation), depending on the mode of transmission of the suspected microorganism, are required.

**Distribution of healthcare-associated infections according to anatomic site**

The characteristic distribution of healthcare-associated infections according to anatomic site in acute-care hospitals in developed countries is as follows: urinary tract infections are the commonest (circa 35%), followed by post-operative wound infections (circa 25%), then bloodstream infections and pneumonia (circa 10% for each), and others that may account for up to 20%. However, it is important to note that the distribution of healthcare-associated infections encountered in any particular facility depends on a variety of factors that constitute the pathogenic “tripod” of healthcare-associated infections. These factors are: host factors (eg. age, underlying illness and co-morbidities, immune status, etc), microbial factors (eg. mode of transmission, virulence, antimicrobial resistance, ability to persist in the environment, etc) and environmental factors (eg. type of ward, invasive instrumentation and life support equipment, procedures performed, antibiotics used, healthcare personnel working within the particular environment, etc). Therefore, in wards such as ICUs in developed countries or in wards in developing countries where the prevalence of HIV infection is high, nosocomial pneumonia might predominate over the other infection categories. In some developing countries the distribution of healthcare-associated infections could be very different with fewer bloodstream infections (since fewer devices are used), more gastrointestinal infections, and a higher rate of postoperative wound infections being observed. Interventions to minimise healthcare-associated infections must therefore be targeted to deal with host, microbe and environment within a healthcare facility. In order to achieve this, it is mandatory that an infection control programme is in place.

**Infection control programmes**

The key components of a successful infection control programme have been defined and the efficacy of these programmes in decreasing nosocomial infections, especially in outbreak situations, is well-established. However, although infection control strategies are generally accepted as being pivotal in the containment of antimicrobial resistance in acute healthcare facilities, it is important to realise that the full impact of these programmes on antimicrobial resistance is far from clear and warrants further study. For instance, infection control programmes are not always necessarily effective in decreasing infections in patients at greatest risk for infection with MDR organisms, and may even paradoxically contribute to the emergence of antimicrobial resistance. Furthermore, the effectiveness of infection control interventions in decreasing the total burden of colonisation of patients with resistant organisms has also not been adequately evaluated.

Infection control programmes in developing countries have increased substantially during the last decade, particularly in Latin America and certain countries in Asia. There are several reasons for this. It has been the experience in many first world countries that where sound infection control programmes are in place, the incidence of hospital-acquired infections can be significantly reduced. Sophisticated care is being offered in many hospitals that lack the basic infrastructure required to minimise the risk of nosocomial infections associated with this care. Nosocomial spread of communicable diseases such as tuberculosis and the burgeoning problem of HIV infection have highlighted the transmission risk of airborne and blood-borne pathogens to patients and healthcare workers. Furthermore, the emergence, persistence, and intra- and inter-hospital spread of MDR organisms have all been facilitated by inadequate infection control practices. Regrettably, good clinical trials comparing the different approaches to, and the impact of
infection control programmes on the control of antimicrobial resistance in hospitals and other healthcare facilities are lacking.\textsuperscript{17} It seems reasonable to assume, however, that if the overall frequency of nosocomial infections is decreased in a healthcare facility, then the need for use of antimicrobial agents may be reduced. Furthermore, well-structured and rational infection control strategies that balance infection control resources with the magnitude of the local problem must surely play an important role in decreasing morbidity, mortality and costs (direct and indirect) to the patient, his or her family, the hospital, and the healthcare sector in general. Infection control programmes in South Africa range from non-existent to excellent. In the majority of our healthcare facilities, these programmes are generally poor. Healthcare-associated (nosocomial) infections are thought to occur in 25\% or more of hospitalised patients in developing countries.\textsuperscript{18} Assuming a conservative nosocomial infection rate of 15\% for South Africa and an associated attributable mortality of 5\%, it could be that healthcare-associated infections rank, either directly or indirectly, among the most important causes of death.\textsuperscript{19,20} It is obvious that the economic impact of nosocomial infections is far greater in developing countries because resources are more limited. Clearly, at a time of economic deprivation, waste of resources through inappropriate antibiotic use and for the treatment of costly healthcare-associated multiply drug resistance is unacceptable. Because advanced medical technology is often lacking in many developing countries, the cost of treatment of these infections is largely due to the cost of antibiotics and the implications of extended hospitalisation. Savings generated as a consequence of intelligent infection control programmes can be more usefully ploughed back in other under-resourced healthcare programmes.

Problems of antibiotic usage and implementation of infection control programmes in developing countries

The burden of infectious diseases such as respiratory tract infections, diarrhoea, sexually-transmitted diseases and HIV/AIDS and associated infections is overwhelming in most developing countries. Starting with the assumption that the bulk of illness in developing countries has an infective aetiology, it is considered cheaper to treat patients empirically (and often incorrectly) with antibiotics rather than to primarily order radiological studies and laboratory investigations. This approach severely undermines the quality of surveillance (disease profiling and antimicrobial resistance data) and the delivery of optimal healthcare. Furthermore, inadequacy and/or scarcity of microbiological support (from the points of view of clinical consultation and laboratory testing), inaccurate results, poor turn-around times, and costs are other frequently cited reasons why laboratory investigations are underused.\textsuperscript{19}

In South Africa, several strategies have been introduced to monitor antimicrobial resistance patterns nationally and to curtail the use of antibiotics. Among these strategies is the establishment of the National Antibiotic Surveillance Forum (NASF) to monitor antimicrobial resistance patterns in clinically significant isolates from either the academic teaching hospitals or from private microbiology diagnostic laboratories, and to provide guidance on antimicrobial susceptibility testing and the appropriate use of antimicrobials. Regrettably, the monitoring of antimicrobial resistance in the vast majority of non-rural, primary, and secondary healthcare institutions and academic hospitals in our country has been largely neglected.

Review of reports describing outbreaks in developing countries is remarkable for the limited use of molecular typing methods for characterising outbreak strains.\textsuperscript{21} The use of in-house molecular typing systems to rapidly assess microbial clonality of multiply drug-resistant organisms and to provide educational feedback can be successfully integrated into infection control programmes and may prove a cost-effective intervention.\textsuperscript{22} Furthermore, molecular typing techniques are not only useful for documenting intra-hospital persistence and transfer of multiply drug-resistant nosocomial organisms, but also inter-hospital and international transfer of nosocomial pathogens.

Severe financial constraints, inadequate staffing, overcrowding in hospitals, inadequate medical and medicinal resources and lack of persuasion of the cost-effectiveness of infection control create difficulties for the effective implementation of basic infection control programmes in healthcare facilities. It follows that where infection control practices are lacking, the containment of the spread of MDR organisms becomes extremely difficult. Infection control programmes should include surveillance, formulation and implementation of policies (particularly with regard to hand washing and use of antisepsics), education and research. Political support for, and persuasion of the cost-effectiveness of such programmes are crucial to their success.

Problems with the detection of nosocomial infections in South Africa

In South Africa, accurate systems to detect nosocomial infections are lacking. Where they do exist, standardised definitions of nosocomial infections are not uniformly applied, making it difficult to draw accurate and consistent conclusions about the data obtained. Most importantly, paucity of accurate data undermines the ability to determine what quality of care is being delivered to patients in various healthcare facilities. It also makes it impossible to persuade hospital administrators that healthcare-associated infections are common, and that accountability must be taken for having failed to take measures to minimise or prevent the transmission of these infections to patients and staff (the latter are called occupational infections, acquired by staff during the delivery of healthcare to patients). It is well established that quality of a healthcare facility’s infection control programme is an overall reflection of the standard of care provided by that institution. In order to reduce healthcare-associated infections and convince authorities to invest in infection control programmes, it is essential to first establish the extent of the problem. This requires surveillance, a system of identification of the prevalent types of microbes, their antimicrobial resistance profiles, and the routes whereby they are spread to cause cross-infections. Once this information is accurately quantified, it is possible to introduce an intervention and subsequently determine how effective that intervention has been. Surveillance can be a very costly and labour-intensive activity, but a simple and highly effective system of automated data entry, involving optical scanning of manually completed questionnaires and analysis of data using appropriate statistical software packages, can make this achievable and is currently being piloted in Gauteng, South Africa.
Strategies to prevent or control nosocomial infections and spread of multi-drug-resistant microorganisms

There are multiple interventions available that may help to minimise or control nosocomial infections as well as the development and spread of microbial resistance to antimicrobial agents. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms may be grouped into those aimed at optimising antimicrobial use and those preventing the transmission of resistant organisms. Interventions aimed at optimising antimicrobial use include: 1) optimising antimicrobial prophylaxis for operative procedures, 2) optimising the choice and duration of empiric treatment, 3) improving antimicrobial prescribing by educational and administrative means, 4) monitoring and providing feedback regarding antibiotic resistance, and 5) defining and implementing healthcare delivery system guidelines for important types of antimicrobial use. Interventions aimed at preventing nosocomial transmission of resistant organisms include: 1) developing systems to recognise and report trends in antimicrobial resistance within institutions, 2) developing systems to rapidly detect and report resistant microorganisms in individual patients and ensuring rapid response by caregivers, 3) increasing adherence to basic infection control policies and procedures, 4) incorporating detection, prevention, and control of antimicrobial resistance into institutional strategic goals and providing the required resources, and 5) developing a plan for identifying, transferring, discharging, and readmitting patients colonised with specific antimicrobial resistant pathogens.

Education

Regrettably, in South Africa, the education regarding infection control of medical students and students in the allied health disciplines is dismal. Curricula need to be reviewed urgently and infection control must be given greater prominence. Education of general practitioners and private sector specialists is, in South Africa, primarily achieved by continuing medical education (CME) seminars, attendance at scientific meetings, participation in departmental meetings at medical schools, and independent sources of information (medical circulars, scientific publications, internet, etc). A formal and compulsory point accreditation system is in place. Strategies are currently being introduced, largely through managed healthcare organisations, to monitor drug-prescribing patterns of individual practitioners and, in the near future, nosocomial infection rates in healthcare facilities. Education of the general public regarding personal hygiene, the concept of nosocomial infection, responsible antibiotic usage and problems of antimicrobial resistance is a challenging task given the low levels of education and literacy of many of our people.

Economics and cost benefits of infection control programmes

Providing proof to health administrators of the cost-effectiveness of infection control programmes is crucial to infection control practitioners if they expect to receive any financial allocation or investment for the establishment of such programmes. Cost benefits of infection control have been demonstrated in a variety of different scenarios, although the quality of some of these data is variable. In a study conducted in Turkey, where each case of nosocomial infection was matched with a non-infected case after controlling for age, sex, and clinical diagnosis of the patients, it was estimated that the medical management of nosocomial infections was costing the hospital sector an additional US$48 million in 1995. The authors concluded that infection control programmes not only pay for themselves, but also generate other direct and indirect benefits to the delivery of healthcare as a whole.23 In an organism-specific study to determine the costs and savings of a 15-component infection control programme to reduce transmission of VRE in an endemic setting, net savings due to enhanced infection control strategies for one year were $189 318. The authors concluded that strategies would be cost-beneficial for hospital units where the number of patients with VRE bloodstream infection (BSI) is at least six to nine patients/year or if the savings from fewer VRE BSI patients in combination with decreased antimicrobial use equaled $100 000 to $150 000 per year.24 In a Canadian study it was estimated that only 52% of hospital prescriptions for antimicrobial drugs were appropriate; this resulted in an expenditure of roughly $300 to $850 million on inappropriate prescriptions.25 The impact of such inappropriate prescribing practices on antimicrobial resistance is significant.

Research priorities

Most of the research on nosocomial infections and the impact of antibiotic use and abuse on the development of resistance has, so far, mainly been carried out in developed countries. Data on the prevalence of nosocomial infections and antibiotic resistance are, for instance, lacking for many areas in sub-Saharan Africa. It is imperative that, in future, significant data from developing countries must be acquired and that such countries are encouraged to participate actively and globally in the fight against the emergence of untreatable pathogens. Developing countries should also work more closely together and:

- create a forum for sharing knowledge and exchanging ideas;
- identify countries with expertise related to research into, or surveillance of, nosocomial infections and antimicrobial resistance;
- identify common infection control-related problems and develop strategies to deal with them;
- gather relevant, high quality data regarding the impact of infection control policy implementation on curtailing and containing antibiotic resistance, and
- encourage multi-centre collaborative work.

Although a high prevalence of endemic antimicrobial resistant organisms is repeatedly reported in healthcare facilities in developing countries, information which describes the origin, patient risks, or impact of antimicrobial resistance is scant. The impact of infection control programmes in these settings of limiting the spread of endemic resistant organisms or preventing infections caused by these organisms is not clearly understood. Developing countries, with a high prevalence of resistant organisms in healthcare facilities but with no, or very rudimentary, infection control programmes, provide an ideal research opportunity to evaluate the effectiveness of infection control programmes and identify those programme-specific activities that have the greatest impact on minimising the
problem of antimicrobial resistance. This can no longer be done in developed countries where infection control activities are already in place.

In this era of evidence-based, budget-constrained, and profit-driven medicine, much more research needs to be done to persuade healthcare workers and administrators that infection control programmes, and particular components within these programmes, are indeed effective in decreasing nosocomial infection rates and containing antimicrobial resistance. The unique contributions of specific infection control interventions to reduce nosocomial infections and contain resistance must be evaluated and documented. Most importantly, more accurate determinations of the costs of nosocomial infections and antimicrobial resistance are urgently needed.

**Conclusion**

As we are seeing increasing numbers of vulnerable individuals who present to our healthcare facilities we should be continuously aware of the consequences of bad infection control practices and the misuse and abuse of the antimicrobial armamentarium. Good infection control practices can usually contain the majority of infections, including those caused by MDR organisms, by simple measures. An infection control programme is as effective as the personnel responsible for its implementation: dedication, knowledge, education, constructive feedback and sensitivity to the needs of both patients and healthcare workers are essential. Furthermore, rational and restrictive antibiotic prescribing strategies together with continuing developments in the search for new antimicrobials must ensure that these so-called miracle drugs will retain their value in the treatment of infections in years to come. Education in infection control practices, nosocomial infection epidemiology and antimicrobial resistance is critically important. The development of these guidelines is a step in the right direction.

**References**

Antimicrobial resistance in nosocomial infections

A Brink

Introduction

Bacterial and fungal resistance is an increasing threat to the successful treatment of nosocomial infections. As bacterial resistance continues to evolve, some pathogens that were once considered routine to treat have become resistant to almost all antimicrobial agents. In particular, the emergence of vancomycin resistance in Staphylococcus aureus and carbapenem resistance in strains of Enterobacter spp and Klebsiella pneumoniae is of great concern. Similarly, increased production and spread of extended spectrum beta-lactamases (ESBL) in Gram-negative bacilli like Escherichia coli are worrisome.

