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Nosocomial infections and antimicrobial resistance in critical care medicine

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Abstract

Objective: To review the human and companion animal veterinary literature on nosocomial infections and antimicrobial drug resistance as they pertain to the critically ill patient.

Data sources: Data from human and veterinary sources were reviewed using PubMed and CAB.

Human data synthesis: There is a large amount of published data on nosocomially-acquired bloodstream infections, pneumonia, urinary tract infections and surgical site infections, and strategies to minimize the frequency of these infections, in human medicine. Nosocomial infections caused by multi-drug-resistant (MDR) pathogens are a leading cause of increased patient morbidity and mortality, medical treatment costs, and prolonged hospital stay. Epidemiology and risk factor analyses have shown that the major risk factor for the development of antimicrobial resistance in critically ill human patients is heavy antibiotic usage.

Veterinary data synthesis: There is a paucity of information on the development of antimicrobial drug resistance and nosocomially-acquired infections in critically ill small animal veterinary patients. Mechanisms of antimicrobial drug resistance are universal, although the selection effects created by antibiotic usage may be less significant in veterinary patients. Future studies on the development of antimicrobial drug resistance in critically ill animals may benefit from research that has been conducted in humans.

Conclusions: Antimicrobial use in critically ill patients selects for antimicrobial drug resistance and MDR nosocomial pathogens. The choice of antimicrobials should be prudent and based on regular surveillance studies and accurate microbiological diagnostics. Antimicrobial drug resistance is becoming an increasing problem in veterinary medicine, particularly in the critical care setting, and institution-specific strategies should be developed to prevent the emergence of MDR infections. The collation of data from tertiary-care veterinary hospitals may identify trends in antimicrobial drug resistance patterns in nosocomial pathogens and aid in formulating guidelines for antimicrobial use.

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Introduction

Nosocomial infections in critically ill human patients are an economic burden to the health care system.[1,2] The estimated annual cost of control and treatment of multi-drug-resistant (MDR) infections in hospitals in the United States of America (USA) is $100 million, while the cost of development of new antibiotics is approximately $30 billion annually.[1] According to the Food and Drug Administration (FDA), the annual cost of dealing with the consequences of antimicrobial drug resistance ranges from $4–5 billion. In Canada, the medical cost of managing antimicrobial resistance has been estimated at $160 million (USD) annually.[2] More significant than the financial cost is the associated morbidity and mortality that occurs in critically ill human and veterinary patients. Because exposure of microorganisms to antimicrobial drugs is a major factor in selection of drug resistance, it is not surprising that bacteria in the hospital environment tend to be more drug resistant than those in the community.[1,3] As a consequence, hospital-acquired infections frequently involve MDR bacteria.[4] Critically ill patients on antimicrobial drug therapy are at greatest risk for infections with MDR bacteria.[4,5]

This review will summarize and compare data from the human and small animal veterinary literature on antimicrobial drug resistance in nosocomial infections,

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with emphasis on critically ill patients. As there is considerable literature in the human field and little information in the veterinary field, much of the data will be drawn from human studies. This review will seek to identify factors that are similar or dissimilar between human and veterinary medicine and assess where extrapolations appear to be justified. Historical perspectives and definitions, modes of action of antimicrobial agents, the significance of transferable drug resistance, and the role of biofilms in antimicrobial drug resistance will be discussed. In addition, epidemiological risk factors, specific types of nosocomial infections, and strategies to minimize antimicrobial drug resistance in the intensive care unit (ICU) will be reviewed.

Historical Perspective and Definitions

Soon after antibiotics had been introduced into clinical practice in the 1930s, the threat of antimicrobial drug resistance became evident.[6] Sir Alexander Fleming was one of the first microbiologists to foresee the potential for penicillin resistance developing *in vivo* with suboptimal doses of the antibiotic.[2,7,8] Resistance to antimicrobial drugs has increased dramatically in hospitalized patients since the 1980s.[7,9] MDR bacteria have emerged and have become a significant concern in human medicine.[6] Notable among these are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β-lactamase producing Gram-negative bacilli and, most recently, strains of *S. aureus* with reduced susceptibility to vancomycin.[8,10–12] In recent years, the increased number of human and veterinary conferences and publications that highlight the promotion of rational use of antimicrobial agents and awareness of antimicrobial drug resistance is a reflection of the concern with MDR infections.

Antimicrobial resistance is developing in both veterinary referral hospitals and general practice; however, the problem at this time appears to be occurring more rapidly in human hospitals.[1,13] The reasons for this difference include the absence of long-term care facilities such as nursing homes, shorter periods of hospital stay especially within the ICU, lower doses of immunosuppressive agents, and a lower prevalence of immunosuppressive diseases such as human acquired immunodeficiency disease (AIDS) in veterinary medicine. These factors all contribute to infection, which in the hospital and ICU setting, are often with MDR organisms. There may also be reduced selection for development of antimicrobial drug resistance in veterinary patients as pet owners may elect euthanasia in very ill patients, which shortens duration of hospitalization. Furthermore, it may also be comparatively easier in a veterinary hospital than a human hospital to implement strategies such as depopulation and sanitization to break the cycle of transmission of nosocomial pathogens.[13] The extensive use of antimicrobial agents, prolonged ICU stays and evolving complexity of emergency medicine and critical care in veterinary referral hospitals increase the possibility that antimicrobial drug resistance may be a serious threat in the near future to the veterinary ICU patient if antimicrobial use is not judicious and appropriate.[14]

While there are various definitions of the term *nosocomial infection*, the main characteristic is that the infection was not present at the time of admission to the hospital.[15,16] A nosocomial infection is defined as one of the following: an infection that occurred more than 48 hours after admission to the hospital; an infection that occurred less than 48 hours after admission, if the patient had been hospitalized within the last 2 weeks prior to the current hospital admission, or if an infection was transferred from another hospital or long-term facility (e.g., nursing home).[15,16] The National Nosocomial Infection Surveillance (NNIS) system of the Centers for Disease Control and Prevention (CDC) defines ICU-associated infections similarly, with the only difference being that they occur after admission to the ICU or within 48 hours of being transferred from an ICU.[17]

Antimicrobial resistance is best measured *in vitro* by minimum inhibitory concentration (MIC), the lowest concentration of an antibiotic that inhibits growth of a bacterium.[3] In veterinary medicine, antimicrobial resistance is defined by *in vitro* susceptibility testing using mainly methods such as disk diffusion and broth microdilution tests.[3] Bacteria that have acquired resistance to more than one class of antibiotics are referred to as MDR.

An Overview of Antimicrobial Drug Resistance

Modes of action of antimicrobial agents and major mechanisms of resistance

The major modes of action of antimicrobial agents are inhibition of the synthesis of proteins, cell walls or nucleic acids (e.g., β-lactams, macrolides, tetracyclines, aminoglycosides); inhibition of cell membrane function (e.g., polymixins); inhibition of DNA-dependent RNA polymerase (e.g., rifampin); disruption of DNA structure (e.g., nitroimidazoles); and interference with DNA gyrase activity and replication (e.g., fluoroquinolones).[18,19] The major mechanisms of antimicrobial drug resistance include enzymatic modification of antibiotics, modification of antibiotic target sites, altered outer membrane permeability to antibiotics in Gram-negative bacteria, active drug efflux pumps, and modification

of biosynthetic pathways that bypass the antibiotic target.[3,18–21] One of the more important mechanisms in nosocomial infections caused by Gram-negative bacteria is the production of β-lactamases.[20] Table 1 shows the main activities of the major antibiotic classes, their modes of action and mechanisms of resistance, and gives examples of bacteria that may become resistant.[3,19,22]

The genetic basis for development of antimicrobial drug resistance is either through spontaneous mutation or acquisition of genes by horizontal gene transfer. The former type of acquired resistance occurs because of single or multiple genetic mutations that arise spontaneously, often through errors in DNA replication. The latter type of acquired resistance involves the uptake of DNA from another bacterium and is of considerable concern as resistance often occurs to multiple drugs and may spread from one bacterium to another.[23]

