

Association of Primate Veterinarians' Guidelines for the Judicious Use of Antimicrobials

Purpose

The Association of Primate Veterinarians (APV) recognizes that antimicrobials are commonly prescribed for prophylactic, therapeutic, and experimental management of nonhuman primates (NHP). While clinicians should use antimicrobials to treat documented cases of illness, the decision to prescribe antimicrobials must take into account the increasing resistance of bacterial populations, leading to decreasing efficacy of critical pharmaceuticals in both human and veterinary medicine. The intent of this document is to provide guidance to veterinarians, research staff, and institutional animal care and use committees (IACUCs) on the use of antimicrobials in NHP.

Background

Antimicrobial stewardship refers to a comprehensive program that “promotes the appropriate use of antimicrobials, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms” (APIC, 2001). The AVMA has published general guidelines to direct the decision to use antimicrobials in an animal (AAFP/AAHA, 2014). The following are considerations for the use of antimicrobials in NHP.

1. Preventive strategies, such as appropriate husbandry, hygiene, and routine health monitoring, should be emphasized. Antimicrobials should never be used as a substitute for good animal health management.
2. Therapeutic alternatives should be considered prior to antimicrobial therapy, such as dietary modification for diarrhea and appropriate cleaning and bandaging of wounds.
3. Appropriate behavioral management of NHP groups is a tool to decrease the incidence of wounding and the need for antimicrobial therapy.
4. The routine prophylactic use of antimicrobials should not be used as a general preventive health strategy (e.g., en masse antimicrobial treatment of clinically normal animals).
5. Antimicrobials important in treating refractory infections in human medicine should be used in animals only after careful review and reasonable justification.
6. Antibiotic resistance in zoonotic agents poses an occupational hazard and public health risk to human caretakers, and potentially their family and the community.
7. Bacterial colonization must be differentiated from bacterial infection. Colonization (or a carrier state) is not an indication for antimicrobial therapy.
8. Culture and sensitivity results should be used to confirm bacterial infection and determine the selection of antimicrobials. Antimicrobial therapy based solely on clinical signs should be avoided.
9. The use of antimicrobials adds non-experimental variables to research studies that must be considered by the PI and IACUC.

Guidelines

Clinical Indications and Alternatives to Antimicrobials

Diarrhea

Diarrhea is a common clinical condition in NHP, resulting in significant morbidity and mortality (Wilk et al., 2008; Taylor et al., 2018). Numerous enteric pathogens can contribute to diarrhea, most prominently *Shigella flexneri*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Escherichia coli*, *Campylobacter jejuni*, and *Klebsiella pneumoniae*. Animals housed in groups may be susceptible to enhanced disease transmission of enteric pathogens, although the risk remains unclear (Balasubramanian et al., 2019). Fecal or rectal culture with sensitivity and/or PCR should be used to identify enteric bacterial infections. Antimicrobial use should be guided by diagnostic results and the zoonotic potential of these microorganisms.

Nonhuman primates may present with noninfectious causes of diarrhea that are responsive to antimicrobial therapies with immunomodulatory properties that may be useful in treating idiopathic chronic diarrhea (Blackwood et al., 2008). To minimize selective pressure leading to antimicrobial resistance, alternatives to antimicrobial therapy should be considered and include increased dietary fiber (Ardeshir et al., 2014), coconut (Wilk et al., 2008), vitamin B supplementation (Izzi et al., 2016), probiotics, bismuth subsalicylate, and fecal transplant (Ferrecchia & Hobbs, 2013). Changes in diet and enrichment should be considered as well. There are reports of gluten-sensitivity in macaques (Bethune et al., 2008) that can be improved with dietary alterations (Sestak et al., 2016). Mild cases of diarrhea without other clinical sequelae may not require treatment, and animals should be monitored closely. Use of multi-drug antimicrobial regimens to treat idiopathic enterocolitis is strongly discouraged. The potential public health consequences of this strategy outweigh potential benefits in most circumstances when human-important antimicrobial agents are utilized in NHPs.

Wounds

Nonhuman primates commonly sustain injuries, and antimicrobial use to manage wounds is common in NHP clinical practice. However, the general principles of antimicrobial stewardship should be followed. Rapid identification and appropriate lavage of wounds can eliminate the need for antimicrobials by reducing contamination. Bandages may be considered to prevent further contamination and promote wound healing. When making the decision to bandage a wound, NHP temperament and the size, location, and character of the wound should be taken into account. If a wound has been sutured, a bandage can provide protection from contamination in the first 24-48 hours, but likely loses utility beyond that point unless it is needed to protect the sutures. Topical treatments to be considered include hydrogel, honey, and silver, although these compounds have not been studied in NHPs specifically (Thomas et al., 2009)

Perioperative period

The use and choice of perioperative antimicrobial agents should be determined by the type of surgical procedure, type of surgical wound, comorbidities of the NHP patient (natural or experimentally-induced), and postoperative husbandry conditions (Trepanier, 2013). The majority of NHP surgical wounds likely fall into the categories of clean (i.e., incisional wound made by the surgeon not involving the respiratory, alimentary, genital, or urinary tracts) or contaminated (i.e., acute conspecific bite wounds) and may not require antimicrobial therapy. There is limited information on the most common bacterial pathogens associated with surgical site infections (SSI) in NHPs. In humans, staphylococci, *E. coli*, *E. faecalis* and *Pasteurella* are the most commonly identified SSI pathogens (WHO, 2018).

