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Citrobacter rodentium

(*Citrobacter freundii* biotype 4280)

Classification

Non-motile, Gram-negative rod

Family

Enterobacteriaceae

Affected species

Mice and gerbils. Possibly Guinea pigs. Hamsters and rats are not susceptible. *C. freundii* is a human pathogen; *C. rodentium* is not zoonotic.

Frequency

Very rare in contemporary colonies. Possibility of outbreaks related to its use as a model organism for human disease. Prevalence in wild or feral populations unknown.

Transmission

Transmitted via the fecal-oral route.

Clinical Signs and Lesions

Disease occurs almost exclusively in weanling mice. Although all strains and stocks of mice examined thus far are susceptible to *C. rodentium* colonization, the nature of the subsequent disease appears to be related to host factors. Clinical signs vary from subclinical hyperplasia of the colonic epithelium to clinically apparent diarrhea and colitis with weight loss, rectal prolapse, runting, and possible death. Genetic background, age, deficits in the immune system, and concurrent infection have all been shown to affect the course and severity of disease. Morbidity and mortality can be high in individual outbreaks. Immunocompetent animals will mount an immune response to the bacterium, leading to protective immunity.

In gerbils, one case report describes *C. rodentium* infection as fatal in most animals infected. In guinea pigs, one case report describes pneumonia, colitis, and septicemia associated with *C. freundii*. The biotype is not specified, so it is possible that *C. rodentium* was not the causative agent.

After gaining entry to the body via the oral route, *C. rodentium* uses the attaching and effacing mechanism to colonize the gastrointestinal tract. The organism attaches to a specialized area of colonic immune tissue known as the cecal patch. From there, the infection spreads to the distal colon. Typical gross lesions include visibly thickened colonic walls, a shrunken cecum, and an absence of normal stool in the colon. On histopathology, early in infection, large numbers of bacteria may be seen adherent to the brush border of the colonic mucosa. As the infection progresses, the presence of the bacteria induces a profound hyperplasia of the colonic mucosa. Peak hyperplasia occurs 2-3 weeks after infection. At the point of the peak hyperplastic response, the bacteria can no longer be isolated from the intestines. Inflammation may or may not be present; age and genotype tends to determine whether or not inflammatory infiltrates are associated with the infection. Two months after infection, lesions have resolved and colonic mucosa appears normal.

Diagnosis

C. rodentium may be cultured on MacConkey agar. Biochemical testing can distinguish *C. rodentium* from *C. freundii* since *C. rodentium* is indole-negative and positive for ornithine decarboxylase (among other tests). *C. rodentium* may be suspected through clinical signs, gross lesions, and the typical appearance of histopathologic lesions, but culture of affected animals is necessary to confirm the diagnosis. Lesions appear very similar to those caused by some *Helicobacter* spp., although *Helicobacter*-associated lesions affect older mice, whereas *C. rodentium* affects weanling mice. However, with immunodeficient mice, this distinction may be lost. PCR to detect *C. rodentium* in feces has been developed, but is not available commercially. Because immunocompetent animals clear infection, colony screening is most effective when performed on 4-5 week old mice. Screening of older colony mice, or of immunocompetent sentinels after more than 8 weeks of exposure, is unlikely to find *C. rodentium* even when present.

Interference with Research

Immunocompetent mice infected with *C. rodentium* make a full recovery after approximately two months. During that period of illness, however, the animals may be ill and unfit for use for research or breeding. The diarrhea and colonic involvement may stunt the growth of the animals, or predispose them to secondary infections. Most immunodeficient mice will not clear the infection and will remain ill and unfit for research, as well as possibly serving as a source of infection for other animals.

C. rodentium is used as a model of human disease caused by pathogenic *E. coli*, so animals with active or prior infections will not be suitable for this research application.

Prevention and Treatment

Citrobacter rodentium is not a spore-former, and spreads slowly among animals in infected colonies. *C. rodentium* is likely to be relatively fragile and does not seem to survive long in the environment. Other than observed epidemiology of the agent, published data to support this claim do not exist, however. As a non-spore-former, *C. rodentium* should be susceptible to most common disinfectants effective against Enterobacteriaceae used in animal facilities. Theoretically, any chemical or mechanical sterilant will be effective against *C. rodentium* in the environment. However, *Citrobacter freundii* isolates have been described as biofilm inhabitants, and this may increase their resistance to environmental decontamination. Enterobacteriaceae are also profligate in their sharing of plasmids and other mechanisms of resistance. This may increase the likelihood that *Citrobacter* isolates are multi-drug or biocide resistant.

Treatment is not recommended. Treatment of animals with antimicrobials may serve to treat illness, but rarely, if ever, resolves the carrier state, nor will antibiotic treatment eliminate bacteria from the bedding or cage surfaces. One report of antibiotic treatment of *C. rodentium* involved the use of enrofloxacin in immunodeficient mice. This treatment decreased colony mortality and allowed enough animals to survive to allow for rederivation of the colony. To obtain animals without *C. rodentium*, animals should be rederived through embryo transfer or hysterectomy into/onto *C. rodentium*-free dams.

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T: +1 877 CRIVER 1 • +1 877 274 8371
E: askcharlesriver@crl.com • www.criver.com