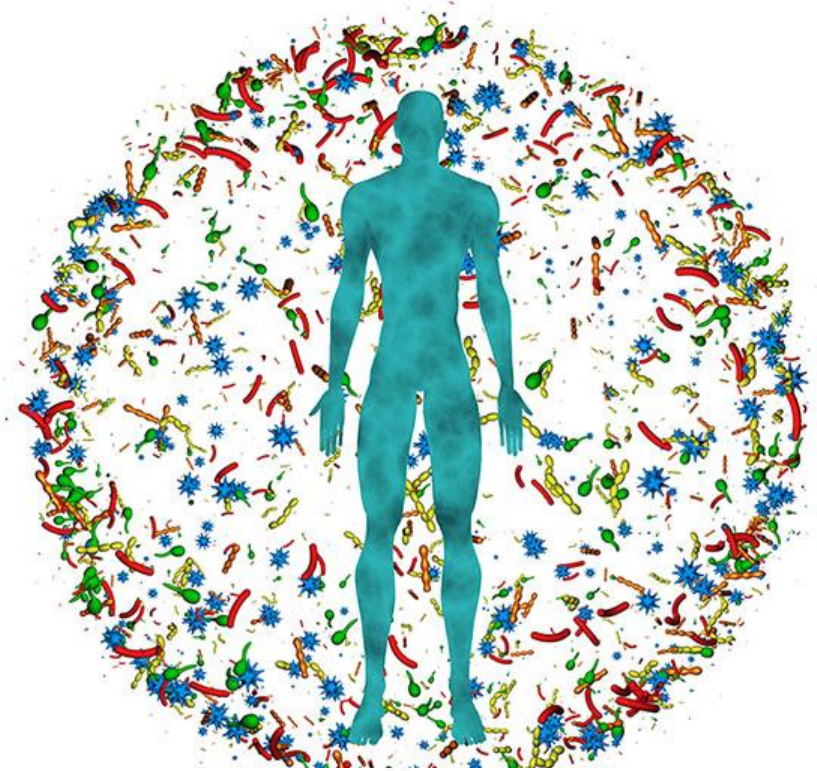


Sepsis & Microbiome

Name: Yeong Kai Yan

Year 2 PhD candidate

Supervisor: Prof. Margaret Ip

Date: 13 Dec 2022

Contents

Introduction of sepsis

- Definition, symptoms and mechanism of sepsis

Microbiome & sepsis

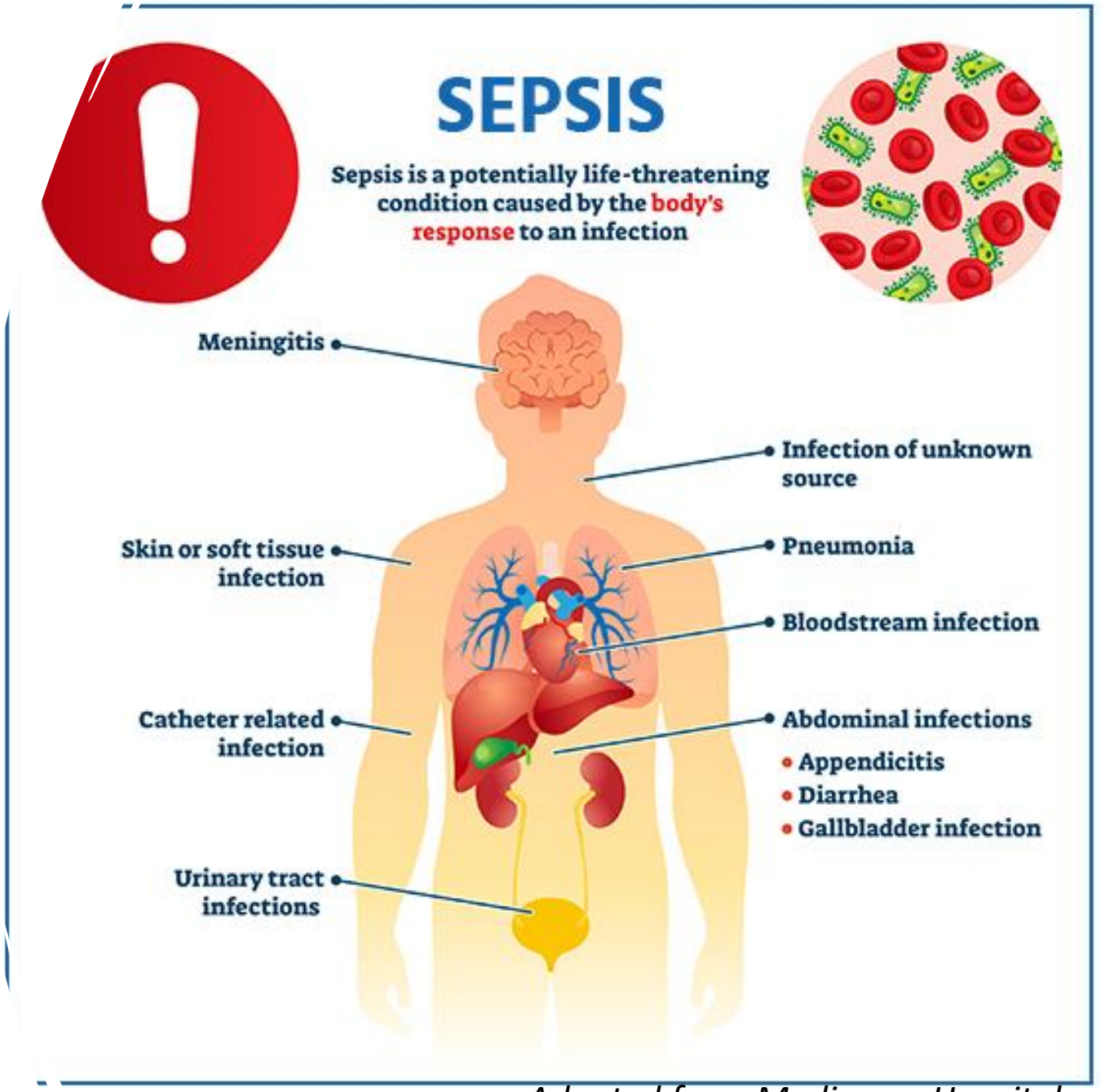
- Does microbiome play a role in sepsis?

Sepsis treatment

- Probiotics/FMT – potential treatment?