Bacterial and fungal resistance may result from:
- mutations at the target site;
- permeability changes in the bacterial cell wall restricting access to target sites;
- biosynthesis of enzymes (ie. beta-lactamases) that cause degradation of drugs;
- or as described recently, as a result of extrusion of antibiotics from the cell interior by multi-drug efflux pumps, and
- resistance may also be attributable to a combination of these resistance mechanisms; this is particularly encountered in Pseudomonas aeruginosa and E. aerogenes.

Several complex factors are driving the increasing prevalence of antibiotic-resistant pathogens in South African hospitals, which include:
- the selection of resistant mutants by antibiotic exposure;
- the transfer of genetic determinants of resistance between bacterial strains, and
- the clonal spread of resistant bacteria among hospitalised patients within and between institutions.

These mechanisms are fuelled by excessive and/or inappropriate antibiotic use and poor compliance with infection control standards. Such practices are enhanced by failure to implement antibiotic policies country-wide.

In South Africa the following patterns of antimicrobial resistance have recently been noted in surveillance studies undertaken in most major centres of the country:
- a dramatic increase in extended spectrum beta-lactamase (ESBL) production, particularly in Klebsiella and Enterobacter spp;
- an increase in carbapenem resistance, including multi-drug resistance in P. aeruginosa and Acinetobacter baumannii;
- an increase in multi-drug-resistant E. coli, and
- emerging resistance among Gram-positive isolates including an increased prevalence of methicillin-resistant S. aureus (MRSA) and emergence of vancomycin-resistant enterococci (VRE).

Inappropriate antimicrobial use

Antibiotic resistance is an inevitable consequence of the inappropriate use of antibiotics, and impacts every hospital to varying degrees. Risk factors for inappropriate use include:
- not using local epidemiological and antibiotic susceptibility data;
- use of broad-spectrum antibiotics (eg. vancomycin) when not absolutely necessary;
- treatment of contamination or colonisation rather than invasive infection;
- inappropriate surgical prophylaxis;
- excessive antimicrobial treatment (ie. continue antibiotics when infection is cured), and
- treating colonisation aggressively especially in patients simply colonised by Gram-positive bacteria such as coagulase-negative staphylococci (CNS) or Gram-negative bacteria such as Acinetobacter spp without any additional evidence of infection.

Trends in the antimicrobial management of nosocomial infections

It is generally accepted that initial appropriate empirical antibiotic therapy for nosocomial infections reduces mortality. Inadequate initial therapy, ie. not covering resistant Gram-positive and/or Gram-negative bacteria and/or fungal infections, is associated with a worse outcome; a delay of 24 - 48 hours (and even as little as six hours) can be associated with increased mortality. Therefore, to avoid this possibility, timely broad-spectrum empiric therapy must be utilised until the pathogen is identified. The dilemma and conflict of interest is that increased use of antimicrobial therapy with this practise (“getting it right the first time”) will inevitably lead to increase in resistance. Subsequently, several trends and possibly controversial strategies have emerged to balance bacterial and clinical efficacy with the emergence of resistance.

Antimicrobial de-escalation - “antibiotic streamlining”

The goal of de-escalation is to prescribe an initial antibacterial regimen that will cover the most likely pathogens associated with infection. Antibiotic therapy is then scaled down or de-escalated or tailored to a narrow spectrum once identity and susceptibility profiles are known. In addition, Gram-positive antibiotics are removed if a Gram-negative organism is cultured and vice versa. The same applies to anti-fungal therapy.

The choice of initial therapy should be based on local surveillance; the problem facing many hospitals, particularly ICUs, in South Africa is the fact that multiply-resistant bacteria are so prevalent that de-escalation to an antibiotic with a narrow spectrum is not always possible. However, if
no pathogen or a less resistant pathogen is identified, it should be mandatory to at least consider discontinuing antibiotic therapy or de-escalating to a narrower spectrum. This dictum needs to be tempered by the fact that in many cases, even critically ill cases with an obvious invasive infection, microorganisms are frequently not cultured.

- **The use of local epidemiology and antibiotic susceptibility patterns - “know your bugs”**
  
  Not using local data is a risk factor for inappropriate use. Initial empiric broad-spectrum treatment should be based on unit-specific antibiograms and in this regard there might be a role for weekly routine surveillance cultures. However, in this regard, the simple isolation of bacteria from surveillance cultures from patients in intensive care units (ICUs) without evidence of systemic infection, is not an indication *per se* for antibiotic treatment.

As an example of an ICU that used local data and to demonstrate the benefits thereof, Ibrahim *et al* implemented a clinical guideline to treat ventilator-associated pneumonia (VAP). ² *P. aeruginosa* and *S. aureus* were identified as the most common pathogens causing VAP in that unit and based on susceptibility patterns; a combination of vancomycin, and imipenem and ciprofloxacin would cover more than 90% of those pathogens. Treatment was given for only seven days unless signs and symptoms of active infection persisted. Following implementation of the clinical guideline, the initial antimicrobial treatment was more frequently appropriate than before the intervention (94.2% vs 48%, p < 0.001). The duration of antimicrobial treatment was statistically shorter during the after period compared with the before period (8.6 vs 14.8 days, p = 0.001). Furthermore, a second episode of VAP (with more resistant bacteria) occurred statistically less often among patients in the after period (7.7% vs 24%, p = 0.030).

- **Shorten duration of therapy**
  
  The optimal duration of treatment for confirmed nosocomial infections is currently not known. However, evidence suggests that shorter courses of antibiotic treatment would suffice. Dennesen *et al* demonstrated that maximal resolution of infection parameters in patients with VAP usually occurs after six to eight days of treatment. ⁷ Certain specific nosocomial infections may require more prolonged treatment, as described more fully below.

It is a well known fact that newly acquired colonisation and subsequent infection with more resistant bacteria occurs during the second week of therapy and as such that excessive antibiotic therapy has an adverse influence on outcome; antibiotics that are continued after an infection has resolved, are harmful in that they predispose to superinfection with more resistant bacteria. Decreasing overall duration of empiric antibiotic use can reduce the incidence of hospital-acquired superinfection with multiresistant bacteria or *Candida* spp and simultaneously reduce antibiotic pressure. Several recent studies serve to prove this:

- Utilising a “clinical pulmonary infection score” and restricting empiric antibiotic treatment for three days for patients with suspected VAP, Singh *et al* demonstrated that excessive antibiotic therapy had an adverse influence on outcome (antibiotics were randomly discontinued for those patients who were formally re-scored at three days and whose scores were inconsistent with pneumonia). ³ These patients had significantly fewer superinfections with antibiotic-resistant bacteria than did those with a more prolonged duration of empiric therapy. The 30-day mortality rate was 13% for patients treated for just three days versus 31% for those who received prolonged therapy (p = 0.06).
- An impressive recent prospective, randomised double-blind trial in 51 French ICUs comparing eight days vs. 15 days of treatment of VAP, demonstrated that compared with patients treated for 15 days, the eight-day group had neither excess mortality (18.8% vs. 17.2%) nor more recurrent infections (28.9% vs. 26%). ² More importantly, with recurrent infections, multiresistant pathogens emerged less frequently with the eight-day group (42.1% vs. 62%, p = 0.04).

From a practical point of view:

- If a response to a particular antibiotic is seen within 48 hours, treatment should be continued for another five to seven days after which it should be discontinued. Prolonged use beyond a week is therefore strongly discouraged.
- In contrast, it is reasonable to discontinue the antibiotic if no response is seen in 48 hours, to then re-culture the patient after source control is reviewed and to switch to another class of antibiotic. If septic markers worsen on an antibiotic, resistance should be considered and a change to another class also made.

- **Clinical application of pharmacokinetic and pharmacodynamic parameters**
  
  Nearly 20 years ago it was shown that when treating cases of VAP, a clear correlation existed between the lengths of time (T) that the serum concentration of the antibiotic exceeded the minimum inhibitory concentration (MIC) of the infecting pathogens (T>MIC) and the time to eradicate the pathogen. If the dosage was changed to achieve a longer T>MIC, the time to achieve bacterial eradication in these severely ill patients, was shorter. ⁷

In contrast to concentration-dependent antibiotics (eg. ciprofloxacin or levofloxacin) where an area under the inhibitory curve (AUC)/MIC ratio of less than 100-125 does not protect against the selection of resistant subpopulations in Gram-negative bacteria, for time-dependent antibiotics (eg. beta-lactams) data suggest that less than 80% time above MIC predicts failure to eradicate microorganisms, as well as likely emergence of resistance. ⁷

Furthermore, sub-inhibitory concentrations are more likely to select for resistance. Rather than using conventional administration, one possible solution might be to administer time-dependent broad-spectrum antibiotics in a continuous infusion over 24 hours in the case of vancomycin, cefepime, piperacillin/tazobactam or as a prolonged infusion over three to four hours in the case of carbapenems (the latter agents are unstable in solution after three to four hours). In the case of concentration-dependent antibiotics such as the aminoglycosides and dependent on toxicity data, a high single daily dose rather than multiple dosing should be considered.

- **Measures to reduce nosocomial infections**
  
  In the past not enough attention has been given to prevent infection. Accepted practices have included:

  - elevation of the head of the bed in ventilated patients;
One of the most recent developments in reducing mortality is intensive insulin therapy in critically ill patients. Van den Berghe et al performed a prospective, randomised, controlled study in 1548 patients over 12 months where sugar maintenance was kept between 4.5-6.1 mmol/L vs 8.3-11 mmol/L. Intensive insulin therapy reduced mortality from 8% with conventional treatment to 4.6% (p < 0.04), the greatest reduction in mortality involved deaths due to multi-organ failure with a proven septic focus; overall bloodstream infection was also reduced by 46%.

Furthermore, several “programmes” have recently been evaluated to reduce nosocomial infections. Implementation of the University of Geneva’s vascular access care programme reduced the overall incidence of nosocomial infections from 52.4 to 34 per 1000 patient days (35%; p < 0.0001); primary bacteraemia due to CNS was reduced by 88%. A prevention of VAP programme in five ICUs, called “WHAP the VAP” and described by Zack et al, reduced the mean rate of VAP episodes per 1000 ventilation days by 57.6%.

**Controversies in the antimicrobial management of nosocomial infections**

- **Combination versus monotherapy - “should antibiotics be combined?”**

A combination of beta-lactams and aminoglycosides is recommended by many scientific societies as standard treatment for Gram-negative infections, particularly for those associated with *Pseudomonas* spp. These recommendations were based on studies undertaken with combination versus monotherapy and the use of the older generation cephalosporins with or without aminoglycosides. However, there is no evidence that a combination of antibiotics increases efficacy or decreases resistance, particularly when therapy is undertaken with newer antimicrobial agents such as the 4th generation cephalosporins (ie. cefepime), beta-lactam/beta-lactamase inhibitor combination agents (ie. piperacillin/tazobactam) and the carbapenems. Controversy still currently exists with regard to whether mono- or combination therapy is optimal for pseudomonal infections, particularly in the critically ill patient.

A recent meta-analysis of 64 randomised studies of 7568 patients demonstrated no difference in mortality rate between patients receiving monotherapy vs combination therapy. Similarly, no differences were observed in patients with pseudomonal infections who were treated with either regimen. The rate of colonisation with multi-drug-resistant pathogens was also similar, while in contrast the rate of superinfections was lower in the monotherapy group. A significantly higher rate of adverse events was seen in the combination therapy group. In this analysis, limited data were available on the optimal therapy for pseudomonal infections. Some recent data suggest that optimal results for this pathogen may best be achieved with initial combination therapy that is then tailored to monotherapy based on microbiological results.

- **Antibiotic cycling - “should antibiotics be rotated?”**

By reducing antibiotic pressure and selection of resistant mutants, antibiotic cycling may impact on the prevalence of resistant organisms in a particular ICU or hospital. One of the recent studies tested the hypothesis that quarterly rotation of empirical antibiotics could decrease infectious complications from resistant organisms in a surgical ICU. For example, for pneumonia, the quarterly rotation schedule of empirical antibiotics included ciprofloxacin with or without clindamycin, piperacillin-tazobactam, a carbapenem and cefepime with or without clindamycin.

Compared to the one-year non-protocol use, rotation resulted in significant reductions in the incidence of antibiotic-resistant Gram-positive infections (7.8 infections/100 admissions vs 14.6/100, p = 0.0001), in antibiotic-resistant Gram-negative infections (2.5/100 vs 7.7/100, p = 0.0001) and in less mortality associated with infections (2.9 deaths/100 admissions vs 9.6/100, p = 0.0001). Furthermore, antibiotic rotation was an independent predictor of survival (OR 6.27, 95% CI 2.78-14.16).

Historical controls have been used in published studies and results could be due to changes in infection control practises. Therefore, further studies are needed to establish or confirm the role of antibiotic cycling in preventing or reducing antibiotic-resistant bacteria. The impact of other variables such as choice of regimen, impact of rotation intervals, single vs multiple drug rotations, effect of rotation in a single ICU and long-term effects of antibiotic rotation has yet to be determined.

A recent review of 11 articles on antibiotic cycling or rotation concluded that due to multiple methodological flaws and lack of standardisation, results of these studies do not permit reliable conclusions regarding efficacy of cycling. Until further studies are done the authors advised against routine implementation of cycling as means of reducing antibiotic resistance rates.

- **Collateral damage from antibiotic therapy - “should certain antibiotics be avoided?”**

“Collateral damage” is terminology used to refer to the ecological effects of antibiotic therapy in nosocomial infections, ie. the selection of drug-resistant bacteria and development of colonisation or infection with such organisms. Various recent epidemiological studies have assessed the risk of such damage:

- Cephalosporins: the results of these studies suggest that use of the 2nd and 3rd generation cephalosporins have been associated with the risk of the emergence and colonisation or infection with vancomycin-resistant enterococci (VRE), ESBL-producing *K. pneumoniae*, multi-resistant *Acinetobacter* spp and an increased incidence of *Clostridium difficile* infection.

- Fluoroquinolones: several case-control studies have shown that prior receipt of quinolones in the previous three months was associated with subsequent MRSA infection although there are little data on the relationship between prior quinolone use and colonisation or infection with VRE. From a Gram-negative point of view, it has been demonstrated that prior quinolone use is a risk factor for subsequent...
infection with quinolone-resistant, ESBL-producing bacteria in nursing homes, nosocomial *Acinetobacter* spp and multi-drug-resistant *P. aeruginosa* in ICU patients. Recent case-control studies also concluded that use of quinolones are a risk factor for *C. difficile* infections, although less commonly than several other antibiotics.

