BAOJ Microbiology

Shimon S, et al. BAOJ Microbiology 2019, 5: 3
5: 047

Mini Review

Microbiome, TMAO, Butyrate, Short Chain Acids in the Internal Medical Health

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Recent Discovery

The gutmicrobiota, now the device is the field of bacteria. Example of the *archaea* is the methane-producing *Methanobrevibactersmithii,* and Recent studies are the has been implicated in irritable bowel syndrome (IBS) with constipation [1]. Methane (CH4) is one of the gases that show the human intestines and is produced by aerobic bacteria fermentation. CH4 is described as having the ability to affect bowel passage speed, reduce the secretion of serotonin and is caused by IBS, diverticulitis and colorectal cancer, and the Role of commensal gut bacteria in inflammatory bowel diseases. Microorganisms are representing *methanobrevibactersmithii*, belonging to the old domain [2,3]. Prolonged bowel candidates produce [4]. The microbiome, with its vast, 100 Billions of cells, produces excretions [5], two of them, the Trimethyl Amine Oxide (TMAO), as intensively studied by professor Stanley Hazen [6], and butyrate, are identified by researchers and serve as a marker

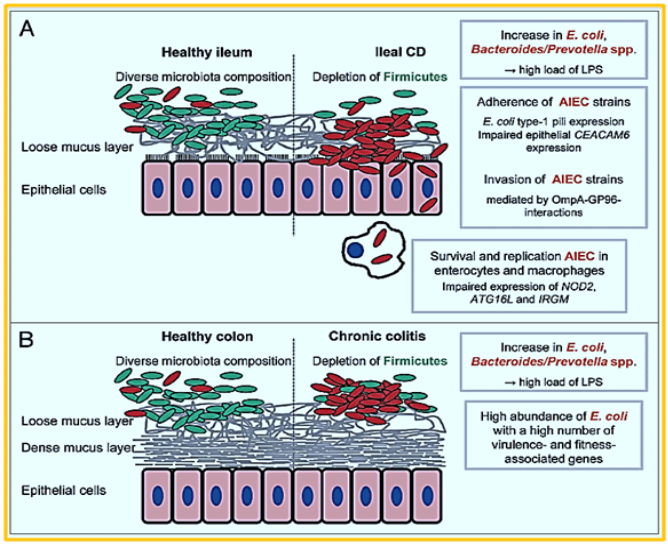

Figure 01:

Figure: Pro-inflammatory effects of gut bacteria in IBD. Crohn disease and ulcerative colitis are characterized by a depletion of Firmicutes in conjunction with an increase of Gram-negative bacteria, namely E. coli and Bacteroides/Prevotellaspp The shift in microbiota composition are associated with high loads of bacterial antigens (mainly LPS). The recognition by the immune system of these antigens and the subsequent initiation of-inflammatory responses may be an essential trigger of IBD. In a subset of patients with ileal CD, adherent-invasive E. coli (AIE C) strains are highly abundant and able to invade and to survive and replicate in host cells. An impaired bacterial clearance by the host may be responsible for disease development in patients with mutations in autophagy-associated genes (A). Direct interactions between bacterial and host cells may be less critical in chronic colitis because the colonic mucosa is protected by a dense mucus layer. Increased concentrations of bacterial antigens resulting from a high abundance of Gram-negative bacteria may drive colitis progression. The exact role in chronic colitis of E. coli strains with a high number of virulence and fitness-associated genes remains to be identified (B). (credit ref. [3]).

In many kinds of research. In this paper we will focus on the butyrate, mainly present in our gut. For example it is reported that Relationship of Serum Trimethylamine N-Oxide (TMAO) Levels with early Atherosclerosis in Humans [7].

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Sub Date: July 11th, 2019, **Acc Date:** July 16th, 2019, **Pub Date:** July 18th, 2019

Citation: Shimon S, Krieger R, Lapidot I, Galina Z (2019) Microbiome, TMAO, Butyrate, Short Chain Acids in the Internal Medical Health. BAOJ Microbiology 5: 047.

Figure 02:

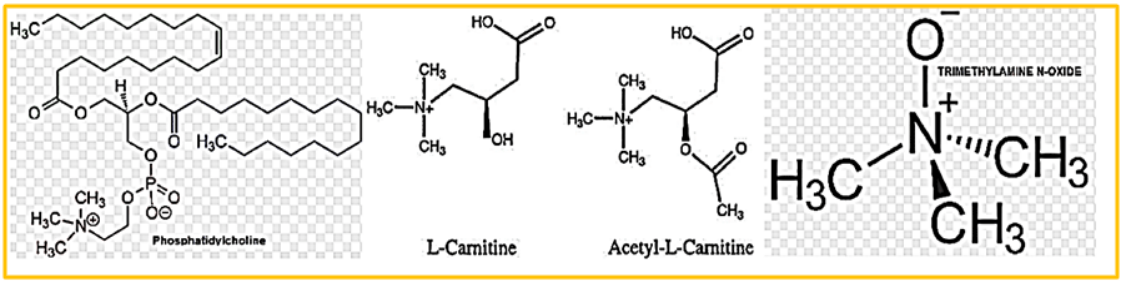

Figure 03:

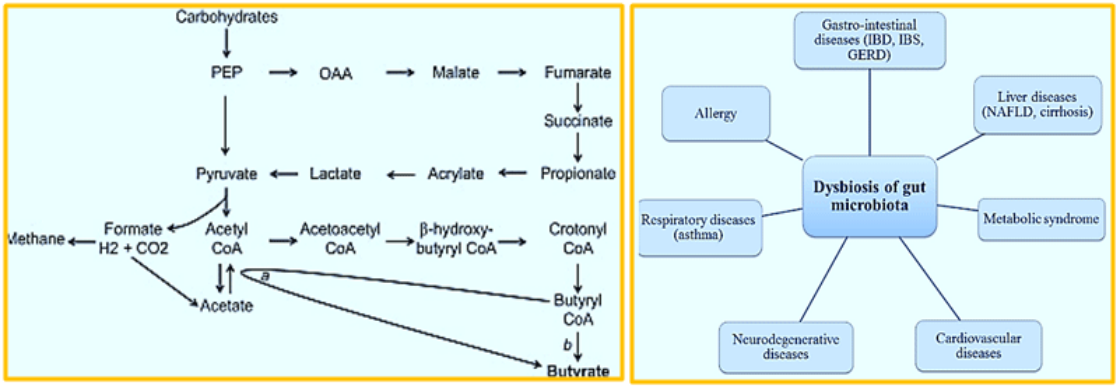

Figure 04:

