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A Review of the Opportunistic Pathogen *Citrobacter Freundii* in Piglets Post Weaning : Public Health Importance

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ABSTRACT

The review study will describe clearly related research about *Citrobacter freundii* in piglet intestines which has been known to play a very important role in animal health and its effects on aspects of public health. Thus, the existence of *Citrobacter freundii* as a pathogenic opportunistic bacterium as a result of weaning plays an important role in formation and maintenance of the intestinal microbiota which affects the health and growth performance of pigs in the future. The review discussed the presence of *Citrobacter freundii* in the intestines of healthy pigs and its presence during the weaning period. The review explains comprehensively related research findings regarding the cytotoxicity of *Citrobacter freundii* and its resistance to several antimicrobials and provide an overview of recent studies that could help facilitate the design of a new strategy for conducting further research on *Citrobacter freundii* in pigs.

Keywords: *Citrobacter freundii*, microbiota, piglets, antimicrobial resistance, public health

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INTRODUCTION

Scraps are home to diverse communities of microbial species that have a symbiotic link to pigs. In maintaining the dietary, physiological, and immunological functions of pigs, the gut microbiot population, or microbiota, has an important role[1]. But the microbial community also comprises species that cause disease such as *Escherichia coli*, *Salmonella*, *Clostridia* and *Citrobacter*. The disease and death of these pathogenic organs will occur. Thus, in the livestock industry the use of prophylactic antibiotics was widely used. Disturbance during pig breeding of the intestinal microbial ecosystem will significantly increase disease risk. Piglets are weaned until a healthy microbial population is formed and the immune system matures in order to speed up their development. Weaning stress will interact with the intestinal microbial ecosystem[2], thus rendering it more vulnerable to post-weaning bacteria [3]. This condition is prevented with prophylactic antibiotics, which decreases the occurrence of GDD, particularly when weaning. Increased antimicrobial resistance has been caused by prophylactic antibiotics and by growth-foster antibiotics and is now a significant global public health problem[4].

Citrobacter Freundii is a *Citrobacter* family bacteria which is a natural environment in both the human and animal intestinal tract[5]. *Citrobacter Freundii* is a member of the genus *Citrobacter*. But that is *C. Freundii* can also contribute to diarrhoea and other human infections[6]. A few *C. Freundii* isolates are characterised by virulence and cause human food poisoning or diarrhea[5]. The major factors of virulence observed in *C.*

caused diarrhoea. *Freundii* are toxins that are homologated to cholera subunitB[5], including toxins such as shiga, a he table toxin.

In order to shape the microbial communities of the pig's intestines, the microbial composition of the intestins is established by various internal and external influences such as diet changes as well as probiotic and prebiotic provision and antibiotic supplementation in the feed [7]. Weaning is therefore an essential period of development and stress in animals in the early stages of life. The intestinal dynamics of piglets, especially *Citrobacter* bacteria during the weaning transition, are therefore interesting because they affect the health and production of growth of piglets. The results of the most recent and relevant research , which focuses on *Citrobacter* in the intestines of piglets, that affect piglets health, will be examined in this review.

Citrobacter the member of *Enterobacteriaceae*

Both *Enterobacteriaceae* members share such bacteriological characteristics. It belongs to the gram-negative , rod-shaped and optional anaerobic community. Species of 1.0 x 2.0-6.0 µm *Citro* bacteria. The bacteria are solitary or colonial, have no capsule and are motile. *C.* In the medium of MacConkey Agar, the *freundii* shaped small, round, dark pink convex colonies. Also recorded were rough or slimy forms. At a certain temperature of 37 °C *Citrobacter* grows optimally[8]. *Citrobacter* is present in a range of environmental sources, including soil and water, and in human and animal digestive tracts. These bacteria rarely cause illness, although some species can lead to infection of the urinary tract, sepsis and

