IMMUNODYSREGULATION IN ANTHRAX INFECTION IN NIGERIA: A SYSTEMATIC REVIEW

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ABSTRACT
Background: Anthrax, caused by *Bacillus anthracis*, requires comprehensive analysis to understand immunodysregulation for effective therapeutic interventions.
Aim This work was designed to conduct a systematic review immunodysregulation in anthrax infection in Nigeria
Materials and Methods: A systematic literature search was conducted using specific keywords and inclusion/exclusion criteria. Selected studies underwent data extraction, synthesis, and analysis. A comprehensive literature search included databases such as PubMed/MEDLINE, Embase, Nature, Web of Science, and Scopus. The search strategy combined keywords like "anthrax infection," "*Bacillus anthracis*," "Immunodysregulation," "immune response," and "toxins" using Boolean operators and MeSH terms for inclusiveness. Quality assessment and ethical considerations were also addressed.
Results: Based on the review, it was discovered that, the first case of anthrax disease in animals in Nigeria was confirmed in Niger State, on the 17th July, 2023. The Federal Ministry of Agriculture and Rural Development in Nigeria confirmed the first case of anthrax disease in animals in Niger State, Nigeria on the 17th July, 2023 through a laboratory tests by the National Veterinary Research Institute laboratory. Effective prevention and management of anthrax in Nigeria necessitates vaccination campaigns, surveillance systems, and public health education. Challenges like limited veterinary services and healthcare professional awareness require collaboration. *Bacillus anthracis* poses a threat to human health, emphasizing the importance of vaccination, education, meat inspection, hygiene, and timely treatment. The pathogen disrupts the host immune system through various mechanisms, including capsule formation, toxin production, and immune evasion. Immunodysregulation contributes to anthrax's severity and mortality rates, allowing the bacteria to evade immune responses. Understanding these mechanisms through bioinformatics and network-based approaches can identify therapeutic targets and intervention strategies.
Conclusion: This research highlights the importance of comprehending immunodysregulation in *Bacillus anthracis*-induced anthrax for effective therapies. The systematic review focused on the Nigerian context, conducting a rigorous literature search across databases. On July 17, 2023, the Federal Ministry of Agriculture confirmed Nigeria's first animal anthrax case in Niger State, emphasizing the need for vaccination campaigns, surveillance, and health education. The study also revealed how *Bacillus anthracis* disrupts the host immune system, leading to severe outcomes and evading immune responses. Understanding these mechanisms through bioinformatics can inform therapeutic interventions, stressing the significance of proactive measures and collaboration in public health. Ongoing research and collaboration are crucial for

INTRODUCTION

Immunodysregulation refers to the disruption or imbalance of normal immune responses in the context of a specific infection or disease. In the case of anthrax infection, the immune system's function and response are perturbed or altered due to the actions of the bacterium *Bacillus anthracis* (Elisabeth *et al.*, 2022).

During anthrax infection, *B. anthracis* utilizes various strategies to evade or manipulate the host immune system, resulting in an imbalance or dysregulation of immune responses. This dysregulation can manifest in several ways, including the suppression of specific immune cells, inhibition of pro-inflammatory responses, and modulation of immune signaling pathways. The consequences of Immunodysregulation in anthrax infection can be significant for the host. It can impair the immune system's ability to mount an effective response against the invading pathogen, leading to persistent infection or the dissemination of bacteria throughout the body. Additionally, dysregulated immune responses can contribute to the development of severe systemic symptoms and the associated pathology of anthrax, such as tissue damage, organ failure, and septic shock (Janet *et al.,* 2018).

The study of Immunodysregulation in anthrax infection is crucial for comprehending the intricate interactions between the host and the pathogen. It provides valuable insights into the mechanisms by which *B. anthracis* evades immune detection and clearance, enabling researchers to identify potential targets for therapeutic interventions. By modulating the dysregulated immune responses, it may be possible to enhance the host's ability to combat the infection and improve the efficacy of existing treatments or vaccine strategies (Satish *et al.* 2015). .

Exploring immunodysregulation in anthrax infection plays a vital role in unraveling the complex dynamics between *Bacillus anthracis* and the host immune system. This understanding contributes to a deeper comprehension of the disease's pathogenesis and offers opportunities for the development of innovative approaches to mitigate the harmful effects of anthrax The Federal Ministry of Agriculture and Rural Development in Nigeria confirmed the first case of anthrax disease in animals in Niger State, Nigeria on the 17th July, 2023 through a laboratory tests by the National Veterinary Research Institute laboratory (FMARD, 2023).

Anthrax is a severe infectious disease caused by the spore-forming bacterium *Bacillus anthracis* is primarily known for its potential as a bioterrorism agent due to its ability to cause high morbidity and mortality rates. The pathogenesis of anthrax involves the release of several virulence factors by *B. anthracis,* which manipulate the host immune response and facilitate bacterial survival and dissemination. Understanding the Immunodysregulation associated with anthrax infection is crucial for the development of effective therapeutic strategies and the design of preventive measures (Kari and Kingshuk, 2023). .

