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Association of Primate Veterinarians Guidelines for the Management of Diarrhea

Purpose

Diarrhea is a common clinical condition that affects nonhuman primates (NHP), with a higher incidence often reported in macaques and marmosets. The etiology may be multifactorial, and both infectious and noninfectious causes should be included in the differential diagnoses. The purpose of this document is to guide veterinarians on the etiologies, diagnostic procedures, and treatment options for diarrhea in NHP. As some cases of diarrhea are idiopathic and refractory to treatment, humane endpoints are an important consideration for management. The purpose of the animal in the colony is also a key factor when considering long-term treatment options.

Background

Diarrhea can be a management challenge for veterinary clinicians at laboratory animal facilities. Infectious etiologies have the potential to spread throughout a colony and may pose a risk of zoonosis. Noninfectious and chronic diarrhea may require symptomatic treatment for an extended duration, especially when a definitive diagnosis is challenging to obtain. Stress-related factors should be taken into consideration, and may include research procedures, type of housing, or social instability with resident or newly introduced animals.

Guidelines

Diagnosis. Recommendations for the diagnostic approach to determine the etiology of diarrhea in NHP vary based on several factors (including but not limited to, severity of disease, clinical signs, and indoor vs. outdoor housing). Enteric diseases due to bacterial infections are a primary cause of morbidity and mortality in both New and Old World monkeys.[15] Diagnosing the primary pathogen can be difficult. However, the diagnostic methodology for NHP does not differ from that used for other veterinary species.

Fecal diagnostics require fresh samples to ensure optimal diagnostic sensitivity. If fresh feces cannot be promptly analyzed, samples should be refrigerated for no more than 24 h. Fecal flotations and direct smears are commonly used to identify intestinal parasites. Pathogenic bacteria can be identified via culture or PCR. Sequential samples taken on each of 3 successive days is recommended for definitive diagnosis.[15]

Complete blood count and serum chemistries are useful diagnostic tools used to determine the severity of disease and to detect systemic complications. Other serum analytes may be helpful components of a diagnostic plan. For example, cobalamin deficiency has been implicated as a causal factor for chronic diarrhea in pigtail macaques.[12]

Depending on the results of initial diagnostic tests, an endoscopic examination of the gastrointestinal tract may be considered. If endoscopic equipment is unavailable, surgical exploration may be indicated. The risk-benefit ratio of exploratory surgery should be carefully evaluated for each individual animal.

Treatment. In cases where an infectious etiology is identified, targeted therapy with antimicrobials may be necessary if the animal has diarrhea along with systemic signs of disease such as dehydration, inappetence, or lethargy. However, antimicrobial administration is not warranted in animals with uncomplicated diarrhea of short duration with no other clinical signs. In general, asymptomatic carriers should not be treated with antimicrobials to avoid development of antimicrobial resistance.

The type of housing is an important consideration in managing and/or treating diarrhea. Animals housed outdoors have greater exposure to transmission vectors such as arthropods, sylvatic reservoirs, or soil. Parasites that require maturation in intermediate hosts or the external environment for infectivity are of greater concern in outdoor housing environments, where cleaning may be less frequent or effective. It may be difficult to administer treatments to animals housed outdoors in large groups. Separating group-housed animals from conspecifics for treatment may disrupt the social organization of the group, while returning an animal to its social group after a long period of separation for medical care may be challenging.

Rehydration therapy and electrolyte replacement. Initial treatment should be directed at stabilizing the animal, which may include correction of fluid deficits and electrolyte imbalances. Sports drinks or oral electrolyte solutions like those used in companion animal or human pediatric medicine can be hung from the animal's cage to allow ad-libitum consumption. Oral rehydration should be used supplementally, even in cases that require intravenous administration.[4] Animals with moderate to severe dehydration due to protracted diarrhea often require subcutaneous and/or intravenous fluid administration of a balanced crystalloid solution.

Dietary interventions. Adjunct treatment for diarrhea often includes dietary therapy to allow normalization of intestinal motility and function and to alleviate dysbiosis. Dietary manipulations can be highly successful if initiated early in the disease course and can often be withdrawn once enteric inflammation and mucosal changes resolve.[15] Treatments include initiation of a highly digestible and bland diet, an increase in dietary soluble fiber, and supplementation with pre- and probiotics.