Sepsis

- Dysregulated host response to infection
- Tissue damage, organ failure and death
- Location
  - Lungs, abdomen, urinary tract, skin or soft tissue



Adapted from Medicover Hospitals

(WHO, 2020; Global Sepsis Alliance, 2020)

Risk group

Weakened immune system

Infant, age <1

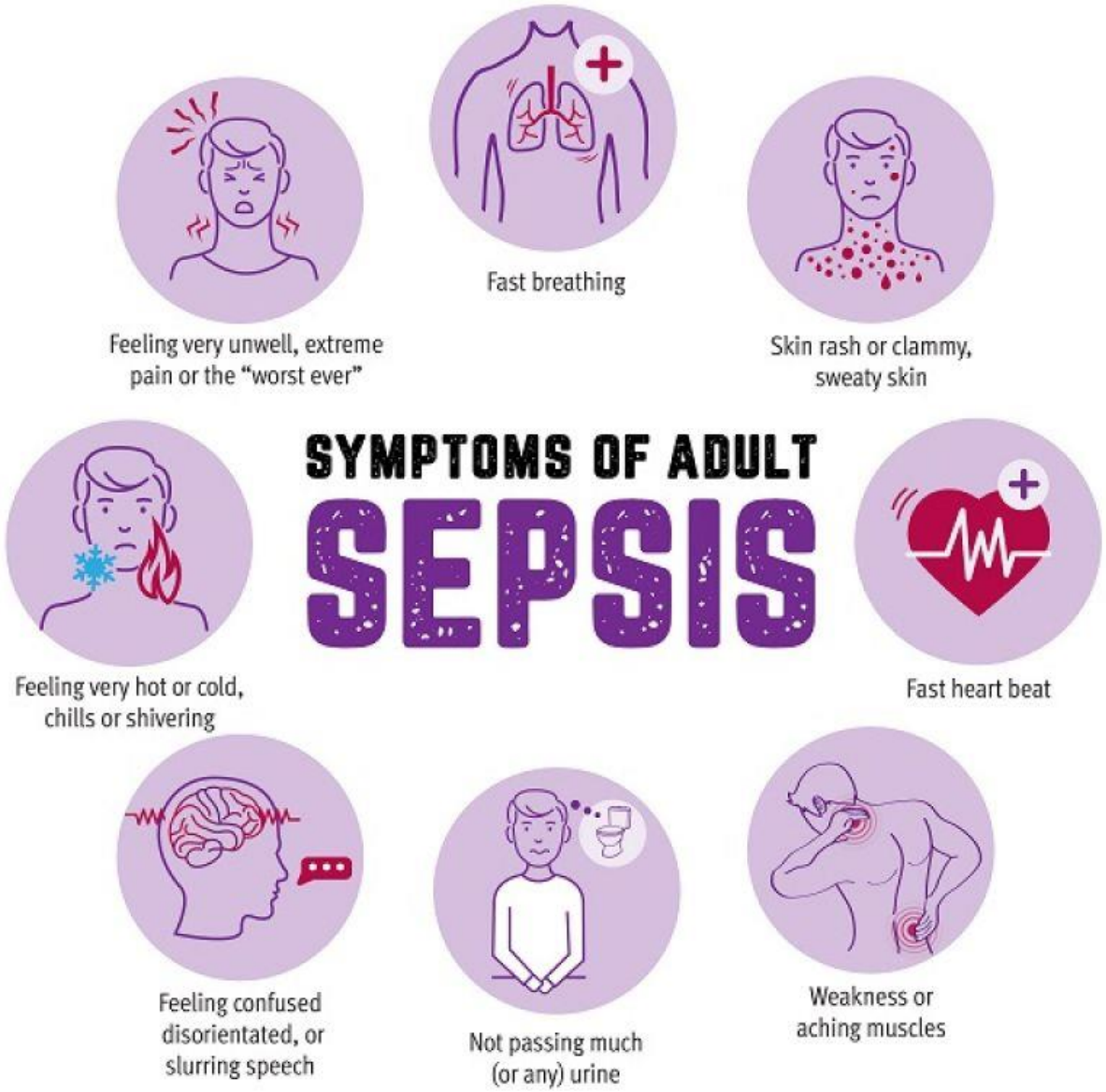
Adult, age ≥65

Immunocompromised patients

Post-sepsis recovery

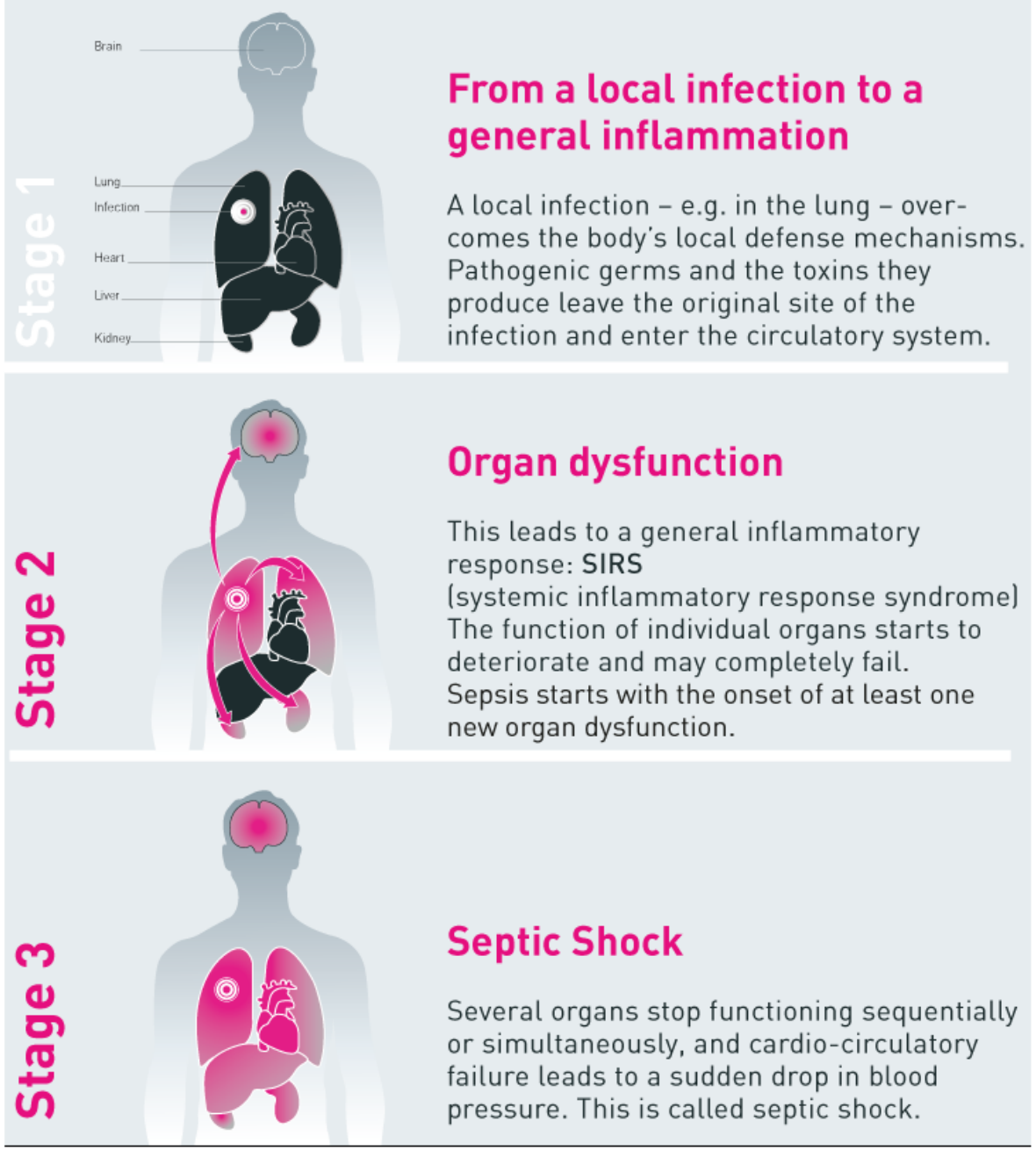
(CDC, 2022)