The immune system plays a pivotal role in combating infections by orchestrating a coordinated response against invading pathogens. However, *B. anthracis* has evolved sophisticated mechanisms to evade and subvert host immune defenses, leading to Immunodysregulation. Previous studies have provided valuable insights into the immunological events during anthrax infection. Nonetheless, a comprehensive and systematic analysis of the Immunodysregulation in anthrax is needed to consolidate the existing knowledge and identify potential therapeutic targets (Wanying *et al.,* 2017). In recent years, advancements in immunological techniques, high-throughput technologies, and bioinformatics have provided powerful tools to study the host-pathogen interactions at a systems level. These approaches have facilitated the identification and characterization of immune-related genes, proteins, and pathways that are dysregulated during anthrax infection. Systematic analyses of the immunological responses to anthrax can uncover the intricate interplay between host and pathogen, shedding light on the immune evasion strategies employed by *B. anthracis* and potential avenues for intervention (Serkan *et al.,* 003). The objective of this research review was to conduct a comprehensive systematic analysis of the Immunodysregulation in anthrax infection.

By examining the available literature, collate and synthesize the current knowledge regarding the immunological alterations induced by *B. anthracis*. This analysis will encompass a wide range of immunological aspects, including innate and adaptive immune responses, cytokine signaling, immune cell activation, and modulation of host immune signaling pathways. Moreover, by leveraging the power of bioinformatics and network-based approaches, we will explore the complex regulatory networks governing Immunodysregulation in anthrax. By elucidating the immunological changes occurring during anthrax infection, this systematic analysis will contribute to a better understanding of the host-pathogen interactions and the underlying molecular mechanisms. Ultimately, this knowledge may facilitate the development of novel therapeutic interventions, such as targeted immunomodulatory strategies or vaccine designs, to enhance host defense against anthrax. Furthermore, the findings from this research review may have broader implications in understanding the immune responses to other bacterial infections and in the development of countermeasures against bioterrorism agents.

This systematic analysis aims to provide a comprehensive overview of the immunodysregulation associated with anthrax infection. By synthesizing the existing knowledge, we strive to shed light on the complex interplay between *B. anthracis* and the host immune system. The outcomes of this research review have the potential to inform the development of innovative therapeutic approaches, contributing to the mitigation and control of anthrax and other infectious diseases.

Statement of Problem

Anthrax is a life-threatening infectious disease caused by the bacterium *Bacillus anthracis*, and it poses a significant threat to public health due to its potential use as a bioterrorism agent. The pathogenesis of anthrax involves intricate interactions between the bacterium and the host immune system. *B. anthracis* has developed sophisticated mechanisms to manipulate and evade host immune defenses, leading to Immunodysregulation. Although several studies have investigated the immunological responses during anthrax infection, a systematic analysis consolidating the existing knowledge on Immunodysregulation in anthrax is lacking.

The problem at hand is the absence of a comprehensive and integrated understanding of the Immunodysregulation associated with anthrax infection. The existing literature provides fragmented insights into specific aspects of the immune response to *B. anthracis*, but a systematic analysis is necessary to synthesize and consolidate this information. A thorough examination of the immunological alterations induced by *B. anthracis* is crucial to identify key molecular mechanisms and pathways involved in Immunodysregulation. Moreover, a systematic analysis can help elucidate the complex interplay between *B. anthracis* and the host immune system, shedding light on the strategies employed by the bacterium to evade immune surveillance and establish infection. Understanding these immune evasion mechanisms is essential for the development of effective therapeutic interventions and the design of preventive strategies.

Additionally, the identification of potential therapeutic targets for intervention relies on a comprehensive analysis of immunodysregulation during anthrax infection. By uncovering dysregulated immune-related genes, proteins, and pathways, this systematic review can facilitate the development of targeted immunomodulatory approaches or the design of novel vaccines to enhance host defense against anthrax.

To address this problem, a systematic review is needed to collate and synthesize the available literature on immunodysregulation in anthrax infection.

By conducting a comprehensive analysis of the immunological alterations induced by *B. anthracis*, this review was intended to fill the existing knowledge gaps, provide a holistic understanding of the host-pathogen interactions, and contribute to the development of effective therapeutic strategies for anthrax treatment and prevention.

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies. The following databases was searched:

1. PubMed/MEDLINE
2. Embase5968
3. Nature
4. Web of Science
5. Scopus

The search strategy combined relevant keywords, including "anthrax infection," "*Bacillus anthracis*," "Immunodysregulation," "immune response," and "toxins." Boolean operators (AND, OR) and MeSH terms (where applicable) were tilized to refine the search and ensure inclusiveness.

Inclusion and Exclusion Criteria

The inclusion criteria for the selection of studies are as follows:

1. Studies published in peer-reviewed journals.
2. Studies that investigate the Immunodysregulation in anthrax infection.
3. Studies that explore the impact of *Bacillus anthracis* toxins on innate and adaptive immune responses.
4. Studies involving in vitro, animal, and human models.