Biogenesis of Butyrate and its effects (credit ref [8]) Colon cancer (CRC) is one of the significant health threats in developed countries. Changes in Nutritional components, such as protein intake and more fats, can increase the risk of CRC. Diet affects CRC in many ways. They regulate the composition and function of the gut microbiota, which there is a fantastic metabolic capacity can produce short-chain acids (SCFAs), such as propionate Acetate, and butyrate. Butyrate is a significant energy source for colon epithelial cells and plays an essential role in maintaining the stability of the gut microbiota and the completeness of the intestinal epithelium. However, there are a number of studies examining the anti-CRC potential of the butyrate. This review summarizes the latest advanced study under the influence of microbial and microbial imbalance Decrease of metabolite and intestinal bacteria caused by a balanced diet on the CRC Development, and discusses the mechanisms of anti-CRC activity induced by butyrate, which are made Instruct people to avoid CRC by improving the structural diet. The gut production of short chain fatty acids (SCFA), especially butyrate, in the Microbial abdomen is required for optimal health, but is often limited by lack of dietary fiber in the diet. We tried to increase production by

butyrate by Complement the diet of 174 healthy young people for 2 weeks with resistance Potato Starch (RPS), Starch Resistant from Corn (RMS), Insulin from Chicory Root, or corn starch control is accessible. RPS resulted in the most significant increase in total SCFA, including butyrate. Although most microbiologists responded RPS with relative abundance increases of Bifidobacteria, those who responded With an increase in Ruminococcusbromii or Clostridium chartatabidum were more May yield higher butyrate concentration, especially when their microbiota were Packed with populations of species that produce a Eubacterium rectale. RMS And insulin caused various changes in fecal communities, but they did not produce Significant increases in stool levels of butyrate. Understanding the butyrogenic effect of these specific intestinal bacterial supplements. It is important to plan more effective and predictable treatments People may enjoy them. More generally, defining metabolic interactions between intestinal bacteria improves our understanding of assembly, maintenance, and outputs from the intestinal microbiota.Today, increasing attention has been given to other ways to prevent or treat diseases. Nutraceuticals are increasingly used for this purpose. Many of them are used as alternative treatments. Classic therapy with synthetic drugs, although very useful, has many side effects. The term "nutraceuticals" means to the link between the nutritional and pharmaceutical fields. Also, recently, many studies have been done to investigate the role of microbiota in maintaining health. There is the hypothesis that some of the health benefits of nutraceuticals are due to their ability to alter the microbiota. The purpose of the review was to highlight the link between the most common nutraceuticals, the microbiota and the health benefits. Recent studies reveal a new mechanistic relationship between the microbiota in the gut and the development of cardiovascular disease (CVD). Dietary substances rich in a western diet [9] (eg, choline, phosphatidylcholine and carnitine) act by intestinal bacteria to form, trimethylamine (TMA), which is converted by hepatic monooxygenases to produce the TMAO metabolites (triethylamine-N-oxide). TMAO in animal studies has been shown to promote atherosclerosis. Clinical studies in humans show that TMAO is closely linked to the risk of MI, stroke or death, and is produced in gut microbiota. Recent studies have shown that the TMAO pathway is linked to improved platelet response and the potential for thrombosis. Studies presented suggest that the colon may participate in the pathogenesis of the cardiometabolic diseases, thrombosis potential, and intestinal microbial may serve as a potential therapeutic target for the treatment and prevention of CVD.

Tmao –A Product of the Digestion in the Gut by Microbiomals

Trimethylamine [10] is created by gut microbiota from nutrients containing l-carnitine, choline, phosphatidylcholine followed by the formation of trimethylamine N-oxide (TMAO) by liver enzymes to increase the plasma level of TMAO-increasing the risk of myocardial infarction and stroke to increase the production of neurotoxin. The incidence of non-alcoholic fatty liver disease (NAFLD), a significant concern for public health, has increased worldwide, and this disease is generally associated with obesity, insulin resistance, diabetes and metabolic syndrome. NAFLD includes pathological spectrum, from isolated steatosis to non-alcoholic stomatitis (NASH), which can progress to fibrosis, cirrhosis, or hepatocellular carcinoma. A combination of genetic, metabolic, environmental, and environmental factors contributes significantly to the formation of the NAFLD disease. However, despite extensive studies made in recent decades, the underlying molecular mechanisms of NAFLD progression remain largely unclear; Common treatment strategies, other than lifestyle changes such as weight loss diets and / or intensive exercise are not yet available, and there is no effective drug for NASH treatment approved by the Food and Drug Administration .Increasingly, studies have confirmed the critical role of gut microbial development in the development and progression of NAFLD, but the underlying mechanisms are unclear Short-chain endogenous fatty acids (SCFA) are produced mainly from dietary carbohydrates by the intestinal microbiota, which consists of many bacteria of intestinal bacteria and / or probiotic bacteria Interestingly, dietary supplements with SCFA, especially butyrate, have been shown to protect against high-fat obesity (HFD), insulin resistance, and liver status in animal models. The ability of butyrate to protect mice from methionine-choline deficiency (MCD) diet-induced diet development to regulate the gut microbiota and luminal gut metabolism has not been determined. We hypothesized that butyrate could weaken the liver steatosis and damage the liver and improve microbiota gut and luminal metabolism in the mouse model of NASH induced by the MCD diet [11].Connections [12] between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). NAFLD is now the leading cause of chronic liver disease in developed countries, and the number of patients in NAFLD patients has increased worldwide. NAFLD often has symptoms similar to other metabolic disorders, including type 2 diabetes and obesity. Recently, the role of gut microbiota in the pathophysiology of many diseases has been exposed. For NAFLD, experiments using microbiota gut transplants for animal models without bacteria showed that the development of the fatty liver disease is determined by intestinal bacteria. Furthermore, the disorder of the microbiota composition of the intestines was observed in patients with NAFLD. There are many mechanisms associated with the microbiome of the intestines to NAFLD, including Dysregulation induced dysbiosis of intestinal endothelial barrier function, which allows the translocation of bacterial components and leads to hepatitis. In addition, various metabolites produced by gut microbiota may affect the liver thereby regulating the NAFLD sensitivity. Therefore, the manipulation of intestinal microbium by probiotics, parabiotics or probiotics has been shown to improve liver phenotype in NAFLD patients as well as rodent models. Thus, further knowledge about the interactions between dysbiosis,