Cefazolin is the most commonly used antimicrobial for perioperative prophylaxis in both human and veterinary medicine due to its safety profile, efficacy against common SSI pathogens, and relatively low cost (Bratzler et al., 2013; Fossum, 2019). Prophylactic perioperative antimicrobials may be recommended in veterinary medicine for animals undergoing neurosurgical procedures (e.g., craniotomies) or receiving implants (Fossum, 2019). The initial dose of antimicrobial prophylaxis should be given no longer than 120 minutes prior to the surgical incision, with the half-life of the chosen antimicrobial taken into consideration. Re-dosing should be considered for procedures exceeding two half-lives of the drug, or if excessive blood loss occurs during the surgical procedure. For cefazolin, redosing NHPs every 4 hours is likely to be effective based on pharmacokinetic data from humans and dogs (Bratzler et al., 2013, Gonzalez et al., 2017). Topical antimicrobial agents should not be applied to surgical incisions (Berriós-Torres et al., 2017).

Both the CDC and WHO recommend against additional doses of antimicrobials following wound closure. Postoperative antimicrobials are not necessary for the vast majority of surgeries in NHPs. Continuation of postoperative antimicrobial therapy should primarily be considered for NHPs at a higher risk of SSI (e.g., dirty/infected wounds, natural or experimentally-induced immune deficiencies, device implantation). Alternatives to antimicrobials for NHPs that disturb an incision include preventing access (e.g., a jacket), increasing enrichment (e.g., grooming boards), and ensuring wound integrity (e.g., debride devitalized tissues, avoid tension). If antimicrobial agents are chosen to be included in the postoperative regimen, first generation cephalosporins should be utilized as a first choice.

Outdoor and/or group housing

Animals housed in pairs or groups have complex social interactions that lead to a balance maintained by affiliative and agonistic encounters. Trauma is a common sequela to maintaining hierarchical order, whether they are indoor- or outdoor-housed. Outdoor-housed animals often require relocation away from their social group to receive necessary treatment, which may include timely and appropriate antimicrobial therapy. When indicated, consideration for novel ways to balance timely return to the social group with delivery of necessary antimicrobials is crucial. Long-acting single-dose antimicrobial therapy may be utilized in these situations, depending on culture and sensitivity results. It is important to note that pharmacokinetics of antimicrobials is species-specific and that data in one species does not necessarily translate into effective dosing for another. One example of this is cefovecin, which does not provide extended plasma levels in NHPs as it

does in companion animals (Raabe et al., 2011). The judicious use of antimicrobials should be weighed against the duration and frequency of administration, the social standing and influence of the individual in the group, the stability of the group in the individual's absence, and the success of reintroduction of the individual following prolonged removal for clinical care. This can be further enhanced beyond clinical practices by consultation with a well-trained and skilled behavior team. This team can identify compatible social partners, monitor social group stability, and intervene to maintain population densities that may reduce social stresses leading to trauma and disease transmission of bacterial pathogens requiring antimicrobial therapy.

Research Indications and Alternatives to Antimicrobials

Immunosuppression

Although uniquely challenging, antimicrobial stewardship remains of critical importance for immunosuppressed patients (Robilotti et al., 2017) and should also be applied to nonhuman primates. Infections can progress rapidly in these patients making early and specific microbial diagnosis necessary both for treatment and stewardship (Abbo & Ariza-Heredia, 2014). Presumptive infections should be confirmed through microbiological investigation. When empirical therapy is implemented, re-evaluation is recommended, ideally in 2-3 days. Re-evaluation should include de-escalation which includes both narrowing of spectrum and discontinuation of agents (Garnacho-Montero et al., 2015). Prophylaxis in research models requiring immunosuppression should be critically evaluated by the IACUC and guided by local surveillance of organisms and their resistance patterns (Wachtman & Mansfield, 2008). In some NHP research models, infections may be an indication of over-immunosuppression (Fechner et al., 2006).

Implanted devices

Chronically implanted devices present a specialized risk for infections in NHP research models. The use of antimicrobials to treat infections depends on the location of the implant, the chronicity of the implant, and clinical signs presented by the affected NHP. Implanted catheters, telemetry devices, and orthopedic implants are at most risk of contamination at the time of surgical implantation. Strict aseptic technique during surgery and validation of the procedures used to sterilize implants are key to preventing device-associated infections. Due to biofilm formation, antimicrobial therapy alone is unlikely to resolve implant-associated infections. Use of antimicrobials to treat infected implants is recommended only as a temporary measure until explantation can be performed, or the study endpoints have been achieved.