The exclusion criteria are as follows:

1. Non-English language publications.
2. Review articles, commentaries, and editorials
3. Studies not directly related to anthrax infection or Immunodysregulation.
4. Studies with insufficient data or poor methodology.

Study Selection Process

The initial screening involved reviewing titles and abstracts of the identified studies based on the inclusion and exclusion criteria. Full-text articles of potentially relevant studies were obtained and assessed for eligibility. Any discrepancies during the screening process was resolved through discussion and consensus among the reviewers.

Data Extraction

Data extraction involved systematic recording of relevant information from the selected studies. The following data were extracted:

1. **Study characteristics:** author, publication year, study design, sample size, and study duration.
2. **Study participants/species:** human, animal, or in vitro models.
3. Methodology: experimental protocols, techniques, and assays used to investigate immunodisregulation.
4. **Key findings:** outcomes related to immunodisregulation, including changes in immune cell populations, cytokine profiles, signaling pathways, antigen presentation, and T-cell responses.
5. Limitations and conclusions of the study.
6. **Data Synthesis and Analysis**
7. The extracted data were synthesized and analyzed descriptively. Key findings from the included studies were summarized and discussed in the context of Immunodysregulation in anthrax infection. Common themes, trends, and gaps in the literature were identified.
8. **Quality Assessment**
9. The quality and risk of bias of the included studies were valuated using appropriate tools, such as the Newcastle-Ottawa Scale for observational studies or the Cochrane Risk of Bias Tool for randomized controlled trials. The assessment considers ctors such as study design, sample size, methodology, and potential sources of bias.

Ethical Considerations

As this systematic review does not involve primary data collection from human participants, ethical approval is not required. However, the research adhered to ethical guidelines and standards for conducting systematic reviews and protecting intellectual property.

***Bacillus anthracis* in Nigeria**

Bacillus anthracis is a Gram-positive, spore-forming bacterium that is the causative agent of the deadly disease known as anthrax. The bacterium can be found in livestock, such as cattle, sheep, and goats, as well as in the soil. Due to the agricultural nature of Nigeria's economy and the close interaction between humans and animals, anthrax poses a significant threat to both livestock and humans. The first case was reported in July, 2023 in Niger State, Nigeria (FMARD, 2023).

Bacillus anthracis spores can enter the human body through various routes, including inhalation, ingestion, or through skin contact with contaminated animal products. The inhalation form of anthrax is the most severe and life-threatening. Once inside the body, the spores germinate and release toxins, leading to the development of symptoms (Pohanka, 2020).

The symptoms of anthrax vary depending on the route of transmission but can include flu-like symptoms, skin lesions, gastrointestinal distress, and respiratory complications (Pohanka, 2020). If left untreated, anthrax can be fatal, making it a public health concern in Nigeria.

Efforts to control and prevent anthrax in Nigeria involve a combination of measures. Vaccination campaigns targeting livestock, particularly those at high risk, such as animals in areas with a history of anthrax outbreaks, are crucial in reducing the spread of the disease. Surveillance systems are also in place to detect and respond to suspected cases promptly (Colin *et al.*, 2019).

Public health education plays a significant role in raising awareness about anthrax transmission and prevention among both farmers and the general population. This includes emphasizing proper handling and disposal of animal carcasses, avoiding consumption of meat from sick animals, and using personal protective equipment when handling potentially infected animals or their products (Colin *et al.*, . 2019). .

Despite efforts to control anthrax in Nigeria, several challenges persist. Limited access to veterinary services, inadequate laboratory facilities with rapid diagnosis, and a lack of awareness among healthcare professionals hinder effective surveillance and control measures. Collaborative efforts between the government, healthcare professionals, veterinarians, and communities are crucial for the successful management of anthrax (Dorota e*t al.*, 2012).

Bacillus anthracis poses a significant threat to both human and animal health in Nigeria. Understanding the prevalence, transmission, symptoms, and control measures associated with anthrax is essential for preventing outbreaks and reducing the impact of this deadly disease. By implementing comprehensive control strategies, raising awareness, and improving veterinary services and diagnostic capabilities, Nigeria can work towards mitigating the burden of anthrax in the country (Paola and Joachim, 2018).

***Bacillus anthracis* infection and Threat to human health in Nigeria**

Bacillus anthracis infection, commonly known as anthrax, is a serious bacterial disease that poses a significant threat to human health in Nigeria. Anthrax is caused by the spore-forming bacterium *Bacillus anthracis*, which primarily affects livestock but can also infect humans. In Nigeria, where agriculture is a crucial economic activity, the risk of anthrax transmission is high due to close contact between humans and infected animals. People who work with livestock, such as farmers, butchers, and veterinarians, are particularly vulnerable to contracting the disease. Additionally, consumption of contaminated animal products, especially undercooked meat, can lead to human infections (Spencer, 2003) .

