Association of Primate Veterinarians Guidelines for MRSA Infections in Nonhuman Primates in Biomedical Research

Purpose

Use of nonhuman primates (NHPs) in biomedical research may include performing invasive surgeries, multiple courses of antibiotics, chronic implantation of research devices, immunosuppression, regular contact with humans, and living in close proximity to conspecifics. These conditions likely put animals at increased risk for opportunistic infections caused by methicillin-resistant Staphylococcus aureus (MRSA). This guideline aims to provide NHP researchers and veterinary staff with information for assessment, treatment, monitoring, and prevention of infections caused by MRSA.

Background

There is paucity of information related to MRSA in NHPs in the published literature. Recommendations must rely on 1) extrapolation from human and non-NHP veterinary literature, 2) the few relevant NHP publications on this matter, and 3) anecdotal reports.

Staphylococcus aureus is a colonizing opportunistic pathogen, and may be carried by hosts without causing disease, including in NHPs. In NHPs, primary infections are rare, but S. aureus is a leading cause of infections when physical (e.g. wounds, incisions) or immunological protective mechanisms are compromised. Methicillin-resistant S. aureus (MRSA) are strains that have acquired mecA or mecC genes that encode production of an altered penicillin-binding protein, PBP2x, which dramatically reduces the affinity for beta-lactam antibiotics, rendering virtually all drugs of this class ineffective. Many clinically relevant MRSA strains have also acquired resistance to other antimicrobials such as lincosamides, macrolides, aminoglycosides, fluoroquinolones, or tetracyclines (5). While methicillin-resistance itself does not confer virulence, MRSA strains may have acquired other virulence genes and are of particular concern because of challenges in treating infections.

MRSA is a significant problem in human healthcare, yet S. aureus is widely present in the healthy human population. The majority of humans will carry S. aureus (including MRSA) transiently, but an estimated 20% of the population will be persistent carriers. The majority of carriers never develop a clinical infection. MRSA carriage has been associated with increased risk of infection in select surgical procedures. Community-associated MRSA in people who have little to no healthcare contact is increasingly reported. In addition, some community MRSA strains appear to progress more rapidly from colonization to infection than strains associated with hospital settings. One important challenge is the ability for S. aureus—including MRSA—to persist in the environment for weeks to months, which necessitates strict environmental control measures in the face of an outbreak. It is imperative to differentiate between “infected” and “colonized” animals. A high prevalence of colonization may be present despite low prevalence of infection within a population.

NHPs, like humans, are natural hosts of S. aureus, with comparable rates of nasal carriage. However, the limited research on S. aureus carriage in NHPs shows that they can carry both nonhuman and human strains (7). Recent studies suggest that humans who work with NHPs may become colonized with strains found in the macaque populations (18, 19). As an opportunistic pathogen, MRSA is of particular concern in NHPs that have implants or other factors that increase the risk of opportunistic infections. Because of the difficulties in finding an appropriate antimicrobial or failure of empirical therapy, these infections can result in morbidity, mortality, the need for intensive treatments, increased treatment costs and interference with research studies. Use of ‘higher tier’ antimicrobials in response to MRSA infections can exert further selective pressure for antimicrobial resistance, resulting in additional management challenges. These drugs also may be associated with more side effects, which could be a concern for research protocols as well as animal welfare. Additionally, as an important human pathogen, MRSA in NHPs represents a potential occupational hazard to human contacts. Laboratory NHPs have many of the same risk factors that predispose humans to MRSA infection, both in its healthcare-associated (indwelling devices, surgical wounds, immunosuppression) and community-associated (living in close proximity to other individuals) forms. Case reports document MRSA infection in previously healthy animals, causing pneumonia (10) and necrotizing stomatitis (11); individual risk factors include immunosuppression (12), cranial implants (13), and chronic exteriorized catheters (14). While clinical NHP infections appear to be rare, when they do occur the impact on research is severe, potentially requiring de-instrumentation or euthanasia.