(NO) oxide can be rapidly transformed from released into the intestinal lumen into nitrate (NO₃⁻). [30] The rich nitrate environment is very beneficial to Enterobacteriaceae growth that covers the gene nitrate reductase [31]. Several enterotoxigenic E pathogens in the family of enterobaceae, namely *Salmonella enterica* serovar Typhimurium. *Coli* (EPEC), caused by pigs, can cause intestinal inflammation, disrupting the composition of microbiota [32, 33]. In studying the *Salmonella typhimurium* model, Arguello *et al.* [34] showed that there was a decline in the populations of bacteria needed, such as bifidobacterium, and lactobacillus, with an increase in pathogenic bacteria as *Citrobacter* and anaerobic decrease, namely *Clostridium*, *Ruminococcus*. Or diallister on weaned piglets' ileal mucosa. Intestinal inflammation due to weaning thus disrupts the intestinal microbiota, promoting in particular Enterobacteriaceae, which promotes the growth of enteropathogenic bacterias. More study is therefore required to understand the effect of colitis on intestinal microbiota impairments in piglets after weaning [35].

Cytotoxicity of *Citrobacter freundii* in Pigs

A study conducted by Bai *et al.*, [5] in a village in China, has found 26 *Citrobacter* isolates into 20 pulse types, and 2 of them from pigs and have cytotoxic activity. The isolates obtained from humans and animals have the same types of pulse. It was also found that one animal and fly isolate had the same type of pulse. This suggests that animals can act as reservoirs for human infection and flies may act as carriers of transmission. Flies are known to transmit bacteria between humans. In a study flies reported that not only as a mechanical vector, but bacteria have been found to multiply in the mouth of flies and excreted through fly feces. Both isolates have cytotoxicity and adhesion activities to HEp-2 cells. Determination of the cytotoxicity of bacteria to cells is carried out by measuring the lactate dehydrogenase produced by the cells. This treatment causes the cells to release 24.3% dehydrogenated lactate (LDH) which causes damage and cell death of > 50%.

Another study conducted by Tschape *et al.*, [15] found the verotoxinogenic properties of *Citrobacter freundii* which contaminated vegetables used in sandwiches in a nursing school. Vegetables contaminated with verotoxin from *Citrobacter freundii* are caused by the use of manure from pig feces in organic gardens. This incident causes severe gastroenteritis and haemolytic uraemic syndrome. Of the 152 people, 36 had positive test results for verotoxin using the ELISA testing method. And surprisingly, 59 isolates were found including *C. freundii* from 72 isolates and the rest were 13 isolates from *E. Coli*. This examination was performed using the dot blot hybridization techniques method on positive stool samples.

Research conducted by Liu *et al.*, [6] in the Maanshan Ahui Province of China isolated *Citrobacter* spp. from patients with diarrhea, foodstuffs, and some of them come from pork and pork. Of the 62 isolates tested, four isolates (including three *C. youngae* and one *C. freundii*) showed the strongest adhesion, with an adhesion index of > 50.25 isolates showed moderate adhesion, with an adhesion index between 1 to 50. Nineteen isolates showed weak adhesion, with adhesion index <1. The remaining isolates showed ambivalent or no adhesion. The lowest adhesion rates of each type of bacteria were *C. kii* (25%), *C. freundii* (77%) and *C. youngae* (88%). There was no significant difference ($P > 0.05$) of any

adhesion between several sources (human and food) of *Citrobacter* isolates.

Another study conducted by Tajeddin *et al.*, [37] regarding the outbreak in the Islamic Republic of Iran, found 19 isolates of *Citrobacter* out of 484 samples tested. Of the 19 *Citrobacter* isolates obtained, two of them carried the *stx1* gene. In his research, this was the first time an outbreak was caused by foodborne illness with *stx1* encoded by the *C. freundii* strain. Since only a small proportion of these strains carry the *stx1* gene, it is possible that other virulence factors exist in these bacteria. Other virulence factors that have been reported for diarrhea associated with *C. freundii* include a heat-stable toxin, cholerae and *aer*. The presence of *stx1* encoded by the *C. freundii* strain in diarrhea in this study is significant, although the clinical impact and role of this emerging strain in human pathogenicity have not been reported. The spread of Shiga toxin-producing phages by horizontal gene transfer can occur via environmental stimulation, as may antibiotics be the cause of this emergence [38].