Based on emerging evidence, the use of 2nd and 3rd generation cephalosporins, particularly in ICUs, should be avoided. Quinolones represent an important option for treatment of *P. aeruginosa* infections but should probably not be used as monotherapy.

**Impact of biofilm production**

Many infections such as endocarditis, osteomyelitis, urinary tract infections, ventilator-associated pneumonia and device-related infections are caused by micro-organisms that colonise these sites by the production of biofilm. Biofilm is defined as a structured community of bacterial cells specialised for surface growth and enclosed in a polymeric matrix. Biofilm provides many benefits to infecting bacteria. This may include protection from immune cells and physical stress whilst the close proximity of bacterial cells enhances quorum sensing and genetic transfer.

Another benefit conferred relates to antibiotic resistance *in vivo* despite the fact that bacteria may be antibiotic sensitive *in vitro*. Biofilm bacteria particularly involved with device infections are therefore inherently antibiotic-resistant and may include pathogens like *P. aeruginosa* and coagulase-negative staphylococci. Several hypotheses exist for this phenomenon of reversible antibiotic resistance. These include that the biofilm matrix may create a diffusion barrier to the antibiotics and that some biofilm bacteria are metabolically inactive and therefore difficult to kill as microbial growth rate affects susceptibility to antibiotic killing. Recent evidence also indicates that biofilm phenotypes exist with changes in bacterial gene expression.

Antibiotic treatment alone in such instances would be inappropriate and debridement of chronic infected bone for example or removal and replacement of devices like central venous catheters could often suffice as treatment.

**Conclusion**

The inexorable increases in antibiotic resistance have led to calls for reduction in inappropriate antibiotic use. The process by which it is to be achieved is not clear and to date there has been no published evidence-based guidelines on interventions to optimise antibiotic prescribing in either the community or hospitals. Several possible strategies have been developed to deal with resistance problems but most measures rely on restrictive or punitive actions and are directed toward prescribers. No consensus exists regarding the measures or combination of measures that are likely to have maximum impact on prescribing rates or quality of care. Furthermore, not enough effort has been made to optimise antibiotic use through dosing and administration strategies, drug selection, duration of therapy, or strategies to measure anti-infective effects *in vivo*.

Until conclusive evidence is found to promote appropriate antimicrobial use, a systematic approach in selecting an antibiotic for nosocomial infections should include the following:

- What are the microbiological considerations?
- Which pathogens are likely to be encountered?
- What are the susceptibility patterns of these pathogens?
- What is the antimicrobial spectrum of the chosen antibiotic?
- What are the pharmacological considerations in the patient?
- What is the pharmacokinetics of the antibiotic - does it reach the site of infection?
- If an MIC is available, what is the pharmacodynamics - is the dose big enough?
- But foremost, is an antibiotic really necessary?

**References**

15. Paterson DL. “Collateral Damage” from cephalosporin or quinolones antibiotic therapy. *Clin Infect Dis* 2004; 38: S341-S345

**Antimicrobial resistance in nosocomial infections**

*South Afr J Epidemiol Infect* 2005; Vol 20 (2)
The diagnosis of hospital-acquired infections or sepsis is often difficult. The ACCP/SCCM Consensus Conference definition of infection refers to the presence of bacteria, viruses, fungi or parasites. Their definition of sepsis suggests that there should be proven or suspected infection in combination with two or more of the four features of the systemic inflammatory response syndrome (SIRS) reflected in Table 1. These non-specific features are not extremely helpful in the clinical situation as they are common to many hospitalised patients even in the absence of infection/sepsis. Consequently, attempts at proving the existence of an infective process are of paramount importance.

Table 1: Systemic inflammatory response syndrome (SIRS)

| Definition: Presence of two or more of the following clinical manifestations: |
| 1. Temperature less than 36°C or greater than 38°C |
| 2. Pulse rate greater than 90 bpm |
| 3. Respiratory rate greater than 20 per minute or hyperventilation as shown by a PaCO₂ of less than 32 mmHg |
| 4. A white blood cell count less than 4000/mm³ or greater than 12 000/mm³, or greater than 10% immature polymorphonuclear leucocytes |

The two questions that need to be answered initially are:
1. Is there an infection (with or without sepsis)?
2. If so, where is the infection?

Although often difficult, the diagnosis of an infection should be based primarily on a diligent review of the patient’s history and charts, and a thorough clinical examination. The awake, co-operative patient may help direct the clinician. Patients who are critically ill, HIV-infected, malnourished, immunosuppressed, very young or very old present a major challenge. Such patients do not always show the classical systemic response to infection, and may need to be investigated for infection/sepsis in the absence of the classical clinical features. Localised infection may also not manifest with systemic features.

Manifestations of sepsis are numerous and varied. Besides the defining features of SIRS, other features to consider include, but are not restricted to the following: hypoxaemia, hyperglycaemia or hypoglycaemia, lactic acidosis, thrombocytopenia, altered level of consciousness, azotaemia, oliguria, anaemia, disseminated intravascular coagulation, and cutaneous lesions.

Traditionally, fever has been regarded as the hallmark of infection. The definition of fever is arbitrary. Some sources define it as a core temperature >38.0°C, and others as two consecutive readings >38.3°C. A new onset of temperature ≥38.3°C is considered a reasonable trigger for investigation.

Numerous non-infectious causes of fever/inflammation may complicate the course of the hospitalised patient. Depending on the clinical situation, some of these, reflected in Table 2, need to be considered and excluded before the diagnosis of an infection is made.

Table 2: Non-infectious causes of fever/inflammation

1. Drug-related
   1.1. Hypersensitivity reactions, eg. antibiotics
   1.2. Local infection at administration site, eg. amphotericin B, potassium chloride and cytotoxic chemotherapies
   1.3. Malignant hyperthermia, eg. succinylcholine, inhalational anaesthetics
   1.4. Neurolept malignant syndrome (antipsychotic neuroleptic medications)
   1.5. Withdrawal syndromes, eg. alcohol, opiates
   1.6. Toxicity, eg. cocaine, Ecstasy
   1.7. Transfusion reactions

2. ‘Inflammatory’ states
   2.1. Collagen vascular diseases
   2.2. Fibroproliferative phase of ARDS
   2.3. Acute or chronic pancreatitis
   2.4. Acute myocardial infarction (Dressler’s syndrome)
   2.5. “Postpericardiotomy” syndrome
   2.6. Tumour lysis syndrome
   2.7. Thyroid storm
   2.8. Acute adrenal insufficiency
   2.9. Transplant rejection

3. Miscellaneous causes
   3.1. Subarachnoid haemorrhage
   3.2. Fat embolism syndrome
   3.3. Pulmonary embolism/infarction
   3.4. Deep vein thrombosis

Immunological markers have been suggested as useful adjuncts in the diagnosis of infections. Of these, C-reactive protein and procalcitonin have been widely studied. Current evidence suggests that both may be useful in diagnosing infections in a wide variety of situations. Procalcitonin is generally regarded as being more accurate. Serial measurements of both parameters appear more useful than absolute values, both in diagnosing infections as well as in evaluating patient response to therapy.

Having decided that infection/sepsis is present, or in the case of uncertainty, potential sites of infection need to be looked for.
Where clinical evidence is clear, directed investigation is necessary, eg. if pus is draining from a post-surgical abdominal wound, then surgical site infection should be suspected and the patient should be investigated and managed for this. However, the site of sepsis is often unclear. Consequently, a thorough investigative screen may be necessary to identify potential sources of sepsis. This constitutes a “septic screen” and may include the following:

1. **Blood cultures**
   Within the first 24-hour period of patient evaluation, two to three pairs of blood cultures should be obtained from peripheral sites by separate venipunctures after appropriate disinfection of the skin.4

2. **Respiratory tract secretions**
   Obtain a sample of lower respiratory tract secretions for microbiology. Expectorated sputum, induced sputum, tracheal secretions, or bronchoscopically obtained material can be used effectively.4

3. **Chest radiograph**
   A chest imaging study should be obtained. An erect portable antero-posterior chest radiograph is often most feasible.

4. **Intra-vascular catheters**
   The site of all intravascular cannulae should be examined for inflammation or purulence. The intravascular cannulae should be removed, the tips cultured, and new cannulae, if necessary, inserted at different sites.

5. **Urine specimens**
   Urine should be obtained for microbiology and culture to diagnose a urinary tract infection.

6. **Wound infections**
   Examine the surgical wound for erythema, purulence, or tenderness. If there is suspicion of infection, the wound should be opened. Gram stain and cultures should be obtained from any expressed purulence or material obtained from deep within the wound site.7

7. **Intra-abdominal infections**
   Where indicated, imaging studies may be necessary to exclude an intra-abdominal source of sepsis. Potential sites include pus collections, infected necrosis of the pancreas and acalculous cholecystitis. An ultrasound, despite its limitation of operator dependence, is a reasonable starting point. If this is not helpful, a CT scan of the abdomen must be considered.13 An exploratory laparotomy may need to be considered if investigative measures are unhelpful.

8. **Sinusitis**
   Patients with prolonged nasotracheal or nasogastric intubation are at increased risk of developing sinusitis.11 Where clinically indicated, imaging of the sinuses should be obtained. Plain radiographs, ultrasound, nasal endoscopy, CT scans or magnetic resonance imaging scans may be used to diagnose acute sinusitis. Of these, CT scans, if possible, appear to be the best.12 Puncture and aspiration of sinuses under sterile conditions may be both diagnostic and therapeutic.

9. **Stool specimens**
   *Clostridium difficile* should be suspected in any patient with fever and diarrhoea who received antibacterial agents or chemotherapy during the preceding three weeks.13 In such patients, stool specimens should be sent for evaluation. Stool cultures for other enteric pathogens are rarely necessary as these infections are rarely hospital-acquired.

10. **Central nervous system (CNS)**
   If altered consciousness or focal neurological signs are unexplained, lumbar puncture should be considered in any patient suspected of having an infection, provided there is no contraindication to lumbar puncture.6 CT scan of the brain, often required prior to lumbar puncture, may also identify other central lesions such as brain abscesses. Neuro-surgical patients with intracranial devices such as shunts or drains are at increased risk of developing CNS infections. Such patients may need removal of infected intracranial devices.

11. **Obstetrics and gynaecology**
   When gynaecological and obstetric sepsis is likely, these sites should be explored as possible sources of infection/sepsis. Puerperal endometritis or infection as a result of foreign bodies such as IUCDs should be considered. Imaging, eg. ultrasonography, looking for retained products of conception, endometrial sampling using eg. Pipelle®, and high vaginal swabs may be considered as part of the screen in at-risk patients.

12. **Infective endocarditis**
   Echocardiography demonstrating valvular vegetations confirms the diagnosis among patients with clinical and microbiological evidence of endocarditis.14

13. **Orthopaedic**
   Osteitis, septic arthritis and prosthetic joint infections secondary to bacteraemia may develop in the hospitalised patient. Radiography and aspiration of joints may be necessary to confirm these diagnoses.

14. **Pleural fluid**
   Pleural collections should be tapped for microbiological evaluation if infection is suspected. An infected haemothorax or empyema of the pleural space needs drainage.

Not all the investigations indicated above need be part of a “septic screen” at initial patient evaluation. Adopting a tiered approach, investigations marked No. 1 to No. 6 above may be considered essential parts of a “first tier” screen and thus performed as “first tier” tests, if applicable. The remaining investigative measures may be adopted as “second tier” tests pending the results of the “first tier” investigations, or they may form part of an initial screen as dictated by the clinical situation and severity of the patient’s illness.

These guidelines are not intended to be prescriptive nor exhaustive, but rather to guide the clinician to consider various sources of infection/sepsis that may not normally be considered. Routine, blind screening of all potential sources is not cost-effective. Each unit needs to tailor an approach based on factors such as the specific patient population, the specific clinical situations, the specific ward and expected pathogens.

This document also does not address the issue of therapy, either empiric or directed, as these decisions are entirely dependent on clinical evaluation, underlying disease and the patient’s condition. The goal of these guidelines is to promote
the rational utilisation of resources and to ensure efficient evaluation of the patient.

References

An overview of nosocomial pneumonia

C Feldman

Definition and incidence

A nosocomial infection is an infection acquired by a patient as a result of hospitalisation or contact with the hospital environment that was neither present nor incubating at the time of the patient’s visit or admission to hospital. Infections are generally considered to be nosocomial if acquired > 48-72 hours following hospital admission. Nosocomial pneumonia (NP) or hospital-acquired pneumonia (HAP) is defined as pneumonia occurring ≥ 48 hours after hospital admission that was neither present nor incubating at the time of admission to hospital.1,2 Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring in a patient undergoing mechanical ventilation that was neither present nor incubating at the time of intubation (occurring > 48 hours after intubation).3 Recently, the term “healthcare-associated pneumonia” (HCAP) has been included in the description of NPs and this entity includes all patients who have been hospitalised in an acute care hospital for two or more days within 90 days of the infection, resided in a nursing home or long term facility, received intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection or attended a hospital haemodialysis clinic.1,2

The common types of nosocomial infection encountered in any institution depend on a number of factors including the type of hospital or ward, the age, underlying illnesses and/or co-morbid conditions of the patient, the severity of illness of the individual cases, and the treatment instituted. In most hospitals urinary tract infections are overall the most common form of nosocomial infection, while NP or HAP is the second or third commonest cause.1,2 However, in areas such as the intensive care unit (ICU), NP predominates. NP is the most common cause of death among patients dying from a nosocomial infection. VAP represents some 80% of hospital-acquired pneumonias and features therefore most commonly in the reviews, guidelines and studies.2

Incidence

The incidence of nosocomial infections in hospitals varies between 0.5-10%. NP is more common in medical and surgical wards than in paediatrics or gynaecology, and is particularly high in the ICU. These infections are a direct cause of increased patient morbidity, mortality, length of hospital stay, and medical costs. HAP has been estimated to add five to nine days to the hospital stay of survivors and to have a crude mortality rate that may be as high as 70% or more.1 The reported incidence of VAP ranges between 7.8-68% (most commonly quoted incidence of between 8-28%).3

Sources of infection

There are three main sources of organisms that cause nosocomial infections. Most commonly, patients become infected through endogenous organisms. These organisms may have been carried by the patient into the hospital, or the patient may have become colonised by these organisms through contact with the hospital environment. Within 48-72 hours of admission to hospital, patients are colonised by hospital organisms, which increase the risk of infection with resistant organisms, even in the absence of pressures of antibiotic use. Two other sources of infection, which are much less common, are by direct contact spread from other patients or hospital staff, and through exogenous sources by contact with inanimate objects in the environment such as drugs, equipment and solutions.