Guidelines

1. **Strict asepsis must be used for all surgical procedures.**
   a. Of primary importance is prevention of infection that must include aseptic surgical technique and appropriate maintenance of surgical sites for implanted devices.
   b. Asepsis is of paramount concern when implanting long-term exposed devices (16). Routine anti-MRSA prophylaxis is not recommended, but in high-risk events (e.g. cranial implantation in a colony with endemic MRSA), targeting MRSA with, for example, a single dose of amikacin peri-operatively, along with a routine antibiotic (e.g. cefazolin) would be reasonable. Additional protocols such as intranasal mupirocin and pre-operative bathing with chlorhexidine should be considered for animals that are known carriers (21). It is important to note that similar protocols used in humans with MRSA infection – even protocols that included the entire household – have shown limited effectiveness, which suggests that additional measures may be necessary. Exposed devices should be regularly attended to with appropriate cleaning protocols (26). Antimicrobial
prophylaxis is an option that should include manufacturer’s recommendations, experience and judicious use of parenteral dosing to achieve therapeutic drug levels throughout the procedure.

2. Identification of carriers
   a. Periodic screening of individual animals and colonies can be performed. However, there should be a plan on how to use the results to avoid panic and unnecessary eradication measures. Mounting published and anecdotal evidence suggests MRSA colonization in NHPs is not an unlikely event if surveillance cultures are conducted.
   b. Identification of carriers or colonized animals is typically performed via nasal swabs. Other areas may be swabbed such as the oropharynx, inguinal, or axillary area. Specific, standardized culture techniques identify if MRSA is present. Consultation with the diagnostic laboratory is required prior to screening to ensure that appropriate methods are used. Routine non-selective culture is not recommended, with possible exception of specific surveillance activities.
   c. Optimal screening practices have not been established. A single nasal swab provides a reasonable overview at the colony level but should not be taken as indicating an animal is definitively MRSA free. Greater sensitivity is achieved through collection of paired nasal and oropharyngeal swabs with serial testing (rectal swabs were not sensitive in the Schauburg et al study (22) and/or serial sampling). The goals of screening should be considered when choosing the screening approach (sites, number of sampling times).
   d. If a high colonization rate (50%) is established, while prevalence of clinical disease remains low, the longitudinal monitoring and environmental assessment should include:
      i. Culturing animals to be subjected to conditions predisposing to opportunistic infections accompanied by a specific follow-up plan, e.g. changing peri-operative practices (amikacin + cefazolin –see above).
      ii. Maintaining appropriate records on carrier animals and tracking their housing situations.
      iii. Adapting standard of care to include submission of suspicious lesions (e.g. abscesses, nonhealing wounds) for MRSA culture and genotyping, or performing routine culture and sensitivity for any lesion, regardless of known colony MRSA status.
      iv. Review SOPs and practices concerning prudent antibiotic use and optimizing antibiotic stewardship.
      v. Effective management strategies for minor operative procedures may include judicious use of antibiotics and relying more on aseptic techniques.

3. Elimination of carriers
   a. A harm-benefit analysis of decolonization is recommended, taking into account factors such as prevalence of MRSA, models at risk, possibility of re-infection, and maintaining a MRSA free colony to reduce the risk of re-exposure.
   b. Elimination of NHP carriers may not be practical due to the following reasons:
      i. In humans, routine decolonization attempts have resulted in failure of treatment, enhanced antibiotic resistance and lack of evidence of a clinical benefit in most situations (3). However, these studies are conflicting with others showing benefits when dealing with community MRSA (23). Further, decolonization efforts are likely to ultimately fail if re-exposure is likely.
      ii. Attempts to decolonize humans have not always resulted in reduced transmission events (5). There is no evidence that decolonization attempts in NHPs are as, or more, effective than in humans.
      iii. The protocol for decolonization in humans includes repeated 1) topical applications of mupirocin into the nares, 2) oral antibiotics based on antimicrobial resistance profiles and 3) chlorhexidine or bleach baths.
      iv. Challenges in applying human procedures in NHP populations:
         1. need to harmonize treatment (treat all animals at the same time);
         2. repeated sedation of animals
         3. addressing the environment and personnel (strain dependent)
         4. practicality of chlorhexidine decolonization baths in known MRSA positive animals following human hospital standard infection control practices (24)
   c. There is currently no extensive published work on this matter in NHPs. Recent attempts to decolonize MRSA from colonized macaques have shown some success, however, the treatment did not appear to be successful in all cases and long-term follow-up was not described (19). Due to the intense nature of the treatment, the overall welfare of the animals should be considered before starting treatment.