environmental factors, diet and their effects on the liver's abdominal axis can improve the treatment of this life-threatening liver disease and its related disorders. The relationship between gut microbial and NAFLD. Non-bacterial (GF) animal models have been used for decades to define the consequences of the absence of gut microbiota, therefore, to establish host physiological functions affected by these bacteria. Among these functions, it has been shown using these animal models that gut microbiota has a role in obesity and related metabolic diseases [13]. Indeed, it was found that GF animals are resistant to obesity caused by various diets, including a high-fat, Western-style diet or even high in sugar, and this effect is correlated with the increased expression of ANGPTL4 genes as well as the activity of AMP-activated protein kinase AMPK) and its target downstream proteins, such as acetyl-carboxylase COA (ACC) [14]. Protein kinase AMPK is an energy sensor that plays a significant role in the transition between glucose and lipid metabolism in various organs. The study of Robot et al. Also confirmed the fat-resistant phenotype in GF mice and showed a decrease in the use of calories and increased lipid secretion in these animals [15]. However, the phenotype resistance to obesity in GF mice was later to be highly dependent on the sugar composition of the diet . We examined the effect of three different diets, namely low fat, high fat and West (WD), on GF and CV (conventional) mice, and disagreed with the role of Angptl4 in protecting GF mice from obesity. More importantly, GF and CV mice showed no difference in body weight on a low-fat diet. Significantly, GF mice have accumulated more body weight and body fat than CV mice with lower energy expenditure on HFD. Finally, WD-fed GF mice showed less body fat than GF mice on HFD, suggesting that the absence of gut microbiota does not usually protect mice from obesity caused by diet. Samuel and others. Showed that short fatty acid (SCFA) - G binding corresponds to a G441 protein receptor that may regulate the effects of gut microbiota on host fat by comparing Gpr41 deficient and wild-type GF mice with and without a fermented microbial model [16] Causal link between bacterial The intestines and obesity were further investigated through microbiota transfer. For the first time, B. the et al. Has demonstrated that transferring a normal kettle microbiota of conventional mice to GF C57BL / 6 mice led to more fat deposition and insulin resistance in the body despite reduced food intake [17]. In line with previous findings suggests that microbial oils help to reap more energy from the diet and that this feature can be transferred by transplantation of fecal microbiota (FMT) [18].

Effect of Microbiome on Cirrhosis of the Liver

Several studies have attempted to map the human microbiology of patients with advanced liver disease. Data on patients who are not supervised are much rarer. A first comprehensive look at the intestinal microbial of cirrhosis patients showed that the composition of fecal bacteria in patients with cirrhosis of the liver was different from healthy controls. Patients with the prevalence of pathogenic potential bacteria, such as Enterobacteriaceae Veillonellaceae and Streptococcaceae, which had a positive correlation with CTP score. Proteobacteria and Fusobacteria were highly enriched along with the reduction of beneficial populations such as Lachnospiraceae which correlated negatively with CTP score [19]. The next analysis of the stool microbiome held at Sierrhotics showed that the composition was significantly different [20].The researchers looked at 54 patients with unsuccessful cytoplasmic patients, and proposed the liver ratio of dysbiosis (CDR), the ratio of autochthons and non-autochthonous doses, as a tool for evaluating pyrolysis. Microbiota and CDR were relatively stable over time in patients whose disease remained unchanged and changed when the underlying disease worsened. CDR for controls was significantly higher in comparison to all cytotropic patients. In 2014, Qin et al [13] analyzed data on the intestinal microbial of patients with cirrhosis and reported two main findings; Patients with cirrhosis changed the gut profile of microbial compared with healthy controls, and most of them (54%) of the highly enriched species were of Bokalian origin, suggesting a massive invasion of the intestines by oral microbial species responsible for this change in the intestinal microbiota seen in cirrhosis of the liver. These findings have presented new perspectives on the role of the liver-oral neck in patients with cirrhosis of the liver.

Microbiota in dental Problem of Periodontal Infections

Human microbiota systems differ from place to place in the body. Diet affects the composition of microbial: long-term diet is Associated with the development of specific enterotypes e.g. higher diets in animal protein and fat with higher levels of many Bacteroides and low levels of *Prevotella* bacteria, high carbohydrate diets but low in protein and animal fat with higher levels of *Prevotella* but lower levels of the Bacteroides [21].The oral cavity is very diverse, dynamic And the unique ecosystem in the human body with a characteristic Feature being the instability of its ecological(Marsh, 2005). The oral cavity is complex A mucous membrane covered with a cartilage layer Diaphragmatic epithelium (eg palate) and non keratinized Epithelium, papillary surface of Tongue and hard non-shed structures of the teeth Above and below the rim of the gums, in contrast Surfaces, grooves and spaces. These sites constitute Separate ecological niches that promote development of microorganisms, with each marble niche unique microbiome. Gingivitis is a type of periodontal disease that occurs when plaque, a natural adhesive tape containing bacteria, builds on the teeth and causes inflammation of the surrounding gum tissue. Plaque produces toxins that stimulate the gums [22]. Dental caries [23] is one of the most common multifactorial diseases affecting the human population. The appearance of tooth decay is determined by co-existence of three main factors: acidic and acidic microorganisms, carbohydrates derived from the diet, and host factors. Socioeconomic

and behavioral factors play an important role in the etiology of the disease. Caries develops as a result of an ecological imbalance of stable oral microbial. Oral microorganisms form a dental layer on the dental surfaces, which is the cause of the caries process, and shows features of a classic biofilm. Biofilm structure appears to be affected by large-scale changes in protein expression over time and in genetic control. Their presence causes a decrease in the pH level below 5.5, resulting in demineralization of the hydroxyapatite enamel crystal and the proteolytic distribution of the structure of the hard tooth tissues. Streptococcus mutans, streptococci and others of the so-called non-stansptococci non-mutant group, Actinomyces and Lactobacillus play a key role in this process. Biofilm Dental is a dynamic, constantly active metabolic structure. Intermittent processes of decrease and increase of pH and biofilm occur, which are followed by the corresponding processes of de-demineralization of the tooth surface. In healthy conditions, these processes are in balance and there is no permanent damage to the tooth enamel surface.

