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The Effects of Anthrax Toxins and Cell Wall on Coagulation and Thrombosis

Project Number	Contact PI/Project Leader	Awardee Organization
1ZIACL090023-11	EICHACKER, PETER	CLINICAL CENTER

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Description

Abstract Text

Despite attempts at aggressive source control in addition to intensive care unit support, mortality in the recent UK outbreak of Bacillus anthracis (B. anthracis) soft tissue infection among intravenous drug abusers was very high (greater than 40% in more than 40 patients). A noticeable finding among many of these patients was a marked coagulopathy and thrombocytopenia. These conditions greatly complicated efforts at debridement in patients. While laboratory evidence of coagulopathy and thrombocytopenia has not been consistently reported on in prior **anthrax** outbreaks, pleural fluid collections and meningitis have frequently been described as hemorrhagic. Thus disruption of coagulation, excessive fibrinolysis and platelet consumption or destruction may play an important role in the pathogenesis of **anthrax**. Understanding the basis for these processes will be important for targeted treatment of **anthrax** in the future. **Anthrax** is associated with several virulence factors, which could potentially contribute to coagulopathy, fibirnolysis and thrombocytopenia or platelet dysfunction. On the one hand, **anthrax** produces lethal and edema toxins (LeTx and ETx respectively). LeTx inhibits is a zinc dependent protease which disrupts MAPK pathways important in innate immunity, cell cycling and replication and other essential host functions. Edema toxin has calmodulin dependent adenyl cyclase activity and increases intracellular cAMP to very high levels. Both toxins have the potential to alter both coagulation, fibrinolysis and platelet function. However, as a gram-positive bacteria, **anthrax** has a peptidoglycan cell wall which could also disrupt these functions via stimulation of inflammatory pathways. While such abnormalities related to LeTx or ETx might be best treated by toxin inhibitors, cell wall induced abnormalities might require alternate forms of therapy such as anti-inflammatory ones. The purpose of the present protocol has been to directly compare the effects of LeTx, ETx and **anthrax** cell wall peptidoglycan on coagulation, fibrinolysis and platelets in a previously developed rat model. In experiments now completed, animals were challenged with 24-hour infusions of one of these three components using methods developed in prior experiments. During infusion, as well as from 24 to 48 hours, animals had serial coagulation, fibrinolysis and platelet studies performed. We previously developed techniques to measure prothrombin (PT) and partial thromboplastin (PTT) times, fibrinogen levels, and thrombin anti-thrombin (TAT) levels in this rodent species. Other measures included tissue factor, protein C, anti-thrombin III, and plasminogen activator inhibitor. In this study **anthrax** cell wall peptidoglycan had marked coagulopathic and inflammatory actions, while similarly lethal doses of LeTx and ETx did not. This work was previously published. (Qiu p, Li y, Shiloach J, Cui X, Sun J, Trinh L, Kubler-Kielb J, Vinogradov E, Mani H, Al-Hamad M, Fitz Y, Eichacker PQ (2013) Bacillus anthracis Cell Wall Peptidoglycan but Not Lethal or Edema Toxins Produces Changes Consistent With Disseminated Intravascular Coagulation in a Rat Model. J Infection Diseases 208:978-89) Based on this work, additional studies have been completed examining the protective effects of anti-inflammatory agents in the setting of **anthrax** cell wall peptidoglycan challenge. In these studies a high and medium dose of corticosteroids were highly protective with **anthrax** PGN challenge. Studies with tumor necrosis factor soluble receptor showed that this highly selective anti-inflammatory agent, was not protective with **anthrax** PGN challenge. A manuscript describing these studies is under review.

Public Health Relevance Statement

Data not available.

Project Terms

Activated Partial Thromboplastin Time measurement · Adenylate Cyclase · Adrenal Cortex Hormones · Animals · **Anthrax** disease · Anti-Inflammatory Agents · Antithrombin III · Antithrombins · Bacillus anthracis · Blood Coagulation Disorders · Blood Platelets · Calmodulin · Cell Cycle · Cell Wall · Coagulation Process · Collection · Consumption · Cyclic AMP · Debridement · Disease · Disease Outbreaks · Disseminated Intravascular Coagulation · Dose · Edema · Fibrinogen · Fibrinolysis · Functional disorder · Future · Gram-Positive Bacteria · Hemorrhage · Hour · Infection · Inflammation · Inflammatory · Infusion procedures · Intensive Care Units · Intravenous · Laboratories · Liquid substance · MAP Kinase Gene · Manuscripts · Measures · Meningitis · Methods · Modeling

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EICHACKER, PETER

Awardee Organization
CLINICAL CENTER

Organization

Name
CLINICAL CENTER

City

Country

Department Type
Unavailable

Organization Type
Unavailable

State Code

Congressional District

Other Information

FOA

Study Section

Fiscal Year
2020

Award Notice Date

Administering Institutes or Centers
CLINICAL CENTER

DUNS Number

CFDA Code

Project Start Date

Project End Date

Budget Start Date

Budget End Date

Project Funding Information for

Total Funding

Direct Costs

Indirect Costs

Sub Projects

No Sub Projects information available for 1ZIACL090023-11

Publications

No Publications available for 1ZIACL090023-11

Patents

No Patents information available for 1ZIACL090023-11

Outcomes

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No Outcomes available for 1ZIACL090023-11

Clinical Studies

No Clinical Studies information available for 1ZIACL090023-11

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History

No Historical information available for 1ZIACL090023-11

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