

Effects of Subclinical Bacterial Infections on Immune Response in Cats

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Abstract This study explores the effects of such infections on the feline immune response, with an emphasis on the underlying molecular and cellular mechanisms. The study examines key components of the feline immune system and how these infections alter immune cell populations, cytokine profiles, and immune activation. Special attention is given to the case study of *Bartonella henselae*, a common bacterial pathogen, and its role in modulating feline immunity. Additionally, the research investigates the clinical and subclinical consequences of immune dysregulation, including increased susceptibility to other infections, autoimmune reactions, and chronic inflammation. Various diagnostic approaches, such as serological and molecular techniques, are reviewed to highlight challenges in identifying subclinical infections. Therapeutic strategies, including antibiotics, immune modulation, and long-term management practices, are discussed as potential solutions for controlling these infections. The findings of this study emphasize the importance of addressing subclinical bacterial infections to improve feline health and reduce veterinary complications. Future research is needed to refine diagnostic techniques and develop more effective treatment protocols, ultimately advancing both clinical practice and public health outcomes in veterinary medicine.

Keywords Subclinical bacterial infections; Feline immune system; *Bartonella henselae*; Immune dysregulation; Veterinary diagnostics

1 Introduction

Subclinical bacterial infections in cats, particularly subclinical bacteriuria, are characterized by the presence of bacteria in the urinary tract without any overt clinical symptoms. These infections are relatively common, especially in older cats and those with comorbidities, with prevalence rates reported to be as high as 29% in certain populations (White et al., 2016). The most frequently isolated bacteria in these cases include *Escherichia coli*, *Enterococcus* species, and *Staphylococcus* species (Teichmann-Knorrn and Dorsch, 2018). Despite the absence of symptoms, subclinical bacteriuria can be associated with specific risk factors such as female sex, lower urine specific gravity, and chronic kidney disease (Puchot et al., 2017; Peterson et al., 2020).

Understanding subclinical infections is crucial for feline health management as they can influence treatment decisions and antimicrobial use. While these infections are often not treated due to the lack of symptoms, they pose a challenge in terms of antimicrobial resistance, which is a growing concern in veterinary medicine (Teichmann-Knorrn et al., 2018). The decision to treat subclinical bacteriuria is complex, as there is currently insufficient evidence to support routine treatment, and inappropriate use of antimicrobials can contribute to resistance (Teichmann-Knorrn and Dorsch, 2018; Dorsch et al., 2019). Moreover, distinguishing between subclinical bacteriuria and bacterial cystitis is essential for effective treatment protocols and antimicrobial stewardship, especially in cats with underlying conditions or those using devices like subcutaneous ureteral bypass systems (Djoneva et al., 2023).

This study attempts to explore the prevalence and clinical implications of subclinical bacterial infections in cats, discuss the associated risk factors, and provide an overview of the impact of these infections on feline health outcomes. By focusing on subclinical bacteriuria, the study aims to provide insights into the necessity and timing of treatment interventions, thereby contributing to more informed clinical decision-making and improved management of feline urinary tract health.

the bacterial load without completely eradicating the pathogen. This state of infection is often identified through laboratory tests rather than clinical observation, as the host does not exhibit the typical signs of illness (Rocha et al., 2018).

3.2 Prevalence and distribution of subclinical infections in felines

Subclinical infections are common in felines, particularly in environments where multiple animals are housed together, such as breeding colonies or shelters. For instance, feline enteric coronavirus (FECV) is known to cause subclinical infections in cats, with many infected individuals showing no clinical signs despite the presence of the virus (Pearson et al., 2019). The prevalence of such infections can vary based on factors like geographic location, population density, and the presence of other diseases that may compromise the immune system (Priolo et al., 2019).

3.3 Common bacterial pathogens responsible for subclinical infections

Several bacterial pathogens are known to cause subclinical infections in cats. For example, *Leishmania infantum*, although primarily a protozoan, can lead to subclinical infections in felines, especially in areas where canine leishmaniosis is endemic. In these cases, cats may harbor the pathogen without showing symptoms, but they can still mount an immune response detectable through laboratory assays (Priolo et al., 2019). Additionally, other pathogens such as cytomegalovirus (CMV) in non-feline models have been shown to persist subclinically, affecting immune responses and potentially influencing the host's susceptibility to other infections (Rocha et al., 2018).