The genetic material in most bacteria consists predominantly of chromosomal DNA, but extrachromosomal DNA in the form of self-replicating, circular, elements called plasmids may be present. R-plasmids carry extrachromosomal DNA that encodes genes for antimicrobial drug resistance and are responsible for a majority of resistances observed, especially in the family *Enterobacteriaceae*.[22]

The acquisition of DNA occurs by three major mechanisms that allow transfer of genetic material among bacteria: transformation, transduction and conjugation.[3] Transformation is the uptake of naked DNA from the environment by a recipient bacterium; this DNA is often provided by a lysed donor bacterium. This process is generally an inefficient means of genetic transfer and likely has a limited role in the development of antimicrobial drug resistance.[22,24] However, it may be of practical significance in naturally competent bacteria that have a high frequency of natural transformation. This is the case, for example, in *Streptococcus pneumoniae*. Transduction is a process in which DNA is transferred between bacteria by viruses (bacteriophages). Again, the exact significance of this mechanism in the spread of resistance genes is not clear. Conjugation involves cell-to-cell contact and transfer of plasmids, which is considered to be the most significant and efficient mechanism promoting transfer of resistance genes among bacteria. It can occur between strains of the same bacterial species or between different species.[3] Conjugative transposons, found mainly in the chromosome of Gram-positive bacteria, can be excised spontaneously and transferred to a recipient bacterium by conjugation in the same way as plasmids.[24]

Resistance genes may also move within a bacterium from one DNA molecule (such as the chromosome or plasmid) to another via transposons and integrons. Transposons or 'jumping genes' are mobile DNA elements which can transfer genes for antimicrobial resistance.[22] Transposons may accumulate on a chromosome or a plasmid, or combinations of transposons may occur.[3] Integrons are genetic elements that encode mainly drug resistance and can be found integrated in the chromosome, in transposons or on plasmids. Resistance gene cassettes are free, circular, closed DNA segments with a recombination site that allows for recognition and insertion at an attachment site in the integron.[3,24] Multiple gene cassettes can integrate into the same integron and cause expression of resistance to multiple antimicrobial agents.[24,25] Transposons and integrons play a crucial role in the development of MDR strains of bacteria and in DNA integration into the chromosome.[23,24]

In summary, there are multiple ways in which bacteria can acquire resistance genes. Mechanisms that involve transmissible resistance genes are of particular significance as these genes can spread, rapidly conferring resistance to bacteria to one or more antimicrobial drugs.

Role of biofilms in drug resistance

Certain bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are able to grow in a matrix of extracellular polysaccharide that irreversibly attaches to a substrate and facilitates further adhesion of microorganisms. This sessile community or microcolony of bacteria is called a biofilm and was first discovered by Van Leeuwenhoek on tooth surfaces.[26] Bacteria that organize themselves into biofilms may become less sensitive to antimicrobial agents because of the protection conferred by the biofilm.[7,27] In human and veterinary medicine, there is considerable concern about biofilm formation and colonization of medical devices (e.g., central venous catheters (CVCs), indwelling urinary catheters, and endotracheal tubes [ETT]) used in critically ill patients.[26,28]

Organisms in a biofilm are structurally and physiologically resistant to antimicrobial agents and are usually associated with nosocomial infections. There are several ways in which bacteria develop antimicrobial drug resistance in biofilms. A reduced rate of diffusion of antimicrobial agents through the biofilm matrix reduces the concentration of the drugs entering the biofilm.[29] Another mechanism of resistance is related to penetration of the antibiotic. Aminoglycosides, for example, are positively charged and have restricted penetration through a negatively charged exopolysaccharide layer in the biofilm.[29] In addition, the slower growth rate of the stationary phase bacteria in the biofilm provides increased resistance to destruction by antimicrobial agents, such as cephalosporins, advanced β-lactams, aminoglycosides and fluor-

Table 1: Summary of major antibiotics, modes of action, mechanisms of resistance and examples of resistant organisms*

Antibiotic class and examples	Mode of action	Target	Examples of resistant bacteria	Major mechanisms of resistance
β-lactam antibiotics				
a. Penicillins	Inhibits cell wall synthesis	Penicillin binding proteins (PBP)	*Enterobacteriaceae*, *Staphylococcus aureus* and other staphylococci	Degradation by β-lactamases
b. Cephalosporins				Decreased affinity of PBP
Glycopeptides				
a. Vancomycin	Inhibits cell wall synthesis	Peptidoglycan in cell wall	*Enterococcus faecium* and other enterococci	Alteration of peptidoglycan precursor with decreased affinity for vancomycin
b. Teicoplanin				
Polypeptides				
a. Polymyxin	Detergent-like disruption of outer membrane	Outer membrane	Rare in Gram-negative bacteria (intrinsic resistance in Gram-positive bacteria)	Modification of lipopolysaccharide
b. Colistin				
Nitrofurans				
a. Nitrofurantoin	Inhibits protein synthesis	Prevent mRNA translation	*Pseudomonas aeruginosa*	Absence of activation by nitroreductase enzyme Decreased cell wall permeability
a. Chloramphenicol	Inhibits protein synthesis	50S ribosomal subunit	*Enterobacteriaceae* Staphylococci	Inactivation by acetylation, active efflux
b. Florfenicol				
Aminoglycosides				
a. Streptomycin	Inhibits protein synthesis	30S ribosomal subunit	*Enterobacteriaceae* (intrinsic resistance in anaerobes)	Inactivation of drug by aminoglycoside-altering enzymes Impaired ribosomal binding Impaired transport of aminoglycoside across cell membrane
b. Neomycin				
c. Gentamicin				
Tetracyclines				
a. Oxytetracycline	Inhibits protein synthesis	30S ribosomal subunit	*Enterobacteriaceae* Staphylococci Anaerobes	Ribosomal protection Active efflux
b. Doxycycline				
Lincosamides				
a. Clindamycin	Inhibits protein synthesis	50S ribosomal subunit	Some Gram-positive bacteria (intrinsic resistance in many Gram-negative bacteria)	Alteration of ribosomal receptor site Active efflux
b. Lincomycin				
Macrolides				
a. Erythromycin	Inhibits protein synthesis	50S ribosomal subunit	*Staphylococcus aureus*	Alteration of ribosomal receptor site Active efflux
b. Tylosin				
Quinolones				
a. Nalidixic acid	Inhibits DNA synthesis	DNA gyrase and topoisomerase IV	*Enterobacteriaceae*	Modification of DNA gyrase Decreased permeability to the drug Active efflux
b. Enrofloxacin				
c. Ciprofloxacin				
d. Orbifloxacin				
Sulfonamides				
a. Sulfamethazine	Inhibits folic acid synthesis	Dihydropteroate synthetase	*Enterobacteriaceae*	Bypass of blocked enzyme by alternate dihydropteroate synthetase with low affinity to sulfonamides
b. Sulfamethoxazole				
Trimethoprim	Inhibits folic acid synthesis	Dihydrofolate reductase	*Enterobacteriaceae*	Bypass of blocked enzyme by alternate dihydrofolate reductase with low affinity to trimethoprim
Nitroimidazoles				
a. Metronidazole	Disrupts DNA structure & inhibits DNA repair	DNA repair enzyme (DNase I)	*Bacteroides fragilis* *Clostridium difficile*	Decreased intracellular activation of drug

*Modified from Prescott, [3] Quinn et al.[19] and Hoffman.[22]

oquinolones, which all kill rapidly dividing cells more efficiently than stationary phase bacteria.[29] Finally, physiological factors such as lower oxygen levels and limited nutrient availability can affect the mode of growth of the biofilm and hence the rate of antimicrobial drug uptake.[29]

Biofilms also provide a suitable environment for the spread of resistance to multiple antimicrobial agents through plasmids that encode for multi-drug resistance.[26,27] Bacteria of more than one species can coexist in the biofilm. For example, *P. aeruginosa* may grow slowly as a base biofilm while *K. pneumoniae* attaches to the *P. aeruginosa* biofilm; this may allow *K. pneumoniae* to grow more rapidly and invade the surface layers of the biofilm. Both organisms are commonly associated with urinary catheters and CVCs.[26]

In central venous catheters, bacterial colonization and biofilm formation on the external surface or the internal lumen often occur within 3 days of placement and originate from the skin insertion site or the hub.[26] Biofilm formation also occurs on the ETT of mechanically ventilated human and veterinary patients and contributes to the development of ventilator-associated pneumonia (VAP).[28] Biofilm development on medical devices will be discussed in greater detail in the sections on specific nosocomial infections.