4. Source and common genotypes
   a. Appropriate use of PPE should prevent any potential bacterial transmission between NHPs and human staff. It is highly likely that MRSA can move between NHPs and humans as human MRSA strains have been identified in NHPs, and MRSA strains found in NHPs have been found in humans closely working with them. Extensive effort at determining bacterial source may not be justified, as by the time it is investigated, it is rarely possible to pinpoint an exact source.
   b. Consultation with an expert in infectious diseases should be considered regarding the typing which might be useful as part of an outbreak response. Any MRSA carrier poses a risk of transmission and subsequent infection for other NHPs or humans.

5. Treatment strategies
   a. Treatment should focus on local wound care when possible.
   b. Alternative treatment modalities such as low-level laser therapy have been attempted with some benefit (25).
   c. An appropriate antimicrobial stewardship program should be employed including antimicrobial use practices for prophylaxis and therapy taking into account antimicrobial resistant trends within the colony and individual-specific culture and sensitivity results. Infected sites should have culture and sensitivity performed whenever possible.
   d. Antibiotic treatment should be implemented when
necessary using the narrowest spectrum of antibiotic appropriate for given infection, and based on the results of culture and susceptibility testing.

e. Focus should be placed on infection control approaches to reduce the risk of infections, which should include consideration of environmental reservoirs of MRSA.

6. Antibiotic susceptibility and choices

a. Base any treatment choice on susceptibility testing. If isolates are known to be MRSA, beta-lactam antibiotics (penicillins, cephalosporins and carbapenems) should not be used regardless of susceptibility results.

b. Monitor susceptibility to agents used in successful decolonization attempts. Consult an infectious disease expert before initiating any attempt to decolonize, including a microbiologist to obtain mupirocin susceptibility testing if mupirocin is to be used as part of a decolonization regimen (5).

c. Employ appropriate antibiotic stewardship. While administration of any antibiotic can promote development of resistant bacteria, enrofloxacin has been linked to increased development of methicillin resistance.

d. Susceptible/intermediate/resistant determinations are based on anticipated serum drug levels. Some antimicrobials with reported resistance may still be useful topically or locally.

7. Maintenance strategies of infected or colonized subject animals

a. There is no uniform strategy. Topical therapy (e.g. chlorhexidine) can by highly effective for superficial infections and should be considered as the first line of treatment whenever possible (26).

b. If an infection is established in an implanted animal, de-instrumentation, resolution of the infection and re-instrumentation may be required, as treatment of infected implants is often unrewarding. IDSA guidelines (7) recommend device removal if onset of symptoms is >3-4 weeks after implantation or device is unstable, but parenteral antibiotic treatment can be attempted if infection is early after implantation. De-instrumentation and re-instrumentation should always be performed in consideration of institutional animal care and use policies.

c. Anecdotally, culture-based antibiotic use as well as re-implanting MRSA colonized animals may still be successful. Re-implantation of actively infected sites is controversial. De-instrumentation, allowing healing time and re-implantation may be more practical, if possible.

d. Effective management strategies include judicious use of antibiotics and relying more on aseptic techniques for minor operative procedures with no increase in infections. Regular follow-up MRSA surveillance is recommended.

References


logical Samples to Monitor *Staphylococcus aureus* Colonization in Great Apes and Lemurs. PloS One, 8(10), e78046–6. http://doi.org/10.1371/journal.pone.0078046


26. APV Cranial Implant Care Guidelines for Nonhuman Primates in Biomedical Research www.primatevets.org

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