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Short Communication

Gut in Sepsis

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Sepsis is a leading cause of hospital admission and mortality. Sepsis is characterized by heterogenous and multifaced dysregulation of host immune response to invading micro- organism, in the presence of multiple organ dysfunction [1]. For decades, gut is considered as source of sepsis, however the mechanism for the same is more complex than previously perceived. Of the several functions performed by intestines, one important function is barrier function. This barrier functions has three levels: 1) biological barrier which consists of microbiota and various functions offered by it; like colonization resistance, protection from pathogens, enterocytes and colonocytes integrity by generating short chain fatty acids, 2) immunological barrier with the help of Gut associated lymphoid tissue (GALT) and various cells of innate and adaptive immune system and 3) mechanical function by tight junctions between the epithelium which regulate paracellular permeability.

Human intestine is home for 100 trillion of bacteria which are with symbiotic relationship with host. These population is dominated by anaerobic bacteria. The composition and concentration of these commensals change at different segments of gastrointestinal tract. In acidic environment of stomach, most of the bacteria are aerobic and 10^2-10^3/ g of gastric content. Similarly, proximal intestine has facultative anaerobes and concentration up to 10^4-10^8 / g of luminal content and in colon predominant bacteria are obligate anaerobes and concentration is 10^{10}-10^{12} / g of stool. Commensals bacteria have symbiotic relationship with host. They help in digestion, provide short chain fatty acids which helps to maintain integrity of lining epithelium, production of vitamin K, help in development and modulation of immune system, protects against pathogens, maintains intestinal homeostasis [2]. Apart from bacteria, there are other commensals like fungi, archae, viruses, bacteria, protozoa. Their exact role in the intestine is not known. The composition of the intestinal microbiota varies among individuals and throughout development, dependent on host and environmental factors [3]. Microbiome in an individual is generally stable and offers resilience to perturbations. More diverse the microbiota is, stiffer the resilience offered. If microbiota fails to offer resilience then dysbiosis occurs. And this can lead to pathobiome.

Disruption of microbiota by use of antibiotics increases chances of blood stream infections and sepsis. In US Health and Retirement study which included 10996 participants showed that there is strong and longitudinal dose- response relationship between dysbiosis and progression to sepsis [4]. Sepsis is heterogeneous and multifaceted dysregulation of the host response to an infecting pathogen, with the presence of organ dysfunction. Complex interactions between the immune and other systems of the host and the infecting microorganism [1]. Any critical illness itself disturbs intestinal microbiota by many mechanisms like antibiotic use, change in pH of intestine, hypoxia, decreased gut perfusion, dysmotility, vasopressors, disturbed intestinal integrity, proton pump inhibitors etc. During such perturbations; commensals such as *Faecalibacterium* species, *Prevotella* species, *Blautia* species, and *Ruminococcaceae* species, decrease in population and Clostridium species, Enterococcae bacteria grow more in number; thus leading to dysbiosis. Gut is being considered as motor of sepsis for many decades. But mechanism of this bacterial translocation remains unproven. Simple theory of bacterial translocation across gut through portal blood stream to systemic circulation resulting in sepsis, looks easy to understand; however it is not supported by clinical data. More likely mechanism is probably transmission of gut derived pathogens or/and pathogen associated molecular patterns

(PAMPs) to mesenteric lymph nodes. Then through lymphatics, they go to lungs, resulting acute lung injury and distress syndrome. When the infection spills over to systemic circulation, then it may cause sepsis and multi organ dysfunction syndrome (MODS) [5]. So in any critical illness, intestinal permeability increases due to damage in intestinal barrier. Pathogens and/or PAMPs is translocated to submucosa and GALT. Focal inflammation sets in that further enhances intestinal permeability through a first vicious cycle. Thus gut becomes a proinflammatory organ. PAMPs get translocated to mesenteric lymph nodes and reach lungs. Pulmonary vasculature is the first vessels bed to encounter these PAMPs. They are recognised by pathogen recognising receptors (PRR) bearing cells of innate and acquired immune system. This triggers acute lung injury and respiratory distress syndrome. When influx of PAMPs is more, it leads to organ injury in various organs and may trigger MODS which will further damages intestinal barrier thus leading to second vicious cycle of sepsis. This gut-lymph theory has emphasised that local bacterial translocation is the first step in the sequence of events. With this background knowledge, there is scope for medical intervention to interrupt this sequence by either preserving microbiota or enhancing intestinal integrity. Preservation of microbiota can be done by avoiding use of unnecessary antibiotics, use of selective non- absorbing antibiotics, use of probiotics, prebiotics or synbiotics. Banking of fecal microbiome and auto-transplantation after dysbiosis can help to restore microbiome. Use of bacterial products like short chain fatty acids can preserve integrity of lining epithelium. Early hemodynamic resuscitation can limit reperfusion injury. Early enteral nutrition prevents bacterial translocation. Immuno-nutrition, use of antioxidants may help to limit epithelial injury. The above measures need to be evaluated in research settings. Role of other members of commensals population like fungi, viruses, bacteriophages, protozoans is still investigational. Biomarkers for intestinal barrier function like serum citrulline, serum intestinal fatty acid binding protein can be studies to use as predictors of sepsis.

Thus, gut plays a pivotal role in sepsis and MODS. Dysbiosis and intestinal barrier injury due to microcirculatory disturbances is the first critical step in pathogenesis. Bacteria and PAMS gain access to intestinal submucosa and initiates intestinal proinflammatory response which leads to further damage to intestinal barrier function. More PAMPs are released in lymphatics and gain access to systemic circulation, thus causing SIRS and MODS. There is need to develop non-invasive methods to predict dysbiosis and intestinal permeability. Gut microbiota will continue to inspire researcher's interest.

Conflict of Interest

None.

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Volume 2 Issue 8 October 2019