Epidemiology of Antimicrobial Drug Resistance

Overview

The main sites of nosocomial infection, representing approximately 80% of all infections, are the bloodstream, respiratory tract, urinary tract, and surgical sites.[30,31] Gram-negative bacilli cause about half of all the infections at these sites, while the remainder are caused by polymicrobial infection or Gram-positive cocci.[30,31] In veterinary medicine, most of the literature published has been on nosocomial infections of the urinary tract or surgical sites.[32–37]

The organisms which are of major concern in human hospitals in the USA include third-generation cephalosporin-resistant *K. pneumoniae*, third-generation cephalosporin-resistant *Escherichia coli*, ciprofloxacin-resistant *E. coli*, ciprofloxacin-resistant *P. aeruginosa*, VRE, MRSA, and oxacillin-resistant coagulase-negative staphylococci.[38] In European human hospitals, *E. coli*, coagulase-negative staphylococci, *S. aureus*, *P. aeruginosa* and *Acinetobacter* spp. are the nosocomial pathogens most commonly associated with bloodstream infections (BSIs), urinary tract infections (UTIs), and surgical site infections (SSIs).[39,40] The differences in nosocomial pathogens noted from different countries and human hospitals are likely multifactorial in origin, attributable to differences in socioeconomic conditions, antibiotic prescribing policies, hospital size, hygiene and sanitation policies, frequency of collection of blood and urine samples for culture, and patient populations with varying risk factors.[41] In addition, length of hospital stay plays a role, as patients with a shorter length of stay have lower SSI rates.[41]

In order to evaluate the extent of nosocomial infections in critically ill animals, organization of surveillance programs, such as the Swiss-NOSO network, would allow monitoring of frequency of nosocomial infections in veterinary hospitals. In Switzerland, the Swiss-NOSO network is a nationwide surveillance group that functions in a similar capacity as the NNIS in the USA. Specifically, this network determines the prevalence of human nosocomial infections in Swiss hospitals and investigates the impact of inter-hospital differences on infection rates.[41] At the present time, there are no such veterinary multi-centered studies; however, individual veterinary institutions are pursuing this area of investigation. Based on these emerging studies, there is evidence of increasing antimicrobial drug resistance in opportunistic nosocomial pathogens recovered from companion animals in veterinary teaching hospitals. An increase in the incidence of MDR *Enterococcus* spp., *P. aeruginosa* and *Enterobacter* spp. associated with canine UTIs from 1984–1998 was reported from the Ontario Veterinary College Veterinary Teaching Hospital (OVC-VTH).[42] In recent years, there have been reports of outbreaks of nosocomial MDR infections in veterinary hospitals, involving both ICU patients and those in the general wards. One study identified *Acinetobacter baumannii* as a nosocomial pathogen that contributed to the death of 2 animals (among 17 dogs and 2 cats) in an ICU in Switzerland.[43] In another study, 2 clusters of MDR *A. baumannii* infections in dogs and cats were identified in a veterinary teaching hospital in Switzerland.[14] These isolates were likely nosocomial pathogens with reduced antimicrobial susceptibility compared to isolates from sporadic infections. Interestingly, cleaning and disinfecting the hospital eradicated one strain but this was quickly replaced by another MDR strain.[14] In other studies, MRSA infections were reported in 11 dogs, 8 of which acquired the infection as a complication of surgical treatment.[44] In addition, MDR *E. coli* was isolated from nosocomial infections in 10 dogs from the veterinary teaching hospital at the University of Queensland.[45] It was not known whether the MRSA infections in the dogs were acquired from human or animal contact. Recently, an outbreak of nosocomial diarrhea due to *Clostridium difficile* in teaching dogs in the small animal clinic at the Ontario Veterinary College was reported.[46] This outbreak was confined to the general wards and did not affect the patients in the ICU due to strict

compliance with ICU entrance rules and handling of patients within the ICU.[46]

Data from the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project suggests that human patients housed in the ICU are at a significantly higher risk of acquiring a nosocomial infection compared to patients housed in other areas of the hospital.[47,48] The frequency of nosocomial infections has been reported to be 2–10 times higher for human ICU patients compared to the general patient population.[17,49] In a large, prospective, multi-centered study, approximately one-half of the ICU patients had microbiological documentation of infection prior to admission to the ICU.[31] It is not known how many animals admitted to a veterinary ICU have microbiological documentation of infection upon admission; however, this predilection for nosocomially-acquired infection in human ICU patients likely applies to veterinary patients as well.

The major impetus for development of antimicrobial drug resistance and MDR bacteria is undoubtedly antimicrobial drug usage; this is particularly evident in the ICU where heavy antimicrobial drug usage occurs.[1,10,50] For example, *P. aeruginosa* isolated from human ICU patients was found to be more resistant to ciprofloxacin, imipenem and ceftazidime than isolates from the general hospital population,[8] and several other examples can be found in the human literature.[51] In the veterinary literature, Hirsh and Jang[32] reported that from 1988 to 1992, increased frequency of resistance of *E. coli* to ampicillin and cephalothin in a veterinary teaching hospital occurred as the use of these antibiotics increased. Prescott et al.[42] reported that *S. aureus* and *S. intermedius* isolates from the OVC-VTH had an increase in resistance to fluoroquinolones (0–12%) over an 8-year period; this increase in antimicrobial-resistant isolates correlated with an increase in the use of fluoroquinolones. A similar trend was also observed at the University of Missouri-Columbia and the University of California.[33,52] Another report noted a significant increase in the proportion of fluoroquinolone-resistant *E. coli* isolates from canine UTIs from 1992 to 2001.[52] Data available from Sweden showed an increase in fluoroquinolone usage in dogs by as much as 50% between 1993 and 1996.[53] Use of the fluoroquinolone enrofloxacin has also been associated with increased numbers of cases of streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis (NF) in dogs in Ontario, Canada.[54] This antimicrobial agent induces a bacteriophage-encoded gene in *Streptococcus canis* that causes accentuated lysis of the bacteria and release of host cytokines that may promote the devastating progression of STSS and NF in dogs.[54]

In a recent study on the relationship between duration of stay in the ICU and development of antimicrobial resistance in rectal *E. coli* from dogs, the frequency of ampicillin resistance increased significantly as the length of stay increased.[55] Most of these dogs were treated with ampicillin for associated medical or surgical problems while hospitalized in the ICU.

Exposure to any antimicrobial agent can alter an animal's normal flora and predispose to bacterial colonization and infection with virulent MDR organisms.[56] This effect is further compounded by the empiric use of antimicrobial agents that have minimal or no *in vitro* activity against the infecting organism; these resistant organisms can then be shed into the environment. Human and veterinary patients who are not receiving antimicrobial drug therapy are also at enhanced risk for acquiring a resistant infection because the use of antimicrobial drugs in other ICU patients affects the risk of infection or colonization of the entire ICU patient population.[57,58] As a result, critically ill patients may become more severely ill when infected with virulent MDR bacteria, especially if suboptimal or inadequate empirical antimicrobial therapy is administered.[8,59,60] These hospitalized patients are often colonized with nosocomial pathogens and many factors, including the selective effects of antibiotics, contribute to their increased risk of infection.[61] As veterinary ICU patients tend to share the same hospital room, the opportunities for transmission of infection are likely to be even greater than is the case with human patients. It was recently reported that hospitalized dogs treated with enrofloxacin for 21 days shed large numbers of MDR *E. coli* in their feces.[58] Contamination of the hospital environment with this MDR *E. coli* was suggested to be a possible source for nosocomial MDR infections in other animals.[58]