Another study conducted by Schmidt *et al.*, [39] showed that *Citrobacter freundii* can produce Shiga-like Toxin II-Related Cytotoxin isolated from patients with diarrhea and meat. In this incident, to determine the presence of *slt*-genes associated with *Citrobacter freundii*, an examination was carried out by colony hybridization, PCR analysis, and nucleotide sequence. In testing based on the toxicity of *Citrobacter freundii* it can produce functional toxins. In his research, he found a similarity with the genes produced by the *Escherichia coli* *slt-II* group. It is suspected that this happened because of the transfer of genes between the two bacteria. Because when the neutralization test was carried out, this study showed that the cytotoxic activity of the *C. freundii* isolates could be neutralized by antibodies against SLT-II produced by *Escherichia coli*. To ensure the existence of a relationship between the generator between the two bacteria was examined using PCR and found that *C. freundii* had different results and determined that *C. freundii* had *slt-IcA* and *slt-IcB* genes toxins. This is because Shiga toxin-encoding phages are highly mobile both in regulation and transverse horizontally due to environmental influences such as exposure to antibiotics [38]. In general, lysogenic phages are important particles in population dynamics within the host, which are useful for killing sensitive bacteria and converting lysogenic to viable bacteria [40].

Guarino *et al.*, [16] have also successfully detected the presence of 18-amino-acid heat-stable enterotoxin produced by *Citrobacter freundii* and which is similar to 18-amino-acid *Escherichia coli* heat-stable enterotoxin. The role of the toxin produced by *Citrobacter* sp. in inducing diarrhea is not known, but the toxin from *Citrobacter* sp. has a biological potency similar to the toxin from *Escherichia coli*. Furthermore, this study indicated the presence of a strain of *Citrobacter* sp. which can produce 75% more toxins than *Escherichia coli*, which isolates *Citrobacter* sp. This optimization was carried out under the same conditions as *E. coli*.

Antimicrobial Resistance Profile of *Citrobacter freundii* in Pig

C. Freundii is a commensal, but unstudied micro-organism, which is mostly isolated from severe nosocomial infections in human beings [31] because it is clinically significant in animal disorders related to a multi-drug resistance [18]. In a study by Evangelopoulou *et al.*, the resistance level of *C* was tested. Pig galbalader

isolated freundi showed resistance to 20 of the 24 antibiotics examined. Antibiotics are amoxicillin (30 µg), aztreonam (30 µg), cefotaxime (30 µg), cefoxitin (30 µg), cefazidime (30 µg), ceftriaxone (30 µg), cefuroxime (30 µg), colistin (50 µg), enrofloxacin (5 µg), gentamicin (10 µg) and enrofloxacin (15 µg), amoxicillin (30 µg), aztreonam (30 µg), cefoxitin (30 µg), cefoxitin (30 µg), Cef Of the antibiotics C of all these. Aztreonam, cefotaxime, tigecycline, and doripenem were not immune to freundi. The test uses the process of disc diffusion [43]. The developmental capacity to acquire resistance genes affects the trajectory of an infection, immune-response prevention and interactions with host pathogens[19]. The key reservoir of multidrug resistance for multiresistant bacteria showed that pigs are the most significant. The use of antimicrobials in the feed helps to excrete gram-negative enteric pathogens which cause pork to contaminate pork products that can lead to consumer infection[44].