Cranial implants for neuroscience research are at a high risk for polymicrobial chronic bacterial colonization with a risk for subsequent adverse sequelae (e.g., meningoencephalitis, cephalic abscess). Resistant bacterial pathogens including MRSA and multi-drug resistant *Enterococcus faecalis* have been documented to colonize cranial implants (De La Gandara et al., 2019; Lieberman et al., 2018; Woods et al., 2017). Biofilm formation in cranial implants is common, especially for implants utilizing acrylic materials, and represents a barrier to both antimicrobials and chemical disinfection. Use of local antimicrobial agents as part of cranial implant maintenance is strongly discouraged, as it encourages development of bacterial resistance (Lieberman, 2018; Woods et al., 2017). Systemic antimicrobial use should be reserved for treating implant infections in which the dura or bone are severely compromised, for animals with clinical signs

of meningoencephalitis, and/or animals with cephalic abscessation observed on imaging, and may require a long duration of therapy (4-8 weeks). Explantation of infected implants is encouraged for animals with current or recurrent clinical signs that do not respond to topical halogen and/or systemic antimicrobial treatment.

IACUC/protocol considerations

Administration of compounds including antimicrobials to animals as part of an experimental protocol must be reviewed and approved by the IACUC (Mohan & Foley, 2019). The investigator should provide sufficient information for the committee to make an informed decision as to the necessity and appropriateness of the specific antimicrobial treatment protocol requested. Antimicrobial usage can be an intended or unintended variable in study designs and as such can affect the reproducibility of experimental results within and between studies and institutions if there are variations in treatment protocols.

Special Considerations for Antimicrobial Use

Decolonization of bacterial carriers

Nonhuman primates may be transient or subclinical carriers of a multitude of potentially pathogenic organisms. Where there is a concern for disease or interference in research, carriage status of individual animals should not be assumed, but rather determined by microbiologic diagnostics including culture or PCR. Depending on the agent, there may be some utility in treating subclinical contacts following a confirmed diagnosis (e.g., to address serious colony health risks posed by an agent such as *S. flexneri*). Routine en masse treatment of subclinical carriers or of groups of animals in an effort to standardize the microbiota, or decolonize them of endemic agents for research purposes should be avoided and poses potentially serious public health concerns that outweigh any perceived benefit. There is little evidence that decolonization persists long-term (Tacconelli et al., 2019). It also remains unclear how efforts to eradicate common GI organisms affects the translatability of NHP research, due to the effects on the microbiota (Manuzak et al., 2020).

A survey of US biomedical research institutions housing NHP and affiliated diagnostic laboratories showed low resistance of bacterial enteric pathogens to commonly used antimicrobials (Kim et al., 2017; Kim et al., 2018). However, multi-drug resistant *S. flexneri* and *E. coli* were isolated from a group of rhesus macaques imported from China (Bolton, 2002). Facilities that obtain NHP from commercial suppliers or other institutions should consider that the antimicrobial use practices, and thus, the antimicrobial resistance profiles, of shipping facilities may have implications for the receiving facility.

In humans, carriage of *S. aureus* increases the risk of infection with an identical strain (Von Eiff et al., 2001). While decolonization has been attempted for organisms such as MRSA, long-term success has not been established in humans or NHP, especially when implanted devices are involved (Soge et al., 2016; Cheleuitte-Nieves et al., 2020). This practice is not recommended, as the impact of subsequent recolonization and selection for bacterial resistance on the patient and the medical facility must be carefully considered (Kauffman et al. 1993; Bradley, 2007; Lo et al., 2018).

Use of important human antimicrobials

The World Health Organization's Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) maintains and categorizes antimicrobials to ensure

prudent use in both human and veterinary medicine. The AWARe Guidelines (<https://aware.essentialmeds.org/groups>) group antimicrobials into first or second choice (Access), those that are first or second options for a limited number of conditions but may be the target for resistance (Watch), and those that should be used only as a treatment of last resort (Reserve). Use of agents included on the Watch list should be minimized and agents on the Reserve list should be avoided in NHP.

Highly resistant bacteria, including methicillin-resistant *S. aureus* and multi-drug resistant *E. faecalis*, warrant special considerations to achieve successful clinical outcomes and prevent further antimicrobial resistance. When human-important antimicrobials are the only treatment options for a resistant infection, the decision to use these drugs must prioritize the negative public health consequences over the research animal model.

Methods to Decrease Antimicrobial Use

CDC recommendations for human healthcare facilities require active antimicrobial stewardship through tracking of infectious isolates and their resistance patterns, as well as success of antimicrobial treatment. These principles can be applied to NHP and laboratory animal facilities. It is recommended that all infected sites have samples collected for culture and sensitivity prior to initiation of antimicrobial therapy. Maintaining an institutional database of culture results and sensitivity patterns allows identification of common pathogens and trends in resistance, facilitating the success of empiric treatment.

Institutions that experience significant morbidity due to bacterial infection should consider preemptive screening of subclinical animals for carriage of agents of concern, such as MRSA. Screening programs should be designed to allow for effective intervention, such as screening in quarantine to allow separation of carriers vs. non-carriers, or screening of surgical candidates to disqualify individuals for device implantation.

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