The use of oral *versus* parenteral antimicrobial drug therapy has been studied in human patients with a variety of infections including respiratory tract infections, skin and soft tissue infections and complicated urinary tract infections.[62–65] It is advantageous to switch from parenteral to oral antimicrobial therapy when this choice is available as it shortens length of hospital stay and associated costs.[63] In long-term facilities (e.g., nursing homes), patients with indwelling urinary catheters develop UTIs that are often treated with oral antimicrobial agents that are well tolerated and less expensive.[65] Oral fluoroquinolones have been used most commonly in human studies conducted in critically ill patients. In early studies, oral ciprofloxacin had a slightly better clinical response than intravenous imipenem in patients with serious bacterial infections.[62] However, adverse effects of oral administration of fluoroquinolones may occur, including nausea, abdominal discomfort, diarrhea and vomiting.[66] These gastrointestinal signs can limit the use of fluoroquinolones

orally, especially in critically ill patients who may be recumbent, inappetant and already manifesting these clinical signs. In addition, fluoroquinolones cause irreversible cartilage erosions and are contraindicated for use in young patients.[66]

Resistance to first-generation fluoroquinolones (e.g., ciprofloxacin) has increased in Gram-negative bacilli such as *E. coli*, *Klebsiella* spp., *P. aeruginosa* and *A. baumannii*, and Gram-positive cocci such as *S. aureus*.[67] This has been evident in human ICU patients in recent years and highlights a major disadvantage of oral antimicrobial agents, particularly fluoroquinolones, in critically ill patients. Under-dosing and overuse of oral agents lead to alteration of the endogenous gastrointestinal flora and more rapid emergence of resistant bacterial populations and shedding of MDR pathogens in the environment.[58,63,67] For example, it has been shown that MRSA carriage is prolonged in patients given sub-inhibitory concentrations of ciprofloxacin because increased expression of fibronectin-binding proteins promotes adhesion to the gastrointestinal tract.[67] As a consequence of the increasing resistance to first-generation fluoroquinolones, newer generation fluoroquinolones such as levofloxacin, gatifloxacin, moxifloxacin and trovafloxin have been developed.[63,64] Trovafloxacin and clinafloxacin had higher eradication rates against complicated soft tissue infections caused by *S. aureus*, *E. faecalis*, and *P. aeruginosa*.[64] In addition, no statistically significant difference was found in clinical response with the use of oral ciprofloxacin versus parenteral aminoglycosides in patients with complicated urinary tract infections.[65] Orally administered antimicrobial agents can be considered as an alternative to parenteral antimicrobial drug therapy in selected infections (e.g., osteomyelitis and septic arthritis) if there is proven clinical efficacy, safety and good tolerance by the patient. Oral antimicrobial therapy also facilitates earlier discharge from the hospital.[68]

Risk factors

ICU patients possess intrinsic risk factors that are inherent to the underlying disease conditions; these factors further predispose these patients to the adverse effects of extrinsic risk factors imposed by the practices of the staff or the hospital. Both intrinsic and extrinsic factors increase the likelihood of acquiring nosocomial infections by as much as 5–10 times that of less critically ill patients in a hospital.[69] One of the important intrinsic risk factors that is inherent to ICU patients is the severity of the underlying disease, which is indexed in human medicine by scoring systems, such as the Acute Physiologic and Chronic Health Evaluation (APACHE II) system.[70] Severe disease processes such as the systemic inflammatory response syndrome (SIRS) may involve multiple organ systems concurrently. Similarly, neonatal, pediatric and geriatric animals may not be immunologically competent or may be directly immunosuppressed from corticosteroids, chemotherapy or radiation therapy.[16] Poor nutritional status and increased metabolic demands (from sepsis, burns, obesity, traumatic injuries and surgery) may also play a role in the acquisition of nosocomial infections in ICU patients.[16,71–73]

Many extrinsic risk factors are implicated in nosocomial infections, but the most significant is increased exposure to medical and surgical devices. These devices serve as conduits for microorganisms from the environment to colonize the patient and facilitate the transfer of microorganisms to multiple organs. The ICU patient is also in close contact with other reservoirs of MDR organisms and hence is at an increased risk of cross-infection through health care workers and fomites.[1,69] Infection via contaminated equipment or instruments is more likely to occur if hospital policies impacting direct patient care are not followed. In human ICUs, many of these policies have been implemented to control outbreaks of MDR infections caused by MRSA and VRE.[69,74,75] The urgent nature of critical care may also promote reduced compliance with strict hygienic procedures such as hand-washing, use of gloves and strict barrier nursing.[74] The CDC Hospital Infection Control Practices Advisory Committee (HICPAC) has published extensive recommendations for reducing nosocomial transmission of VRE that include details of implementing barrier nursing and isolation procedures.[75]

Other important extrinsic risk factors for nosocomial infections are associated with therapeutic intervention. As discussed earlier, the widespread use of antimicrobial agents in at least 25% of all hospitalized human patients selects for resistant opportunistic pathogens that have a tremendous impact on increasing colonization and altering a patient's normal flora. *C. difficile*-associated diarrhea (CDAD) is almost always associated with prior antibiotic use in human patients, specifically cephalosporins.[76] Recently, an outbreak of CDAD in client-owned dogs and teaching dogs housed in a small animal clinic was associated with antimicrobial drug use in only a small number of the affected dogs.[46] In a tertiary referral veterinary hospital or university veterinary teaching hospital, increased use of corticosteroids and chemotherapeutic agents to treat neoplasms and immune-mediated diseases imposes increased risk of infection to patients. Immunosuppressive drug therapy may impair the host's defenses against infection, thereby predisposing these critically ill patients to nosocomial infections, some of which may be caused by MDR microorganisms.[77]

Blood Stream Infections

Most BSIs that are nosocomially-acquired in human ICUs are associated with the use of intravascular devices such as CVCs.[78,79] In human patients, the mortality associated with catheter-related bloodstream infections is reportedly as high as 10%, and is usually associated with endocarditis, septic shock, and metastatic lung infection.[78,80] The risk factors that predispose critically ill human and veterinary patients to CVC-related infections are listed in Table 2.

Indwelling CVCs are used extensively in human and veterinary ICU patients to allow noninvasive phlebotomy, to administer fluids, blood products, parenteral nutrition and medications, and to allow for hemodynamic monitoring of parameters (e.g., central venous pressure). These indwelling devices are a potential port of infection directly to the bloodstream and also provide a surface for biofilm formation. Organisms that have been identified on the external surface of CVCs from human patients include Gram-negative bacilli, *Candida albicans*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* and *E. faecalis*. The organisms tend to be MDR Gram-positive and Gram-negative bacteria and fungi that can lead to hematogenous systemic infection.[47,78] Catheter-related bloodstream infections (CR-BSIs) can be detected in human and veterinary patients with a CVC. In human patients, CR-BSIs are identified based on the following: clinical signs of infection, (e.g., fever, hypotension, tachycardia, leukocytosis), no other obvious source of a BSI, and recovery of the same organism from peripheral blood as from the CVC.[79] Detection of CR-BSIs in veterinary patients is based on similar clinical findings.

Colonization of intravenous or arterial catheters occurs primarily extra-luminally from bacteria present on the patient's skin around the catheter insertion site or from the hands of the introducer or nurse.[79,81–83] Sources of intraluminal colonization include seeding of the catheter from a hematogenous route, infusion of a contaminated solution (e.g., propofol, partial parenteral nutrition) and over-guidewire exchange.[82] Strict observation of aseptic technique with intravascular catheter placement and appropriate maintenance of the catheter and care of the catheter site are important to reduce contamination of the hub and subsequent colonization of the catheter.[82,83] About two-thirds of catheter-related infections are caused by coagulase-negative staphylococci and *S. aureus*.[84] In the veterinary literature, organisms cultured from intravenous catheters from dogs include *S. aureus*, *Streptococcus* spp., *Klebsiella* spp., *Serratia* spp., *E. coli*, *Acinetobacter* spp., *Citrobacter freundii* and *Enterobacter* spp.[77,85,86] *Enterobacter* spp. and MDR *Serratia* spp. have also been reported from outbreaks of CR-BSIs in companion animals.[86]

The risk of infection may increase with the duration of catheter dwell time. In one study, the rate of infection doubled in human ICU patients from 5% to 10% as the duration of catheter dwell time increased from 3 to 7 days.[79] However, a meta-analysis of 12 human studies