The spores of *Bacillus anthracis* can enter the human body through inhalation, ingestion, or contact with broken skin. After gaining entry into the body, these spores can undergo germination and subsequently release toxins, leading to the development of a severe illness. The severity of the infection depends on the route of exposure and the immune response of the individual. Cutaneous anthrax is the most common form in Nigeria, characterized by the development of a painless skin lesion that progresses to a black eschar. Inhalation and gastrointestinal forms of anthrax are less frequent but more severe. Inhalation anthrax presents as a severe respiratory illness, while gastrointestinal anthrax manifests as a result of consuming contaminated meat, causing symptoms such as nausea, vomiting, abdominal pain, and bloody diarrhea (David e*t al.,* 2013).

Anthrax not only poses a direct threat to human health but also has the potential for bioterrorism. The spores can be intentionally disseminated, leading to outbreaks with devastating consequences. Therefore, it is essential for Nigeria to have effective surveillance systems, diagnostic capabilities, and public health infrastructure to promptly identify and respond to anthrax cases (Pohanka, 2020).

Prevention and control of anthrax in Nigeria require a multi-faceted approach. Vaccination of livestock, especially in high-risk areas, is crucial to reducing the reservoir of the bacteria. Public awareness campaigns should educate individuals about the risks associated with handling infected animals or consuming contaminated products (Colin *et al.,* 2019). Proper meat inspection, hygiene practices, and safe disposal of infected carcasses are essential in minimizing transmission. Timely diagnosis and treatment are vital for positive patient outcomes (Dorota e*t al.,* 2012) Prompt administration of antibiotics, such as ciprofloxacin or doxycycline, can effectively treat anthrax. Healthcare professionals should be trained to recognize and manage cases appropriately. *Bacillus anthracis* infection, or anthrax, is a significant threat to human health in Nigeria, primarily affecting individuals in close contact with livestock. Preventive measures, including livestock vaccination, public education, and improved surveillance, are necessary to reduce the incidence of anthrax and mitigate its impact on both human health and the agricultural sector (David e*t al.,* 2013).

The mechanisms by which *Bacillus anthracis* disrupts the host immune system during anthrax infection

Bacillus anthracis the causative agent of anthrax, possesses several mechanisms through which it disrupts the host immune system during infection. These mechanisms involve both direct interference with immune cells and evasion of host immune responses. Below are key mechanisms (Marta, 2005):

Capsule Formation: *Bacillus anthracis* produces a protective capsule composed of a unique sugar polymer called poly-D-glutamic acid. This capsule inhibits phagocytosis, the process by which immune cells engulf and destroy pathogens, by making the bacterium less accessible to immune cells (Taro, 2004).

Toxin Production: *Bacillus anthracis* produces three toxins: lethal toxin (LT), edema toxin (ET), and protective antigen (PA). These toxins disrupt signaling pathways involved in immune cell function. PA forms a pore on the surface of host cells, facilitating the entry of LT and ET. LT disrupts signaling pathways involved in immune cell function, impairing the host's ability to mount an effective immune response (Marta, 2005).

Suppression of Inflammatory Responses: *Bacillus anthracis* produces factors that suppress the production of pro-inflammatory cytokines, which are important for coordinating immune responses. By inhibiting the release of these cytokines, the bacterium can dampen the immune system's ability to recognize and eliminate the infection (Taro 2004).

Inhibition of Phagocytosis: *Bacillus anthracis* secretes factors that interfere with the process of phagocytosis. These factors can impair the ability of immune cells, such as macrophages, to engulf and destroy the bacteria, enabling the pathogen to evade immune surveillance (Clarkson, 2003).

Escape from the Immune System: *Bacillus anthracis* is capable of hiding within host cells, such as macrophages, which normally serve as a defense against invading pathogens. By residing within these cells, the bacterium can avoid detection and destruction by the immune system (Taro, 2004).

The specific immunological alterations induced by *Bacillus anthracis* during anthrax infection

Bacillus anthracis the causative agent of anthrax, induces several immunological alterations during infection. These alterations affect both innate and adaptive immune responses, cytokine signaling, immune cell activation, and modulation of host immune signaling (Elisabeth *et al.*, 2022).

Innate Immune Responses: *Recognition and Phagocytosis: Bacillus anthracis* is recognized by pattern recognition receptors (PRRs) on host cells, such as Toll-like receptors (TLRs). This recognition triggers phagocytosis by phagocytic cells like macrophages and neutrophils. *Activation of Inflammatory Response:* Recognition of *Bacillus anthracis* components leads to the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which contribute to inflammation (Pohanka, 2020). .

Adaptive Immune Responses: *Antigen Presentation:* Antigen-presenting cells, particularly dendritic cells, capture and process *Bacillus anthracis* antigens. These antigens are presented to T cells, initiating adaptive immune responses. *T Cell Activation:* T cells specific to *Bacillus anthracis* antigens recognize the presented antigens and become activated. This activation leads to the expansion and differentiation of effector T cells, including cytotoxic T cells and helper T cells. *Antibody Production:* B cells recognize *Bacillus anthracis* antigens and differentiate into plasma cells, which produce specific antibodies, such as anthrax toxin-neutralizing antibodies (Colin e*t al.,* 2019). .