Routes of infection

Organisms causing NP may enter the respiratory tract through various routes:2
a) aspiration of oropharyngeal contents, including bacteria colonising the upper respiratory tract (thought to be the commonest mechanism);
b) inhalation of airborne pathogens (a much less common route presently with optimum care of ventilator circuits and with the increased use of heat and moisture exchangers);
c) haematogenous route (possibly associated with bacterial translocation), and
d) extension from a contiguous site (occurring only in specific situations).

Pathogenesis of NP

A number of factors play a role in the development of NP. The major factors involved in the pathogenesis of the infection are bacterial colonisation of the upper respiratory and gastrointestinal tracts and subsequent aspiration of these oropharyngeal organisms into the lower respiratory tract.1,3 Other factors which may also contribute, although occurring much less frequently, include translocation of gastrointestinal bacteria, with haematogenous spread of enteric Gram-negative bacteria to the lungs.1

a) Colonisation

Colonisation of an epithelial surface is said to be an important precursor of infection in any particular site, and it has been shown that adherence of bacteria to the epithelium, or epithelium-associated structures is an important determinant of colonisation by many bacteria. Adherence takes place through the interaction of bacterial components (termed adhesins) and complementary epithelial structures (termed receptors). In healthy individuals several factors are present which help prevent respiratory tract colonisation by Gram-negative organisms (there is inherent “colonisation resistance”). In seriously ill patients many of the factors preventing colonisation are perturbed, and in addition,
aspects of treatment enhance both the colonisation process and the subsequent risk of development of pneumonia. Colonisation of the oropharynx and upper respiratory tract, the normally sterile trachea and the endotracheal tube in intubated patients is a source of microorganisms that may subsequently be aspirated into the lower respiratory tract causing HAP or VAP.\(^1,3\) Among factors enhancing respiratory tract colonisation are pre-existing pulmonary disease, institutionalisation, intubation, mechanical ventilation, corticosteroid and antibiotic use and malnutrition.\(^3\) Prior antibiotic treatment is one of the main factors related to oropharyngeal colonisation by pathogens that commonly cause NP. More recently, it has been recognised that dental plaque is an important source of oral bacterial colonisation that can harbour respiratory pathogens and the amount of plaque and its rate of colonisation have been found to increase in time in patients in the ICU setting and to be a potential reservoir of respiratory pathogens in institutionalised elderly.\(^4,6\) This finding suggests that improvements in oral hygiene in the institutionalised elderly and the ICU could be associated with a decreased incidence of HAP/VAP.\(^4,9\) Colonisation of dental plaque, as well as the interior of the endotracheal tube, is associated with biofilm formation, which encases the microorganisms and allows adhesion to abiotic surfaces and protection against antibiotic action.\(^3,9\)\(^1\)\(^2\)\(^1\)\(^7\)\(^8\) Embolisation of biofilm containing bacterial pathogens may occur from the endotracheal tube to the alveoli during suctioning, bronchoscopy and from airflow forces during mechanical ventilation.\(^3\)\(^9\)

Other possible reservoirs of pathogenic organisms are the sinuses and the gastrointestinal tract.\(^3\)\(^4\) Within 24-72 hours of ICU admission, the stomach and small bowel become colonised with Gram-negative bacteria, which may also serve to colonise the oropharynx through retrograde flow. Factors that may enhance this retrograde process include the supine position, and the presence of a nasogastric tube.

Two aspects of ICU practice may possibly enhance gastrointestinal colonisation with Gram-negative organisms, and be associated with an increased incidence of NP. These factors are the techniques of feeding and the type of stress ulcer prophylaxis used (if such agents are instituted).\(^3\)\(^5\) Factors that increase gastric pH may enhance gastric colonisation with Gram-negative organisms. While there has been some debate as to whether this enhances the risk of NP, a recent meta-analysis suggests that this may well be the case. Techniques of feeding may also be important. Continuous drip feeding may similarly be associated with increase in gastric pH, and subsequent problems of colonisation and infection. This needs to be counterbalanced by the recognition that although the pH effect may be lessened by bolus feeding, the latter may possibly enhance another component of disease pathogenesis, namely aspiration.

While most Gram-negative organisms colonise the oropharynx before reaching the lower respiratory tract, the one exception is *Pseudomonas aeruginosa* which has been shown to be able to colonise the trachea directly without prior oropharyngeal colonisation.\(^3\) Injury to the trachea (eg. by endotracheal tube) may enhance attachment and growth of this organism in the trachea.

The exact factors that allow colonisation to proceed to invasive infection are unknown. It is thought that many of the host “defects” that lead to colonisation may also allow the progression of colonisation to invasive disease.

**b) Aspiration**

The other major step in the pathogenesis of NP is aspiration of oropharyngeal organisms into the lower respiratory tract.\(^1\)\(^2\)\(^3\) Many aspects of the underlying disease process or therapy may enhance the risk of aspiration. It is important also to bear in mind that even the presence of an endotracheal tube with inflated cuff in a ventilated patient does not prevent aspiration into the lower respiratory tract. Subglottic secretions pooled above the tube cuff containing bacteria may readily enter the trachea by leakage around the endotracheal tube cuff. Other factors that may be important in the ICU in predisposing to aspiration include the supine nursing position, and various techniques of feeding, including placement of a nasogastric tube. In non-ventilated patients, factors that may predispose to aspiration include neurological disorders, head trauma, altered levels of consciousness, and sedation.

**c) Translocation**

Another route by which nosocomial pulmonary infections is said to occur occasionally is through translocation of bacteria across anatomically intact bowel mucosa.\(^3\) Subsequent pneumonia would occur through blood spread of these organisms. The importance of this mechanism has not been proven beyond doubt, but it certainly is less important than the other routes described above.

### Predisposing factors to NP

There are a number of risk factors that have been identified that may predispose to NP (Table 1).\(^3\)\(^4\) Specific risk factors for VAP that have been documented in various studies include: age ≥ 60 years, underlying chronic obstructive lung disease, coma or impaired level of consciousness, various therapeutic manipulation, intracranial pressure monitoring, organ failure, large volume gastric aspiration, prior antibiotic usage and therapy that raises the gastric pH (eg. the use of H\(^-\)\(_2\)O).

**Table 1: Factors predisposing to nosocomial pneumonia**

- **General factors**
  - Inadequate hand washing of staff
  - Advanced age
  - Obesity
  - Underlying systemic disease
  - Underlying lung disease
  - Altered level of consciousness
  - Immunosuppression
  - Colonisation
  - Aspiration
  - Lengthy hospitalisation
  - Surgery
  - Tracheostomy
  - Antibiotic therapy
  - Viral respiratory tract infection

- **Additional factors in the intensive care unit**
  - Intubation
  - Mechanical ventilation
  - Supine nursing position
  - Acute respiratory distress syndrome
  - Techniques of feeding
  - Stress ulcer prophylaxis
receptor antagonists and antacids) resulting in gastric colonisation, particular seasons (autumn and winter), more frequent ventilator tube changes, re-intubation, mechanical ventilation \( \geq \) two days, tracheostomy, and supine nursing position. Antibiotic therapy is an important risk factor for severe VAP that needs highlighting. Several studies have suggested not only that prior antibiotic therapy has an important ecological impact in the ICU, being associated with the selection of nosocomial infections with *Pseudomonas aeruginosa* and other resistant Gram-negative organisms, but also that it is the only independent factor shown on multivariate analysis to adversely influence the mortality of such infections.\(^\text{12}\)

**Microbiology**

Numerous studies have been undertaken documenting the common causes of NP. The usual microbial pathogens involved are different from those causing community-acquired pneumonia and are influenced primarily by three main factors:

- a) the time of onset of the pneumonia;
- b) the severity of the underlying illness and the infection, and
- c) the presence or absence of risk factors for specific pathogens.

Early onset HAP or VAP is most commonly defined as infection occurring within four days of hospitalisation or intubation, whereas late onset HAP or VAP is that occurring five or more days after hospitalisation or intubation.\(^\text{1}\) Early onset bacterial NP occurring during the first few days is more frequently due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus* and *Moraxella catarrhalis*.\(^\text{13}\) This category of pneumonia is therefore aetiologically more similar to community-acquired pneumonia. Late-onset bacterial pneumonia is more commonly due to methicillin-resistant *S. aureus* and aerobic enteric Gram-negative bacilli. The latter include *Enterobacter* spp, *Escherichia coli*, *Klebsiella* spp, *Proteus* spp, and *Serratia marcescens*. *S. pneumoniae*, *S. aureus* and the enteric Gram-negative bacilli are described in many of the guidelines for NP management as so-called “core pathogens” that must be considered as possible cause, and covered for, in all cases of NP.

*P. aeruginosa* and *Acinetobacter anitratus* infections are a particular problem in the ICU, being an important cause of VAP. These infections occur somewhat later in the ICU course. Specific risk factors for infections with these latter organisms include intubation, prolonged hospital or ICU stay, severe underlying illnesses, underlying structural lung disease, prior antibiotic use, high dose corticosteroid use and severe NP. Risk factors for multi-drug-resistant pathogens are shown in Table 2 and include previous antibiotic therapy, previous surgery, ICU admission, ventilatory support and coma.\(^\text{1}\)

Specific risk factors for *S. aureus* infections include coma, head trauma, neurosurgery, burns, diabetes mellitus and renal failure. Specific risk factors for anaerobic infections include thoraco-abdominal surgery, impaired swallowing, witnessed aspiration and dental sepsis. Elderly residents of long-term care facilities have a spectrum of pathogens that more closely resembles that of late-onset HAP or VAP. Some cases of bacterial NP are polymicrobial in aetiology (up to 50% or more of cases).\(^\text{1}\) Other pathogens that may also cause

<table>
<thead>
<tr>
<th>Micro-organisms</th>
<th>Approximate frequency (%)</th>
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<tr>
<td><strong>Gram-negative bacilli</strong></td>
<td>40 - 75%</td>
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<td><em>Pseudomonas aeruginosa</em></td>
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<tr>
<td><em>Acinetobacter</em> spp</td>
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<td><em>Enterobacter</em> spp</td>
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<td><em>Haemophilus influenzae</em></td>
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<tr>
<td><strong>Gram-positive cocci</strong></td>
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<td><em>Staphylococcus</em> spp</td>
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<td><em>Enterococcus faecalis</em></td>
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<tr>
<td><strong>Anaerobes</strong></td>
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<td><strong>Fungi</strong></td>
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<tr>
<td><em>Candida</em> spp</td>
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<tr>
<td><em>Aspergillus</em> spp</td>
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<td><em>Legionella</em> spp</td>
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<tr>
<td><em>Moraxella catarrhalis</em></td>
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Markers of severe HAP include the need for admission to ICU, and evidence of respiratory failure, rapid radiographic progression, severe sepsis with hypotension and presence of multiple risk factors. Markers of a severe infection include the presence of a respiratory rate > 30 breaths/minute, respiratory failure, sepsis, infection complications, cavitation on chest radiograph, and need for mechanical ventilation.

Risk factors for resistant pathogens include previous antibiotic therapy, previous surgery, ICU admission, ventilatory support and coma.

**Diagnosis of nosocomial pneumonia**

While many cases of NP occur in non-ventilated patients and are diagnosed clinically and on the basis of chest radiographic changes, the rate of NP is higher in mechanically ventilated patients.

Much has been written on the subject of diagnosis of NP in mechanically ventilated patients, and an ongoing heated
debate continues in the literature about the relative merits and de-merits of invasive diagnostic techniques for accurate diagnosis. Not all patients with fever and pulmonary densities and clinical manifestations suggestive of VAP have a pulmonary infection. Thus some workers have suggested that clinical judgement alone does not permit accurate diagnosis, and argue that invasive diagnostic techniques such as bronchoscopy with protected specimen brush techniques or broncho-alveolar lavage are required. These techniques are relatively invasive and expensive, and require a certain level of expertise. There is also little evidence that they have the ability to influence the outcome of VAP. At least one study in ICU has clearly documented that it is the initial, empiric antibiotic therapy, instituted at the onset of the pneumonia, which impacts positively on the outcome of the infection. Any subsequent changes in antibiotic treatment that occur once the results of initial invasive diagnostic testing become available 24-48 hours later have no influence on the prognosis. Also, there are many experts who believe that the diagnosis of VAP on clinical grounds may be as sensitive as other methods. For this reason the current guideline does not recommend routine invasive diagnostic testing for VAP in ICU patients.

Furthermore, since it is the initial antibiotic treatment that is by far the most important, many ICUs practice continuous surveillance of patient colonisation in the unit and with the onset of clinical features of pneumonia, institute empiric antibiotic therapy, based on the previous microbiological data obtained from the recent prior screening.

A new infiltrate developing in a patient with pyrexia and fever who has purulent secretions is often taken as indicative of pneumonia. Additional pointers that may indicate the presence of pneumonia include an increase in respiratory rate, unexplained tachypnoea or hypoxia, a change in the ventilatory mechanics of the patient on a ventilator, and a change in the volume, colour, character or flora of the sputum or respiratory tract secretions.

The most commonly used clinical definition of nosocomial pneumonia includes the following: New or progressive radiographic shadowing; Plus at least two of the following: Fever ($\geq 38.3^\circ C$) or hypothermia ($< 35^\circ C$); Leucocytosis ($> 12000/mm^3$) or leucopenia ($< 4000/mm^3$); Purulent respiratory secretions. A number of investigators have attempted to develop more sensitive indices to improve clinical judgement in the diagnosis of VAP. One such indicator system is the Clinical Pulmonary Infection Score (CPIS) of Pugin and colleagues, which attempts to assist in the diagnosis of NP using a combination of readily available clinical, bacteriological and radiological parameters (seven variables are included in the scoring system, namely temperature, blood leucocyte count, volume and purulence of tracheal secretions, oxygenation ($PaO_2/FiO_2$ ratio), pulmonary radiology and semi-quantitative cultures of tracheal aspirates).

Even if the NP is diagnosed on clinical grounds, without invasive diagnostic techniques, it still remains important to obtain a fresh specimen of respiratory tract secretions at the time of diagnosis, where possible from the lower respiratory tract (eg. through a sterile suction catheter in patients who are intubated) before initiating antibiotic treatment, even if surveillance is practiced. Blood cultures should also be taken and may be helpful in such cases. However, microorganisms are often not recovered by either of these diagnostic investigations. Antibiotic treatment should be appropriately tailored, once the culture results are obtained. Several units have investigated the use of improved sampling techniques, including techniques such as blind bronchoalveolar lavage which, although having increased diagnostic ability, are less invasive and perhaps more easily performed by the average intensivist.