Symptoms of sepsis



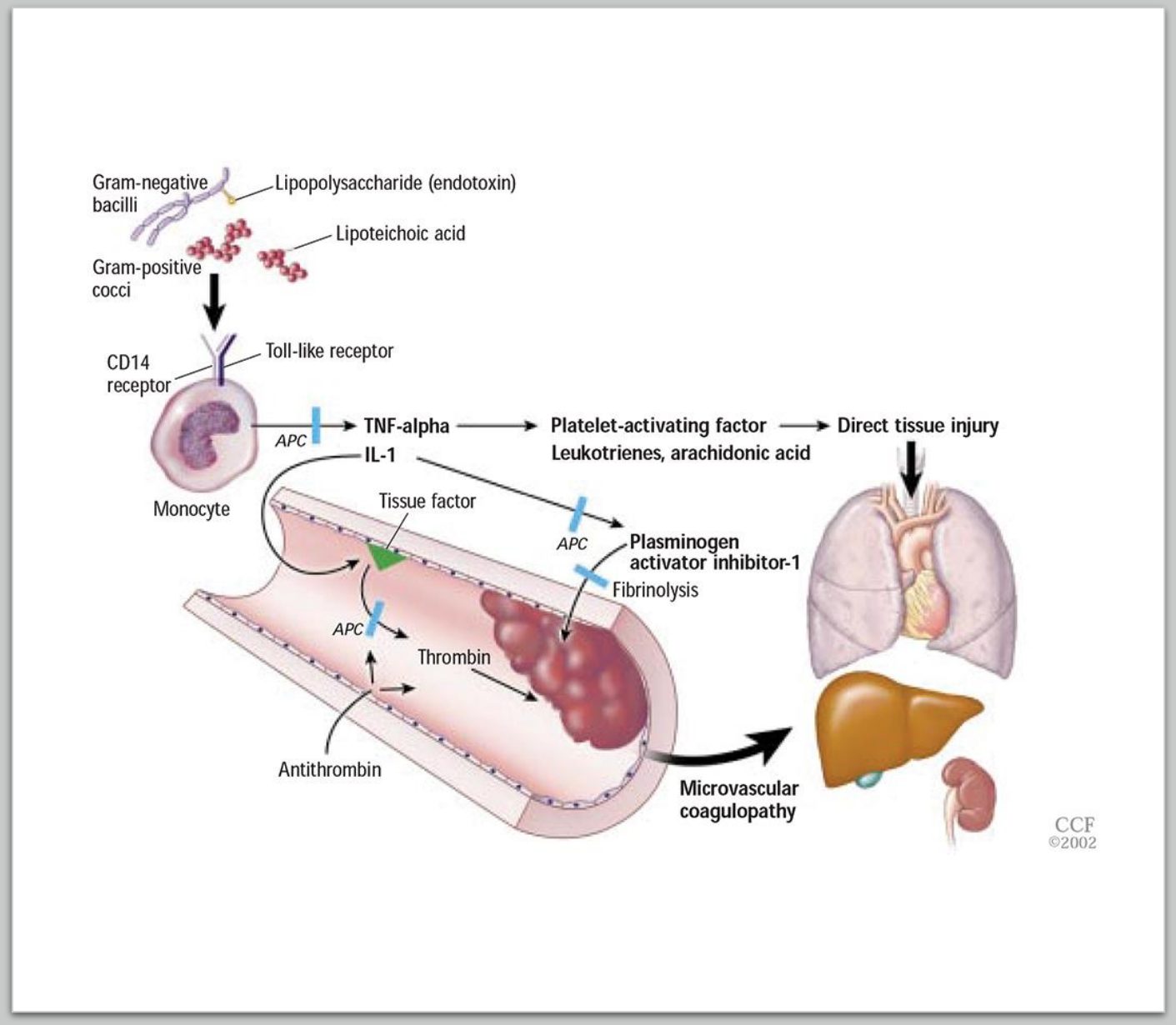
(WHO, 2020; Queensland Health, 2020)

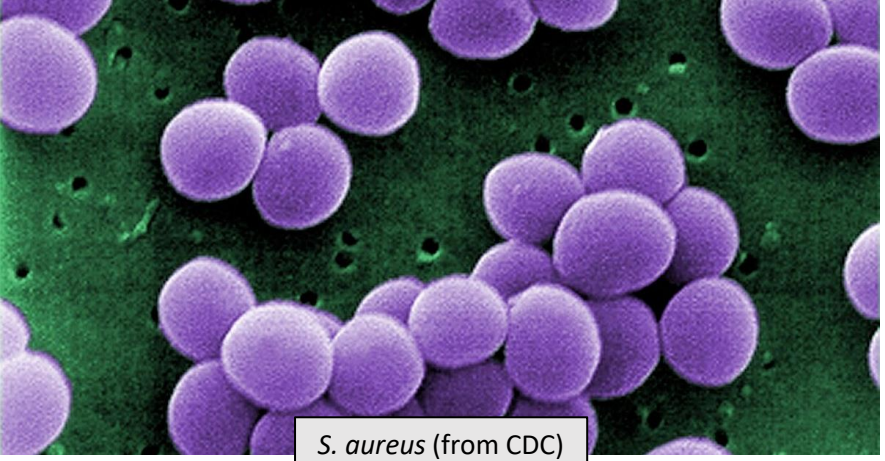
Stages of sepsis



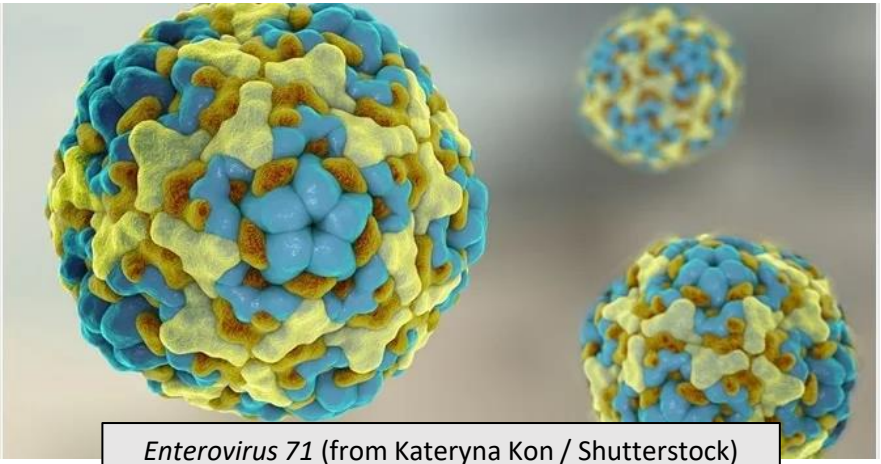
Mechanism of sepsis

- Outer membrane component trigger activation of host immune system
- Activated B cells then leads to production of cytokines
- Production of toxic downstream mediators
- Sepsis occurs when release of proinflammatory mediators > response needed for systemic response
- The mediators damage endothelial lining and promote capillary leakage
- Cytokines also induce production of adhesion molecules on endothelial cells and neutrophils, promote further endothelial injury
- Activated neutrophils release nitric oxide – vasodilator that leads to hypotension and septic shock