In summary, subclinical bacterial infections in cats are defined by the presence of bacteria without clinical symptoms, are prevalent in certain environments, and can be caused by various pathogens, including those that are typically associated with other species. These infections can influence the host's immune response and overall health.

4 Impact of Subclinical Infections on Immune Response

Subclinical bacterial infections in cats, particularly those caused by *Bartonella henselae*, can significantly impact the feline immune system. These infections often go unnoticed due to the absence of overt clinical symptoms, yet they can lead to chronic immune activation and alterations in immune cell populations.

4.1 Changes in immune cell populations during subclinical infections

Subclinical infections can lead to notable changes in immune cell populations in cats. For instance, a study on a cat with *Bartonella henselae* infection revealed a marked increase in intermediate and lymphoblastic lymphocytes, along with reactive macrophages, indicating an immune response despite the lack of severe clinical symptoms (Nivy et al., 2022). This suggests that even in the absence of overt disease, the immune system is actively responding to the presence of the pathogen.

4.2 Cytokine imbalances and chronic immune activation

Chronic immune activation due to subclinical infections can result in cytokine imbalances. *Bartonella henselae*, for example, is known to manipulate host immune responses, potentially leading to prolonged immune activation (Figure 2) (Thibau et al., 2022). This persistent activation can cause an imbalance in cytokine production, which may contribute to the development of immune-mediated conditions such as hemolytic anemia, as observed in some infected cats (Nivy et al., 2022). The ongoing immune response, even in the absence of symptoms, highlights the pathogen's ability to evade complete immune clearance and maintain a state of chronic infection.

4.3 Case study: *Bartonella henselae* and its effects on feline immunity

Bartonella henselae serves as a prime example of how subclinical infections can affect feline immunity. In a documented case, a cat with *Bartonella henselae* infection exhibited persistent fever and lymphadenopathy, alongside immune-mediated hemolytic anemia, despite being subclinical for a significant period (Nivy et al., 2022). This case underscores the pathogen's potential to cause significant immune dysregulation, even when the infection is not overtly symptomatic. The study also highlights the effectiveness of a combination treatment with

pradofloxacin and doxycycline in resolving clinical signs and achieving negative PCR results for *Bartonella henselae*, suggesting a potential therapeutic approach for managing such infections.

In summary, subclinical infections in cats, particularly those caused by *Bartonella henselae*, can lead to significant immune alterations, including changes in immune cell populations and cytokine imbalances. These infections can persist without obvious symptoms, yet they have the potential to cause chronic immune activation and related health issues.

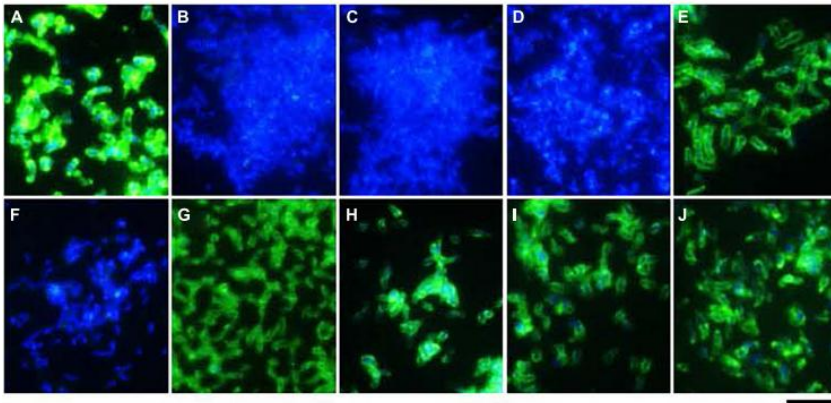


Figure 2 Surface expression of BadA in various *B. henselae* strains (immunofluorescence microscopy) (Adopted from Thibau et al., 2022)

Image caption: Surface expression of BadA was analysed via immunofluorescence microscopy using specific anti-BadA IgG antibodies (green). Bacterial DNA was counterstained using DAPI (blue). The illustrated *B. henselae* strains are (A) Marseille, (B) Marseille 1BadA-T, (C) Marseille 1BadA-D, (D) ATCC49882T var-1, (E) ATCC49882T var-2, (F) Berlin-I, (G) G-5436, (H) 88-64 Oklahoma, (I) FR96/BK38, and (J) FR96/BK3. Expression is observed for strains Marseille, ATCC49882T var-2, G-5436, 88-64 Oklahoma, FR96/BK38, and FR96/BK3, detected by the characteristic green halo. Strains ATCC49882T var-1 and Berlin-I do not express BadA, nor do the negative control strains Marseille 1BadA-T and Marseille 1BadA-D. Scale bar: 5 μ m (Adopted from Thibau et al., 2022)