Cytokine Signaling: *Modulation of Cytokine Production: Bacillus anthracis* secretes factors that can modulate cytokine production, potentially suppressing the host immune response. For example, the anthrax toxin produced by *Bacillus anthracis* can inhibit the production of certain cytokines, including interferons (Dorota *et al.,* 2012).

Immune Cell Activation: *Macrophage Activation:* Macrophages play a crucial role in anthrax infection by phagocytosing the bacteria and producing pro-inflammatory cytokines. However, *Bacillus anthracis* can also interfere with macrophage function by inhibiting phagocytosis and inducing cell death. *Neutrophil Recruitment: Bacillus anthracis*infection can lead to the recruitment of neutrophils to the site of infection, where they help control bacterial growth through phagocytosis and the release of antimicrobial peptides (Paola and Joachim, 2018).

Modulation of Host Immune Signaling Pathways: *Suppression of Inflammatory Signaling: Bacillus anthracis* produces toxins that interfere with host immune signaling pathways, including the inhibition of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. This interference can suppress the production of pro-inflammatory cytokines (Spencer, 2003) .

Contributions of Immunodysregulation to the pathogenesis and clinical outcomes of anthrax infection, such as disease severity, progression, and mortality rates

Immunodysregulation plays a significant role in the pathogenesis and clinical outcomes of anthrax infection, influencing disease severity, progression, and mortality rates.

By disrupting the immune system's normal functioning, anthrax can evade immune responses, leading to detrimental consequences. Anthrax is caused by the bacterium *Bacillus anthracis*, which produces various virulence factors. One such factor is the protective antigen (PA), which enables the bacterium to enter host cells. PA combines with lethal factor (LF) or edema factor (EF) to form lethal toxin (LT) or edema toxin (ET), respectively. These toxins impair immune cell function and disrupt signaling pathways involved in the immune response (Marta, 2005).

Immunodysregulation occurs as a result of LT and ET's actions on immune cells. LT inhibits the activation of immune cells, such as macrophages and dendritic cells, by disrupting intracellular signaling pathways. This impairs antigen presentation, cytokine production, and the overall immune response. ET disrupts the function of immune cells by increasing cyclic adenosine monophosphate (cAMP) levels, affecting cellular processes and impairing immune cell function.

These immunodysregulatory effects have significant implications for anthrax infection. Firstly, the evasion of immune surveillance allows *Bacillus anthracis* to proliferate rapidly, leading to increased bacterial load and disease severity. Uncontrolled bacterial growth can result in widespread tissue damage, organ failure, and septic shock (Taro, 2004).

Furthermore, the dysregulation of cytokine production can lead to a cytokine storm, characterized by an excessive and uncontrolled release of pro-inflammatory cytokines. This dysregulated immune response can contribute to tissue damage, systemic inflammation, and multi-organ dysfunction, exacerbating disease severity and progression (Clarkson, 2003).

Immunodysregulation also affects the adaptive immune response. By impairing antigen presentation and T-cell activation, anthrax inhibits the development of an effective immune memory response. This hampers the clearance of the infection and increases the risk of recurrent or persistent disease Guangyan *et al.,* 2020).

Additionally, Immunodysregulation may contribute to the mortality rates associated with anthrax infection. By disabling immune cells and impairing the immune response, anthrax can render individuals more susceptible to secondary infections, further compromising their health and increasing mortality rates. (Pohanka, 2020).

Immunodysregulation caused by anthrax toxins disrupts multiple aspects of the immune response. This evasion strategy allows *Bacillus anthracis* to proliferate, induce tissue damage, and cause severe systemic effects. The dysregulated immune response, including cytokine storms and impaired adaptive immunity, contributes to disease severity, progression, and increased mortality rates (Colin *et al.,* . 2019). .

The key molecular mechanisms and pathways employed by *Bacillus anthracis* to manipulate and evade host immune defenses, leading to Immunodysregulation during anthrax infection

Bacillus anthracis he causative agent of anthrax, employs several key molecular mechanisms and pathways to manipulate and evade host immune defenses, resulting in Immunodysregulation during infection. These strategies allow the bacterium to establish a successful infection and overcome the host's immune response (Dorota *et al.,* 2012).

One crucial mechanism employed by *B. anthracis* is the production of a complex cell wall that contains several components capable of interfering with the immune system. The bacterial cell wall comprises various surface proteins, such as the protective antigen (PA), edema factor (EF), and lethal factor (LF). These proteins contribute to the formation of anthrax toxin, which is a potent immunosuppressive virulence factor. Anthrax toxin disrupts various host immune signaling pathways, ultimately leading to Immunodysregulation (Paola and Joachim, 2018) .

Upon entering the host, *B. anthracis* releases the anthrax toxin, which binds to specific host cell receptors. The binding of PA to its receptor triggers endocytosis and the internalization of the toxin complex into host cells. Within the host cell, LF and EF are released, enabling them to modulate key signaling pathways (Spencer, 2003).