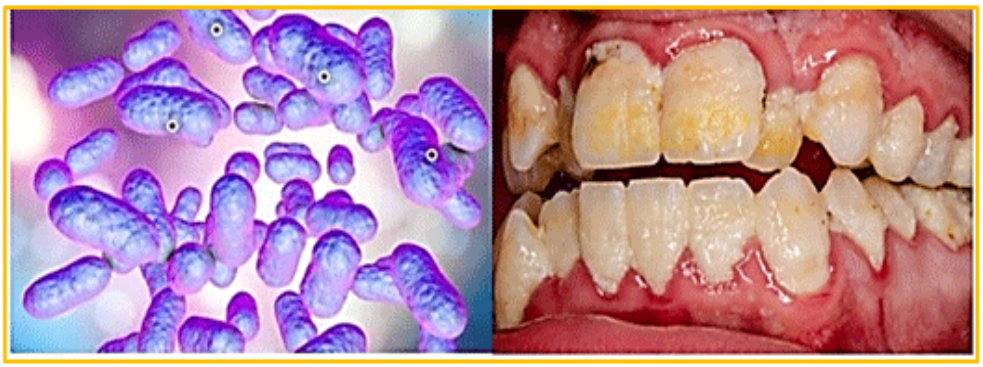

Figure 05:

The Oral Bacteria *Prevotella* intermedia and its Link to Gout and Hyperuricemia (credit ref. [24])

The Microbiome and Butyrate Regulate Energy

Metabolism and Autophagy in the Mammalian Colon

The microbial is characterized by large-scale sequencing efforts, but it is unknown whether it regulates host metabolism in general versus specific tissues or some bacterial important metabolites. Here, we show that microbiota has a substantial impact on energy Homeostasis in the colon vs other tissues. This issue is specific due to colonocytes using bacterial-derived bigotries as their primary source of energy. Colonocytes of the genre Mice are in a deprived energy state and exhibit a decrease in expressions of enzymes that precipitates Major steps in mediated metabolism include TCA cycle. As a result, there is marked Decrease in NADH / NAD +, oxidation phosphorylation, ATP levels, resulting in 5' adenosine monophosphate-activated protein kinase (AMPK) Activation, Cyclin-dependent kinase inhibitor 1B (p27Kip1) phosphorylation, and autophagy. On adding butyrate to germ free Colonocytes, it saves their deficit in mitochondrial respiration and prevents them Autophagy pass. The exact way is certainly due to butyrate acting as an energy source rather than as a Histone deacetylases (HDAC) inhibitor. On the other hand, intestinal bacterial degeneration of butyrate proteins. In patients with symptomatic atherosclerosis and type 2 diabetes, metabolites of gut bacteria may be behind the role of the microbial of the intestines in cardiovascular health[25], as the triglycerides of trimethylamine in the production of nitric oxide (TMAO) Trimethylamine (TMAO) promotes atherosclerosis in animal models and is associated with cardiovascular risk in humans. Humans with metabolic and inflammatory diseases often harbor lower levels of gutted butyrate bacteria. However, it is not known whether variation in these levels organisms is associated with a causal relationship with the development of the disease and whether the diet changes the effect of These bacteria are on health. Here we show that the abdomen stands out associated with butyrate-producing bacteria Species (rasbora sp.) Is correlated reverse with the development of atherosclerotic lesion the mouse population is genetically diverse. We use apolipoprotein-free rat E mice in impaired colony With synthetic bacterial communities that differ in their ability to produce butyrate Prove that the intestinal interact with plant dietary polysaccharides affect Gene expression in the gut, direction of metabolism from glycolysis towards fatty acid Utilization,

(i) lower systemic inflammation, and

(ii) Improving arteriosclerosis. Furthermore, the colon of Butyrate reduces endotoxemia and the development of atherosclerosis. Overall, our results demonstrate how microbiota-based diet interactions can be altered cardiovascular disease, and offer interventions aimed at increasing the representation of Bacteria that produce butyrate may provide protection against atherosclerosis. However, the role of bacteria producing butyrate in the development of atherosclerosis is unclear.

A new study of mice, led by the Department of Bacteriology at the University of Wisconsin in Madison, Wisconsin, shows that bacterial butyrate prevents atherosclerosis by maintaining colon function. To investigate the role of butyrate in atherosclerosis, the researchers colonized mouse-free transgenic mouse model of atherosclerosis and apolipoprotein E-mice deficient - with defined microbial communities that had a different genetic background. Eight human intestinal bacteria with limited ability to produce butyrate have been tested, with or without the known butyrate producer Rosabary intestines. Cardiovascular Health: The Role of Gut Microbiota-Generated Short-Chain Fatty Acids in Metabolic and the role of fatty acid Microbiota generated short-chain fatty acids metabolic cardiovascular. Here we evaluate the evidence linking short-chain fatty acids (SCFA) to metabolic risk for cardiovascular health [26] and disease (CVD) and present the latest evidence of possible biological mechanisms. SCFA, produced mainly from bacterial fermentation of dietary fiber, appears to be critical mediators of the positive effects caused by gut microbial. Not only does dietary fiber ferment regulate the activity of bacteria in the intestines, but SCFA also directly correspond to host health through a variety of specific tissue-related mechanisms for intestinal barrier function, glucose homeostasis, immunomodulation, appetite regulation and obesity. With the increased burden of obesity around the world, the role of macrobiotics generated in SCFA-generated protection against the effects of dense energy diets offers a new and intriguing avenue for regulating metabolic health risk to CVD.

