

重症病態の腸内細菌叢とシンバイオティクス治療

清水 健太郎

大阪大学医学部附属病院 高度救命救急センター

略歴

1973年 愛知県生まれ。1998年大阪大学医学部医学科卒業。2000年国立大阪病院消化器内科レジデント 2003年大阪大学医学部附属病院 高度救命救急センター医員 2009年大阪大学医学部附属病院 中央クオリティマネジメント部特任助教 2012年米国 Brigham and Women's Hospital Research Fellow 2014年大阪大学医学部附属病院 高度救命救急センター助教

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侵襲時の腸内細菌叢と腸管内治療

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要約

1. 重症病態での腸管の役割

敗血症は感染症によって重篤な臓器障害が引き起こされる緊急性の高い状態であり、多臓器不全から致命的な転機をたどる病態である。世界全体で年間5000万近い患者が発症し、うち1000万人以上が死亡するとされている(1)。2017年に、WHOはSepsis(敗血症)の診断・治療・管理の改善を決議した(2)。日本では年間約10万人が罹患し、40億ドル以上の医療費負担となっている(3)。敗血症は疾患と異なる病態の概念であり、悪性新生物、心疾患、脳血管疾患、COVID-19などの疾病にかかわらず肺炎や尿路感染症などの敗血症が引き起こされる。

救急・集中治療領域の代表的疾患である敗血症だけでなく重症外傷、熱傷などの大きな「侵襲」が生体に加わると全身性炎症反応(systemic inflammatory response syndrome: SIRS)が引き起こされ多臓器不全に進行する。全身性炎症反応は急性期に共通した概念で、菌などの外来異物や外傷による自己組織によって免疫系が起動され、炎症性のTh1型の免疫反応、抗炎症性のTh2型の免疫反応や制御性T細胞の活性化が生じる(4)。侵襲により免疫が破綻すると感染症は重篤化するため、その予防・診断と治療が必要とされている。

腸管は、侵襲時の重要な標的臓器であり、IgAなどに代表される腸管免疫の低下、腸管バリア破壊によるバクテリアトランスロケーション、腸管膜リンパを介した炎症性サイトカインの全身循環への流入などが引き起こされると考えられている。これらの腸管機能不全は、“the motor of critical illness”として全身の多臓器不全の進行に中心的な役割を果たすと考えられている(5)。

2. 侵襲による腸内細菌叢の変化

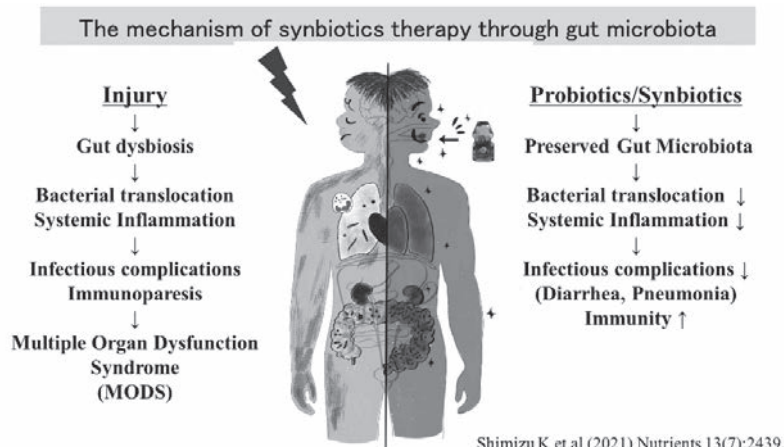
健常人の腸管内の最優勢菌は *Bacteroides* や *Bifidobacterium* などの無酸素環境下でのみ増殖できる偏性嫌気性菌である。最優勢の偏性嫌気性菌に比べると、大腸菌等の酸素環境下でも生存できる通性嫌気性菌は、1/1000以下に過ぎない。しかし、重症病態になると、腸内細菌叢は減少し、通常検出されない、MRSA (methicillin-resistant *Staphylococcus aureus*)、真菌などが、検出される。定量的に腸内細菌叢を評価すると、便中の総偏性嫌気性菌数は健常人に比べ有意に減少していた (6)。便中の有機酸の中でも短鎖脂肪酸 (酢酸, プロピオン酸, 酪酸) は著しく減少し、便中の pH は有意に増加していた (7)。

腸内細菌叢の構成割合に関しては、16S リボゾーム RNA 遺伝子 (16S rRNA) を用いた網羅的なメタゲノム解析が行われる。ICU 患者では早期から腸内細菌叢や腸内環境の崩壊が受傷後数時間の内に進行し、以後数週間にわたって継続する (7)。便中の *Blautia*、*Faecalibacterium*、*Clostridium* などの通性嫌気性菌の減少が顕著である (8)。