Mortality

The overall mortality for NP, reported in the literature, ranges between 24-76%. In one study NP contributed to 60% of deaths from nosocomial infection. ICU patients with NP have a two- to 10-fold risk of death compared with patients without pneumonia. The overall “attributable mortality” for VAP in one study was 27%, and this figure rose to 43% when organisms such as *P. aeruginosa* or *Acinetobacter spp* were involved.

Treatment of NP

Antibiotic therapy should never be instituted for colonisation alone, which occurs in most cases as early as 12 hours, but should only be initiated once the presence of an active infection is diagnosed. It has been extensively documented that an important factor in the prognosis of sepsis, in general, and NP, in particular, is the appropriateness of the initial empiric antibiotic therapy. The early initiation of antibiotics (within 24 hours and preferably 12 hours) to which the causative organisms are sensitive is associated with the best outcome of various infections, including NP.

In the choice of empiric antibiotic therapy, consideration should be given to what antibiotics the patient has had in the recent past (in the past 90 days) and an agent from a different class should be used. Factors to consider in empiric therapy include:

- Whether the pneumonia is of “early” or “late” onset;
- The severity of illness of the individual patient, including a consideration of whether the patient is in or out of the ICU, and
- Whether there are any specific risk factors for infection with severe Gram-negative pathogens such as *Acinetobacter* and *Pseudomonas* spp.

In order to optimise the empiric antibiotic management of nosocomial infections, it is imperative for the attending doctor to be fully aware of the common pathogens most frequently isolated in any particular ward situation (the so-called “ward epidemiology”), as well as to be familiar with the usual microbial susceptibility patterns of the common isolates (so-called “microbial ecology”). This knowledge is facilitated by local surveillance studies.

In patients who are not in the ICU with an early and/or mild to moderately severe NP, and without specific risk factors for resistant pathogens such as *Pseudomonas* and *Acinetobacter* spp, initial antibiotic treatment should target the so-called core pathogens. This may be accomplished with one of the following agents:

- 3rd generation cephalosporin (eg. in regional centres outside the central academic and private sectors)
Since the outcome of most infections is directly related to the patients responding well to the antibiotics. For CAP, an aminoglycoside may be stopped after five to seven days in patients who have a lower risk of infection. The antibiotic described above, may be more appropriate and have a lower risk of infection. For more severe infections or when the infection is due to a more resistant organism, combination therapy, usually with the addition of an aminoglycoside to a beta-lactam or fluoroquinolone-containing regimen, may be associated with a lower 30-day mortality. The antibiotic described above, may be more appropriate and have a lower risk of infection. However, antibiotic therapy should always subsequently be tailored (“narrowed” or “de-escalated”) once the results of the microbiological testing become available. De-escalation therapy is often said to be important for the following reason: “Narrow is nice, if you can live with it, whereas broad is bad except when you need it.”

Duration of therapy
The general consensus is that treatment of NP, including VAP, has traditionally been longer than is required. The currently recommended treatment duration is five to seven days.

Prevention of NP
The various factors that can be attended to in an attempt to decrease the incidence of NP, and in particular VAP, are extensive. Most of these factors will be self evident when one re-examines the predisposing factors to these infections and an understanding of aspects of disease pathogenesis would lead to the implementation of logical preventive strategies for NP. Some of these techniques have not been shown to be of definite benefit and remain largely experimental (eg. selective digestive decontaminations), and others are still under research (eg. acidification of feeds). Table 4 shows some of the factors that may be addressed in an attempt to prevent NP in general and in particular measures for the specific prevention of VAP. Regular hand washing and the use of alcohol rubs are simple, effective and cost-effective measures to decrease the risk of nosocomial infections. Recently, an evidence-based clinical practice guideline for the prevention of VAP was recently published and concluded that the orotracheal route of intubation, change of ventilator circuit only with each new patient or with contamination, closed endotracheal suction systems, use of heat and moisture exchangers, and semi-recumbent nursing position were the most effective. Continuous subglottic drainage and kinetic beds could also be considered. However, one recent experimental study documented little benefit from continuous subglottic drainage and, in addition, there was significant evidence of trauma to the tracheal mucosa/submucosa at the site of aspiration. Strategies aimed at eradication of endotracheal tube biofilm and bacterial colonisation and improved oral care are more recent strategies suggested that may be associated with a decrease in VAP and/or HAP, respectively.

Conclusion
Nosocomial infections are the almost obligatory consequence of advanced technology in medicine. While many highly specialised techniques to prevent such infections are being recommended or are under investigation, our challenge remains to convince medical staff that simple techniques, such as regular and effective hand washing, improved mouth-care and oral hygiene in patients in the ICU and perhaps long-term care facilities and strict adherence to cross infection techniques may be just as important in the prevention of nosocomial infections.
### Table 4: Factors that may play a role in the prevention of nosocomial and ventilator-associated pneumonia

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Methods of prevention</th>
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<tbody>
<tr>
<td>Colonisation</td>
<td>Hand washing*</td>
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<tr>
<td></td>
<td>Aseptic techniques*</td>
</tr>
<tr>
<td></td>
<td>Stress ulcer prophylaxis (avoid gastric alkalinisation)</td>
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<tr>
<td></td>
<td>Appropriate enteral feeding techniques</td>
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<tr>
<td></td>
<td>Distal feeding</td>
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<tr>
<td></td>
<td>Acidification of feeds</td>
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<td></td>
<td>Overnight feed switch-off</td>
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<td></td>
<td>Judicious antibiotic use*</td>
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<tr>
<td>Aspiration</td>
<td>Subglottic aspiration**</td>
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<td></td>
<td>Semi-recumbent positioning of patient*</td>
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<tr>
<td></td>
<td>Distal feeding</td>
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<tr>
<td></td>
<td>Small-bore feeding tube</td>
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<tr>
<td>Translocation</td>
<td>Cardiovascular stabilisation</td>
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<tr>
<td></td>
<td>Early enteral feeding</td>
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<tr>
<td>Intubation</td>
<td>Oral endotracheal tube*</td>
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<td></td>
<td>Oral gastric tube*</td>
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<tr>
<td></td>
<td>Avoid unplanned extubation*</td>
</tr>
<tr>
<td></td>
<td>Aseptic tracheal suction*</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Less frequent tube changing*</td>
</tr>
<tr>
<td></td>
<td>Heat and moisture exchangers with bacteriological filters*</td>
</tr>
<tr>
<td>Topical antibiotic</td>
<td>Selective decontamination of the digestive tract (SDD)</td>
</tr>
<tr>
<td></td>
<td>Tracheobronchial tree antibiotics</td>
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<tr>
<td>Additional</td>
<td>Judicious antibiotic use*</td>
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<tr>
<td></td>
<td>Kinetic bed therapy</td>
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<tr>
<td></td>
<td>Mobilisation of tracheobronchial secretions</td>
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<tr>
<td></td>
<td>Immune reconstitution</td>
</tr>
<tr>
<td></td>
<td>Application of general infection control measures*</td>
</tr>
</tbody>
</table>

* Particular interventions that are of proven value and cost-effective

** Recent studies have suggested that this technique may be ineffective and moreover be associated with trauma to the trachea

### References


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Overview of nosocomial pneumonia

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Introduction

The urinary tract is the commonest site of nosocomial infections, accounting for 40% of infections. Sixty-six to 86% of these infections follow instrumentation of the urinary tract, particularly catheterisation. In the USA, each hospital-acquired urinary tract infection adds approximately $675 to the costs of hospitalisation. When bacteraemia develops, this additional cost increases to at least $2800, and patient mortality may be as high as 30%. Decreasing the inappropriate use of indwelling urinary catheters, using a closed drainage system, and ensuring that the catheter is removed as soon as it is no longer necessary, remain the main interventions in reduction of nosocomial urinary tract infections.

Definitions

The urinary tract is usually sterile except for the distal urethra.

Colonisation is defined as the presence of micro-organism/s in the urine without clinical manifestations (dysuria, fever, etc).

Urinary tract infection (UTI) is defined as invasive disease by microorganisms, inducing an inflammatory response and symptoms and signs such as fever > 38°C, urgency, frequency, dysuria without any other cause. Positive urinary culture is expected unless the patient has received antibiotics.

Nosocomial urinary tract infection (NUTI) refers to a UTI acquired in a hospital setting. In two-thirds of cases the bacteria causing these infections are endogenous.

Epidemiology

The risk of acquiring a UTI depends on the method and duration of catheterisation, the quality of catheter care, and host susceptibility. Reported infection rates vary widely, ranging from 1-5% after a single brief catheterisation to virtually 100% for patients with indwelling urethral catheters draining into an open system for longer than four days. Host factors which appear to increase the risk of acquiring catheter-associated UTIs include advanced age, debilitation, and the postpartum state.

Routes of infection

Microorganisms may enter the bladder of the catheterised patient and cause either asymptomatic bacteriuria or NUTI in several ways:

- At the time of catheter insertion where organisms may be pushed into the previously uninfected bladder, or following removal of the catheter.
- Extra-luminal colonisation of the catheter with ascension of organisms into the urinary tract. This route of infection becomes more evident after the first week of indwelling catheterisation as gastrointestinal tract bacteria migrate and colonise the perineal and meatal-urethral surfaces. Endogenous organisms are the ones that are most frequently associated with infection through the extra-luminal route.
- Intra-luminal colonisation of the catheter with ascension of microorganisms. Closed systems are designed to minimise intraluminal infection by preventing exogenous contamination. However, in practice, it is difficult to maintain a truly closed system since the collection bag must be emptied frequently. Such manipulations of the closed system by healthcare workers may allow cross-infection with organisms on the hands of personnel or from containers. Exogenous organisms are therefore most frequently associated with the intra-luminal route.
- Acquisition of infection via the lymphatic or haematogenous route is a proven, though minor, portal of entry.

Microbiology

Catheter-associated UTIs are caused by a variety of pathogens, including *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterococcus*, *Pseudomonas*, *Enterobacter*, *Serratia*, and *Candida*. Many of these microorganisms are part of the patient’s endogenous bowel flora, but they can also be acquired as a consequence of cross-infection from other patients or hospital personnel, as well as from exposure to contaminated solutions or non-sterile equipment. Regular hand washing by healthcare personnel, minimisation of manipulations of the closed drainage system, and strict aseptic practices are therefore all important strategies to decrease the risk of developing NUTIs. Urinary tract pathogens such as *Serratia marcescens* and *Burkholderia cepacia* have special epidemiological significance. Since these microorganisms do not commonly reside in the gastrointestinal tract, their isolation from catheterised patients suggests acquisition from an exogenous source.

The same organisms are responsible for asymptomatic bacteriuria and symptomatic UTI so it is impossible to differentiate between infection and colonisation by the organism involved. Common pathogens include:

- *Escherichia coli* (50% of infections)
- *Staphylococci*
  - *Staphylococcus aureus* (including MRSA)
  - Coagulase-negative staphylococci
- *Enterococci*
  - *Enterococcus faecalis*
- *Pseudomonas aeruginosa*

G Paget, S Naicker, O Perovic, Johannesburg Hospital.
It is important to have a profile of the commonest pathogens that cause NUTIs in a particular healthcare facility, as well as knowledge of their antimicrobial susceptibility patterns.

**Diagnosis**

**Non-catheterised patients**

In non-catheterised patients, the clinical and microbiological diagnosis of a NUTI is essentially the same as the diagnosis of community-acquired UTI, ie. significant bacteriuria associated with signs and symptoms of infection.

**Catheterised patients**

Diagnosis of UTI in catheterised patients is problematic in that many of the usual laboratory and microbiological parameters are unreliable indicators of infection in the presence of a catheter. The presence of an indwelling urinary catheter can mask or mimic the classical signs and symptoms of UTI, in particular significant bacteriuria, pyuria and suprapubic pain:

- Significant bacteriuria: catheters readily become colonised so catheter urines will frequently yield cultures (often mixed cultures).
- Pyuria: irritation from a catheter can result in pyuria despite the absence of infection. Conversely, even if infection is present causing pyuria, the altered pH in catheter urine and in urine following infection with certain organisms such as *Proteus* spp can lyze white blood cells so they may not be detectable.
- Suprapubic pain: the presence of the catheter can cause suprapubic pain in some individuals.

Clinical symptoms are the key to diagnosis of infection in catheterised patients.

Symptoms indicative of infection in immunocompetent patients include fever and haematuria.

**Laboratory diagnosis**

Because colonisation of catheters is common, specimens should only be taken from catheterised patients when the patient is febrile.Specimens should be taken from the catheter, not from the bag, which readily becomes colonised. Catheter urines frequently yield mixed cultures; while this does not necessarily mean that the infection is polymicrobial, it gives an indication of the types of pathogen that need to be covered by antibiotic therapy.

**Alternatives to indwelling catheters**

The suprapubic catheter as an alternative to permanent/implanted long-term catheterising has not proved its superiority.

The penile sheath as an alternative to permanent/implanted catheterisation is preferable when medically possible.

Intermittent catheterising is preferable to using indwelling catheters.

Suprapubic ultrasonography is preferable to catheterisation to measure the vesical residue.

**Treatment**

**Urinary colonisation**

This is not an indication for systemic antibiotic treatment, whether the patient is catheterised or not, diabetic, elderly, or presenting with urinary bladder dysfunction due to neurological disorders. Nevertheless, treatment of urinary colonisation may be necessary in some specific cases:

- When it leads to a risk of morbidity and mortality in: neutropaenic, immunosuppressed, and pregnant patients.
- In patients in a preoperative situation: surgery and urological explorations, implanting prostheses.
- In patients with a joint, vascular, or cardiac prosthesis, when undergoing invasive procedures.

**All bacterial NUTIs**

All bacterial NUTIs should be treated, irrespective of whether the patient has a urinary catheter or not.

**Antibiotic therapy**

The reasonable choice of antibiotic therapy depends on the nature of the micro-organism(s) and its (their) susceptibility to antibiotics. In case of severe parenchymatous infection (pyelonephritis, prostatitis, orchi-epididymitis), the immediate empiric treatment must rely on data from knowledge of local ecology. This treatment should be systematically reviewed after obtaining culture data. It is mandatory to choose an antibiotic with the narrowest possible spectrum, so as to prevent the selection of resistant bacteria.

