InflammAging: Bacterial Toxins and Systemic Inflammation

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A leaky gut is the immunological gateway to autoimmunity and neurodegenerative disorders.

The identification of systemic bacterial toxins provides a therapeutic opportunity to prevent circulatory inflammation that leads to chronic clinical conditions and rapid aging.

Maintaining a healthy intestinal barrier is a vital step in a long and healthy life.
Learning Objectives

- Review the effect of systemic lipopolysaccharides and cytolethal distending toxin B on the pathogenesis of various, chronic, clinical conditions in the human body.
- Expertly assess intestinal permeability and systemic bacterial toxins.
- Utilize available treatment options for repairing and maintaining the intestinal barrier.
We suggest that the exposure of microglia to systemic inflammation at critical periods, such as middle age, may set the stage for CNS vulnerability to neurodegeneration and other neural disorders associated with neuroinflammation.
Intestinal Permeability
Systemic Bacterial Toxins
Systemic Inflammation
Autoimmune Reactivity
Pathogenic Gut Bacterial Toxins

- Lipopolysaccharides (LPS) an endotoxin from gram-negative bacteria such as *Escherichia coli, Salmonella, Shigella, Pseudomonas, Helicobactor, Legionella, Wolbachia*

- Cytolethal Distending Toxin-B is released by coliform bacteria, namely *Escherichia coli, Salmonella, Shigella* and *Campylobacter jejuni*, the pathogens that cause irritable bowels and small intestinal bacterial overgrowth (SIBO)
Systemic LPS plays a role in multiple disorders
LPS can cause damage to epithelial cells and tight junctions.

Increased intestinal permeability allows more LPS to enter the blood stream.
Contact with bacterial products such as LPS, induces enterocytes to release several proinflammatory cytokines and chemokines, such as IL6 or IL8. This results in the recruitment of further immune competent cells into the intestinal mucosa, increasing the inflammatory cascade.

Gut, 2002; 51:842-848.
Systemic LPS Disorders

Neurological disorders:

- Maes et al. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuroendocrinol Lett, 2008; 1(29):117-124.
The findings of the present study suggest that lipopolysaccharide increases permeability of the blood–brain barrier and diameter of pial arterioles via the activation of inducible nitric oxide synthase.

Cytolethal Distending Toxin B

10 times more inflammatory than LPS
Cytolethal Distending Toxin (CDT) Subunits

- **CdtB**: Pathogenic
- **CdtC**: Ability to attach to receptors on the surface of intestinal epithelial cells
- **CdtA**:
Bacterial Cytotoxins

By binding to CdtC and CdtA, CdtB can attach to the host cell wall and then infiltrate the cell.
Vinculin

Junctional adhesion molecule

Claudin

Actin

α-actinin

Talin
Entry of CDT to submucosa

Release of cytoskeletal proteins

Desmoglein

Release of tight junction proteins

Entry of food antigens to submucosa

Antibody against bacterial cytotoxin

Antibody against cytoskeletal proteins

Antibody against tight junction proteins

Antibody against food antigens
Further, both the number of *C. jejuni* exposures and levels of SIBO correlate with loss of vinculin in the intestinal wall. This represents a breakthrough in understanding the roles of *C. jejuni* infection and the CdtB toxin in contributing to impairment of gut function.

*Dig Dis Sci, 2015; 60:1196-1205.*
Here we show that chronic exposure to the genotoxin cytolethal distending toxin (CDT) of Gram-negative bacteria promotes genomic instability and acquisition of phenotypic properties of malignancy in fibroblasts and colon epithelial cells.
What the...
Clinical Assessments for Systemic Bacterial Toxins and Damaged Intestinal Barrier
Assessing Antigenic Intestinal Permeability

- **Lipopolysaccharides IgG, IgA, IgM:**
  - Gut dysbiosis (too much gram-negative bacteria in ratio to gram-positive bacteria)
  - Systemic LPS infiltration

- **Ocludin/Zonulin IgG, IgA, IgM:**
  - Tight junction breakdown

- **Actomyosin IgA:**
  - Epithelial cell damage


Acute Phase of Gut Dysbiosis

Early Onset of Gut Dysbiosis

Chronic state of Gut Dysbiosis
✓ Long-term reactivating gut dysbiosis
✓ Early onset tight junction damage
✓ Early onset gut dysbiosis (with IgG on the rise)
✓ Early onset tight junction damage (with IgG on the rise)
Early onset gut dysbiosis
Intestinal barrier intact
✓ Long-term reactivating gut dysbiosis
✓ Intestinal barrier intact
Epithelial cell damage
Tight junction damage
gut dysbiosis

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>IN RANGE (Normal)</th>
<th>EQUIVOCAL*</th>
<th>OUT OF RANGE</th>
<th>REFERENCE (ELISA Index)</th>
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<td>Actomyosin IgA **</td>
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<td>Lipopolysaccharides (LPS) IgM</td>
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</table>
✓ Long-term CdtB
✓ Early onset epithelial cell damage
- **Recent onset CdtB** (with IgG on the rise)
- **Epithelial cells intact**