5 Clinical and Subclinical Implications of Immune Dysregulation

5.1 Immune suppression and increased infection susceptibility

Subclinical bacterial infections in cats can lead to immune suppression, making them more susceptible to other infections. The immune system's ability to respond to pathogens is compromised, as seen in studies where immune checkpoints like TIGIT are upregulated, leading to reduced immune function and increased vulnerability to infections (Souza-Fonseca-Guimaraes et al., 2023). Additionally, dysbiosis in the microbiota, often caused by antibiotic use or dietary changes, can further impair immune responses, increasing the risk of chronic diseases and infections (Tizard et al. 2017).

5.2 Autoimmune reactions induced by subclinical infections

Subclinical infections can also trigger autoimmune reactions in cats. The immune system may mistakenly target the body's own cells, leading to autoimmune diseases. This phenomenon is partly due to the dysregulation of immune responses, where the balance between immune activation and suppression is disrupted. For instance, changes in the microbiota can influence the development of autoimmune diseases by altering immune responses (Tizard et al. 2017). Moreover, the presence of persistent bacterial infections can mimic self-antigens, potentially leading to autoimmunity (Souza-Fonseca-Guimaraes et al., 2023).

5.3 Chronic inflammation and its impact on feline health

Chronic inflammation is a significant consequence of immune dysregulation caused by subclinical infections. Persistent inflammatory responses can lead to tissue damage and contribute to the development of chronic diseases. In cats, chronic inflammation has been linked to conditions such as atopic dermatitis and respiratory allergies (Tizard et al. 2017). Furthermore, the presence of reactive oxygen species (ROS) as a response to

bacterial infections can exacerbate inflammation, leading to further health complications (Brown et al., 2021). Chronic inflammation not only affects the immediate health of cats but can also have long-term impacts on their overall well-being and quality of life.

In summary, subclinical bacterial infections in cats can lead to immune suppression, increased susceptibility to infections, autoimmune reactions, and chronic inflammation. These immune dysregulations have significant implications for feline health, potentially leading to chronic diseases and reduced quality of life.

6 Diagnostic Approaches to Subclinical Infections in Cats

6.1 Techniques for identifying subclinical bacterial infections

Identifying subclinical bacterial infections in cats can be challenging due to the absence of overt clinical symptoms. Traditional diagnostic methods often rely on the isolation of pathogens from biological samples, such as blood, urine, or tissue cultures (Woodhouse et al., 2024). However, these methods may not always detect subclinical infections due to low pathogen loads or intermittent shedding. Advanced techniques, such as polymerase chain reaction (PCR), have been employed to enhance detection sensitivity by amplifying bacterial DNA from samples, allowing for the identification of specific bacterial species even in low concentrations (Zottler et al., 2017; Maekawa et al., 2019).

6.2 Advancements in serological and molecular diagnostics

Recent advancements in serological and molecular diagnostics have significantly improved the detection of subclinical infections in cats. Serological tests, such as enzyme-linked immunosorbent assays (ELISA), have been developed to detect specific antibodies against pathogens, providing a non-invasive and efficient diagnostic tool. For instance, the detection of antibodies against the lung nematode *Aelurostrongylus abstrusus* in cats using ELISA has shown high sensitivity and specificity, making it a reliable method for diagnosing subclinical infections (Zottler et al., 2017). Molecular diagnostics, including next-generation sequencing and quantitative PCR, offer precise identification and quantification of bacterial pathogens, further enhancing diagnostic accuracy (Mesa-Sanchez et al., 2020).

6.3 Limitations and challenges in detecting subclinical infections

Despite these advancements, several limitations and challenges remain in detecting subclinical infections in cats. One major challenge is the potential for cross-reactivity in serological tests, which can lead to false-positive results, as seen in cases where antibodies against other nematodes were detected in cats tested for *A. abstrusus*. Additionally, the variability in immune responses among individual cats can affect the reliability of serological assays. Molecular diagnostics, while highly sensitive, can be limited by the availability of specific primers and the need for specialized equipment and expertise. Furthermore, the interpretation of results can be complicated by the presence of commensal bacteria or transient infections that do not necessarily indicate a subclinical disease state (Zottler et al., 2017; Sierra et al., 2020).