Lethal factor (LF) is a protease that cleaves and inactivates critical proteins involved in host immune responses, such as mitogen-activated protein kinase (MAPK) signaling pathways. By disrupting MAPK signaling, LF inhibits the production of pro-inflammatory cytokines, impairs neutrophil function, and reduces antigen presentation, thus hampering an effective immune response (David *et al.*, 2013).

Edema factor (EF) is an adenylate cyclase enzyme that elevates cyclic adenosine monophosphate (cAMP) levels within host cells. Increased cAMP suppresses host immune cell functions, including phagocytosis, cytokine production, and T-cell proliferation, thereby promoting immunodysregulation (Marta, 2005).

Furthermore, *B. anthracis* produces a capsule composed of poly-D-glutamic acid, which aids in evading phagocytosis and complement-mediated killing by the host's immune system. The capsule interferes with the opsonization process, reducing bacterial recognition and clearance by immune cells (Taro, 2004).

Bacillus anthracis employs various molecular mechanisms and pathways to manipulate and evade host immune defenses during anthrax infection. These include the production of anthrax toxin, which disrupts host immune signaling pathways, as well as the formation of a protective capsule that hinders recognition and clearance by immune cells. By utilizing these strategies, *B. anthracis* can successfully evade host immune defenses, leading to immunodysregulation and the establishment of infection (Clarkson, 2003).

Utilization of bioinformatics and network-based approaches to analyze and visualize the complex regulatory networks underlying Immunodysregulation in anthrax, with the aim of identifying potential therapeutic targets and intervention strategies

Bioinformatics and network-based approaches play a crucial role in analyzing and visualizing complex regulatory networks associated with Immunodysregulation in anthrax. By leveraging these techniques, researchers can identify potential therapeutic targets and develop intervention strategies (Guangyan *et al.*, 2020)..

Data Integration: Bioinformatics allows for the integration of various data types, such as genomics, transcriptomics, proteomics, and metabolomics, to gain a comprehensive understanding of Immunodysregulation in anthrax. By combining these diverse datasets, researchers can identify key regulatory elements and interactions within the immune system (Iuliia and Altino, 2021).

Network Construction: Network-based approaches involve the construction of interaction networks to represent the complex relationships between genes, proteins, and other molecular entities involved in immunodysregulation. These networks capture the regulatory mechanisms and signaling pathways that contribute to the disease (Xuting *et al.*, 2022).

Network Analysis: Once the network is constructed, researchers can apply various network analysis techniques to extract meaningful insights. For example, identifying central nodes (hubs) and densely connected regions (modules) can reveal critical regulators and functional clusters within the regulatory network (Xuting *et al.*, 2022).

Identification of Therapeutic Targets: Analyzing the network topology and incorporating functional annotations can help pinpoint potential therapeutic targets. Nodes that occupy central positions in the network or are associated with dysregulated pathways could be promising candidates for drug development or intervention strategies Xuting *et al.*, 2022).

Visualization: Visualizing the complex regulatory networks aids in understanding the overall structure and dynamics of Immunodysregulation in anthrax. Visualization tools enable researchers to explore the network at different levels of detail, facilitating the identification of key components and their interactions (Iuliia and Altino, 2021).

Critical research gaps and future directions for investigation in understanding and addressing Immunodysregulation in anthrax infection, including the development of novel therapeutic approaches and the design of preventive measures to enhance host defense against anthrax

Understanding and addressing Immunodysregulation in anthrax infection presents several critical research gaps and potential future directions. These areas of investigation aim to develop novel therapeutic approaches and design preventive measures to enhance the host defense against anthrax.

Elucidating the mechanisms of Immunodysregulation: One crucial research gap involves a lack of comprehensive understanding of the immunological dysfunctions that occur during anthrax infection. Investigating the intricate interplay between *Bacillus anthracis* he causative agent of anthrax, and the host immune system is vital. This research can focus on identifying the specific immune cells, signaling pathways, and immunomodulatory factors involved in the dysregulation of the host immune response (Elisabeth *et al.,* 2022).

Unraveling the role of immune evasion strategies: *Bacillus anthracis* employs various immune evasion strategies to subvert the host immune system. Uncovering these mechanisms and understanding how the pathogen evades immune surveillance is crucial for the development of effective therapeutics and preventive measures. Research in this area can explore the virulence factors employed by the bacterium, such as toxins and surface molecules, and their impact on immune cell function and signaling (Janet *et al.,* 2018).

Developing targeted immunotherapies: Novel therapeutic approaches for anthrax should aim to modulate the immune response effectively. Investigating and identifying immunomodulatory agents that can restore immune homeostasis and counteract immunodysregulation is an important research direction. These therapies may include immunomodulators, immune checkpoint inhibitors, or monoclonal antibodies targeting specific immune cells or signaling molecules involved in anthrax infection (Satish *et al.,* 2015).

Enhancing host defense through vaccination: Another critical area for investigation is the development of effective anthrax vaccines that promote a robust and protective immune response. Research should focus on improving current vaccine platforms, such as recombinant protein-based vaccines, attenuated strains, or DNA vaccines, to elicit a strong and durable immune response against *Bacillus anthracis.* Additionally, exploring novel vaccine adjuvants or delivery systems can enhance vaccine efficacy and induce long-lasting protective immunity.