### Test Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>IN RANGE (Normal)</th>
<th>EQUIVOCAL*</th>
<th>OUT OF RANGE</th>
<th>REFERENCE (ELISA Index)</th>
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<td>Array 22 - Irritable Bowel/SIBO Screen</td>
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<tr>
<td>Cytoskeletal Proteins IgM</td>
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<td>0.3-1.7</td>
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- Long-term reactivating CdtB
- Mounting epithelial cell damage
Our results ... suggesting that in patients with ocular neurodegenerative diseases, peripheral damage, as a systemic infection or chronic inflammatory process, could accelerate disease progression, and should be taken into account in order to select an appropriate therapy to revert, block or slow-down the degenerative process.

Cell Death and Disease, 2018; 9:350.
Clinical Approaches to

Systemic Bacterial Toxins and
Damaged Intestinal Barrier
and Maintaining a
Healthy Gut
The 4 “R” Program

- **Remove** pathogens
- **Replace** digestive enzymes and stomach acid
- **Reinoculate** with probiotics
- **Regenerate** damaged intestinal mucosa

**Extra Credit**

- **Retest** to see the gains
- **Retain** by adhering to a GI supportive lifestyle
Healing Protocol for Antigenic Intestinal Permeability

- Remove the triggers
  - Food sensitivities
  - Drugs like antibiotics and NSAIDS
  - Dysbiosis, pathogens
  - Toxins
  - Stress
  - Alcohol
Healing Protocol for Antigenic Intestinal Permeability

- Replace enzymes and deficiencies
  - Digestive enzymes (brush border, DPP-IV)
  - Basic Nutrients and Antioxidants (B vitamins with emphasis on folates*, retinoic acid, ascorbate, mixed tocopherols, zinc, selenium, molybdenum, manganese, and magnesium)

Healing Protocol for Antigenic Intestinal Permeability

- **Reinoculate**
  - **Probiotics**: Lactic acid producers: Lactobacilli (*acidophilus, plantarum, casei, salivarius, sporogenes*), Bifidobacteria, Streptococci
  - **Soil-derived organisms**: Bacilli (*laterosporus, subtilis*)
  - **Saccharomyces boulardii**: (yeast against yeast)
  - **Prebiotics**: Foods that support the growth of probiotics:
    - Bran
    - Psyllium
    - Resistant starch (high amylose)
    - FOS (onions, garlic, rye, blueberries, bananas, chicory)
    - Inulins (chicory and artichoke)
Healing Protocol for Antigenic Intestinal Permeability

- **Repair**
  - L-Glutamine
    - Dosage: 1 – 20 grams a day. Typical dose is 3-6 grams per day
  - N-acetyl glucosamine
    - Dosage: 3- 8 grams per day
  - Glutathione and N-acetylcysteine (NAC) and Glycine
    - Dosage Glutathione: 100mg PO bid or IV push 3-6 cc weekly
    - Dosage NAC: 1500 mg per day
    - Dosage Glycine: 3-6 grams per day

Healing Protocol for Antigenic Intestinal Permeability

- **Repair**
  - **Vitamin A (Retinoic Acid)**
    - Dosage: 25,000 - 50,000 units a day. DO NOT use if pregnancy is a possibility.
  - **Vitamin D3**
    - Achieve blood levels between 50 – 70 ng/ ml.
  - **Zinc (carnosine, citrate)**
    - Dosage: 10 – 90 mg a day with meals*
    - *Note that prolonged use of zinc requires supplementation with copper to prevent copper deficiency. The suggested ratio is 1 part of copper for every 15 parts of Zinc.
Healing Protocol for Antigenic Intestinal Permeability

- **Repair**
  - **Essential Fatty Acids (especially high-EPA fish oil)**
    - Dosage: 3-6 grams per day
  - **Quercetin and flavonoids (tight junctions)**
    - Dosage: 500-1000 mg per day
  - **Boswellia serrata**
    - Dosage: 300-900 mg per day
  - **Curcuma longa (curcumin, turmeric)**
    - Dosage: 500-1500 mg per day
Healing Protocol for Antigenic Intestinal Permeability

▪ **Repair**
  ▪ **Demulcent botanicals:**
    ▪ Aloe vera (aloë leaf gel)
    ▪ Althea off. (marshmallow)
    ▪ Glycyrrhiza g. (licorice)
    ▪ Ulmus f. (slippery elm)
      ▪ Dosages vary


If you PREVENT this
MUCOSAL IMMUNE ABNORMALITIES
IMBALANCED GUT FLORA
INTESTINAL BARRIER DYSFUNCTION
SYSTEMIC INFLAMMATION
NEUROINFLAMMATION
NEUROINVASION
NEURODEGENERATION

You can PREVENT this

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Thank you