Antimicrobial Resistance in the ICU

David Liss, RVT, VTS (ECC, SAIM)
Veterinary Training and Consulting, LLC
South Pasadena, CA

The development of nosocomial infections and subsequent antimicrobial resistance to commonly used antimicrobial drugs has prompted heavy discussions the fields of human and veterinary critical care. Proper care of patients and biosecurity are extremely important in preventing, recognizing, and treating resistant infections in patients admitted to the hospital. Patients are at higher risk for becoming colonized with microbes, developing overt infection, and developing a multi-drug resistant infection. The morbidity and mortality of these infections is higher than simple, uncomplicated infections. Taking proper precautions and being cognizant of the state of veterinary ICU's, with regards to hospital-acquired infections, requires veterinary medical personnel to pay attention to resistance patterns, enhance biosecurity in their facilities and recognize and promptly treat patients with potentially life-threatening infections.

Nosocomial infections

A nosocomial infection, or hospital-acquired infection, refers to colonization and subsequent physiologic response to a microbe that was not present in the patient's flora prior to hospitalization. The definition involves a documented infection with an organism not present prior to hospital admission. Typical locations for nosocomial infections to develop include invasive devices, surgical sites, development of pneumonia, and gastrointestinal overgrowth situations. Noscomial infections can be categorized into urinary tract infections, bloodstream infections, surgical site infections, pneumonia's and diarrheas. The urinary tract and bloodstream infections can be further classified into catheter-associated bloodstream/urinary tract infections, identifying the invasive device as the culprit for the infection. Colonization is not the same as infection, and colonization may not lead to infection. However, colonization must be present for infection to occur. As invasive devices contribute to a large amount of hospital-acquired infections, these devices must be monitored on a regular basis. Recommendations include: checking the devices every 24-48 hours for signs of inflammation, removing unnecessary invasive devices, using antimicrobial impregnated devices when possible, maintaining closed systems to prevent breaks in sterility, washing hands and wearing gloves when dealing with invasive devices, and preventing soiling of these lines with bodily fluids. Urinary catheters should not be placed in patients for convenience, but rather for a legitmate need. In addition, while multiple IV catheter devices may be necessary, removing unused catheters prevent access ports for bacterial or microbial invasion. Surgica site infections can also develop through suture lines, and in the dermal, subcutaneous, or potentially muscular layers of a surgical incision. If kept local, these may be easily treated; yet, invasion of a body cavity may result in peritonitis or pyothorax. Patient hygiene is very important in maintaining clean surgical sites. Patients should be kept free of soil, and incisions monitored for redness, heat, swelling, discharge, or missing sutures/staples.

Pneumonias and bacterial diarrheas develop in a slightly different fashion to the surgical site, urinary tract and bloodstream/intravenous catheter related infections. Noscomial pneumonia is most often associated with mechanical ventilation and is termed ventilator-acquired (or associated) pneumonia (VAP). VAP can be a devastating consequence of mechanical ventilation and is often multi-drug resistant (MDR). VAP is thought to develop through colonization of gastrointestinal and oral flora that migrate into the bronchi and small airways through invasive devices such as endotracheal tubes, and a paralyzed mucociliary apparatus. Patients undergoing mechanical ventilation should be intubated with sterile ET tubes (after initial rapid sequence induction and stabilization of vent settings), they should be kept with their head elevated to prevent aspiration, oral care should be instituted on a regular basis, secretions should be cultured if they are suspected to be related to an occult infection, and patients should be monitored closely for the development of VAP. VAP is an extremely serious consequence of mechanical ventilation and can lead to sepsis and septic shock. Bacterial diarrhea, often caused by Clostridium difficile, is a major problem in human ICU's and is being seen in veterinary ICU's as well. As C. difficile infections are contagious, this infection can spread amongst several patients in an ICU population.

Antimicrobial resistance

Microbes have various ways to confer resistance to a class or classes of antimicrobial agents. These involve one or more of the following three categories: interfering with the ability of a drug to bind to a receptor, changing the integrity of the drug to prevent action, and preventing the drug from reaching therapeutic concentrations near the microbe. Drug binding alterations affect the mechanism of action of the drug and can be mutations in ribosomal binding sites (affecting aminoglycosides, chloramphenicol, tetracyclines, macrolides, and lincosamide drugs), nucleic acid synthesis proteins (affecting fluroquinolones) or enzymes that affect cell wall synthesis (affecting β-lactam drugs). Destruction or alteration of the antimicrobial molecule include the production of β-lactamases which destroy the killing ability of penicillin/cephalosporin drugs, and the conjugation of aminogylcosides. Many bacteria produce β-lactamases presently including: Staphyloccocus, Bacillus, Pseudomonas, Proteus, Klebsiella, E. Coli, and Salmonella sp.

There are several studies documenting the increase in resistance patterns amongst bacterial species such as Pseudomonas, E.Coli and S. Aureus. It appears that antimicrobial use has a direct impact on resistance, as evidenced by a 2002 Canadian study documenting

increased resistance amongst antimicrobials that were prescribed more often than those that were being utilized less. There have been conflicting studies over the past several years repeating and refuting these findings. A summary of some evidence includes: study documenting fluroquinolone resistance mechanisms in bacteria, a study in the UK finding increased resistance to E.Coli organisms, and a French study that documented 60% of S. Aureus strains resistant to β-lactam drugs, and a 2% resistance to fluroquinolones.