**Antibiotic rationale**

The antimicrobial agent chosen should:

- always be active against Gram-negative organisms (particularly *Escherichia coli*) as well as Gram-positive organisms
- achieve high concentrations in renal parenchyma
- be renally excreted

Second-generation cephalosporins have the required broad spectrum and many of the potential pathogens are still sensitive to these agents. Other agents active against likely pathogens include the aminoglycosides and the fluoroquinolones.

**Empirical therapy**

Definitive antibiotic treatment will depend on blood and urine culture and sensitivity results but the following may be useful empirical choices. It is imperative that urine and, if necessary, blood cultures, are sent to the laboratory before antimicrobial therapy is initiated.

In patients who are not severely ill:

- amoxicillin/clavulanic acid or
- a fluoroquinolone such as ciprofloxacin or ofloxacin or levofloxacin or
- a second-generation or third-generation cephalosporin; a cephalosporin may be preferable in pregnant women, or
Patients can be switched to oral therapy with a fluoroquinolone such as ciprofloxacin, ofloxacin or levofloxacin if culture results support the change of regimen. The switch to oral therapy can be made when the patient has no nausea and vomiting, no fever and no evidence of sepsis. Once culture results are known, antibiotic therapy can be adjusted if necessary. Treatment for a minimum of seven days is required.

In patients who are severely ill with urosepsis:

- 3rd generation cephalosporin
- cefepime
- piperacillin/tazobactam
- amikacin (or other aminoglycoside), monitoring blood levels
- ciprofloxacin/ofloxacin/levofloxacin

Avoid fluoroquinolones in children and pregnancy and rather consider a 3rd or 4th generation cephalosporin.\(^{13,14}\)

If infection with an ESBL-producing microorganism is suspected, treatment with a carbapenem (eg. ertapenem) should be initiated. This is particularly likely to occur in elderly residents of long-term care facilities. Carbapenems may also be used as part of directed therapy based on microbiological testing.

**Length of treatment**

This depends on the site of infection. Treatment should be shorter for UTIs without parenchymatous infection or in patients without a urinary catheter, for a minimum of seven days. Pyelonephritis requires a 10-14-day treatment regimen.

**Device specific issues**

- Routine and programmed catheter change is not recommended.
- Lavage/irrigation (outside of urological procedures) is not recommended.
- Antibiotic-coated catheters have not proved their efficacy.
- Silver-coated catheters have not proved their efficacy.
- It is not necessary to instil antiseptics in urine bags.
- Adding an ‘antimicrobial’ to the lubricant when inserting the catheter is not necessary.
- Published data does not support superiority of silicone versus Foley’s type rubber urinary catheters for prevention of NUTIs.

For catheterised patients

- It is mandatory to use closed systems.
- Insertion of a permanent catheter must be performed under strict aseptic technique.
- Urine bags must be kept below the patient for gravity flow.\(^{\ast}\)

**References**

Nosocomial bloodstream infection

M Mer

Bloodstream infection (BSI) is a serious problem in many hospitalised patients and is referred to as being primary where there is no obvious source, or secondary, arising as a complication of infection elsewhere (such as pneumonia, urinary tract, skin and soft tissue, intra-abdominal, device-related, etc). Several of these entities are dealt with in greater detail in the context of this document.

The micro-organisms responsible include Gram-positive and Gram-negative bacteria and/or fungi. The most common Gram-positive organisms include *Staphylococcus aureus*, coagulase-negative staphylococci and enterococci whilst the most common Gram-negative organisms include *Enterobacter* spp, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp and *Acinetobacter* spp.

BSIs represent about 15% of all nosocomial infections and affect approximately 1% of all hospitalised patients. The incidence of BSIs has increased substantially over the past two decades and the impact on patient outcome is significant. BSI increases the mortality rate, prolongs hospital and intensive care unit (ICU) stay, and generates substantial extra costs.

A recently published large study spanning three years and evaluating close to 5 000 adult ICU admissions revealed a median time between ICU admission and development of a BSI of 7.4 days (range 3.9-14 days). The most commonly isolated organism was *Staphylococcus aureus* (18% of isolates), followed by coagulase-negative staphylococci (11%) and *Enterococcus faecalis* (8%). Antibiotic-resistant organisms were isolated in 12% and infections with more than one organism in 22% of cases.

A focus of infection could be identified in a third of cases, the most common being pneumonia, followed by vascular catheter-related and urine. Increased risk of developing an ICU-acquired BSI was associated with a higher APACHE II score and admission to a trauma or neurosurgical ICU. Development of an ICU-acquired BSI was associated with a significantly higher risk of death with 45% of patients who had a BSI dying compared with 21% of those without BSI.

The results relating to focus of infection are similar to those noted in the EPIC (European Prevalence of Infection in Intensive Care) study, the one difference being that BSI was most commonly noted to be associated with a central line, followed by pneumonia and urinary tract infection.

The principles involved in the management and therapy of BSIs include seeking a potential source of origin and, if present, institution of appropriate source control measures, use of appropriate antimicrobial therapy, and suitable supportive interventions and care. The importance of source control cannot be overemphasised.

Several studies have shown that approximately 50% of patients with nosocomially acquired BSIs, and up to 70% of those with fungaemia, receive inadequate initial therapy. Even after the final microbiological report is issued, 8-20% of patients with BSIs still receive inadequate antimicrobial treatment. Factors involved in the initial antimicrobial choice should include consideration of site of infection, environmental exposure together with a knowledge of prevalent and likely pathogens, and whether or not the patient is immunosuppressed. If empiric treatment is begun, this should subsequently be reviewed and, if necessary, amended.

References

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positive blood cultures on antibiotic therapy. *APMIS* 1995; **103**: 37-44


Intravascular catheter-related infection guidelines

M Mer

Introduction and background

Intravascular devices are an integral component of modern-day medical practice. They are used to administer intravenous fluids, medications, blood products and parenteral nutrition. In addition, they serve as a valuable monitor of the haemodynamic status of critically ill patients.

Over the past two decades the focus of research and development in this field has been on the physicochemical properties of catheters, looking at such aspects as improved catheter materials, tensile strength, rupture resistance, biocompatibility and the creation of catheter micro-environments hostile to invading organisms.

Intravascular devices have represented a major advance in terms of patient comfort and care, but with them has come the burden of complications, including a variety of local and systemic infectious complications. In general, intravascular devices can be divided into those used for short-term (temporary) vascular access and those used for long-term (indwelling) vascular access. Long-term intravascular devices usually require surgical insertion while short-term devices can be inserted percutaneously. The main focus of this guideline relates to short-term catheters.

Magnitude of the problem

Catheter-related infections (CRI) remain among the top three causes of hospital-acquired infections, with a mortality of up to 25%, and result in prolonged hospitalisation and increased medical costs. Central venous catheters (CVCs) account for an estimated 90% of all catheter-related bloodstream infections (CRBSI). Reported rates of bloodstream infection range from four to 30+ per 1 000 central catheter days.

Given the magnitude and seriousness of the problem of CRI, it is essential for healthcare workers to have a clear understanding of the diagnosis, pathogenesis, prevention and treatment of this problem and of new developments in the field. Most of these infections can be reversed with appropriate diagnosis and treatment, and many can be prevented.

Definitions for CRIs

Definitions relating to intravascular catheter sepsis have been put forward by various workers, but many have complicated matters and been confusing. This has in part related to the fact that definitions used for surveillance and research purposes have differed from those used for clinical diagnosis. The Centers for Disease Control and Prevention have suggested sensible definitions which incorporate both clinical and laboratory evidence of catheter sepsis. These should be universally used in the definition of intravascular catheter sepsis and are documented in modified form in Table 1.

Table 1: Definitions for catheter related infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Catheter colonisation</td>
<td>growth of $\geq 15$ colony-forming units (semiquantitative culture) or $\geq 10^7$ colony forming units (quantitative culture) from a proximal or distal catheter segment in the absence of local or systemic infection</td>
</tr>
<tr>
<td>Local infection</td>
<td>erythema, tenderness, induration or purulence within 2 cm of the skin insertion site of the catheter</td>
</tr>
<tr>
<td>Catheter-related blood stream infection</td>
<td>isolation of the same organism, i.e. the identical species as per antibiogram, from culture (semiquantitative or quantitative) of a catheter segment and from the blood of a patient with accompanying clinical symptoms and signs of bloodstream infection and no other apparent source of infection</td>
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</table>

Pathogenesis of CRIs

The skin around the insertion site is the most common portal of entry. Following placement, a fibrin sheath develops around the catheter which promotes the adherence of pathogens (biofilm layer). Skin organisms then migrate from the insertion site along the external surface of the catheter to colonise the distal intravascular tip and ultimately cause bloodstream infection.

Contamination of the catheter during its manipulation by medical and nursing personal is the second most common portal of entry for microorganisms. Less common causes include haematogenous dissemination from a distal infectious focus, administration of contaminated infusates as well as contaminated transducer kits, disinfectants and infusion lines.

Microbiological profile of CRIs (Table 2)

The microbiology of CRI reflects a predominance of skin organisms such as coagulase-negative staphylococci and *Staphylococcus aureus*. Contamination from the hands of medical and nursing personal is frequently responsible for infection with such organisms as *Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia* and *Candida* species. Emerging pathogens include species of *Enterococcus*, *Micrococcus*, *Achromobacter*, non-tuberculous mycobacteria and fungal organisms.
Use of the endoluminal brush allows samples to be taken via the orange leucocyte cytospin (AOLC) test. Newer diagnostic culture techniques include that of the culturing microorganisms from the catheter surface into a medium for sonication and vortexing methods, which involve extracting a catheter segment is regarded as significant. Quantitative techniques for culturing the catheter include the at > 15 colony-forming units from a proximal or distal catheter is the semiquantitative roll-plate method. Growth of more colonies are isolated from the blood drawn from the predominant. The diagnosis is suggested when five-fold or particularly useful where luminal colonisation is seen in less than half the cases. The laboratory components include culture of blood and the catheter. Contamination or purulence at the catheter insertion site is seen in less than half the cases. The laboratory components include culture of blood and the catheter.

Diagnosis of CRI

Establishing a diagnosis of CRI involves both clinical and laboratory components. The clinical features are generally non-specific and include fever, rigors, hypotension and confusion. If there is no apparent source of sepsis in a patient with an intravascular line (especially a central venous catheter) and if the sepsis appears to be refractory to antimicrobial therapy or is of abrupt onset or associated with shock, the possibility of CRI needs to be considered.

Fundoscopy should always form part of the clinical examination as focal retinal lesions are common in patients with CVC-derived candida infection, even when blood cultures are negative.

Contamination or purulence at the catheter insertion site is seen in less than half the cases. The laboratory components include culture of blood and the catheter.

Blood cultures are central to the diagnosis of CRBSI. Two to three 10 ml samples, ideally from separate peripheral venepuncture sites should be sent to the laboratory.

Paired quantitative cultures, which involve taking blood from both the catheter and a peripheral site, may be particularly useful where luminal colonisation is predominant. The diagnosis is suggested when five-fold or more colonies are isolated from the blood drawn from the vascular catheter as compared with the concurrent peripheral sample.

The most widely used laboratory technique for culturing the catheter is the semiquantitative roll-plate method. Growth at ≥ 15 colony-forming units from a proximal or distal catheter segment is regarded as significant.

Quantitative techniques for culturing the catheter include the sonication and vortexing methods, which involve extracting microorganisms from the catheter surface into a medium for culturing. Newer diagnostic culture techniques include that of the endoluminal brush and the Gram stain and acridine-orange leucocyte cytospin (AOLC) test. Use of the endoluminal brush allows samples to be taken via the lumen of the catheter whilst the catheter remains in situ. High sensitivities and specificities have been reported in the diagnosis of CRI with this technique. The technique does not require sacrifice of the catheter, but there is still a delay before culture results are known. There is also a concern that the process of brushing may lead to embolisation of infected biofilm. The place of the endoluminal, brush in clinical practice is still to be fully determined.

The Gram stain and AOLC test is a recently described method for rapidly diagnosing CRBSI without catheter removal. The test is performed on blood samples drawn from the CVC and has been reported to have high sensitivities and specificities. The method compares favourably with other diagnostic methods, particularly those that require the removal of the catheter and may permit early targeted antimicrobial therapy.

Preventive strategies for CRI

Strict adherence to hand washing and aseptic technique remains the cornerstone of prevention of CRI.

Several other measures have been reported to confer additional protection, some of which need to be considered in the preventive strategy. These include infusion therapy teams, maximal use of barrier precautions during catheter insertion, cutaneous antimicrobials and antiseptics, site of catheter insertion, types of catheter and catheter-site dressings.

Infusion therapy team

The presence of an infusion therapy team whose task is to insert and maintain catheters has been shown to decrease the rate of CRBSI by up to eight-fold and limit overall costs. Similarly, strict adherence to protocols for catheter insertion in the intensive care unit (ICU), wards and theatre is also beneficial in decreasing the rates of CRI.

Maximum sterile barriers

Careful hand washing together with the use of sterile gloves, a mask, gown and cap and a large drape have been associated with a greater than six-fold decrease in CVC-related sepsis. The use of this practice cannot be overemphasised.

Cutaneous antimicrobials and antiseptics

Given the important role of cutaneous microflora in the pathogenesis of CRI, measures to reduce cutaneous colonisation of the insertion site are of vital importance. For skin decontamination prior to catheter insertion in a three-group trial comparing the efficacy of treatment, 2% chlorhexidine gluconate was associated with a four-fold decrease in CRBSI as compared with 10% povidone-iodine and 70% alcohol.

Tunnelling of CVCs

This involves placing the proximal segment of the catheter under the skin at a distance from the point of entry to the vein. A lower rate of CRBSI has been reported in one study in critically ill patients. More data are required to support this observation.

Common organisms associated with catheter-related infections

- Coagulase-negative staphylococci
- Staphylococcus aureus
- Candida species
- Acinetobacter species
- Pseudomonas aeruginosa
- Stenotrophomonas maltophilia
- Klebsiella species
- Enterobacter species
- Serratia marcescens
- Citrobacter freundii
- Enterococcus species
- Bacillus species (especially JK strains)

Table 2: Common organisms associated with catheter-related infections

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Silver-chelated subcutaneous collagen cuffs

These cuffs may be attached to percutaneously inserted CVCs and are designed to act as both a mechanical barrier to the migration of microorganisms and an antimicrobial deterrent (through the effect of silver ions).

They have been shown to lower the risk of catheter colonisation and CRBSI in critically ill patients. The anti-infective effect is short-lived, however, as the collagen to which the silver ions are chelated is biodegradable. Other drawbacks include cost and the need for specialised training.