S. aureus (from CDC)



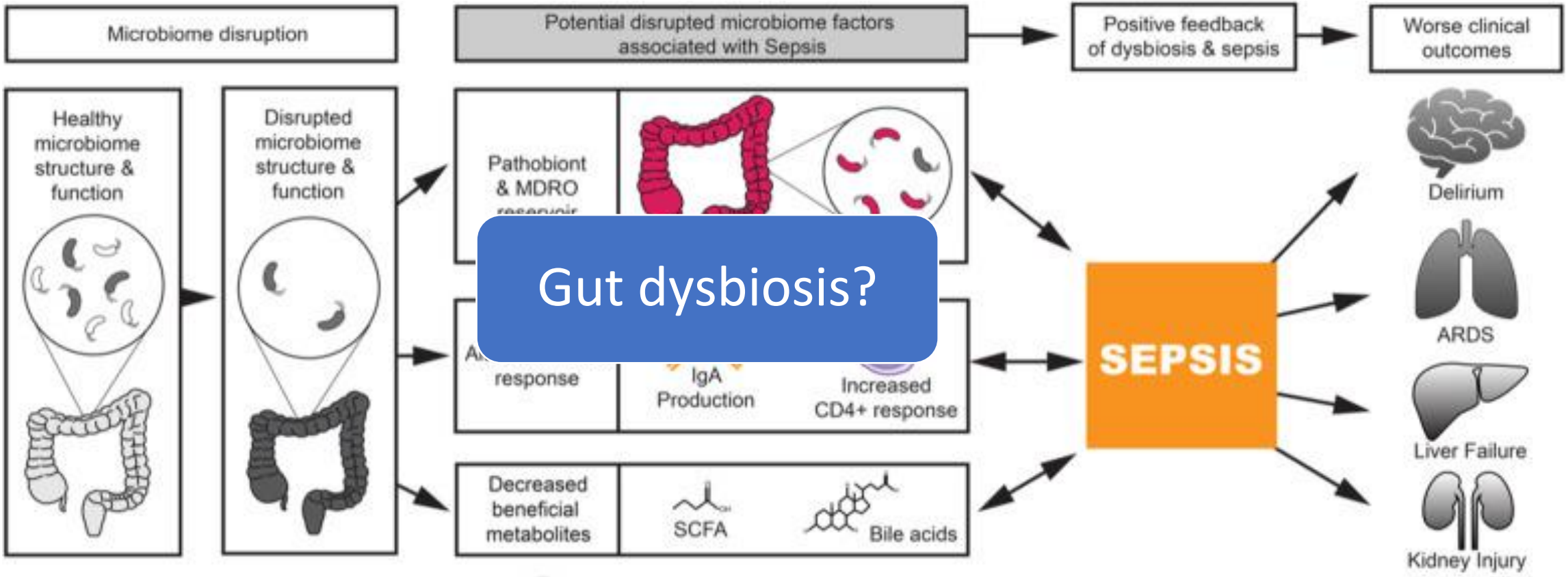
Enterovirus 71 (from Kateryna Kon / Shutterstock)

C. albicans (Kabir, Hussain, & Ahmad, 2012)

Common causes of sepsis

- Bacteria
  - *S. aureus, S. pyogenes, Klebsiella spp., E. coli*
- Virus
  - Enterovirus, influenza viruses, COVID-19, dengue viruses
- Fungi
  - *Candida spp., Aspergillus spp.*

Does the microbiome play a role in sepsis?



Gut dysbiosis?

Gut dysbiosis

- Higher risk of sepsis
  - Decrease in microbial diversity
  - Higher abundance of Enterococcus
- ¾ of patients were observed to have increased abundance of pathogens *E. faecium, K. pneumoniae, E. cloacae, and E. coli* (Ravi et al., 2019)
- 103 stool samples of sepsis patients compared to matched controls on ICU and haematology units (Rao et al., 2021)
  - 23S rRNA gene sequencing
  - Higher abundance of *Enterococcus*

Intensive Care Med (2017) 43:59–68
DOI 10.1007/s00134-016-4613-z

ORIGINAL

Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study

Jacqueline M. Lankelma[1*], Lonneke A. van Vught[1], Clara Belzer[2], Marcus J. Schultz[3], Tom van der Poll[1,4], Willem M. de Vos[2,5] and W. Joost Wiersinga[1,4]

Intensive Care Med (2018) 44:1203–1211
https://doi.org/10.1007/s00134-018-5268-8

ORIGINAL

Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection

Daniel E. Freedberg[1*], Margaret J. Zhou[2], Margot E. Cohen[3], Medini K. Annavajhala[4], Sabrina Khan[4], Dagmara I. Moscoso[1], Christian Brooks[1], Susan Whittier[5], David H. Chong[6], Anne-Catrin Uhlemann[4,7] and Julian A. Abrams[1,8]

MICROBIAL GENOMICS

RESEARCH ARTICLE
Ravi *et al.*, *Microbial Genomics* 2019;5
DOI 10.1099/mgen.0.000293

MICROBIOLOGY SOCIETY
OPEN DATA OPEN MICROBIOLOGY

Loss of microbial diversity and pathogen domination of the gut microbiota in critically ill patients

Anuradha Ravi[1], Fenella D Halstead[2,3], Amy Bamford[2,3], Anna Casey[2,3], Nicholas M. Thomson[1], Willem van Schaik[4], Catherine Snelson[3], Robert Goulden[5], Ebenezer Foster-Nyarko[1], George M. Savva[1], Tony Whitehouse[3,6], Mark J. Pallen[1,6,7,*,†] and Beryl A. Oppenheim[2,3†]