Table 2: Summary of risk factors associated with nosocomial BSI, VAP, UTI and SSI

BSI	VAP	UTI	SSI
Neutropenia	Advanced age	Female gender	Malnutrition, obesity
Immunosuppression	Obesity	Pregnancy	Extremes of age
ICU hospitalization	Chronic lung disease	Debilitating disease	Diabetes mellitus
Parenteral nutrition	Previous pneumonia	Diabetes mellitus	American Association of
Mechanical ventilation	Sepsis	Hyperadrenocorticism	Anesthesiologists' score >3
Multi-lumen catheter	Head trauma	Immunosuppression	Multi-organ failure
Site of catheter	Stress ulcer prophylaxis	Renal insufficiency	Time of clipping and aseptic preparation before surgery
Catheter dwell time	Paralytic agents	Renal transplant	
Frequent dressing changes	Enteral nutrition	Antibiotic therapy	Duration of surgery and anesthesia
	Multiple transfusions	Frequent measurement of urine	Emergency *versus* daytime surgery
	Immunosuppression	Duration of catheterization	Multiple operations during the same
	Tracheostomy	Poor placement technique	anesthesia
	Reintubation	Contaminated drainage system	Tissue trauma
	Frequent ventilator circuit changes	Colonization of peri-urethral area	Central lines
			Drains
	Multiple central lines		Tracheostomy
	Urinary catheter		Infections at remote sites
	Postoperative infection		Immunosuppression, corticosteroids

Sources: adapted from Eugster et al.,[36] Weber et al.,[69]Lane et al.,[79] Sitges-Serra et al.,[80] Mathews et al.,[83] Johnston[86] Craven et al.,[102] Ibrahim et al.,[103] Acka et al.,[104] Sedor and Mulholland,[107] Leone et al.,[109] Sotto et al.,[111] Vasseur et al.,[121] Beal et al.[122] and Nicolson et al.[123]
BSI, bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; SSI, surgical site infection.

indicated that prophylactic catheter changes every 3 days *versus* every 7 days did not decrease the incidence of catheter-related colonization or bacteremia in humans.[87] A prospective veterinary study showed that intravenous catheters can remain in place for more than 3 days (up to 10 days, based on study limitations) in a peripheral vein, providing strict aseptic technique is observed during catheter placement followed by vigilant catheter care.[83] Interestingly, veterinary contamination rates were less in catheters with dwell times beyond 3 days when compared to those in place for 3 days or less.[83] Catheters that are used short term are more likely to be extra-luminally contaminated and can be cultured by a semi-quantitative method of rolling of the tip of the catheter on an agar plate and counting the number of colony-forming units (CFU) per catheter segment. This method has been shown to be highly sensitive.[79] It is more important with long-term use catheters to culture both the tip and the subcutaneous segment to yield results with high sensitivity. A more quantitative method involves sonicating the catheter in broth or flushing broth through the catheter and performing serial dilutions before culturing on blood agar.[88] Both methods involve removal of the central catheter; however, this is not always feasible in veterinary or human medicine, and may not be necessary as the CVC may not be the cause of an infection in all suspicious cases. Another method to diagnose a CR-BSI without removal of the CVC involves obtaining positive blood cultures from the CVC and peripheral blood. This method also yields results with very good sensitivity and specificity.[88]

The management practices of CR-BSIs are universal among human and veterinary patients and involve a decision between removal of the central line, initiating antibiotics, obtaining frequent blood cultures (e.g., central and peripheral samples) and observing the patient closely.[88,89] In any critically ill human or veterinary patient, the catheter site should be inspected carefully prior to removal for signs of erythema, swelling, purulence or pain at or below the insertion site.[79,83,90] In addition, if the patient is persistently febrile with no identifiable source of fever, and blood cultures are negative, the catheter should be removed and the tip cultured. Appropriate antimicrobial drug selection should be judiciously selected based on the knowledge of nosocomial pathogens present in that particular ICU; this should be based on results from surveillance studies, which should be routinely performed.[79,89] Fortunately in veterinary medicine, MRSA and VRE are not prevalent nosocomial pathogens as they are in human critical care medicine. Empirical antimicrobial treatment (with a parenterally administered β-lactam/β-lactamase inhibitor, second- or third-generation cephalosporin) may be necessary depending on prior antibiotic therapy, the critical nature of the patient and the suspected organisms. Antibiotic therapy should be chosen appropriately, pending culture and susceptibility results.[89] Guidelines for initiating empirical antimicrobial therapy in critically ill patients with suspected CR-BSIs include: the presence of an indwelling catheter for >48 hours, evidence of catheter site infection, fever (>103.5°F or >39.5°C), hypotension (systolic blood pressure <90 mmHg), tachycardia, and leukocytosis.[90] Nosocomial infections caused by *Candida* spp. are uncommon but account for approximately 8% of nosocomially-acquired BSIs.[90] Immunosuppressed patients (e.g., after a renal transplant) with an indwelling catheter are at greater risk of candidemia. Clinical signs of fungemia are similar to those described for CR-BSIs and documentation of yeast from Gram-stain of preliminary blood cultures or urine sediment is useful in suspicious cases. Intravenous fluconazole should be considered in patients with suspected fungemia; although approximately 10% of *C. albicans* isolates from nosocomial BSIs are reportedly resistant to fluconazole.[90] Fundamentally, the decision to use antimicrobial drug prophylaxis in human and veterinary patients should be limited to those at greatest risk of acquiring a nosocomial infection. The duration of antimicrobial drug therapy ranges from 7 days to weeks and is based on several factors including the severity of illness, the presence of bacteremia or endocarditis, the organism identified and the results of repeated blood cultures.[79]

A comparative trial in human patients reported that catheters made of polyetherurethane (PEU-Vialon) were substantially less phlebitogenic than were catheters made of teterafluorethylene hexafluoropropylene (FEP-Teflon). However contamination rates with either catheter material were low.[90–92] Teflon catheters are used commonly in veterinary medicine, although they are less flexible, less durable, and more reactive to the surrounding tissue than Vialon or silicone catheters and also have an increased risk of thrombophlebitis when compared to Vialon or silicone catheters.[91,92–96] Thrombophlebitis not associated with bacterial infection is as significant as thrombophlebitis associated with infection due to bacterial skin flora or other microorganisms, and removal of the catheter is recommended.[83] Teflon catheters are not recommended for long-term use because of the increased risk of thrombophlebitis. Although silicone catheters are more expensive and complicated to insert, they are recommended by some clinicians for short and long-term use in veterinary medicine to reduce the risk of CR-BSIs.[95,96] However, Vialon catheters inserted both centrally and peripherally have proven to be equally as effective in preventing thrombophlebitis and resisting infection.[83]

The use of antiseptic-coated (e.g., chlorhexidine and silver-sulfadiazine) or antibiotic-coated catheters is controversial in critically ill human patients receiving total parenteral nutrition or in immunocompromised patients.[82] There are no veterinary studies assessing the use of these catheters, although widespread use in veterinary patients may not be indicated due to shorter duration of hospitalization and prohibitive costs. Based on animal studies, silver-coated catheters decrease the adherence of microorganisms to the catheters and hence reduce biofilm formation and CR-BSI rates.[82] Variable success rates have been reported with antimicrobial coated catheters (which are coated externally and not endo-luminally), as they provide protection for relatively short periods of time (up to 2 weeks).[82] In addition, they may select resistant bacterial flora or cause hypersensitivity reactions. Other strategies to reduce CR-BSI infections are identified in Table 3.

Pneumonia and Ventilator Associated Pneumonia

VAP is defined as pneumonia that occurs in human and veterinary patients who are mechanically ventilated, and is characterized by the presence of new or persistent radiographic infiltrate, fever, leukocytosis and isolation of a pathogen.[97] VAP occurs when there is aspiration of secretions containing bacteria that normally colonize the oropharnygeal area into the lower respiratory tract.[97] In critically ill patients, colonization is more likely to occur because of increased adherence of microbes and a diminished capacity to clear microbial pathogens. The depressed consciousness of critically ill patients with neurological disorders such as meningitis, encephalopathies, intracranial neoplasms and hemorrhage, further predisposes them to aspiration and nosocomial pneumonias.[98] Some of the characteristics of the respiratory tract of critically ill human and veterinary patients that may contribute to increased colonization include impaired immunologic defenses, abnormal epithelial surfaces, poor mucociliary clearance and pro-inflammatory bacterial enzymes (such as elastase and fibronectin-reducing proteases).[99] Other patient risk factors associated with a higher mortality from VAP are shown in Table 2.