Multidrug resistance can be caused by the transfer of resistance genes from the various resistor genes encoded in a resistant microbe to different bacterial species encoding related antimicrobial classes[45]. Resistance to antimicrobials can be transmitted to both pathogenic and commensal pathogens[46,47], such as gram-negative bacteria[48-55] and gram-positive pathogens[56-62]. Antimicrobial resistance can also be transmitted by animal products as a virulence factor[63-67]. This can have major effects on the growth of bacteria in natural bacterial populations and may contribute to infectious diseases [19] as a way to escape the immune system. Pathogenic microorganisms may also live indefinitely or temporarily in a pig's bile blood and become a multidrug reservoir of Gram's negative bacteria, which may contaminate pork products and infect consumers.

Liu et al. also tested 82 isolates[6] in an alternative analysis. Freundi against 17 antibiotics belonging to 10 classes of antibiotics using the CLSI recommended disc diffusion process. The 82 isolates of mainly C. Freundi have been immune to β-lactams, in particular penicillin (41.5%), cephalosporins (19.5%–98.8%) and monobactam (25%). Resistance to two quinolones: ciprofloxacin (7.3%) and levofloxacin (2.4%), aminoglycosides (2.4%–11.0%); phenicol (2.4%), sulfonamides (6.1%), tetracycline (8.5%), and nitrofurantoin (13.4%) respectively. The prevalence of resistance to cephalosporins of first generation, such as cefazolin, was 98.8% and cefoxitin of second generation was 74.4%. In general, ceftriaxone (28.0%), ceftazidim (29.3%) and cefepime (19.5%) were less resistant in this sample; in the present study, 26 isolates were multi drug (MDR), with an antibiotic resistance of three or more different class (MDR) groups.

Another study by Liu et al.[68] which isolates *Citrobacter*, found 21 isolates of *Citrobacter* after E from pork samples, pig faeces and pork farms. 10 isolates were multidrug resistant out of 27 isolates obtained from *Citrobacter*. High frequencies of gentamicin (98% of the isolates), streptomycin (98%), tetracycline (98%), chloramphenicol (98%), kanamycin (96%), doxycycline (70%), ciprofloxacin have been presented. (74.1%), nalidixic acid (97.4%), ampicillin (64.7%), and amoxicillin-clavulanic (60.8%) percent. (94.0%), nalidixic acid (94.1%) and trimethoprim (94.1%). In general, sulfamethoxazole, trimethoprim, tetracycline, gentamicin, streptomycin and chloramphenicol resistant isolates. In his study, 50% of the *Citrobacter* isolates isolated from

pork, but some have different antibiotic resistance profiles and are characterised by different resistant genes, to 100% homology with environmental isolates. Several recent studies have found that *Citrobacter* isolated from pork samples and hog farm conditions have antibiotic resistance[69,70]. *Citrobacter* Research has shown that pork and pig farms can be sources of resistant bacteria which can be passed on to humans by meat products in industrial chains.

CONCLUSION

In this review it can be concluded that the microbial ecosystem in the digestive tract of piglets plays an important role in physiological functions and antibody formation. The presence of digestive tract disorders caused by factors such as stress as a result of weaning can disrupt the microbiota system in the digestive tract of piglets. This can provide opportunities for pathogenic opportunistic bacteria such as *Citrobacter freundi* to grow rapidly to form colonies that can cause disease. *Citrobacter* has the ability to produce toxins that are resistant to heating and produce shiga-like toxins which of course can disrupt the balance of the microbiota composition in the intestines of pigs. In addition, these bacteria also have the ability to mutually transfer toxin coding between other bacterial groups such as *E. coli*. Many recent studies also reveal that in general *Citrobacter freundi* is MDR which causes these bacteria to be difficult to control with certain antibiotics. In addition, the threat of *Citrobacter freundi* which is MDR can also act as a foodborne disease in meat that can potentially be transmitted to humans and have an impact on public health. In addition, these bacteria can also pollute the environment such as soil and water. The importance of further understanding about the threat of *Citrobacter freundi* which is MDR requires special attention to determine the policy of using antibiotics in a pig farm.

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