Gut dysbiosis

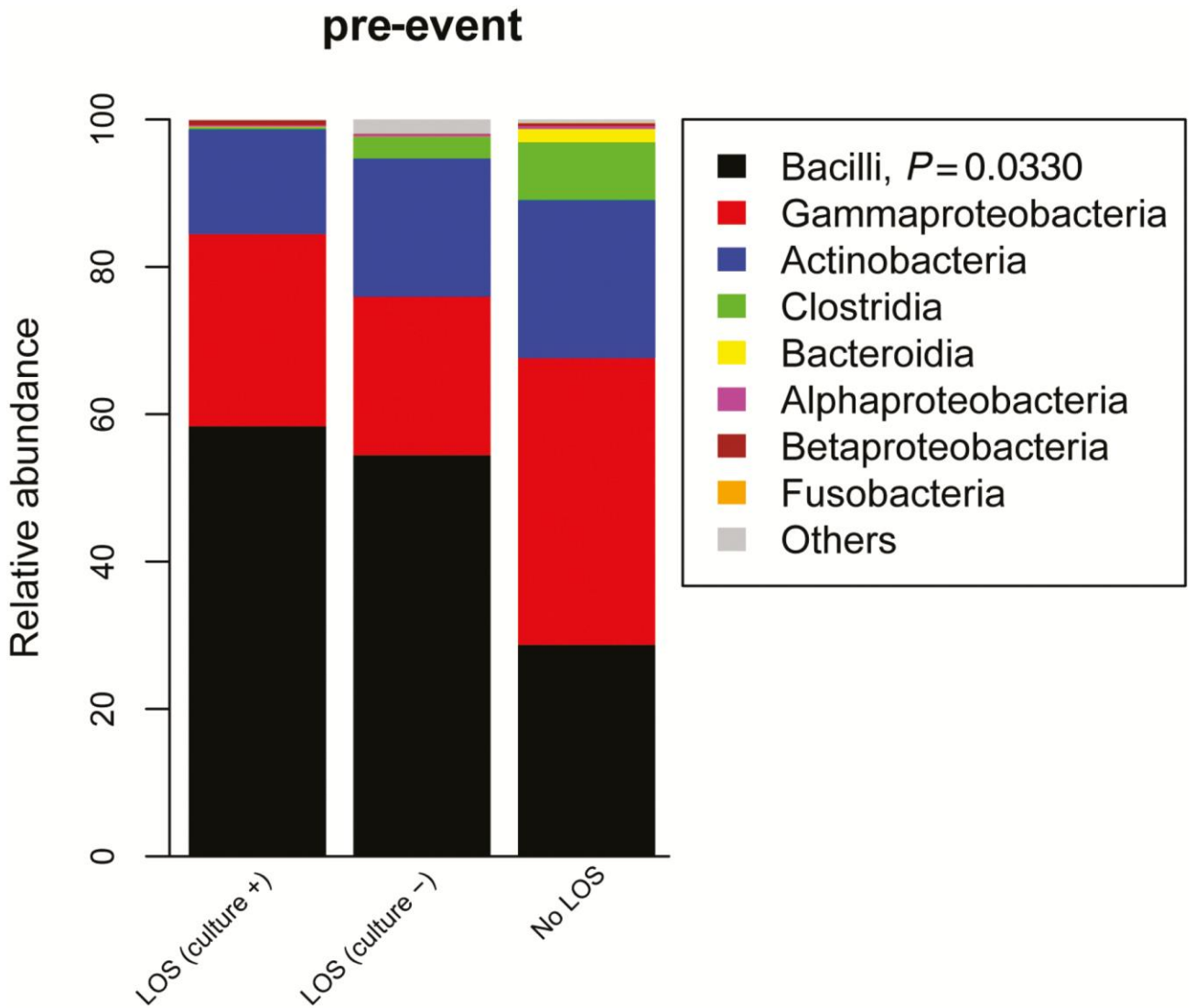
Before onset of sepsis, the guts of preterm infants with late-onset sepsis (LOS) were:

- dominated by Bacilli and a lack of anaerobic bacteria

16S rRNA sequencing on fecal samples

- 71 preterm infants with LOS and 164 unaffected preterm infants

- However, this also showed that infants without LOS has a more balanced in bacterial abundance and diversity



Bacterial taxa on class level according to late-onset sepsis (LOS) status before the onset of sepsis

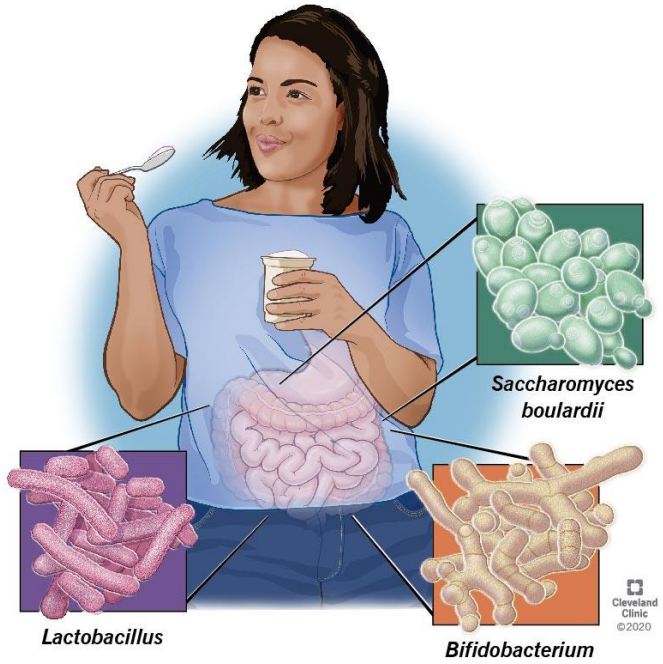
(Graspeuntner et al., 2018)

Sepsis treatment

- Early diagnosis and appropriate clinical management of sepsis are crucial to increase the likelihood of survival.
- Antibiotics
  - Rise of antibiotic resistance
  - Side effects: rash, dizziness to life-threatening allergic reactions and *Clostridium difficile* infections

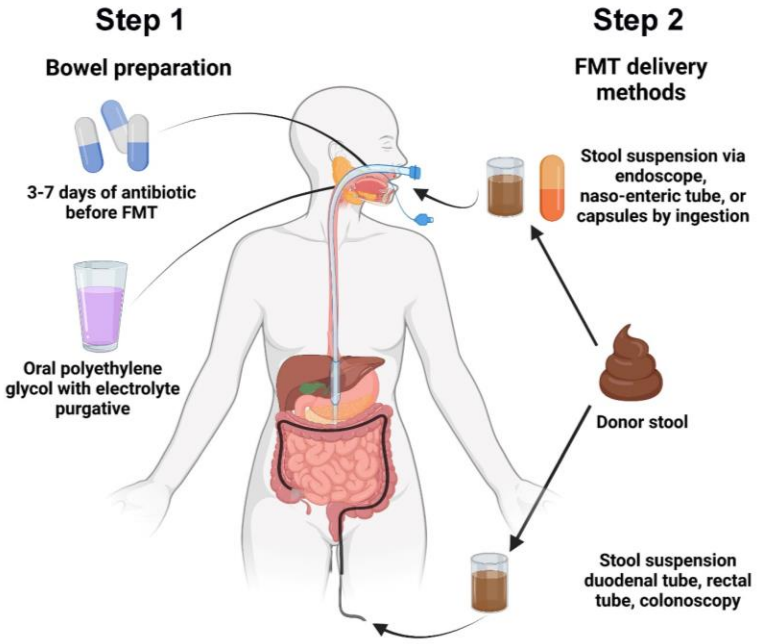
How about potential therapeutics for sepsis through microbiome?