Microbiome in chronic kidney disease

The human gut is now recognized as an essential metabolic organ activated by microbiota in the gut. This paper refers to changes in the intestinal microbiome [27] in patients with chronic kidney disease (CKD) and its outcomes. We describe the main poisons of uraemic, p-cresol sulfate, some indoxyl and N-oxid trimethylamine, produced by intestinal microbial, and how these metabolites contribute to the development of CKD and related cardiovascular diseases. Translocation of endotoxin from the intestines into the bloodstream contributes to inflammation in CKD. Targeting the microbial in the intestines to restore symbiosis may prove to be a powerful strategy in reducing the inflammation and production of these toxins. What progress does she emphasize? This highlights the importance of intestinal bowel contact and how the microbial landscape has changed in the intestine and contributes to dysmetabolism and inflammation in CKD. Recent findings linking the bowel derived from oral toxicity to the progression of CKD, cardiovascular disease, and mortality have also been discussed. Finally, we briefly explain targeted treatments that have been studied to restore intestinal symbiosis in CKD.

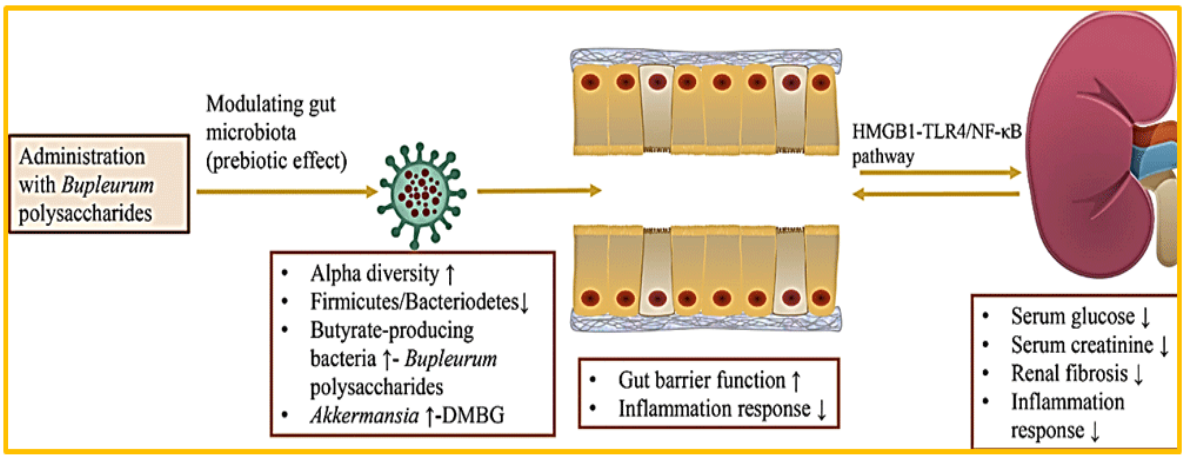

Figure 06:

Investigating Microbial Effect on the Kidney (Credit Ref. [8])

Intestinal dysbiosis activates the renal angiotensin-kidney system that contributes to primary diabetic nephropathy. Much interest is nowadays focused on intestinal microbiota due to their pleiotropic functions in human health and disease. This intestinal community can stimulate a wide range of host activities and function as a microbial organ by creating bioactive metabolites and participating in a series of metabolic-dependent pathways. Alternatives in the composition of microbiota in the intestines, known as intestinal dysbiosis, are apparently associated with several diseases, especially diabetes, and its complications. Here we focus on the relationship between the microbiota in the intestines and diabetic nephropathy [28] (DN), since the latter is one of the leading causes of chronic kidney disease. The activation of the renin-angiotensin system (RAS) is a critical factor for the onset of DN, and emerging data has demonstrated an excitatory and mediating role of microbiota in the gut for this system in the

context of metabolic diseases. The purpose of this survey is to highlight several research updates on the fundamental interactions between the microbiota in the intestines, their metabolites, development and progression of DN, together with the study of novel approaches to targeting this intestinal community as a therapeutic perspective in the clinical management of DN patients. The Microbiota-dependent Glutamine Trimethylamine N-Oxide (TMAO) pathway contributes to both the development of renal failure and the risk of death from chronic kidney disease. People with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD) progression beyond traditional risk factors. However, the mechanism (s) through which CKD is linked to coronary heart disease and improved atherosclerosis is not sufficiently distinguished. Although the role of uremic toxins in the pathogenesis of cardiovascular disease and kidney progression in CKD has been discussed for some time, the exact participants involved, their mechanisms of action are unclear. Recent research has shown the involvement of the colon in a generation of metabolites exhibiting auric toxicity. Furthermore, disorders in the composition of the intestinal microbial community in both human CKD and experimental CKD are associated with significant elevations of intestinal terrestrial toxins. These changes were also associated with increased systemic inflammatory burden, so they are suspected of playing a role in the pathogenesis of cardiovascular disease and kidney progression in subjects with CKD. Bacterial and structural components, such as lipopolysaccharide, 3 and metabolites, such as indoxyl sulfate, p-cresyl sulfate, amines, ammonia, have been identified as potential byproducts and bacteria capable of initiating proinflammatory cytokines / charades schemes see the definition of CKD and end-stage renal disease. , It has been hypothesized that colonic toxins-microbiota-derived toxins may be used both for therapeutic purposes and assessment tools for kidney disease in this injury population [29,30]. However, a demonstration of the role for specific epidemiological toxins in CVD pathogenesis was indirect. Our group has recently identified a new mechanistic relationship between microbial metabolism of intestinal nutrients containing dietary trimethylamine and pathogenesis.[31] CVD. Correctly, microbial-mediated microbial metabolism of phosphatidylcholine, choline or L-carnitine has been shown to generate trimethylamine-N (TMAO), and in many clinical studies, TMAO levels have been associated with cardiovascular risks. [32,33,10,13] Furthermore, studies on animals have revealed that TMAO is mechanistically linked to the development of atherosclerosis through various pathways. [34], animal model and human clinical studies show an essential role for TABA microbiota in the formation of TMAO-containing nutrients including choline and phosphatidylcholine, 9,10L-carnitine, 8 and more recently,γ-butyrobetaine, [35] and to a lesser extent,TMAO is indicated by the kidney, and previous studies have reported that TMAO is elevated in patients with impaired renal function [36]. Recent studies on case-control and longitudinal studies have shown an impressive association between trimethylamine N-Oxide (TMAO) and risk of cardiovascular disease in a variety of groups. TMAO is mainly derived from choline and carnitine through the action of intestinal microbiota, which metabolizes these ingredients to trimethylamine (TMA). TMA is absorbed in turn and travels through the portal cycle to the liver, where it is oxidized by monooxygenases containing flavin, mainly FMO3, to TMAO. In studies in mice, the addition of dietary choline, carnitine, ferritin (γ-butyro-betaine), or even TMAO alone was sufficient to improve the accumulation of macrophage cholesterol and the formation of an atherogenic plaque, and support a causal relationship. TMAO also has considerable effects on cholesterol metabolism in bile acid cells. This is therefore an attractive hypothesis that TMAO may represent an excellent marker for the mechanism of CVD risk in patients with impaired renal function. In one large study of patients with renal function, we reported that a prognostic value of TMAO for a 3-year risk prediction for adverse cardiovascular events (myocardial infarction, stroke, or death) remained significant after adjustment for renal function.9 However, Thus, the risk of long-term mortality of TMAO among CKD subjects should be directly examined. Interestingly, plasma TMAO levels among seemingly healthy donors have been identified in a prospective multicenter study aimed at identifying contributing factors associated with late implant function among recipients of kidney transplants. [37,38] No direct TMAO function was reported that affects renal functional impairment. In this paper, we sought to examine both the prognostic value of TMAO in CKD subjects and the potential contribution of cloth formation associated with dietary nutrition involved in the development and progression of CKD.