Prevention

Prevention of nosocomial infections occurs through a plethora of interventions which include veterinary staff, veterinary facilities, and patient care. These will be discussed here:

Veterinary staff hygiene

Staff hygiene is of utmost importance in attempting to prevent nosocomial infections. First and foremost handwashing needs to be revisited. The proper handwashing technique is

1. Remove all hand jewelry,
2. Use warm (not hot!) water to wet hands and remove all soil prior to soap
3. Apply liquid soap and lather vigorously
4. Continue to wash hands with soap for 30 seconds (while singing happy birthday!)
5. Rinse the soap from the hands
6. Grab paper towels from a drop-down dispenser
7. And turn off the water using the paper towel.

It is important to understand that handwashing (in this situation) is not an aseptic preparation of the hands and does not substitute for sterile gloves or aseptic technique. Use of alcohol-based sanitizers are effective in killing skin microbes and must contain at least 70% alcohol and hands must be free of soil or other organic debris. A 2004 study found a superior advantage to 1% chlorhexidine gluconate + 61% ethanol compounds (Avagard®, 3M) over alcohol-based solutions.

Fomites

Fomites are inanimate objects that are capable of carrying infectious organisms. Common fomites in veterinary facilities include: stethoscopes, thermometers, neckties, solid soap bars, telephones, etc. Veterinary personnel need to be aware of objects that touch multiple patients with no cleaning in-between, and others that are near infectious patients and are never disinfected. Simple measures can be taken to clean fomites or prevent patient-patient contact including: cleaning stethoscope bells in between patients, using disposable thermometer covers, using hand-operated soap dispensers, cleaning all surfaces/equipment in an ICU. Invasive devices should be monitored regularly for signs of inflammation/infection and removed when not needed.

Disinfection

Disinfectants are commonly used in veterinary facilities and several products exist. A complete review of disinfection is beyond the scope of this talk, but the ideal disinfectant will be bacteriocidal, virucidal, and fungicidal. Disinfectants typically do not work through biofilms or organic soil, so this must be removed prior to disinfection. Additionally, disinfectants must be applied for the manufacturer recommended contact time. Common disinfectants in veterinary hospitals include: alcohols, glutaraldehyde, and quaternary ammonium compounds (benzalkonium chloride). Newer disinfectants (Accelerated hydrogen peroxide) may provide superior disinfection compared to traditional chemicals.

Compound	Mode of action	Antimicrobial activity	Contact time	Notes
Chlorines (Hypochlorite) Bleach	Not fully known	Bacteriocidal Viracidal Sporocidal	10 minutes	1:10-1:100 dilution required Removes biofilms
Gluraladehyde	Alters DNA, RNA, and protein synthesis	Bacteriocidal Fungicidal Sporocidal Virucidal	20-30 minutes for *M. Tuberculosis*	
Peroxides (H202) Accelerated Peroxide	Produces hydroxyl radicals that attack membrane lipids and DNA	Bacteriocidal Fungicidal (Yeast) Virucidal Sporocidal	At least 5 minutes	Accelerated product 1-5 minute contact time Addition of H2O2 to urinary bags did NOT lower incidence of CAUTI

Iodophors (Iodine)	Penetration of cell wall and destruction of cell components	Bacteriocidal (NOT Gram -) Mycobacteriocidal Virucidal Prolonged contact = Fungicidal + Sporocidal	Recommended = 10 minutes	Dilution very important
Quaternary ammonium compounds	Denaturation of proteins	Fungicidal Bacteriocidal Virucidal NOT Sporocidal	Minimum 3 minutes-Recommended = 10 minutes	Increased water hardness Inactivated by cloth materials absorbing active compounds
Alcohols	Denaturation of proteins	Bacteriocidal Virucidal Fungicidal NOT Sporocidal	Minimum 3 minutes-Recommended = 10 minutes	Up to 20 minutes for fungi MUST be 60-90% Isopropyl alcohol best

Biosecurity

Additional measures, beyond handwashing and disfinection, involve planning and building of an ICU to maximize prevention of infectious disease transfer, and other facility-wide implements such as footbaths, hand sanitizers placed around the facility, staff compliance, and availability of isolation units and personal protective equipment (full barrier protection- gowns, gloves, bouffant caps, shoe covers) for use in specific patients. Surveillance programs are also important in monitoring resistance patterns and hot-zones within the facility

Care bundles

Care bundles (namely the bundle used in preventing, recognizing, and treating Ventilator-associated pneumonia (VAP), have been widely developed in human medicine to gain control of these nosocomial infections. Most involve hygiene precautions, prescribed treatment interventions, and protocols to quickly recognize and treat the development of VAP, catheter-related infections, or other nosocomial infections.

Antimicrobial use guidelines

Some antimicrobial use guidelines have been developed to help reduce resistance through the over-use and inappropriate use of antimicrobials. Some of the guidelines include: minimize the use of empirical therapy when possible, target the specific organism with specific antimicrobials (use a drug with gram-negative coverage only if suspect a gram-neg infection), use appropriate pharmacokinetics and dosing (appropriate doses and dose intervals), use drugs with appropriate tissue penetration for suspected infection site, and de-escalate from stronger drugs when culture/susceptibility data returns.

References available upon request