Probiotics



- Obtain beneficial microbes like *Lactobacillus rhamnosus GG (LGG), Bifidobacterium longum (BL)*
- Treat nosocomial infections

Fecal microbiota transplant



- Transfer fecal microbiota from donor to intestinal tracts of recipient
- Treat *Clostridioides difficile* infection

Prebiotics

- Food for probiotics which enhances their survival and colonization in the colon
- Can be used with probiotics as synbiotics

Probiotics

Manzanares *et al. Critical Care* (2016) 20:262
DOI 10.1186/s13054-016-1434-y

Critical Care

RESEARCH Open Access

Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis

William Manzanares[1], Margot Lemieux[2], Pascal L. Langlois[3] and Paul E. Wischmeyer[4*]

- According to a meta-analysis on probiotic therapy in critical illnesses published between 1980 and April 2016
- 30 clinical trials that enrolled 2972 patients were identified for analysis (Manzanares, Lemieux, Langlois, & Wischmeyer, 2016)
- Probiotics were associated with a significant reduction in
  - infections (risk ratio 0.80, 95 % confidence interval (CI) 0.68, 0.95, P = 0.009; heterogeneity I 2 = 36 %, P = 0.09)
  - incidence of ventilator-associated pneumonia (risk ratio 0.74, 95 % CI 0.61, 0. 90, P = 0.002; I 2 = 19 %)

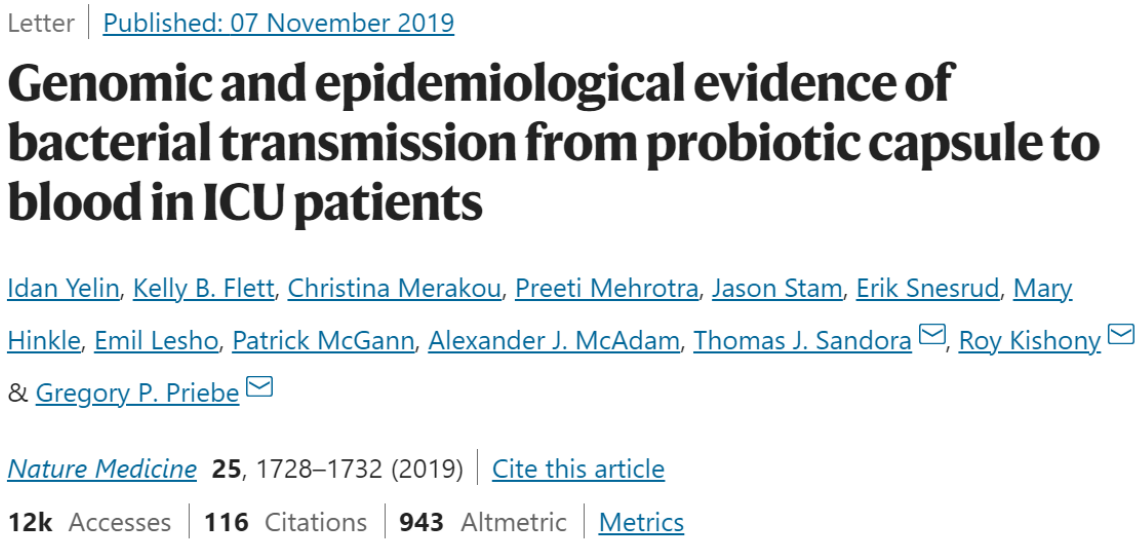
Probiotics

However, there are cases where probiotics can potentially cause adverse effects on ICU patients

- *Lactobacillus* bacteraemia (Land et al., 2005; Yelin et al., 2019)
- *Bacillus clausii* bacteremia after ≥3 days of probiotics on immunocompromised patients

Other studies

- Fungemia – *S. boulardii* supplements (Rannikko et al., 2021)



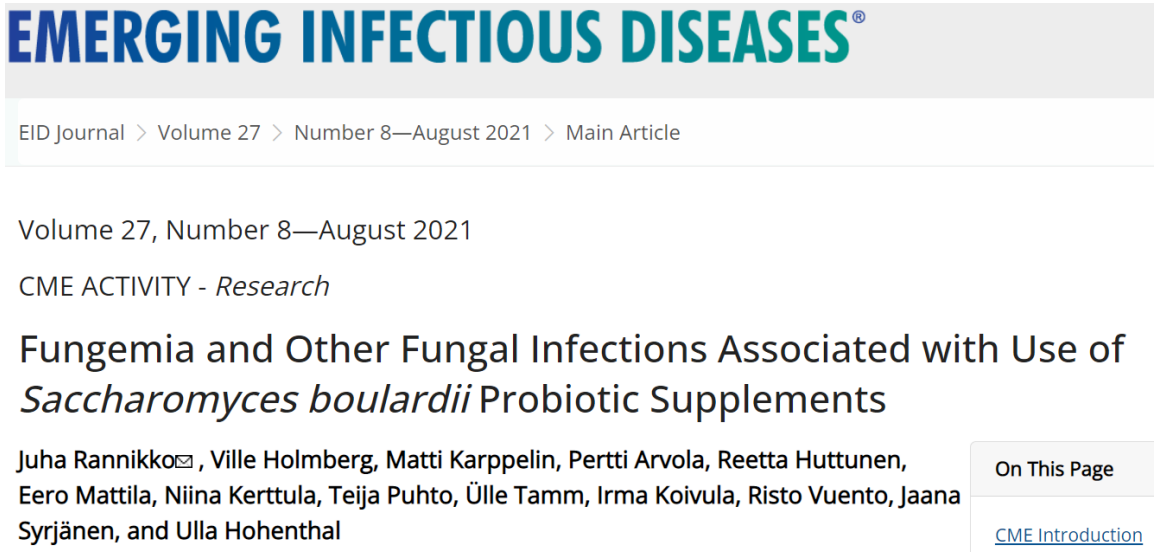
Letter | Published: 07 November 2019

Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients

Idan Yelin, Kelly B. Flett, Christina Merakou, Preeti Mehrotra, Jason Stam, Erik Snesrud, Mary Hinkle, Emil Lesho, Patrick McGann, Alexander J. McAdam, Thomas J. Sandora, Roy Kishony & Gregory P. Priebe

Nature Medicine **25**, 1728–1732 (2019) | Cite this article

12k Accesses | **116** Citations | **943** Altmetric | Metrics



EMERGING INFECTIOUS DISEASES®

EID Journal > Volume 27 > Number 8—August 2021 > Main Article

Volume 27, Number 8—August 2021

CME ACTIVITY - *Research*

Fungemia and Other Fungal Infections Associated with Use of *Saccharomyces boulardii* Probiotic Supplements

Juha Rannikko, Ville Holmberg, Matti Karppelin, Pertti Arvola, Reetta Huttunen, Eero Mattila, Niina Kerttula, Teija Puhto, Ülle Tamm, Irma Koivula, Risto Vuento, Jaana Syrjänen, and Ulla Hohenthal

On This Page

CME Introduction

Fecal microbiota transplant (FMT)

- Case reports showing evidence of sepsis treatment (Li et al., 2014)
  - A 29 year-old patient with severe diarrhoea
  - intervened with 20-day of antibiotics, probiotics, but fever and diarrhoea didn’t subside
  - FMT was administered and septic symptoms subsided

Therapeutic Modulation and Reestablishment of the Intestinal Microbiota With Fecal Microbiota Transplantation Resolves Sepsis and Diarrhea in a Patient