Heart Burns

Stomach Acid Drugs May Be a Risk of Bacterial Infections, FDA Warns

Gastric acid can cause a lot of people great pain, but it also serves an essential purpose in the body: it interferes with infections and begin their pathways. Now, a new study says that drugs that suppress the production of stomach acid can cause people to become more susceptible to complications of gastrointestinal infections, including an increased risk of death. Clostridium difficile: A nightmare for modern medicine. Clostridium difficile, or C. difficile, is the most common cause of infectious diarrhea in the world. It is a dry, anaerobic bacteria found in the soil, in human feces, and in fences such as hospitals, nursing homes, and children's homes. Like anaerobic bacteria, they do not need oxygen to survive and thus live well in the colon. The bacteria can persist in the patient's environment for months or even years in spore form, with heat and dryness. Symptoms of CDI include diarrhea, dehydration, fever, loss of appetite, abdominal pain or tenderness. Because the bacteria are so flexible, they are challenging to manage.

Not all contact with C. difficile results in infectious diarrhea. Among those disabled by the bacteria, only 40-60% will develop symptoms. For diarrhea-related infection to develop, specific circumstances must occur. Initially, there is some form of disturbance to the average balance of bacteria born in the colon. Antibiotic use is a risk factor in this area, as these drugs affect the levels of all the bacteria in our body, even the good ones, leaving room for pathogenic bacteria to grow. After the disorder, a person must have a C. exposure to the skin that thrives on doubling the colon, which now lacks its good protective bacteria. Finally, the growing population of bacteria produces toxins, leading to infection and associated diarrhea. Unfortunately, CDI becomes more frequent and severe on a global scale. Most people who cope with this infection will be able to recover completely, even if they do not receive treatment; However, those who are older or have a weak immune system should seek medical help ASAP if they suspect an infection. While the symptoms can be unpleasant, they will usually disappear in a few weeks.

Pass It on: Acid-Suppressant Drugs May Decrease the Ability of Stomach Acid to Protect You from Illness

Cellulitis

Microbiota of skin in patients hospitalized for Cellulitis and Association with result [39].Microbiota skin plays a crucial role in the pathogenesis of several skin diseases, but its role in cellulitis mains unknown. The researchers studied the microbiota in the skin in patients with cellulitis, examined whether its analysis could help determine the causal pathogen, and examined whether the composition of the macrobiotics of the skin was linked to clinical outcomes. Bacterial infections and microspheres - cellulitis were introduced. According to reports from Amsterdam, the Netherlands, by the editors of News Rx, the study states that "skin microbiota has a crucial role in various skin diseases, but its role in cellulitisis still unknown. We examined the microbiota skin in patients with cellulitis and studied whether its analysis could help determine the pathogen Causal, and examined whether the composition of microbiota skin was associated with clinical outcomes. The researchers found significant interpersonal differences in microbiota composition in the skin of patients with cellulitis. The dominant cases were Staphylococcus and Streptococcus the dominant general. In most patients, there was an active link between the microbiota of the affected lesion and the microbiota of the different organ. Overall, the composition of microbiota cellulitis cannot be distinguished from the microbiota of skin controls. There was no consistent association between the results of traditional culture and microbiota signatures in the skin in patients with cellulitis. Finally, we found that the composition of microbiota or variety was not associated with clinical parameters and outcomes in patients with cellulitis. Cellulitis is a common cause of hospitalization [40]. In the United States there are approximately 650,000 hospitalizations for annual cellulitis, which accounts for 1% of the admission and $10 billion. Most patients when hospitalized are treated with combinations of antibiotics with a broad spectrum of Gram positive, Gram negative and anaerobic coverage. The Infectious Disease Society of America recommends hospitalization for patients for cellulitis under certain circumstances, but there is little clinical evidence to actually guide the decision to admit. The goal of this study is to determine the mortality rate of patients with cellulitis to determine if the rate is low enough to support a narrow approach to empirical antibiotics and to support the potential management of many patients in these patients.