Understanding host-pathogen interactions at the molecular level: Investigating the intricate molecular interactions between *Bacillus anthracis* and host immune cells is crucial for identifying potential therapeutic targets. This research can involve studying host-pathogen protein-protein interactions, host cell receptor recognition, and downstream signaling events. A deeper understanding of these interactions can guide the development of targeted therapeutics and preventive strategies (FMARD , 2023).

Addressing Immunodysregulation in anthrax infection requires extensive research to fill critical gaps in knowledge.

Investigating the underlying mechanisms of Immunodysregulation, unraveling immune evasion strategies employed by *Bacillus anthracis* developing targeted immunotherapies, enhancing host defense through vaccination, and understanding host-pathogen interactions at the molecular level are important future directions for advancing our understanding and ability to combat anthrax (Kari and Kingshuk, 2023). .

Pathophysiology of *Bacillus anthracis* Infection

Bacillus anthracis, the causative agent of anthrax, possesses unique pathophysiological features. It produces several virulence factors that contribute to its pathogenicity. Here is a detailed description of the pathophysiology of *Bacillus anthracis (*Pohanka, 2020) SA:

Spore Infection: *Bacillus anthracis* can survive in the environment as spores, which are resistant to harsh conditions. When spores enter the body through inhalation, ingestion, or skin contact, they encounter an environment conducive to germination (Colin *et al.,* 2019) .

Germination and Vegetative Growth: Once inside the host, the spores germinate and transform into vegetative bacteria. This process is triggered by specific environmental cues, such as the presence of suitable nutrients and favorable host conditions. The vegetative form of *Bacillus anthracis* begins actively replicating and spreading locally (Dorota *et al.,* 2012).

Production of Virulence Factors: *Bacillus anthracis* produces several virulence factors that contribute to its pathogenicity (Paola and Joachim, 2018).

a. Protective Antigen (PA): PA is a critical component of anthrax toxin. It forms a heptameric pore on the host cell surface, allowing the entry of the other two components of the toxin.

b. Edema Factor (EF): EF is an adenylate cyclase enzyme that disrupts cellular signaling pathways by generating excessive cyclic AMP (cAMP). Elevated cAMP levels lead to edema formation and impair host immune responses.

c. Lethal Factor (LF): LF is a zinc-dependent metalloprotease that cleaves and inactivates key proteins involved in host defense mechanisms. It disrupts signaling pathways, leading to tissue damage and cell death.

Localized and Systemic Effects (Spencer,. 2003)

a. Cutaneous Anthrax: When *Bacillus anthracis* enters the body through skin abrasions or wounds, it causes localized infection. It proliferates, forms a characteristic black eschar, and may disseminate to regional lymph nodes. Without appropriate treatment, cutaneous anthrax can progress to systemic anthrax.

b. Gastrointestinal Anthrax: Ingestion of contaminated meat results in gastrointestinal anthrax. *Bacillus anthracis* spores survive the acidic environment of the stomach and germinate in the intestines, causing severe inflammation, ulcers, and systemic dissemination.

c. Inhalation Anthrax: Inhalation of *Bacillus anthracis* spores is the most severe form of anthrax. The spores are phagocytosed by alveolar macrophages and transported to the mediastinal lymph nodes, where germination occurs. Bacterial growth, combined with the release of toxins, leads to hemorrhagic mediastinitis, respiratory failure, and systemic infection.

Laboratory Diagnosis of *Bacillus anthracis* infection

Accurate and timely laboratory diagnosis of *Bacillus anthracis* infection is crucial for effective management. Several laboratory techniques and tests are employed to identify and confirm the presence of *Bacillus anthracis* (David *et al.,* 2013).

Microscopic Examination

a. Gram Staining: *Bacillus anthracis* appears as large, Gram-positive, and spore-forming rods under a microscope (Marta, 2005).

b. Spore Staining: Specialized staining techniques, such as the Schaeffer-Fulton or Dorner's method, can detect the presence of spores in clinical samples (Taro, 2004).

Culture

a. Blood Agar: *Bacillus anthracis* can be cultured on blood agar plates, where it forms large,

gray-white colonies with a characteristic "ground-glass" appearance (Clarkson, 2003).
b. Selective Media: Specific selective media, such as MacConkey agar supplemented with polymyxin B, can inhibit the growth of other bacteria while allowing the growth of *Bacillus anthracis* Guangyan *et al.,* 2020). .

Biochemical Testing (Iuliia and Altino, 2021):

a. Catalase Test: *Bacillus anthracis* exhibits negative catalase activity, which differentiates it from other catalase-positive bacteria.
b. Motility Testing: *Bacillus anthracis* is non-motile, and this characteristic can be determined using motility media.

Serological Tests

a. Enzyme-Linked Immunosorbent Assay (ELISA): ELISA tests can detect specific antibodies against *Bacillus anthracis* antigens in patient serum.
b. Immunofluorescence Assay (IFA): IFA can detect the presence of *Bacillus anthracis* antigens in clinical samples using specific fluorescent-labeled antibodies.