また、腸内細菌叢と感染合併症や予後との関連を解析すると、健常腸内細菌叢の大部分を示す総偏性嫌気性菌数と病原菌である大腸菌や緑膿菌などの通性嫌気性菌数が最も関連していることが明らかになった (9)。これは、抗菌薬で病原菌を減らすことだけでなく、プロバイオティクス・プレバイオティクスなどを用いて腸内細菌叢を保つ治療の妥当性を示唆するものでもある。

3. 腸管内治療による腸内細菌叢の安定と感染性合併症の予防と治療

敗血症患者 72 人を対象としてシンバイオティクス (*Bifidobacterium breve*、*Lactobacillus casei*、オリゴ糖) を入院後 3 日以内に開始したところ、投与群は非投与群に比して、投与菌のみならず *Bifidobacterium* 属、*Lactobacillus* 属全体、及び総菌数が経時的に有意に上昇した (10)。また、便中の短鎖脂肪酸のひとつである酢酸は 1 週目に急激に有意に上昇した。感染合併症に関しては、下痢 (6.3% vs. 27.0%) および人工呼吸器関連肺炎の投与群の発症率 (14.3% vs. 48.6%) が有意に低かった (投与群 vs. 非投与群; $p < 0.05$)。メタアナリシスにおいても、人工呼吸器装着患者を対象とした 1127 人を対象とした研究で下痢および人工呼吸器関連肺炎の発症率に有意に効果があると報告されている (11, 12)。プロバイオティクス・シンバイオティクス療法は、重症患者の腸内細菌叢を維持することで免疫応答を調整し腸肺連関による合併症を防ぐ可能性を示唆している (図)。



4. 難治性下痢症の診断と腸内細菌叢再構築としての糞便微生物移植の効果

クロストリジオイデス・ディフィシル感染症（CDI）は、欧米では重篤な医療関連感染である。日本は難治性の CDI 患者が少ないが（13）、CDI の中でも難治性の症例は、糞便微生物移植（FMT：fecal microbiota transplantation）を行うことによって腸内細菌叢の多様性が回復し、症状が有意に改善したことが本邦でも報告されている。非クロストリジウム・ディフィシル感染症でも崩壊した腸内細菌叢を再構築することで難治性の下痢症例が改善した報告がなされていることから、CDI 症例だけではなく、非 CDI 症例でも、腸内細菌叢を再構築することで下痢を改善させる可能性があり、当センターでは糞便微生物移植の臨床研究を行っている（jRCTs051220110）。

参考文献

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-11.
2. Sepsis. World Health Organization. [Available from: <https://www.who.int/news-room/fact-sheets/detail/sepsis>].
3. Oami T, Imaeda T, Nakada TA, et al. Temporal trends of medical cost and cost-effectiveness in sepsis patients: a Japanese nationwide medical claims database. *J Intensive Care*. 2022;10(1):33.
4. 大須賀章倫, 小倉裕司, 中島紳史, et al. 重症外傷による免疫反応 自然免疫系と獲得免疫系による制御バランス. *日本救急医学会雑誌*. 2013;24(4):181-91.
5. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. *Shock*. 2007;28(4):384-93.
6. Shimizu K, Ogura H, Goto M, et al. Altered gut flora and environment in patients with severe SIRS. *J Trauma*. 2006;60(1):126-33.
7. Yamada T, Shimizu K, Ogura H, et al. Rapid and Sustained Long-Term Decrease of Fecal Short-Chain Fatty Acids in Critically Ill Patients With Systemic Inflammatory Response Syndrome. *Journal of Parenteral and Enteral Nutrition*. 2015;39(5):569-77.
8. Ojima M, Motooka D, Shimizu K, et al. Metagenomic analysis reveals dynamic changes of whole gut microbiota in the acute phase of intensive care unit patients. *Digestive diseases and sciences*. 2015;61(6):1628-34.
9. Shimizu K, Ogura H, Hamasaki T, et al. Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome. *Digestive diseases and sciences*. 2011;56(4):1171-7.
10. Shimizu K, Yamada T, Ogura H, et al. Synbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: a randomized controlled trial. *Crit Care*. 2018;22(1):239.
11. Batra P, Soni KD, Mathur P. Efficacy of probiotics in the prevention of VAP in critically ill ICU patients: an updated systematic review and meta-analysis of randomized control trials. *J Intensive Care*. 2020;8:81.
12. Shimizu K, Hirose T, Ogura H. Efficacy of probiotics in the prevention of diarrhea in ventilated critically ill ICU patients: meta-analysis of randomized control trials. *J Intensive Care*. 2021;9(1):62.
13. Yamagishi Y, Mikamo H. [Recent epidemiology of *Clostridium difficile* infection in Japan]. *Jpn J Antibiot*. 2015;68(6):345-58.