Antiseptic hubs

These have been designed to protect against hub colonisation. A four-fold decrease in catheter-related sepsis has been demonstrated with their use.

A major limitation, however, is that protection is only conferred against organism migration along the internal surface of the catheter. They do not protect against the migration of skin organisms along the external surface.

Dressings

There has been an ongoing debate concerning the best method of catheter dressing. This has essentially revolved around the relative merit of gauze versus transparent firms. In a meta-analysis of catheter dressing regimens, CVCs on which a transparent dressing was used were associated with a significantly higher incidence of catheter tip colonisation but a non-significant increase in CRBSI.

Treatment principles of CRI

Treatment depends on the stage of infection and the pathogen. As a general rule, if CRBSI is suspected, the catheter must be removed and replaced only if necessary.

Most of the infectious complications are self-limited and resolve after removal of the catheter. Indications for antibiotic therapy include persistent sepsis, despite catheter removal, evidence of septic thrombosis of the great veins, clinical or echocardiographic evidence of endocarditis, metastatic foci of infection, underlying valvular heart disease (especially prosthetic valves) and an underlying immunosuppressed state.

In terms of specific pathogens and CRBSI, Staphylococcus aureus and Candida species require special mention. In the setting of uncomplicated Staphylococcus aureus CRI, the catheter should be removed and at least two weeks (and preferably four weeks) of parenteral antibiotics given. There is a high relapse rate if given for a shorter duration.

Systemic antifungal therapy (together with removal of the catheter) should be given in all cases of catheter-related candidaemia in view of the potentially significant sequelae. Amphotericin B and fluconazole (except for fluconazole-resistant organisms such as Candida glabrata and Candida krusei) for at least 14 days have been shown to be equally effective. Newer antifungal agents may also be considered.

Specific catheter types and infection

Specific catheter types that will be reviewed include short peripheral intravenous catheters, peripheral arterial catheters, central venous catheters, pulmonary artery catheters and peripherally inserted central venous catheters.

Short peripheral intravenous catheters

These remain the most commonly used intravenous device. There is a significant risk of contamination 72-96 hours after insertion. The insertion site should be upper extremity or external jugular vein. A greater risk of infection with lower extremity sites and with cutdowns exists.

Peripheral arterial catheters

These catheters are associated with less infection than pulmonary artery catheters (PACs), CVCs and short peripheral catheters. This may be explained by high arterial flow around the catheter, which probably decreases the adherence of microorganisms.

Central venous catheters

CVCs account for an estimated 90% of all CRBSI. Non-tunneled (percutaneously) inserted CVCs are the most commonly used catheters.

A host of risk factors for CVC-related infections have been reported, including duration of catheterisation, location of the catheter (internal jugular reportedly having a higher rate of CRI than the subclavian vein), the presence of sepsis, type of dressing, multi-lumen catheters (increased frequency of manipulation), less stringent barrier precautions during placement, experience of personnel inserting the device and the administration of parenteral nutrition.

The duration of central venous catheter use has remained controversial. As a consequence, scheduled replacement remains widely practiced. The duration of catheterisation has been shown to be a risk factor for infection in several studies. Despite the controversy, no catheter should be left in place longer than absolutely necessary. Over the past few years, antimicrobial impregnated catheters have been introduced in an attempt to limit CRI and increase the time that CVCs can safely be left in place. A recent meta-analysis concluded that chlorhexidine-silver sulfadiazine CVCs appear to be effective in reducing CRI.

Recently published guidelines have, however, been vague and non-specific with respect to the role of antimicrobial impregnated, catheters and when they should be considered for use. A further concern about the use of these catheters relates to the possible development of antimicrobial resistance and, where used, a continued surveillance for resistance is required.

A recently completed randomised prospective double-blind study in a multidisciplinary ICU and spanning approximately 35 000 catheter hours has addressed many of these issues. This study compared a 14-day placement of standard triple-lumen versus antimicrobial-impregnated CVCs on the rates of CRI. The study demonstrated no

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**Intravascular catheter-related infection**

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difference in CRI rates between the two types of catheter, and that standard CVCs could safely be left in place for 14 days (together with appropriate infection control measures). In this study, the use of parenteral nutrition was not noted to be a risk factor for CRI and there was no difference in infection related to catheter insertion site (internal jugular versus subclavian vein).

A recommended protocol addressing the insertion and maintenance of CVCs is shown in Table 3.32,33

**Table 3: Protocol for insertion and maintenance of central venous catheters**

- Clean the skin around the insertion site over a wide area by rubbing for two minutes with sterile gauze or cottonwool soaked in a chlorhexidine gluconate-containing solution. Sterile gloves must be worn.
- The doctor, wearing a mask and cap, scrubs up (using a chlorhexidine gluconate-containing scrub solution) and then dons a sterile gown and gloves.
- The doctor then cleans the area again and drapes widely to include the patient’s head, neck, chest, limbs and torso down to the pelvis. Only the portion necessary for catheter insertion should be left exposed.
- The “flush” (heparin 1 000 iu 19 ml sterile saline) is drawn up avoiding any contamination by the doctor after cleansing of the stopper on the heparin container. The doctor draws up the “flush” with a sterile syringe needle, while the assistant holds the vials.
- Once the line has been inserted, a sterile piece of gauze soaked in a chlorhexidine gluconate-containing solution is applied over the insertion site and adjacent area for approximately 30 seconds.
- The area is then dried with sterile gauze and an adhesive gauze dressing with a central non-adherent pad applied.
- The dressings are changed daily and the insertion site inspected and cleaned in a sterile fashion. Cleaning includes removal of old blood, clots, exudates and crusts and the application of a chlorhexidine gluconate-soaked piece of sterile gauze to the insertion site for approximately 30 seconds, before drying and dressing the area.
- Any signs of local infection (red, hot, swollen, painful, purulence) must be reported.

**Pulmonary artery catheters (PACs)**

Varying rates of infection have been reported with PACs (Swan-Ganz catheters) but most are similar to CVCs. Where higher percentages have been reported, this has been attributed to the number of manipulations performed. The “Hands-Off Catheter” in which the catheter is enclosed in a contamination-proof shield enabling the doctor to prepare, test and insert it without exposure to external contamination, has been associated with a decrease in systemic infection.58 Most PACs are heparin-bonded which reduces catheter thrombosis and microbial adherence.59 These catheters may be left in place for up to seven days if necessary,55,60 by which time the patient frequently no longer requires this form of catheter. With the increasing popularity of non-invasive haemodynamic monitoring devices PACs are being less frequently used.

**Peripherally inserted central venous catheters (PICCs)**

PICCs provide an alternative to subclavian or jugular vein catheterisation and are inserted into the superior vena cava or right atrium via the cephalic and basilic veins of the antecubital fossa. As compared to other CVCs, they are associated with few mechanical complications, an apparent lower rate of infection and decreased cost.62,63 The duration of time that those catheters can be left in place safely has not been determined, although they have been used successfully for extended periods.

**Guidewire exchanges**

A recent meta-analysis of CVC replacement strategies revealed that guidewire exchanges were associated with greater risk of CRI but fewer mechanical complications than new-site replacement.62 If guidewire exchange is used, meticulous aseptic technique is necessary. The procedure should not be performed in the setting of confirmed or clinically suspected sepsis. In general, guidewire exchanges are not recommended unless vascular access represents a problem.

**Recommendations regarding the insertion, maintenance and use of intravascular devices**

The basic principle revolves around strict adherence to aseptic technique at all times (insertion, maintenance use).

Recommendations for replacement of intra vascular catheters:
- Standard central venous and acute haemodialysis catheters after 14 days
- Peripheral venous catheters after three to four days
- Arterial lines after 30 days unless removal is indicated beforehand

**Additional recommendations to limit infection**

- Lines used for the administration of blood products must be replaced within 24 hours.
- Lipid-containing parenteral nutrition solutions should be completed within a 24-hour period.
- Parenteral nutrition must be administered via a single dedicated port with the administration line being replaced at 24-hour intervals (performed as a sterile procedure).
- Administration sets such as those used for the delivery of inotropes and antibiotics should be replaced at 72-hour intervals, or before if clinically indicated.
- The day on which lines are changed should be clearly noted on the ICU chart or in the medical records.
- Bridges and their attached lines, transducers and continuous flush devices can be replaced at seven day intervals, provided there is strict adherence to aseptic technique.
- Aseptic technique also extends to care of ports and caps attached to intravascular devices and includes the spraying of a chlorhexidine gluconate-containing solution following manipulations.

**Conclusion**
Intravascular CRI remains a major problem. Stringent adherence to aseptic technique and infection control measures remain the cornerstone of prevention.

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Nosocomial intra-abdominal infection

DC Grolman, G Richards

Introduction

Peritonitis may be primary, secondary or tertiary and it may be community-acquired (CA) or nosocomial. Primary peritonitis, the entity whereby spontaneous infection of the peritoneum with *Streptococcus pneumoniae* occurs, does not occur as a nosocomial phenomenon. Tertiary peritonitis which is defined as ongoing intra-abdominal sepsis, despite apparently adequate surgical intervention, can occur either as a consequence of nosocomial or CA sepsis and has a high mortality. The term ‘nosocomial infection’ is designated to describe infections acquired in-hospital and are defined as “infections which become evident >48 hours after admission”. Nosocomial infections are more frequently caused by organisms which are resistant to many antimicrobial agents. Intra-abdominal infections include diffuse peritonitis, localised organ infection, localised multiple or diffuse abscesses, and combinations of these clinical conditions.

Nosocomial intra-abdominal infections (IAIs) may be post-operative (PO) or non post-operative (NPO). NPO nosocomial infection usually occurs in the elderly and in patients whose immunity is compromised. This includes patients with diabetes mellitus, AIDS, cardiac failure, respiratory insufficiency, renal or hepatic dysfunction, and those on chemotherapy or corticosteroid therapy. The aetiology of NPO nosocomial IAI is similar to that of secondary peritonitis, ie. CA IAI, and common causes are perforated peptic ulcers, ischaemic colitis, pancreatitis and cholecystitis, although appendicitis and diverticulitis also occur. Acute cholecystitis and typhlitis which occur only rarely in the community are found significantly more frequently in hospital. Acute cholecystitis usually occurs in patients who have not been fed enterally for prolonged periods of time and who are on total parenteral nutrition and may be the result of vascular insufficiency to the gallbladder and/or sludging of the biliary system, secondary to failed enteral feeding or increased pigment load (haemolysis, haematoma resorption, etc). Typhlitis occurs in patients on chemotherapy with neutropenia and is frequently associated with perforation.

PO nosocomial IAI generally occurs as a result of contamination of the peritoneal cavity during or after surgical intervention. The source of these infections is predominantly gastro-intestinal, but may also be gynaecological, urological or hepatobiliary. Contamination that occurs at the time of surgery is usually due to inadequate bowel preparation or an inability to prepare the bows, such as occurs in emergency operations for trauma or in cases of intestinal obstruction or ischaemia. Contamination that occurs post-operatively is usually as a result of the breakdown of intestinal suturing sites. Causes here include ischaemia, distal obstruction, malignancy, impaired healing due to immunocompromise or malnutrition, and poor surgical technique. Dehiscence or breakdown of gastrointestinal anastomoses and repairs may occur as a consequence of following other causes of nosocomial IAI or in circumstances where there has been inadequate source control. Device-associated IAI is well known. It usually occurs in association with peritoneal dialysis (PD) catheters, but has also occasionally been seen with ventriculo-peritoneal shunts and shunts for ascites and portal hypertension.

Risk factors for treatment failure and death in intra-abdominal sepsis

- Advanced age
- Concomitant serious disease
- Poor nutritional status
- Immunocompromise
- Associated malignancy
- Delay to definitive surgery
- Inadequate source control
- Nosocomial onset

Microbiology

Organisms cultured in nosocomial IAI are generally the same as those found in CA IAI. The most common organisms encountered are Gram-negative bacilli (such as *Escherichia coli* and *Klebsiella*), enterococci and anaerobic bacteria (such as *Bacteroides* and *Fusobacterium*). However, these organisms are much more frequently resistant to antibiotics commonly used for CA infections. Infections with bacteria found almost exclusively in the nosocomial setting, such as staphylococci and *Acinetobacter* spp, are also frequent. There is, in addition, a higher prevalence of fungal IAI, in particular *Candida* spp.

Commonly encountered resistant organisms

- Extended spectrum beta-lactamase producers (ESBLs). These are usually *Klebsiella*, *Enterobacter* and *E. coli*.
- Enterococci, including those which are glycopeptide-resistant although these are infrequent in SA (VRE and VREF).
- *Pseudomonas aeruginosa*.
- *Staphylococcus aureus*, especially those resistant to cloxacillin (MRSA).
- Coagulase-negative staphylococci (CoNS).
- *Candida* spp.
- Device-associated infections are frequently due to resistant *S. aureus*, CoNS, *Enterococcus faecalis*, *Enterococcus faecium* (including glycopeptide-resistant
strains), ESBL producers and fungi.

Risk factors for infection with resistant organisms

- Prolonged pre-operative hospital admission.
- Pre-operative antibiotics for more than two days.
- Patients with frequent exposure to antibiotics (so-called healthcare-associated patients).
- Diabetics.
- Cystic fibrosis patients.
- Chronic obstructive airways disease patients.
- HIV patients.
- Patients from long-term care facilities, ie. old age homes, frail care facilities, step-down facilities, rehabilitation centres.
- Need for recurrent laparotomies.

Treatment of nosocomial intra-abdominal infections

Surgery

Surgery remains the mainstay of the treatment of nosocomial IAI, as with CA IAI. Source control is the cornerstone in treating these infections successfully and failure to achieve this is associated with a very high mortality.

Relook laparotomy is no longer controversial, but in fact mandatory in cases of diffuse peritonitis or multiple intra-peritoneal abscesses. Extensive evidence now exists to support the routine re-opening of the abdomen for inspection, lavage and drainage. Relook laparotomies should be performed every 48-72 hours for septic abdomens; however, in cases where packs have been left in the abdomen or where mesenteric ischaemia is suspected, relook should occur as early as 24 hours. Relooks should be continued until at least one negative laparotomy is performed. Failure to relook such patients would constitute medical negligence.