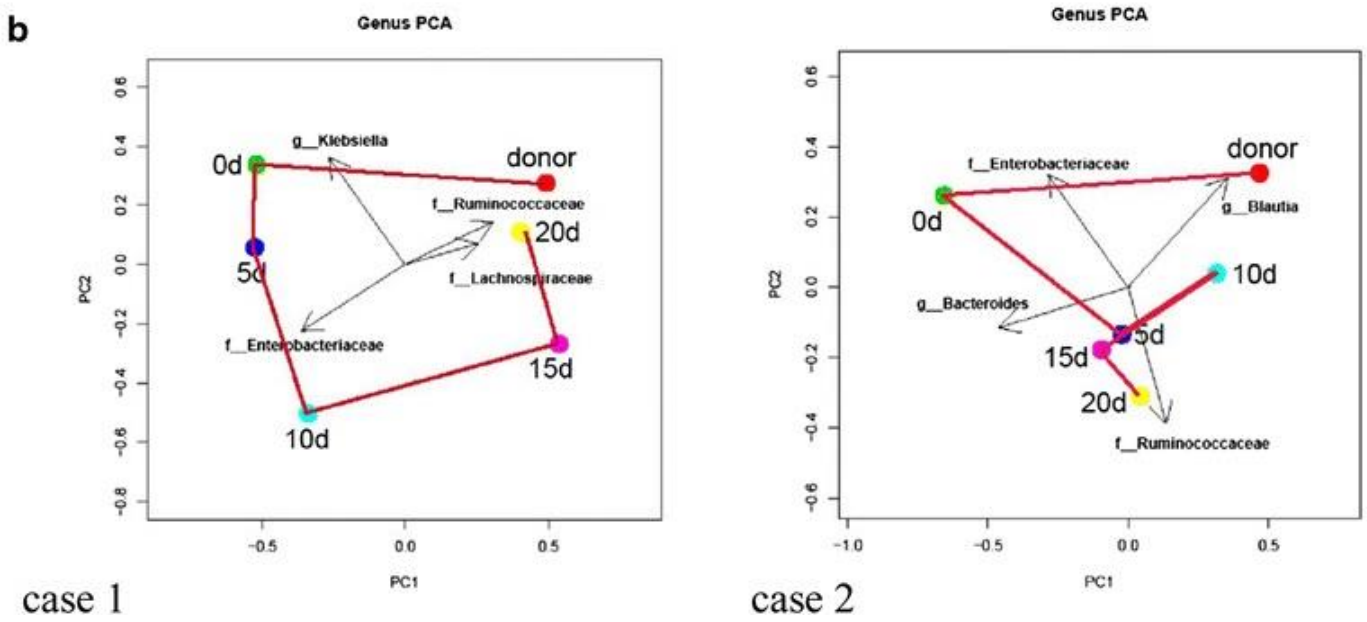
Li, Qiurong MD, PhD[1]; Wang, Chenyang MA[1]; Tang, Chun BA[1]; He, Qin MA[1]; Zhao, Xiaofan BA[1]; Li, Ning MD[1]; Li, Jieshou MD[1]

Author Information

American Journal of Gastroenterology: November 2014 - Volume 109 - Issue 11 - p 1832-1834
doi: 10.1038/ajg.2014.299

Fecal microbiota transplant (FMT)

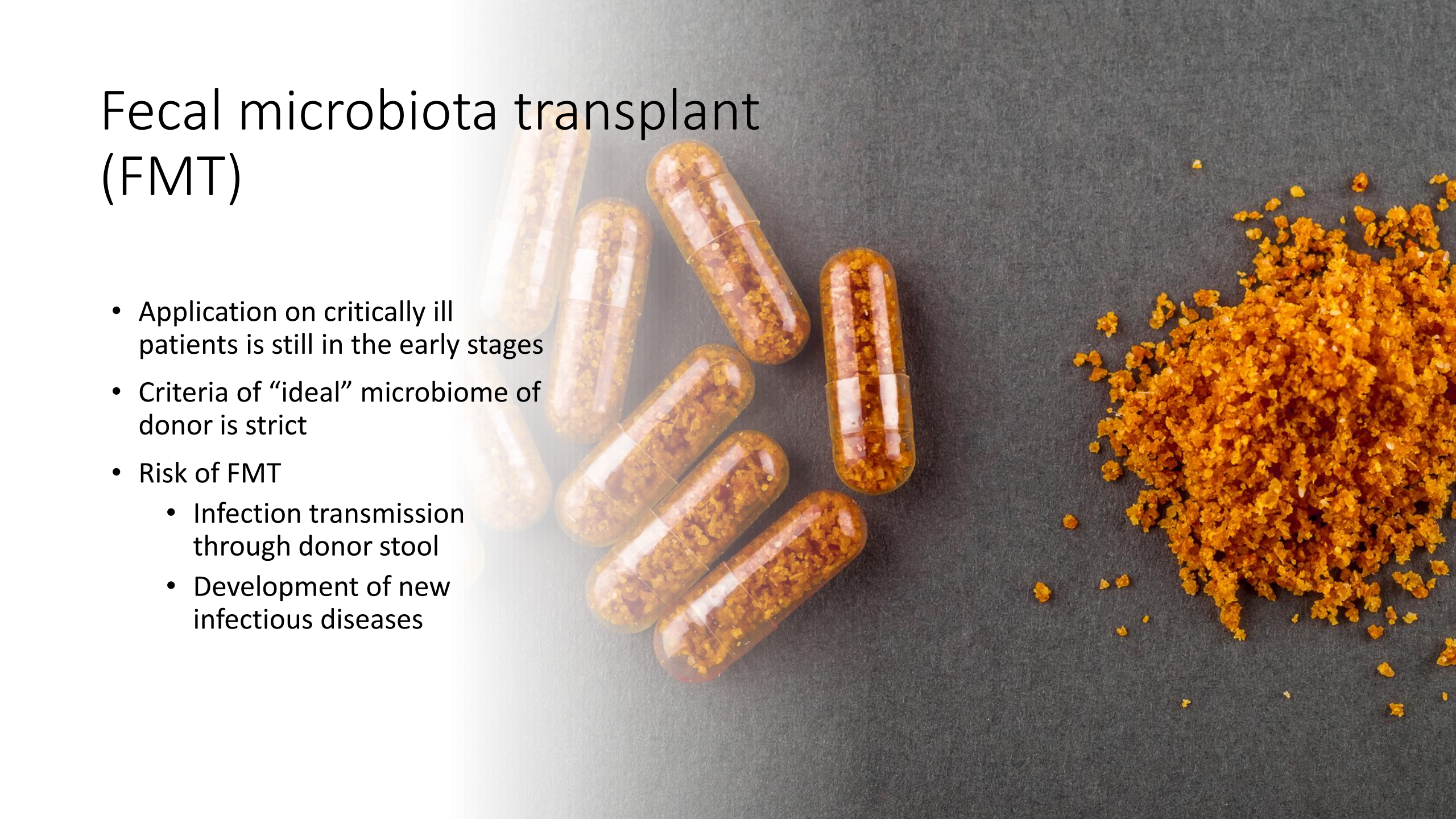
- Another case report on two patients
- A 65-year-old and an 84-year-old developed multiple organ dysfunction syndrome (MODS), septic shock and severe diarrhoea
- After receiving FMT,
  - gut microbiota of both patients tend to have similar microbiota with that of their donors
  - MODS and diarrhoea were alleviated