Gut microbiota and synbiotic therapy in critically ill patients

Kentaro Shimizu

Osaka University Hospital, Trauma and Acute Critical Care Center, Osaka

Brief curriculum vitae

- 2014 Assistant Professor in Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine
- 2012 Research fellow in Department of Surgery, Brigham and Women's Hospital, USA
- 2009 Appointed Assistant Professor in Department of Clinical Quality Management, Osaka University Hospital
- 2003 Medical doctor in Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine
- 1999 Junior Resident and Resident in Department of Gastroenterology, National Hospital Organization Osaka National Hospital
- 1998 Junior resident in first department of medicine, Osaka University Hospital
- 1998 M.D. Osaka University Medical School, Osaka, Japan

Abstract

1. Role of the gut in critical illness

Sepsis is a highly emergent condition in which severe organ damage is caused by infection, leading to multiple organ failure. Worldwide, nearly 50 million cases occur annually, of which more than 10 million die (1). More than 50% of hospital deaths are due to sepsis, which is a healthcare burden (2). In 2017, WHO has also made a number of recommendations to improve the diagnosis, treatment, and management of sepsis (3). In Japan, about 100,000 people are affected annually, costing the country more than \$4 billion in healthcare costs (4). Regardless of whether the disease is a malignant neoplasm, cardiac disease, cerebrovascular disease, or COVID-19, they often result in sepsis, including pneumonia and urinary tract infections.

In addition to sepsis, which is a typical disease in the emergency/intensive care field, severe trauma, burns, and other major "injury" to the body can induce a systemic inflammatory response syndrome (SIRS), which can progress to multiple organ failure. The systemic inflammatory response is a common concept in the acute phase, in which the immune system is triggered by foreign substances such as bacteria or self-tissue from trauma, resulting in both the activation of inflammatory Th1-type immune responses, and anti-inflammatory Th2-type immune responses and regulatory T cells (5). As immune system is disrupted by injury and infections become severe, prevention, diagnosis and treatment for SIRS are needed.

The gut is an important target organ following injury, which could cause reduced

gut immunity represented by IgA and other factors, bacterial translocation due to disruption of the intestinal barrier, and influx of inflammatory cytokines into the systemic circulation via the intestinal lymph. These intestinal dysfunctions are thought to play a critical role in the progression of systemic multiple organ failure as "the motor of critical illness" (6).

2. Dramatic changes in the gut microbiota following injury

The most dominant bacteria in the intestinal tracts of healthy people are the obligate anaerobes such as *Bacteroides* and *Bifidobacterium*, which can grow only in an anaerobic environment. The number of facultative anaerobes that can survive in an aerobic environment, such as *Escherichia coli*, is less than 1/1000 of the predominant bacteria. However, in critically condition, the number of gut microbiota is reduced, and usually undetectable organisms such as MRSA (methicillin-resistant *Staphylococcus aureus*) and fungi can be detected. Quantitative evaluation of the gut microbiota showed that the total number of total commensal anaerobic bacteria in the stool was significantly reduced compared with healthy subjects (6). Among the organic acids in the feces, especially short-chain fatty acids (acetic acid, propionic acid, and butyric acid) were significantly decreased, and the pH of the feces was also significantly increased (7).

Comprehensive metagenomic analysis using the 16S ribosomal RNA gene is indicated the proportion of gut microbiota. There was a marked decrease in the number of facultative anaerobic bacteria such as *Blautia*, *Faecalibacterium*, and *Clostridium* in the feces (8). Analysis of the gut microbiota revealed that the total number of commensal anaerobes and the number of pathogenic bacteria were most associated with infectious complications and prognosis (9). This suggests the relevance of treatment that not only reduces pathogenic bacteria with antimicrobial agents, but also maintains the gut microbiota with probiotics and prebiotics.

3. Stabilization of gut flora and prevention for infectious complications by intestinal therapy

When 72 patients with sepsis were started on synbiotics (*Bifidobacterium breve*, *Lactobacillus casei*, oligosaccharides) within 3 days of admission, the number of not only the administered bacteria but also the total bacteria increased significantly over time (10). In addition, acetic acid, one of the short-chain fatty acids in the feces, increased significantly during the first week. Regarding with infectious complications, the incidence of diarrhea (6.3% vs. 27.0%) and ventilator-associated pneumonia was significantly lower in the treated group (14.3% vs. 48.6%) (treated vs. not treated; $p < 0.05$). A significant effect on the incidence of diarrhea and ventilator-associated pneumonia was also reported in meta-analyses in a study of 1127

intubated patients with mechanical ventilators in the ICU (11, 12). It is suggested that probiotic/synbiotic therapy may modulate the immune response and prevent complications through gut-lung axis by maintaining the gut microbiota in critically ill patients (Figure).

4. The effect of fecal microbiota transplantation for refractory diarrhea

Clostridioides difficile infection (CDI) is a serious healthcare-associated infection in Europe and the United States. There are few patients with refractory CDI in Japan (13). It has been reported that fecal microbiota transplantation (FMT) restored the dysbiosis the gut microbiota and significantly improved symptoms. As there is a possibility that diarrhea can be improved not only in CDI patients but also in non-CDI patients by reconstructing the gut microbiota, we are conducting a clinical study of fecal microbiota transplantation for refractory diarrheal patients at our center (jRCTs051220110).