Conclusions

The overall mortality rate for patients with cellulitis is 1.1% and for patients in the United States the rate was 0.5%. This rate compares the mortality rates of low-risk conditions that are often managed as outpatients or in observation units. Although well described, only about a third of this mortality appears to be attributable to cellulitis. In general, our results support a narrow approach to empirical antibiotics, and may support alternatives to hospitalization, such as admission to antimicrobial surveillance or medication. One may wonder if some cases of cellulitis limit themselves and do not require antimicrobial agents. It should be noted that clinical trials in the pre-antibiotic era, in which the effects of horse serum and ultraviolet light were examined, showed 70% cure rates.[41] On the other hand, it was shown that non-empiric antibiotic deficiency is associated with prolonged treatment duration and hospital stay. [42] Recommendations. Streptococci and S. aureus are the most common pathogens identified in patients with cellulitis, and accumulation of evidence from serological studies for recovery assessment shows that 70% of Streptococci.[43,44] patients are seen with asymptomatic pathogens (Table 3). In contrast to diabetic foot infections, diabetic foot infections are not usually caused by atypical pathogens.[45] In the Netherlands, the preferred small spectrum agent, covering both S.Taurus and other Streptococci - beta-mutual, is fluoxyloxyline. Approved streptococcal infections can be treated with benzyl penicillin or penicillin. Co-amoxiclav and clindamycin are alternative options. Clindamycin is recommended in the case of beta-lactam allergies, streptococcal inhibitor and staphylococcal toxin. Clindamycin is also thought to have better tissue penetration than beta-lactams. However, clindamycin is highly concentrated among cells and studies to measure tissue concentrations have been used in homogeneous tissues and so have been measured in intracellular clindamycin. This estimates the appropriate clindamycin levels in the external fluid, whereas extracellular beta-lactam concentration is mostly diluted by extracellular volume released. Note that there are strains of sorus aureus have resistance for clindamycin, showing inhibition of in vitro growth but resistance in vivo [46,47]. in the Netherlands, around 10% of S. aureus from patients selected in

the general practice patients (not possible) resistance to clindamycin, From 3% for flucloxacillin. This makes less clindamycin preferable as an empirical choice. The evidence does not favor one agent over the other, although there is a significant lack of evidence in this area [48]. One study found that primatinice was slightly more effective than penicillin in a non-blind trial, but did not take into account that penicillin did not cover S. Auros. 3, 92 beta-lactam was as effective as non-beta-lactam in a cohort study [49]. A meta-analysis comparing penicillin or cephalosporin with macular or lincosamides (such as clindamycin) found similar efficacy between the two groups. In addition, three innovative antibiotics have recently been approved by the European Medicines Agency for the treatment of skin infections: oritavancin and Dalbavancin, two glycopeptides (lipo) and tedizolid , oxazolidinone, all show strong activity against MRSA, similar to vancomycin and linezolid [50]. Oritavancin and dalbavancin have two half-lives of more than two weeks, and therefore require only one intravenous dose to reach non-inferior healing rates up to a two-week course of vancomycin.8,813 if this actually reduces the number of admissions or total treatment costs remains to be assessed .

Microbiome and Blood Sepsis

Research showed [51]some bacteria can enter Red Blood Cells (RBCs) directly, and persevere in a nutrient-rich environment; It has been shown that *Staphylococcus aureus*, a species commonly found in both human and patient health, can utilize present Fe (RBC) as a dietary source [52]. Yamaguchi et al. (2013) also showed that Streptococcus pneumonia, a bacterium involved with the onset of *sepsis pneumonia*, became more viable when incubated with erythrocytes. It is also reported that *Rosella* and *Melitensis,* the adverse cause of brucellosis, and *Francisellatularensis*, Gram-negative bacteria that causes tularemia, also have the ability to invade and persist in erythrocytes. Regarding the exact location of microorganisms in human blood, current evidence suggests that the bacterial product can survive within erythrocytes and leukocytes. Chlamydia pneumonia, intracellular bacterium and the main diabetes mellitus of pneumonia, was found to host mononuclear blood cells (PAC) in the blood [53]. Other bacteria, such as S*taphylococcus aureus*, can also invade white blood cells (WBCs). Already in 2000, Gresham et al. [54] showed that these bacteria live and retain their virulence in neutrophils. Thwaites and Gant [55] also suggested that WBCs, particularly neutrophils, can be used as "Trojans" by providing protection against human antibodies, thus facilitating the distribution of S. aureus to various sites in the body. Moreover, when Païssé et al. [56] analyzed the microbial in the blood of healthy people, most of the bacterial DNA (93.74%) was found in the BC coat, which consists mostly of WBCs and platelets. Participants in the study were also identified. Similarly, some bacteria can enter RBCs directly, and persevere in a nutrient-rich environment; It has been shown that Staphylococcus aureus, a species commonly found in both human and patient health (Grice et al., 2009), can utilize present Fe (RBC) as a dietary source (Yamaguchi et al., 2013). Yamaguchi et al. also showed that Streptococcus pneumonia, a bacterium involved with the onset of sepsis pneumonia, became more viable when incubated with erythrocytes. It is also reported that Rosella and Melitensis, the adverse cause of brucellosis, and Francisellatularensis, Gram-negative acteria that causes tularemia, also have the ability to invade and persist in erythrocytes [57]

References

1. Kim G, Deepinder F, Morales W, Hwang L, Weitsman S, et al (2012) Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. Dig Dis Sci 57(12): 3213-3218.

2. Sahakian AB, Jee SR, Pimentel M (2010) Methane and the gastrointestinal tract Dig Dis Sci 55(8): 2135-2143.

3. Loh G, Blaut M (2012) Role of commensal gut bacteria in inflammatory bowel diseases. Gut Microbes 3(6): 544-555.

4. Stephen AM, Wiggins HS, Englyst HN, Cole TJ, Wayman BJ, et al (1986) The effect of age, sex and level of dietary fibre from wheat on large-bowel function in thirty healthy subjects. Br J Nutr 56(2): 349-361.

5. Sekirov I, Russell SL, Antunes LC, Finlay BB" Gut Microbiota in Health and Disease"; Physiol Rev 90(3): 859-904.

6. Stanley Hazen (2019) "Gut Microbiota –An Active Participant and Therapeutic Target for Cardiometabolic Disease", Friedman Speaker Series.

7. Randrianarisoa E, Lehn-Stefan A, Wang X, Hoene M, Peter A, et al (2016) "Relationship of Serum Trimethylamine N-Oxide (TMAO) Levels with early Atherosclerosis in Humans"; Scientific Reports 6: 26745.