Some animals present with persistent diarrhea for which no underlying organism can be isolated, and clinical signs do not resolve with treatment. There are anecdotal and published reports of macaques presenting with clinical signs similar to those seen in humans with celiac disease, an autoimmune enteropathy caused by the ingestion of glutens from wheat, barley, and rye.[5] In these cases, commercially prepared nonhuman primate gluten-free hypoallergenic diets may provide some benefit.[2,5,15]

Miscellaneous symptomatic treatments. Antimotility drugs help to shorten the duration of diarrhea, but are contraindicated in infectious etiologies because they may allow time for proliferation of pathogens. Gastroprotectants and antiemetics may be indicated in cases of diarrhea coupled with vomiting.

Diarrhea can be painful, so analgesic therapy should be considered as part of the treatment plan. Opioids exert beneficial

effects by prolonging intestinal transit time, thus increasing fluid absorption and anal tone while decreasing propulsive peristalsis and fluid secretion. If a bacterium or toxin is the suspected etiology, opioids should be used with caution as they may allow time for proliferation of bacterial pathogens and increase toxin absorption. Nonsteroidal anti-inflammatories may cause gastrointestinal ulceration and acute renal failure in dehydrated animals and have been associated with diarrhea in humans,[8] so this class of analgesics should be used cautiously.

Animals with diarrhea, especially those that are dehydrated, may have anorexia. Rehydration often resolves inappetence. Offering highly preferred foods with a high fluid content such as oranges, grapes, or melons helps maintain hydration status and caloric intake. Increased intake of water may be achieved by adding commercially available fruit juice flavors, either to a water bottle placed on the cage or via syringe feeding if the animal has been trained for this behavior.

Antimicrobial drugs. Fecal or rectal bacterial culture with antibiotic sensitivity testing, and perhaps microscopic fecal examination and PCR gastrointestinal panels, are essential to guide clinicians to the most appropriate antibiotic therapy. In cases of severe acute diarrhea, empirical antibiotic choices may be considered while awaiting bacterial culture results. Nonhuman primates presenting with chronic or recurring diarrhea may respond to antibiotics that are thought to modulate the patient's intestinal immune system.[3,10,20] However, these antibiotics have been reported to cause bacterial dysbiosis,[17,25] and relapse may occur within 30 d after treatment cessation.[3] Risks of long-term antimicrobial treatment include selection for drug resistant microorganisms such as MRSA.[14,18]

Humane Endpoints/IACUC Considerations

The animal's overall well-being must be considered when evaluating and treating diarrhea. If diarrhea is an expected or potential complication associated with the research, the approved IACUC protocol should describe humane endpoints, which should be based on the animal's condition, progression, and prognosis. The specifics of the research study and usefulness of data collected from a debilitated animal should be considered. Animals should be evaluated at regular intervals for both objective assessments (body condition score, weight loss, and bloodwork) and subjective assessments (activity and behavior) as markers for endpoints. Animals unable to maintain weight or body condition should be considered for euthanasia, as should young animals that fail to follow the typical growth curve for the species. Animals that are obtunded and unable to return to normal mentation with treatment and support should be euthanized. Fecal scoring systems have been described in the literature and may be useful for tracking response to treatment when more quantitative monitoring plans are required.[3,26] These criteria are important to include in a study plan and should also be used in clinical situations unrelated to the research.

New World Primate (NWP) Considerations

Chronic diarrhea and intractable weight loss are major concerns in callitrichids, leading to high morbidity and potential death.[23] Various disease processes with nonspecific clinical signs have been inappropriately labelled as 'Marmoset Wasting Syndrome,' which may obscure the identification of unique or multifactorial etiologies.[9,11,19] In marmosets, corticosteroids such as budesonide have demonstrated potential as a solo or adjunct therapy for IBD-like conditions.[19] Anti-tumor necrosis factor (TNF) agents and aminosalicylates have been useful in treating IBD and related conditions in humans, with interest growing in microbiome manipulation to improve clinical outcomes.[7,13,24] These compounds have undergone limited investigation but may be important considerations in the future.

Common marmosets are also particularly sensitive to dysbiosis, which may precipitate chronic diarrhea.[22,23] Contributing factors include host environment, diets that differ significantly in composition from that of wild callitrichids, and antibiotic administration.[1,16] Fecal transplantation has been used in marmosets to treat diarrhea attributed to infectious bacteria and dysbiosis.[21,27] Gut microbiota composition analysis may give insight into the pathogenesis of chronic diarrhea.[16,23] It may also guide the development of probiotics that more closely match the natural flora of marmosets, and potentially present new treatment options for diarrhea.[6] Supportive therapy, as described above, remains a mainstay of clinical care in marmosets with diarrhea.

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