Surgery for intra-abdominal sepsis

The following are the objectives of surgery in these patients:
- drainage of pus collections,
- debridement of septic and necrotic tissue,
- specimen collection for culture and sensitivity,
- irrigation, and
- prevention of further contamination:
  - source control,
  - faecal diversion with exteriorisation of stomas,
  - drainage/lavage abdominal techniques,
  - open-abdomen techniques, eg. sandwich, Bogota bag, and
  - relook laparotomy

Antimicrobial therapy

Antibiotic therapy should be commenced empirically based on knowledge of the commonly encountered bacteria in this situation, as well as awareness of the particular surveillance data of one’s own hospital, bearing in mind the prevalence of certain organisms and their antimicrobial sensitivities. The general principle that antibiotics should be used sparingly applies. One should use the narrowest spectrum antibiotics possible and monotherapy where possible. This needs to be balanced against the increasing evidence from the literature, which clearly shows an increased mortality, should there be a delay in commencement of antibiotics or if the regimen used

is found to be inappropriate. Bare et al found a doubling in the mortality rates in a large retrospective analysis comparing patients deemed to have received appropriate versus inappropriate therapy (12% vs 23%) in patients with IAI. Sendt et al showed an almost four-fold increase in the number of patients requiring re-operation (3% vs 11%) when initial antibiotic therapy was found to be inappropriate. Not surprisingly, his group also showed a more than doubling of the incidence of patients requiring a second antibiotic regimen (12% vs 27%). Burke et al showed that initial inappropriate antibiotic therapy was associated with the need for more prolonged antibiotic administration. Davey et al showed in their study that inappropriate antibiotic therapy initially, almost doubled the final average cost of hospitalisation.

Where possible, therapy should be culture-driven. Prior to culture results, therapy should be commenced with a broad spectrum agent or multiple agents, to cover all commonly occurring pathogens, bearing in mind your individual unit’s antibiotic resistance patterns. On receipt of the culture results, therapy should be de-escalated to the narrowest spectrum possible, and superfluous agents stopped. Repeated cultures should be performed at subsequent relook laparotomies.

Duration of therapy should be guided by clinical response. Shorter courses of antibiotics are now advocated, with no evidence having been shown that therapy beyond five to seven days is beneficial. Evidence, however, does exist that prolonged course therapy increases bacterial resistance.

If the clinical response is not optimal, always review source control. This is also the case if repeated cultures grow the same organisms, especially if these appeared sensitive to the patient’s antibiotics regimen.

There is also emerging evidence that antifungal preventative therapy may be beneficial. This has been conclusively shown in cases of necrotising pancreatitis. There is also proven benefit for antifungal prophylaxis in complicated IAI, ie. those with delayed initial surgery, those with anastomotic dehiscence, those requiring repeated relook procedures and those requiring multiple courses of antibiotics.

Antibiotic therapy for nosocomial IAI

- Therapy should, as far as possible, be culture-directed.
- Repeated cultures should be taken at each relook operation.
- Empircic therapy should be based on the most likely pathogens. The following factors are relevant:
  - site of origin of sepsis,
  - knowledge of your unit epidemiology,
  - concomitant medical pathologies, especially allergies, liver dysfunction and renal failure, and
  - previous antibiotics.
- Considerations in determining appropriate antibiotic therapy are:
  - usually requires broad spectrum or multiple agents,
  - spectrum of activity of antibiotics used,
  - timing of therapy (early),
  - dose and dosing interval - monitor levels where possible,
  - drug interactions and tolerability,
  - prior antibiotic treatment in the past two months, and
- de-escalate therapy where possible.

**Currently recommended antibiotic regimens**

The following antibiotics are currently advocated for use in nosocomial IAI. This represents the opinion of the authors, in consultation with the Nosocomial Infection Guideline Committee as stated in this publication, and a panel of expert specialists. It is based on the current incidence and sensitivity reports of microbiological laboratories in the government and private sectors of South Africa:

- levofloxacin or ciprofloxacin
- cefepime
- piperacillin/tazobactam
- ertapenem
- imipenem/cilastatin or meropenem
- teicoplanin or vancomycin
- metronidazole or clindamycin

Initial therapy should target Gram-negative bacilli and anaerobes where relevant. The fluoroquinolones, piperacillin/tazobactam or cefepime are usually appropriate, in combination with metronidazole where indicated. However, anaerobic infections are far less frequently encountered than with CA infection. Additional anaerobic cover is not necessary with the carbapenems or with piperacillin/tazobactam. These agents are not recommended if a strong likelihood exists that the infection may be due to an ESBL-producing pathogen. In this case ertapenem or another of the carbapenems is preferred; however, the latter should be reserved as far as possible for the non-fermenters *Pseudomonas aeruginosa* and *Acinetobacter*. Should there be a significant chance that the infection is due to a pseudomonal infection, an aminoglycoside or quinolone has been traditionally added to the carbapenem. However, there is no evidence to support this practice.

A glycopeptide (vancomycin or teicoplanin) should be added empirically, should there be a significant chance of staphylococcal infection (MRSA or CoNS).

In the scenario of nosocomial IAI, where cultures reveal an isolated enterococcal infection, this should always be treated. These organisms are resistant to quinolones, cefepime and ertapenem. Imipenem, meropenem or piperacillin/tazobactam may be used. However, frequently the only agents that are effective are the glycopeptides. Linezolid and dalfopristin/quinapristin should be reserved for VRE and vancomycin-resistant *E. faecium* (VREF) infections, respectively, but may be used as second line therapy for staphylococcal infection, which does not respond to glycopeptide therapy.

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Risk factors for surgical wound infection

Bacteria may produce toxins which increase their ability to invade their host. In addition, they may produce a biofilm, which prevents the host's defences from reaching them.

Infection usually occurs after contamination of the surgical site at the original surgery. Occasionally there may be seeping from a distant site to the incisional site, eg. haematogenous spread to a haematoma during an episode of bacteraemia, contamination of the operative site during another procedure (eg. needle aspiration) or via a drain site.

Usually, it requires a significant inoculum of bacteria to establish a surgical site infection, that is >100,000 organisms per gram of tissue. With more virulent organisms, eg. staphylococci or when foreign material is left in the wound site, only 100 organisms may be adequate to begin infection. Bacteria may produce toxins which increase their ability to invade their host. In addition, they may produce a biofilm, which prevents the host's defences from reaching them.

Introduction

Surgical site infections may be divided into organ/body cavity infections and skin/soft tissue infections (SSTI). This article will cover nosocomial guidelines for superficial surgical wound infections, ie. infections of the skin, skin-related structures and soft tissues. SSTIs may be further divided into those which are truly superficial, ie. involving only the skin and subcutaneous tissue; and deep SSTIs which also involve fascia and muscle.

These guidelines were specifically mandated to concentrate on nosocomial infections. However, when one is discussing surgical site sepsis, it is all in reality nosocomial.

Superficial SSTI occurs by definition within 30 days of a surgical operative incision. It is characterised by pain, tenderness, swelling, erythema and purulent drainage from the wound site. Deep SSTI is defined as sepsis in the surgical site as above, but involving the muscle and/or fascial layers, with or without superficial extension as well. It also classically occurs within one month of the operation, but may present as late as one year later, in the case of implants or prostheses having been inserted. These deeper infections may present as those superficial SSTI mentioned above, or may be more insidious. They may be found on investigation for a septic focus, without external signs. Occasionally, they are found on radiological investigation or incidentally at re-operation.

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Risk factors for surgical wound infection

- Patient factors:
  - elderly

- Hospital factors:
  - prolonged pre-operative stay
  - recent exposure to antibiotics
  - inappropriate prophylactic antibiotics
  - operating theatre ventilation and temperature
  - duration of operation
  - Foreign materials implanted
  - surgical drains
  - blood transfusion peri-operatively
  - poor surgical technique (tissue trauma, tissue tension, failure to eradicate dead space, improper haemostasis, excessive electro-coagulation, tissue vascular compromise, failure of adequate debridement)
  - inadequate antisepsis (skin preparation, sterilisation of instruments, scrub technique, inappropriate antiseptic solutions, improper draping)

Prevention of surgical site infections

- Antiseptic bathing or showering
  Pre-operative antiseptic washing has been shown to decrease the skin microbial count. There is no definitive evidence, however, that this decreases post-operative wound infection.

- Pre-operative shaving
  There is definitive evidence that shaving should be performed as close to the operating time as possible. Micro-cuts and abrasions become colonised with bacteria, which are then present within the skin at the time of surgery. Shaving more than 24 hours before the surgery has been shown to increase SSTI to more than 20%.

- Surgical site antisepsis
  Proper surgical site preparation with an antiseptic solution is essential. Preparations that are chlorhexidine-based, alcohol-based or iodine-based are all acceptable, provided that these are in concentrations as recommended by the FDA and are appropriately stored, expiry dates monitored, etc.

- Theatre and instrument preparation
  Guidelines exist for clinics and hospitals for the setting up and maintenance of operating theatres. Guidelines are also available for the positioning of theatres within the hospital, in order to control access into theatre, monitor unsterile corridors and supervise central sterilisation units. Individual theatres should be able to adjust

DC Grolman, Critical Care Specialist Surgeon/Intensivist, Sandton Medi-Clinic, Johannesburg.
G Richards, Associate Professor, Department of Medicine, Director: Intensive Care, University of the Witwatersrand and Johannesburg Hospital Johannesburg.
Correspondence to: Dr DC Grolman, PO Box 68730, Bryanston 2021
E-mail: grolman@iafrica.com

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ventilation, temperature control and humidification. Evidence does exist that laminar airflow with high efficiency particulate air filters, does decrease sepsis rates.

- **Surgical attire**
  The wearing of scrub suits, surgical caps, shoe covers, gowns, masks and gloves are standard worldwide. Whilst only the wearing of gloves has been shown to actually reduce the incidence of SSTI, it makes common sense to institute the other measures.

- **Aseptic technique**
  This has been definitively shown to decrease the incidence of SSTI and meticulous adherence to asepsis is essential. Aseptic technique has been shown to be of particular importance in the scenario of the implantation of devices and the insertion of catheters.

- **Pre-operative handwash/scrubbing**
  This has definitively been shown to decrease the incidence of post-surgical SSTI. The exact choice of scrub agent has not, however, been shown to have a significant impact on SSTI. As with operative skin site preparation above, alcohol, iodine and chlorhexidine solutions are all acceptable. There is minor evidence that an alcohol-chlorhexidine combination scrub may be more efficacious at diminishing skin microbe count. Scrubbing technique, duration of handwash and technique of drying, have all been shown to be important. Most important is the actual gloving technique, making sure not to contaminate the outer surface of the gloves when donning them.

- **Prophylactic antibiotic usage**
  The administration of antibiotics in a prophylactic manner prior to surgery has been shown to decrease the incidence of post-surgical wound site sepsis in certain circumstances. Ideally these should be given by the intravenous route. Instillation of antibiotics directly into the wound has not been shown to be effective. The best time to administer these antibiotics is within 30 minutes of the commencement of the operation. It is imperative that the antibiotic is 'on board' prior to incising the skin. Once the skin has been incised, penetration of the antibiotics into the site has been shown to be poor. A single dose of antibiotic has been shown to be adequate in most cases. This should only be repeated if the duration of the operation exceeds the half-life of the selected antibiotic. Benefit has not been seen in further antibiotic dosing. In previous years, it was believed that continuing the antibiotics for five days was required or until all drains were removed. This is not the case and may actually be detrimental. Most clean surgical procedures do not require prophylactic antibiotics at all. Benefit has been demonstrated in cases in which hollow viscerae which are colonised by bacteria are opened. This includes upper airway, gastro-intestinal, gynaecological and urological surgery. Should the plan be not to violate these areas, but where there is a chance that this could accidentally occur, antibiotics should be given. Benefit has also been seen in areas of surgery where blood supply to those specific tissues is poorer than average. Examples here are orthopaedic and neurological surgery. In addition, benefit from antibiotic prophylaxis has been demonstrated in cases in which prostheses are to be implanted. This includes joint arthroplasty, bone internal fixation, cardiac valve surgery, pacemaker insertion, vascular graft insertion, chemotherapeutic port insertion, various mesh implantations, shunt insertions and cosmetic implant surgery. Antibiotic prophylaxis is also advised in cases in which the development of sepsis would be catastrophic. This includes certain neurologic, spinal, cardiac and vascular operations. An example would be surgery in which the dura mater is to be opened.

The choice of antibiotic depends on the site of surgery and the potential pathogens to be encountered. The vast majority of surgical site infections are caused by normal skin commensals, usually *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS). For patients coming into hospital from the community for elective surgery, prophylaxis with an anti-staphylococcal penicillin, such as amoxicillin-clavulanate, is recommended. For *penicillin* allergic patients, clindamycin is a reasonable alternative. In bone surgery, a first generation cephalosporin such as cephalozolin is preferred because of better bone penetration. In patients who have been hospitalised or on antibiotics recently, those currently in hospital and those from long term care facilities, the possibility of colonisation with a resistant organism must be considered. The usual culprit here is methicillin/resistant *Staphylococcus aureus* (MRSA). Appropriate prophylaxis here would be vancomycin or teicoplanin. Linezolid should be reserved at this stage for therapy only. In patients undergoing hollow visceral surgery or mucous membrane surgery, subsequent infections are usually caused by the endogenous flora of these sites. Usual pathogens are Gram-negative aerobic bacilli, enterococci, and occasionally anaerobes. Infections by staphylococci, *Pseudomonas* spp, *Proteus* spp, clostridia, streptococci and *Candida* spp are also not uncommon. Selection of an appropriate prophylactic antibiotic should be based on this knowledge. Patients from the community can usually be adequately covered with amoxicillin-clavulanate or a 2nd generation cephalosporin. Metronidazole or clindamycin may be added as indicated. Patients who have been hospitalised for a prolonged period of time, may well justify MRSA cover and the use or ertapenem or piperacillin/tazobactam. Those who have been in ICU need to be covered for MRSA, *Pseudomonas*, *Enterococcus* and *Acinetobacter*. Here vancomycin or teicoplanin should be combined with a single dose of meropenem or imipenem/cilastatin.

- **Prophylactic eradication of *Staphylococcus aureus***
  As previously stated, staphylococcus remains the major pathogen in general. MRSA remains the major nosocomially acquired organism in skin and soft tissue infections. Twenty to 30% of normal persons harbour *S. aureus* in their nostrils. These patients have been shown to have a higher incidence of SSTI. Hence it would be prudent to swab the noses of high risk elective surgical cases, and to eradicate this organism with topical mupirocin pre-operatively. In addition, patients transferred from other hospitals and institutions, should all be swabbed for MRSA (groin, axillae, nares). Finally, one needs to be reminded that it is the healthcare personnel who are the major carriers of MRSA and all staff should also be swabbed intermittently, especially after outbreaks of MRSA in one's unit.
References