In humans, pneumonia is the second most common nosocomial infection and the most common in the ICU and is the leading cause of death.[100–102] Pneumonia is three to twenty-one times more likely to develop 48 hours after a critically ill patient is intubated, with mortality rates that are two to five times higher than in unintubated patients.[102] Early-onset VAP is defined as occurring within the first 4 days of mechanical ventilation; after this, it is considered late-onset VAP.[103] In humans, early-onset VAP is caused by bacterial

Table 3: Summary of strategies recommended to reduce BSI, VAP, UTI and SSI

BSI	VAP	UTI	SSI
Handwashing	Handwashing	Handwashing	Antiseptic skin preparation
Alcohol hand cleansers	Semi-recumbent position	Decrease catheter duration	Reducing duration of anesthesia
Maximal sterile precautions	Chlorhexidine oral rinse	Good catheter hygiene	
Thorough skin preparation	Saline airway lavage	Cleansing peri-urethral and perineal areas	Reducing duration of surgery
Chlorhexidine skin cleanser	Continuous suction of subglottic area		Gentle tissue handling
Catheter insertion and management by skilled personnel	Adequate endotracheal tube cuff pressure	Closed collection systems	Appropriate perioperative antibiotic therapy
		Aseptic sampling via ports	
		Intermittent catheterization	Decreasing number of personnel in operating room
Decreased catheter manipulations	Heat and moisture exchangers	Medicated catheters	
	Routine ventilator circuit changes	Judicious use of antibiotics	Minimizing use of central lines and drains
Changing over a guidewire	In-line suction catheters		
Reduced number of access ports	Drainage of circuit condensate		
	Careful use of feeding tubes		Adequate surgical drainage and debridement
Fixation of catheter to reduce movement	Removal of unnnecessary invasive devices		Reducing length of hospital stay
Antiseptic-coated or antibiotic-coated catheters	Avoiding unnecessary antibiotics		

Sources: adapted from Smarick et al.,[35] Eugster et al.,[36] Wenzel and Edmond,[78] Sitges-Serra and Girvent,[80] Coolman et al.,[81] Elliott[82] Dodek et al.,[97] Bonten et al.,[99] Bowton,[100] Sedor and Mulholland,[107] Maki and Tambyah,[108] Leone et al.,[109] Saint and Chenoworth,[110] Vasseur et al.,[121] Nicols[124] and Whittem et al.[126]
BSI, bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; SSI, surgical site infection.

pathogens that are present at the time of intubation, such as *S. pneumoniae* and *S. aureus*. Nosocomial bacteria such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii* and MRSA have been more commonly associated with late-onset VAP.[101]

A significant proportion of early-onset and late-onset VAP in the ICU is caused by *P. aeruginosa*.[103] Mechanical ventilation for one week or longer and previous use of third-generation cephalosporins, fluoroquinolones, or imipenem are 2 of the most important risk factors for colonization with a MDR pathogen such as *P. aeruginosa*.[101,104] In one study, most cases of VAP due to *P. aeruginosa* were caused by endogenous infections from the upper respiratory tract of the patient.[105] However, in another study, cross-contamination occurred in approximately 50% of the patients, with sinks and contaminated bronchoscopes identified as potential reservoirs of this opportunistic MDR pathogen.[102] There have been no comparable recent studies done in veterinary medicine; however, the increasing use of mechanical ventilation in dogs and cats warrants research into the epidemiology and microbiology of VAP in these critically ill patients.

The choice of antimicrobial agents used for prophylaxis for nosocomial pneumonia and VAP should be based on knowledge of the drug resistance of the most common and virulent pathogens observed from surveillance studies done in the critical care unit.[100] Empiric therapy with third- or fourth-generation cephalosporins, monobactams (aztreonam), piperacillin/tazobactam, or imipenem/cilastin is recommended in human patients with nosocomial pneumonia.[106] Empirical antimicrobial therapy should be initiated in veterinary patients with clinical signs of infection, which may include: fever (>103.5°F or >39.5°C), hypotension (systolic blood pressure <90 mmHg), leukocytosis and radiographic evidence of infiltrate consistent with pneumonia. This prophylactic strategy has been shown to improve outcome in human studies but inevitably also promotes colonization by MDR pathogens.[102] Inappropriate administration of broad-spectrum antimicrobial agents increases the likelihood of colonization with MDR Gram-negative organisms such as *P. aeruginosa*, *Stenotrophomonas maltophila* and *Acinetobacter* spp., and Gram-positive organisms such as *S. pneumoniae* and MRSA.[102,103] Strategies that can be employed to reduce the risk of nosocomial pneumonia and VAP are shown in Table 3.

Urinary Tract Infections

Approximately 25% of human ICU patients have an indwelling urinary catheter placed to improve nursing care, prevent urine scalding and skin infections in incontinent patients, facilitate bladder emptying in patients with neurological disorders of the lower urinary tract, to irrigate the bladder, and to measure urine output.[107] In veterinary medicine, the frequency and justification for urinary catheter placement are comparable to those in human medicine. The duration of catheterization varies depending on the reason for requiring a urinary catheter, but is usually discontinued, when possible, with evidence of a UTI. Approximately 30–40% of all nosocomial infections are UTIs that follow catheterization.[107] In addition, UTIs are the source of approximately 15% of all bloodstream infections in human patients.[108,109]

Catheterization allows a portal of entry for bacteria from the environment or from the patient's intestinal or colonic flora. An ascending UTI can occur via the lumen of the catheter, from perineal and periurethral contamination, or along the exterior of the catheter (extra-luminally).[108] This leads to a planktonic population of bacteria proliferating in the urine.[26] Biofilm growth also occurs at the tip of the urinary catheter and forms a protective barrier that allows a community of resistant bacteria to persist. Urinary catheter biofilms have a unique ability to alter the local pH, especially if urease-producing bacteria such as *Proteus* spp., *P. aeruginosa* or *K. pneumoniae* are present.[110] The alkaline pH created by the production of ammonia leads to mineral deposition (e.g., calcium phosphate, magnesium ammonium phosphate or struvite) in the catheter biofilm that could potentially block the urinary catheter within 4 to 5 days.[26]

Intraluminal contamination of the urinary catheter occurs by microorganisms refluxing from contaminated urine in the collection bag or a breakage in the closed drainage system.[108] The most effective way to avoid nosocomial UTIs in human and veterinary ICU patients is to employ urinary catheterization only when necessary and to remove the catheter as quickly as possible. When catheterization is necessary, the catheter should be placed using sterile technique and should be attached to a closed-collection system.[107,108,110]

The major risk factors associated with developing a nosocomial UTI are duration of catheterization and number of urinary catheters placed.[107,109,111] In human patients, the percentage of catheterized ICU patients that develop a nosocomial UTI range from 50% to 100%, as duration of catheterization increases from 10 to 30 days.[107] Short-term urinary catheters tend to be associated with single microbe UTIs, whereas long-term catheters tend to be associated with polymicrobial infections.[109,111] Other risk factors for nosocomial UTIs are shown in Table 2.