(Wei et al., 2016)

Fecal microbiota transplant (FMT)

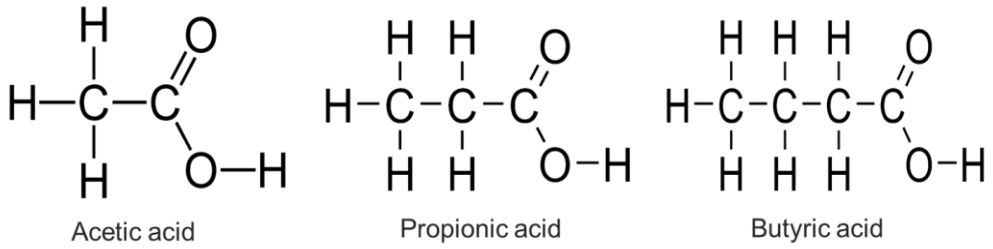
- Application on critically ill patients is still in the early stages
- Criteria of “ideal” microbiome of donor is strict
- Risk of FMT
  - Infection transmission through donor stool
  - Development of new infectious diseases



Prebiotics

- Prebiotics are food to probiotics – beneficial for survival of probiotics
- Mortality higher in sepsis patients with lower abundance of butyrate-producing bacteria (Valdés-Duque et al., 2020)
  - produces a short-chain fatty acid (SCFA) → have immunomodulating and protective effects from the intestinal microbiota

- SFCAs play a key role in promoting intestinal barrier integrity (Mittal & Coopersmith, 2014; Yamada et al., 2015)
  - naturally produced by host metabolic pathways
  - mainly synthesized in the colon through polysaccharide fermentation by anaerobic bacteria
  - can potentially treat sepsis



Prebiotics

- Based on a meta-analysis, 11 trials, with 1106 infants, reported sepsis rates
- The mean morbidity rate for the infants receiving prebiotics was 17.4% compared with 27.4% in the controls.
- A significant decrease(p=) in risk ratio of 0.64 among the group of preterm infants receiving prebiotic treatment compared with that of the control group

European Journal of Clinical Nutrition (2019) 73:657–670
https://doi.org/10.1038/s41430-018-0377-6

REVIEW ARTICLE

Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis

Cheng Chi[1] · Nicholas Buys[2] · Cheng Li[1] · Jing Sun[3] · Chenghong Yin[1]

Received: 1 July 2018 / Revised: 25 October 2018 / Accepted: 26 November 2018 / Published online: 19 December 2018

Conclusion

- Normal microbiota is crucial as first line defense against pathogens in the human body
- Since sepsis arises from microbial infection, microbiome plays a key role even though a direct link between them is vaguely understood
- Evidence is accumulating for the human microbiome to be associated with the development of sepsis and its complications
- More research attention is needed on studies and clinical trials that aim to stabilize dysbiotic microbiota

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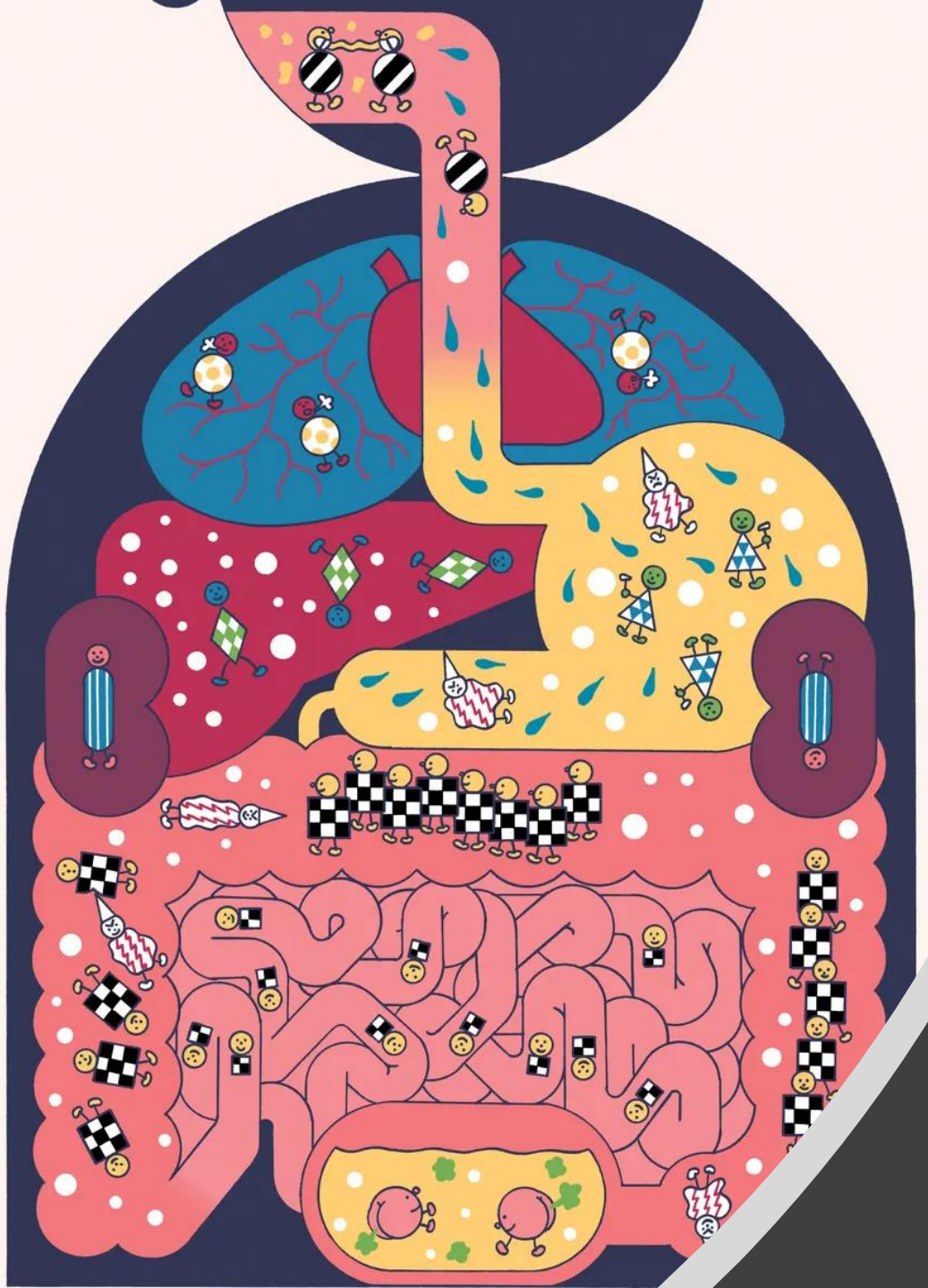

Thank you