In summary, while significant progress has been made in the diagnostic approaches for subclinical bacterial infections in cats, ongoing research and development are needed to address the existing limitations and improve the accuracy and reliability of these diagnostic tools.

7 Therapeutic Strategies for Managing Subclinical Bacterial Infections

7.1 Antibiotic use and resistance in subclinical infections

The use of antibiotics in managing subclinical bacterial infections in cats is a double-edged sword. While antibiotics can effectively reduce bacterial load and prevent the progression of infections, their overuse or misuse can lead to antibiotic resistance. This resistance complicates future treatment efforts and poses a significant challenge in veterinary medicine. The development of resistance is particularly concerning in subclinical infections, where symptoms are not overt, leading to potential underestimation of the infection's severity and inappropriate antibiotic use. Therefore, judicious use of antibiotics, guided by sensitivity testing, is crucial to prevent the emergence of resistant bacterial strains.

7.2 Immune modulation and supportive therapies

Immune modulation through dietary supplements and probiotics offers a promising alternative or adjunct to antibiotics in managing subclinical infections. For instance, the administration of *Bacillus subtilis* and chitin has been shown to enhance systemic and mucosal immunity in fish, suggesting potential applications in other animals, including cats (Sangma and Kamilya, 2015). These supplements can stimulate various immune parameters, such as oxygen radical production and lysozyme activity, which are critical for an effective immune response. By boosting the immune system, these therapies can help control bacterial infections naturally, reducing the reliance on antibiotics and minimizing the risk of resistance development (Gjini and Brito, 2016).

7.3 Prevention and long-term management of subclinical infections

Preventing subclinical infections in cats involves a multifaceted approach that includes maintaining good hygiene, regular veterinary check-ups, and appropriate vaccination schedules. Long-term management also benefits from dietary interventions that support immune health. The use of probiotics and immunostimulants, as demonstrated in studies with fish, can be adapted for feline health to enhance resistance against infections (Sangma and Kamilya, 2015). These strategies not only help in managing existing infections but also in preventing new ones, ensuring the overall well-being of cats. Implementing these preventive measures can significantly reduce the incidence of subclinical infections and the associated complications, promoting a healthier feline population (Hodille et al., 2017).

In summary, managing subclinical bacterial infections in cats requires a balanced approach that includes careful antibiotic use, immune modulation through dietary supplements, and preventive strategies to ensure long-term health and reduce the risk of antibiotic resistance.

8 Concluding Remarks

Subclinical infections in cats can significantly influence their immune responses, often without overt clinical symptoms. For instance, cats infected with feline enteric coronavirus (FECV) typically exhibit strong systemic IgG and mucosal IgA responses, which diminish after the virus is cleared, indicating a robust humoral response that helps control the infection. Similarly, domestic cats exposed to SARS-CoV-2 develop a strong antiviral response, characterized by an increase in CD8⁺ cells and upregulation of antiviral genes, effectively clearing the virus within a week without significant clinical signs. These findings highlight the capacity of feline immune systems to mount effective responses to subclinical infections, which may not always manifest in noticeable symptoms but still engage significant immune activity.

Future research should focus on further elucidating the mechanisms underlying the immune responses to subclinical infections in cats. Investigating the role of specific immune cells and signaling pathways, such as those involved in the production of reactive oxygen species (ROS) in response to bacterial infections, could provide deeper insights into feline immunity. Additionally, exploring the potential of dietary supplements, such as probiotics and immunostimulants, to enhance immune responses in cats could offer practical applications for improving feline health and resistance to infections. Clinical practice could benefit from developing diagnostic tools that better identify subclinical infections and assess immune responses, allowing for more targeted interventions.

Understanding the immune responses of cats to subclinical infections has important implications for both public health and veterinary medicine. Cats can act as reservoirs for various pathogens, including those that affect humans, such as SARS-CoV-2 and FECV2 3. By enhancing our knowledge of how cats respond to these infections, we can better manage the risks of zoonotic transmission. Moreover, improving the health and immune resilience of domestic cats through informed veterinary practices can reduce the prevalence of infections and their potential spread to other animals and humans. This underscores the need for continued research and collaboration between veterinary and public health sectors to safeguard both animal and human health.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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