An important source of organisms contributing to nosocomial UTIs is the patient's endogenous gastrointestinal flora. The selection that antimicrobial therapy exerts increases colonization with enteric Gram-negative bacilli such as *E. coli* and *Klebsiella* spp.[111,112] The risk of acquiring a nosocomial UTI by these pathogens increases because of increased number of fecal bacterial shedding and because perineal contamination can lead to an ascending UTI, especially in female dogs and cats.[112]

The rate of hospital-acquired *E. coli* UTIs in human patients in Europe and North America has progressively increased over the last 10–20 years.[111] For example, over a 10-year period in the Netherlands and in France, the rates increased from 25% to 34% and from 32% to 45%, respectively.[111] In many human ICU patients, cephalosporins are used as empirical thrapy for UTIs, leading to the emergence of extended spectrum β-lactamase (ESBL) resistance by members of the *Enterobacteriaceae* family.[113]

At the Ontario Veterinary College, the rate of *E. coli* UTIs reported from dogs housed in the ICU was approximately 10% of all the positive urine cultures collected from dogs with an indwelling urinary catheter.[114] All of the dogs with MDR *E. coli* UTIs had been treated with antibiotics (usually ampicillin or a cephalosporin) for a medical or surgical problem.[114] Urinary catheter-associated UTIs are the most significant reservoir of MDR nosocomial pathogens, especially *Enterobacteriaceae*.[108,111] Nosocomial UTIs caused by a MDR strain of *K. pneumoniae* were reported from the veterinary teaching hospital at Colorado State University.[112] Over the 5-year period of this study, 62% of the dogs had been treated with antimicrobial agents prior to development of a nosocomially-acquired UTI. In addition, 44% of the dogs had a history of urinary tract manipulation, while 90% had been housed in the ICU for at least one night.[112]

Strategies that can be employed to prevent or reduce catheter-related UTIs are shown in Table 3. Intermittent catheterization in spinal-cord injury or neurogenic bladders is recommended as the risk of infection with a single catheterization is about 1% compared with 10–50% with a dwell time of one week.[107] However, the risk of nosocomial UTIs in patients with spinal cord lesions increases with increased daily frequency of intermittent catheterization, incomplete bladder emptying (residual volume should be <100 mL) and non-sterile catheter placement technique.[115,116] In a recently published veterinary prospective study,[35] aseptic technique, cautious placement, and appropriate handling and maintenance of urinary catheters minimized the risk of developing a catheter-associated UTI to 10% when there was a short duration of catheterization (<3 days).

The administration of routine antimicrobial drug prophylaxis is not recommended during urinary catheterization as this predisposes to resistant bacterial infections, which are more likely to occur with longer duration catheterizations.[35] Unfortunately, clinical application of this principle is difficult as ICU patients may be on concurrent antimicrobial agents for ongoing medical problems, such as soft tissue injuries, orthopedic and surgical lesions. Based on these risks for potential nosocomial infection, the use of antimicrobial agents in these situations requires close scrutiny. Adjustment of empiric antimicrobial therapy in patients with suspected UTIs can be facilitated by the use of Gram-stains of urinary sediments. Gram-stains provide rapid assessment and have high positive and negative predictive values when a clinically relevant UTI is present with $>10^3$–10^4 CFU/mL.

Surgical Site Infections

SSIs represent approximately 15% of all nosocomial infections in hospitalized human patients and are the third most frequently reported nosocomial infection.[117] The majority of these nosocomial infections occur in the peritoneal cavity, skin and soft tissues and are usually polymicrobial and resistant to antimicrobial drug therapy. Some of the organisms isolated in human medicine include *Enterococcus* spp., *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, *P. aeruginosa* and anaerobic bacteria, such as *B. fragilis* and *Clostridia*.[117]

Multiple risk factors predispose surgical patients in both human and veterinary medicine to the development of postoperative infection and sepsis and are shown in Table 2. The risk of infection also increases with increasing degree of bacterial contamination of the surgical wound.[36] Among the factors that determine if the surgical site will become infected are the competency of the patient's defense mechanisms and the skill of the surgeon.[118] It has been stated that surgeons are the most important immunomodulating agent, and antibiotics cannot replace the performance of a skilled surgeon.[119] Other factors contributing to bacterial contamination include the duration of surgery, the viability of the tissue, and the degree of contamination.[36,120,121] In 2000, a veterinary study identified risk factors associated with development of postoperative infections in clean wounds.[122] Significant risk factors were time of surgical site clipping and aseptic preparation before surgery, duration of surgery, duration of anesthesia independent of surgical time, emergency versus daytime surgery, use of propofol, and inappropriate perioperative antimicrobial drug therapy.[122] These same authors

in 2002 retrospectively examined the development of post-operative wound infections in clean-contaminated wounds.[123] The overall infection rate (5.9%) was similar to previously published data for human and veterinary patients.[123] Some of the higher infection rates were noted in intact males and in animals with concurrent endocrinopathies, such as diabetes, hypoadrenocorticism, and hypothyroidism.[123]

A comprehensive prospective study of SSIs in dogs and cats found that duration of postoperative hospitalization and total duration of hospitalization were significantly associated with development of postoperative infection.[36] The median duration of stay for veterinary patients that developed an infection was 4 days. As reported in human patients, these authors also found that longer duration of postoperative stay in the ICU was associated with a higher frequency of post-operative SSIs.[36] An additional finding was that the risk of a surgical site infection was 1.3 times higher for each additional person in the operating room. This is an important consideration in teaching institutions where the interesting cases tend to require very invasive and prolonged surgery times and attract large viewing audiences.

The value of preoperative and intraoperative antimicrobial drug prophylaxis has been debated since the 1950s. In the 1960s, Burke experimentally demonstrated in animal models that the prophylactic efficacy of an antimicrobial agent (e.g., penicillin) was optimized when it was present in the tissues at the time of bacterial contamination by skin flora (e.g., *S. aureus*).[124] In humans, the administration of parenteral prophylactic antimicrobial agents in the immediate perioperative period has now become standard procedure. This is typically done at the time of incision, with an additional dose administered Intraoperatively 2 hours later, if applicable.[124,125] When a similar protocol was administered to dogs undergoing elective orthopedic surgery (with peri-operative penicillin or a first-generation cephalosporin [cefazolin]) compared with dogs that did not receive antimicrobial therapy, a lower infection rate was reported.[126] Perioperative antibiotics were administered to these dogs within 30 minutes prior to surgery, with a second dose repeated if the surgery exceeded 90 minutes. No further antibiotics were administered thereafter.[126] It is important to keep in mind that these were invasive, complicated and prolonged surgical procedures and therefore have higher risks of infection compared with routine, elective procedures. In a recent study, it was found that veterinary patients subjected to clean-contaminated surgical procedures and receiving perioperative antibiotics were 6–7 times less likely to develop post-operative surgical site infections than without antimicrobial prophylaxis.[36] The authors reported the use of a cephalosporin parenterally, such as cefazolin, during the immediate preoperative period (i.e., <24 hours), was beneficial to the patient.[36] A 1988 study demonstrated that there was a low prevalence of postoperative infections in dogs undergoing clean surgical procedures without the use of antibiotics.[121] Currently, antibiotics are not recommended for clean surgical procedures, with infection rates less than 2%. Exceptions to this rule are procedures for prosthetic insertion (e.g., total hip replacement) and neurosurgery, as infections in these procedures would have serious consequences. Prophylactic antibiotics, therefore, should not be administered for routine surgical procedures as infection rarely occurs with strict aseptic technique.[126]

Initial management of patients with SSIs depends on the location, extent, and collection of appropriate fluid or tissue samples for Gram-staining and culture and susceptibility testing. Management of patients with peritonitis includes fluid resuscitation, supportive care and empiric antibiotic therapy. Empiric antimicrobial therapy for peritonitis should include broad-spectrum antibiotics, including: fluoroquinolone-metronidazole, aminoglycoside-metronidazole or clindamycin combinations, second- (e.g., cefoxitin) or third-generation (e.g., ceftazidime) cephalosporins, β-lactam/β-lactamase inhibitors (e.g., ticarcillin/clavulanic acid), or carbapenems (e.g., imipenem).[125] After culture and susceptibility results are received, the antimicrobial therapy should be specific for the organism(s) identified. For soft tissue infections, empiric antimicrobial drug therapy should also be broad-spectrum and should be directed primarily at Gram-positive and anaerobic organisms. Extended-spectrum β-lactams and penicillins, clindamycin and combinations of these antimicrobial agents are appropriate.[124,125]