Molecular Methods

a. Polymerase Chain Reaction (PCR): PCR can amplify and detect specific DNA sequences of *Bacillus anthracis* This technique provides rapid and highly sensitive identification of the pathogen (Xuting *et al.,* 2022) .
b. Whole Genome Sequencing (WGS): WGS allows comprehensive genomic analysis of *Bacillus anthracis* aiding in strain typing and epidemiological investigations (Xuting *et al.,* 2022).

Knowledge gaps on Immunodysregulation in Anthrax Infection

Mechanisms of immunodysregulation: Anthrax is caused by the bacterium *Bacillus anthracis* which produces several virulence factors. While some research has been conducted on the immunological response to anthrax infection, there may still be gaps in our understanding of the precise mechanisms by which *B. anthracis* manipulates and dysregulates the immune system.

Host immune response: Anthrax can lead to a range of immune responses, from mild to severe. Further studies may be needed to investigate the specific immune pathways and cellular components involved in anthrax immunodysregulation, including the interplay between innate and adaptive immune responses.

Immune evasion strategies: *B. anthracis* has evolved various mechanisms to evade the immune system, allowing the bacterium to establish infection and cause disease. Identifying the specific strategies employed by *B. anthracis* to circumvent immune detection and clearance could provide insights into immunodysregulation and potential targets for therapeutic intervention.

Biomarkers of Immunodysregulation: Identifying reliable biomarkers that can indicate the degree of Immunodysregulation in anthrax infection could be valuable for diagnosing and monitoring disease progression. Developing robust biomarkers could help clinicians assess the effectiveness of treatments and predict patient outcomes.

Immunomodulatory therapies: While antibiotics are the primary treatment for anthrax, there is ongoing research to develop immunomodulatory therapies that can target the immunodysregulation associated with anthrax infection. Further investigation is needed to determine the efficacy and safety of these therapies in clinical settings.

Long-term immune consequences: Anthrax infection can have long-lasting effects on the immune system, potentially leading to immunological alterations even after the infection has been cleared. Understanding the long-term consequences of anthrax immunodysregulation could have implications for the management of survivors and the development of post-infection therapies.

To bridge these knowledge gaps, further research, including laboratory studies, animal models, and clinical investigations, will be necessary. It's important to consult recent scientific literature and seek expertise from specialists in the field to obtain the most up-to-date information on immunodysregulation in anthrax infection.

CONCLUSION

In conclusion, this systematic review focused on immunodysregulation in anthrax infection. The findings highlight the complex interactions between the host immune system and the anthrax-causing bacterium, *Bacillus anthracis*. The review provides valuable insights into the immunological mechanisms involved in anthrax pathogenesis and the potential implications for developing effective therapeutic strategies.

RECOMMENDATION

1. Based on the findings of this systematic review, several recommendations can be made to further enhance our understanding of immunodysregulation in anthrax infection. Firstly, there is a need for more comprehensive studies that investigate the dynamic changes in immune responses at different stages of anthrax infection. Longitudinal studies could provide valuable insights into the temporal patterns of immune dysregulation and guide the development of targeted interventions.
2. Additionally, it is crucial to explore the potential role of immunomodulatory therapies in mitigating immunodysregulation associated with anthrax infection. Further preclinical and clinical research should be conducted to evaluate the efficacy and safety of immunomodulatory agents, such as immune checkpoint inhibitors or cytokine-based therapies, in improving the outcomes of anthrax infection.
3. Furthermore, efforts should be made to identify novel biomarkers associated with immunodysregulation in anthrax infection. The discovery of reliable and specific biomarkers could aid in early diagnosis, monitoring disease progression, and assessing the effectiveness of therapeutic interventions. Advanced techniques, such as transcriptomics, proteomics, and metabolomics, should be employed to identify potential biomarkers and unravel the underlying molecular pathways involved in anthrax-induced immune dysregulation.

Contributions to Knowledge

1. This systematic review makes several important contributions to the current knowledge on immunodysregulation in anthrax infection. Firstly, it provides a comprehensive and up-to-date synthesis of the existing literature, consolidating the available evidence on the immune responses and dysregulation associated with anthrax infection. The review identifies key immunological processes involved in anthrax pathogenesis, shedding light on the complex interactions between the host immune system and the bacterium.
2. Furthermore, this review highlights the gaps in our current understanding of immunodysregulation in anthrax infection, emphasizing the need for further research. By outlining specific recommendations, it guides future studies to address these gaps and generate new knowledge in the field. The proposed directions for research, such as longitudinal studies, evaluation of immunomodulatory therapies, and identification of biomarkers, have the potential to advance our understanding of anthrax immunopathogenesis and inform the development of innovative therapeutic approaches.

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a. Mathew Folaranmi OLANIYAN : Conceptualized the idea, research design, literature search, review, synthesis and preparation of manuscript

b. Musa Abidemi MUHIBI : literature search and review of manuscript

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