Microbiome Patterning in Sepsis

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Disclosures

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Life-threatening infection: a complex system

[Diagrams showing interactions between different components representing a life-threatening infection]
The microbiome and sepsis: a vicious cycle

Haack and Wiersinga, Lancet Gastroenterol Hepatol, 2017
Fay, et al, BBA Molecular Basis of Disease, 2017
Alverdy and Luo, Front Microbiol, 2017
What discriminates a healthy microbiome from a pathobiome?

Understanding BOTH composition and function will be essential to enable prophylactic and therapeutic intervention.
Microbiome health and risk of sepsis

A

Microbiome diversity

Hospital discharge (no infection)  Hospital discharge (infection)  Hospital discharge (eg, Clostridium difficile infection)

Robust microbiome  Dysbiosis  Dysbiosis  Dysbiosis

B

Risk of sepsis

Baseline risk of sepsis  High risk  Higher risk  Highest risk

Time

Haack and Wiersinga, Lancet Gastroenterol Hepatol, 2017
Bacteroides fragilis

Gram negative anaerobe, ubiquitous in mammalian intestine
1-2% of human gut microbiome
Adapted for colonization of the mucous layer of the colon

COMMENSAL
Polysaccharide coat

PATHOGEN
B. fragilis toxin (BFT)

WT NTBF

WT ETBF

T cell repertoire

colitis
colonic malignancy
acute diarrhea
undernutrition
sepsis

Huang, J.Y. et al, Anaerobe 2011
Bacteroides fragilis toxin (BFT) injures the colonic epithelium

Casterline, 2017
**B. fragilis** toxin contributes to lethal sepsis

Why would a symbiont have strain variants that express an injurious toxin?
Does competition between toxigenic and non-toxigenic *B. fragilis* occur in humans?

**TABLE 2. Proportions of B. fragilis isolates containing bft**

<table>
<thead>
<tr>
<th>Subject</th>
<th>0 mo</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
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B. fragilis vertical transmission model

mate | abx inoculate | birth | wean
--- | --- | --- | ---
age: | -3 | -1 | 0 | 3 | 4 | 5

![Graph showing log CFU/g feces over age (weeks).](image)

<table>
<thead>
<tr>
<th>CF age</th>
<th>ETBF?</th>
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Neonatal colonization with ETBF leads to histopathologic evidence of colitis.
Neonatal exposure to ETBF and BFT confers protection against lethal sepsis

Casterline, 2017
Early life impacts the microbiota and immunity

- Vertical transmission of microbiota
- Horizontal transmission of microbiota

- Decreased vertical transmission
- Decreased horizontal transmission
- Decreased maintenance

- Replete ancestral microbiota
- Depleted microbiota

- Innate immunity
- Adaptive immunity

- Mature adaptive immune response
- Increased incidence of autoimmune and inflammatory diseases
- Altered maturation of adaptive immunity:
  - Decreased tolerance
  - Increased reactivity

Blaser, Nat Rev Immuno, 2017
The microbiome in sepsis

Unique host and microbiome

Both early imprinting and events in life shape microbiome

NOT STATIC!

Understanding risk and designing prevention and therapy will require knowledge of functional impact of microbiome
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