When a septic focus is identified, surgical intervention to remove the source of infection should be immediate. With septic peritonitis, exploratory laparotomy allows peritoneal lavage, debridement, resection, or drainage of the source and may rarely need to be repeated. The extent of debridement of surgical soft tissue infections depends on the depth of the infection and may be extensive depending on the amount of nonviable or necrotic tissue present; multiple debridements may be necessary.[124,125] The goal of surgery should be to reduce the load of microorganisms, remove necrotic tissue, and to maintain adequate tissue perfusion to allow oxygen, nutrients and immune cells to reach the affected site.[117,124,125]

Strategies to Reduce or Prevent Antimicrobial Drug Resistance in the ICU

Some specific strategies to reduce antimicrobial drug resistance in BSIs, UTIs, VAP and SSIs have already

been suggested. The ultimate goal is prevention of infection.[5] The major strategies employed to reduce antimicrobial drug resistance in the ICU include limiting the use of antimicrobial agents, optimizing their effectiveness, and strict hygienic and isolation procedures.[2,127,128] Some of the practices recommended for antimicrobial drug therapy include ensuring adequate dosing and frequency of administration, obtaining appropriate samples for Gram-stains and cultures, treating for an appropriate duration, avoiding negative drug interactions, using combination therapy where warranted, and monitoring drug levels when appropriate (e.g., aminoglycosides).[1,129,130]

To reduce the incidence of MDR organisms in an ICU and the risks of nosocomial infection, the judicious use of adequate and appropriate antibiotic therapy is warranted. This may require limiting the use of antimicrobial agents based on hospital practice guidelines or protocols, or the restriction of certain antimicrobial agents or antimicrobial drug classes from general use (unless warranted by antimicrobial susceptibility results or a clinical problem, [e.g., carbapenems and aminoglycosides]).[69,129,130] However, in order to avoid inadequate and ineffective treatment, broad-spectrum antimicrobial agents should be instituted early in the course of treatment of patients with an identified septic focus.[59] Broad-spectrum antimicrobial therapy is not warranted with nonseptic causes of fever and leukocytosis, such as neoplasia or immune-mediated diseases (e.g., hemolytic anemia, thrombocytopenia and polyarthritis).

Use of broad-spectrum antibiotic therapy may produce a more effective clinical response in ICU patients with nosocomial infections by targeting the bacteria causing the infection.[1,129,130] Namias et al. showed that the use of imipenem/cilastin and gentamicin to treat sepsis in a surgical ICU was effective in reducing mortality by 50% and did not lead to emergence of resistant bacteria.[131] This choice was made based on surveillance information that 95% of the Gram-negative rods in that particular ICU were susceptible to this antibiotic combination. The authors continued this antibiotic combination for greater than 72 hours only if the culture and sensitivity results confirmed susceptibility; this was changed to a less expensive, narrower-spectrum antibiotic protocol if supported by susceptibility results.[131]

Some important principles that should serve as guidelines for antimicrobial therapy are as follows: microbiological specimens for Gram-staining and culture and susceptibility should be collected before antimicrobial therapy is initiated, prophylaxis should be short (<5 days), the spectrum should be kept as narrow as possible, and the reasons for treatment should be documented while the response to treatment is evaluated and monitored.[40,132] Optimizing antimicrobial drug use in the ICU can be achieved in a variety of ways, one of which includes consultation with a microbiologist or an infectious disease specialist.[1,127,129] In addition, the choice of empiric antibiotics in the critically ill patient should be based on surveillance information from the ICU and on site-specific choices (e. g., peritonitis, catheter-related sepsis, pyothorax, urinary tract infections, osteomyelitis or endocarditis).[1,133] Further guidelines for empiric antibiotic selection in critically ill veterinary patients are published elsewhere.[128,134]

Other important strategies to prevent or reduce nosocomial infections are aimed at reducing hospital spread of these pathogens, and identifying and preventing the spread of MDR pathogens that may be introduced on entry to the ICU from an outside hospital. These strategies include appropriate isolation and barrier nursing of suspected MDR infection carriers until culture and susceptibility results are available, reducing length of ICU stay, minimizing the use and duration of indwelling CVCs, urinary catheters and other invasive devices, and maintaining stringent aseptic and hygienic conditions in the handling and management of these devices.[1,47,135]

Hand-washing has been studied extensively and is the single most effective control measure to reduce cross-colonization or horizontal spread of MDR nosocomial pathogens.[47,135,136] The value of this practice was recognized over a century ago in Hungary by Semmelweis who determined the importance of hands as a source of transmission of infectious diseases in the hospital setting.[49] When hand-washing is not possible because sinks are not in close proximity or there are time constraints due to frequent handling of critically ill patients, alcohol-based disinfectants are very useful. Recently, alcohol-based disinfectant handwashes have been introduced and when used as directed, they have shown reduction in bacterial numbers by 88% compared with 50% with soaps and water.[137]

The use of gloves and gowns are reported to control the spread of resistant organisms from infected to non-infected patients. However, these barriers must be removed prior to touching equipment or other patients. A suggested rule of thumb includes the following: when one turns his/her back on the infected patient for the last time, all contaminated material (e.g., bandages, body fluids etc.) should be disposed of, the gown and gloves removed and disposed of in an appropriate container, and lastly, thorough hand-washing sanitation and departure from the patient area should be promptly initiated.[128] All bodily fluids are presumptively infected until proven otherwise to avoid spread prior to identification of potential infection. Patient isolation is a

potential way of containing nosocomial (or other) infection to a limited area.[128]

Other steps that are valuable include regular surveillance cultures of the ICU environment and cultures from clinical cases (particularly of indwelling urinary catheters, intravenous catheters with suspected infection, or MDR isolates). Identification of sources or sites of concern (e.g., sinks, clippers, cage doors), improvement of the quality of empiric antimicrobial drug choices and education, and dissemination of this information to clinicians and ICU personnel are also valuable.[1,5,47,77]

Conclusions

The emergence of antimicrobial-resistant bacterial pathogens is of global concern. The widespread and heavy use of antimicrobial agents in critically ill patients has been a key reason for the increased development of MDR nosocomial infections, which are associated with high morbidity and mortality. Reports of MDR infections in veterinary hospitals are increasing; however, specific guidelines for prevention, especially in veterinary ICUs, have not yet been established. In order to prevent MDR infections from increasing in veterinary hospitals, it is necessary to use the human literature as a basis for guidelines for minimizing the problem in animals. It appears that the implementation of surveillance studies, strict adherence to infection control practices, and prudent antimicrobial choices may reduce the development of antimicrobial drug resistance. To reduce community-acquired resistance to antibiotics, it is the responsibility of veterinarians to limit the use of antimicrobial agents to help decrease the emergence of MDR pathogens that become a community problem. In addition, general practitioners should use judicious selection of appropriate first-line antibiotics for community-acquired infections as published and limit the use of antimicrobial drug classes beyond this unless there is culture and susceptibility evidence for their administration. This practice has an impact on drug resistance of the bacteria seen by the critical care practitioner as severely ill patients are often admitted to referral hospitals after antimicrobial drug therapy has already been initiated. The importance of reducing antimicrobial drug usage was noted by Low et al.[138] who stated the following: ''The antibiotic era led to the widespread use and abuse of antimicrobials and to the global antimicrobial-resistance crisis that exists today. Although there is little we can do to prevent the evolution of resistance or to reverse it once it is established, we can reduce selection intensity (drug consumption): this may help impede the spread of antibiotic-resistant organisms in humans and animals.''

Self-Quiz Questions

1. Give three mechanisms of horizontal transmission of resistance genes in bacteria?

Answers: Transformation, transduction and conjugation.

2. List 5 risk factors that predispose ICU patients to each of the following:
   (i) bloodstream infections
   (ii) ventilator-associated pneumonia
   (iii) urinary tract infections
   (iv) surgical site infections

Answer: See Table 2.

3. List 5 strategies that can be employed to reduce the frequency of the following nosocomial infections:
   (i) bloodstream infections
   (ii) ventilator-associated pneumonia
   (iii) urinary tract infections
   (iv) surgical site infections

Answer: See Table 3.

4. When is it justified to use prophylactic broad-spectrum antimicrobial agents in ICU patients?

Answer: In cases of documented positive culture (e.g., peritonitis) and in cases of sepsis in which there is a high index of suspicion of bacterial infection, pending culture and sensitivity results.

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