8. Catinean A, Neag MA, Muntean DM, Bocsan IC, Buzoianu AD (2018) "An overview on the interplay between nutraceuticals and gut microbiota."; PeerJ 6: e4465.

9. Bergeron N, Williams PT, Lamendella R, Faghihnia N, Grube A, et al (2016) Diets high in resistant starch increase plasma levels of trimethylamine- N-oxide, a gut microbiome metabolite associated with CVD risk. Br. J. Nutr 116(12): 2020–2029.

10. Shimon Shatzmiller (2019) "Microbiota in the Onset of Heart Diseases the Role of Trimethylamine N-oxide (TMAO)" EC Microbiology 15(7): 641-645.

11. Ye J, Lv L, Wu W, Li Y, Shi D, et al (2018) "Butyrate Protects Mice Against Methionine–Choline-Deficient Diet-Induced Non-alcoholic Steatohepatitis by Improving Gut Barrier Function, Attenuating Inflammation and Reducing Endotoxin Levels". Front. Microbiol 9: 1967.

12. Safari Z, G¹ rard P (2019) "The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD)"; Cellular and Molecular Life Sciences 76(8): 1541-1558.

13. Gerard P (2016) Gut microbiota and obesity. Cell Mol Life Sci 73(1): 147-162.

14. Backhed F, Manchester JK, Semenkovich CF, Gordon JI (2007) Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA 104(3): 979-984.

15. Rabot S, Membrez M, Bruneau A, Gerard P, Harach T, et al (2010) Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. Faseb J 24(12): 4948-4959.

16. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, et al (2008) Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA 105(43): 16767-16772.

17. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, et al (2004) The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 101(44): 15718-15723.

18. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, et al (2009) The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med 1(6): 6ra14.

19. Oikonomou T, Papatheodoridis GV, Samarkos M, Goulis I, Cholongitas E (2018) "Clinical impact of microbiome in patients with decompensated cirrhosis" World J Gastroenterol 24(34): 3813-3820.

20. Bajaj JS, Hylemon PB, Ridlon JM, Heuman DM, Daita K, et al (2012) Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. Am J Physiol Gastrointest Liver Physiol 303(6): G675-G685.

21. Shi M, Wei Y, Hu W, Nie Y, Wu X ,et al (2018) The Subgingival Microbiome of Periodontal Pockets With Different Probing Depths in Chronic and Aggressive Periodontitis: A Pilot Study. Front. Cell. Infect. Microbiol 8: 124.

22. Huang S, Li Z, He T, Bo C, Chang J et al (2016) Microbiota-based Signature of Gingivitis Treatments: A Randomized Study. Sci. Rep 6: 24705.

23. Struzycka I (2014) "The oral microbiome in dental caries."; Pol J Microbiol 63(2): 127-35.

24. Arweiler NB, Netuschil L (2016). The Oral Microbiota. Adv Exp Med Biol 902: 45-60.

25. Kasahara K, Krautkramer KA, Romano KA, Kerby RL Org E, et al (2018) Interactions between Roseburia intestinalis and diet modulate atherogenesis in a murine model. Nat Microbiol 3(12):1461-71.

26. Chambers ES, Preston T, Frost G, Morrison DJ (2018) Role of Gut Microbiota-Generated Short-Chain Fatty Acids in Metabolic and Cardiovascular Health "Curr Nutr Rep 7(4): 198-206.

27. Wing MR, Patel SS, Ramezani A, Raj DS (2015)" Gut microbiome in chronic kidney disease"; Exp Physiol 101(4): 471-477.

28. Feng Y, Weng H, Ling L, Zeng T, Zhang Y, et al (2019)" Modulating the gut microbiota and inflammation is involved in the effect of Bupleurum polysaccharides against diabetic nephropathy in mice"; International Journal of Biological Macromolecules 132: 1001-1011.

29. Mafra D, Lobo JC, Barros AF, Koppe L, Vaziri ND, et al (2014) Role of altered intestinal microbiota in systemic inflammation and cardiovascular disease in chronic kidney disease. Future Microbiol 9(3): 399-410.

30. Lee CT, Hsu CY, Tain YL, Ng HY, Cheng BC, et al (2014) Effects of AST-120 on blood concentrations of protein-bound uremic toxins and biomarkers of cardiovascular risk in chronic dialysis patients. Blood Purif 37(1): 76-83.

31. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, et al (2013) Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 19: 576-585.

32. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, et al (2013) Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 368(17): 1575-1584.

33. Wang Z, Tang WH, Buffa JA, Fu X, Britt EB, et al (2014) Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide.Eur Heart J 35(14): 904-910.

34. Bennett BJ, de Aguiar Vallim TQ, Wang Z, Shih DM, Meng Y, et al (2013) Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. Cell Metab 17(1): 49-60.

35. Koeth RA, Levison BS, Culley MK, Buffa JA, Wang Z, et al (2014) G-butyrobetaine is a pro-atherogenic intermediate in gut microbial metabolism of l-carnitine to TMAO. Cell Metab 20(5): 799-812.

36. Bain MA, Faull R, Milne RW, Evans AM (2006) Oral L-carnitine: metabolite formation and hemodialysis.Curr Drug Metab 7(7): 811-816.

37. Robert R, Guilhot J, Pinsard M, Longeard PL, Jacob JP, et al (2010) A pair analysis of the delayed graft function in kidney recipient: the critical role of the donor.J Crit Care 25(4): 582-590.

38. Tang WHW, Wang Z, Kennedy DJ, Wu Y, Buffa JA, et al (2015)"Gut Microbiota-Dependent Trimethylamine N-Oxide (TMAO) Pathway Contributes to Both Development of Renal Insufficiency and Mortality Risk in Chronic Kidney Disease"; Circulation Research 116(3): 448-455

39. Cranendonk DR, Hugenholtz F, Prins JM, Savelkoul PHM (2019) "The Skin Microbiota in Patients Hospitalized for Cellulitis and Association With Outcome"; Clinical Infectious Diseases 68(8): 1292-1299.

40. Gunderson C, Cherry B, Fisher A (2018) "Mortality of Hospitalized Patients With Cellulitis: A Systematic Review And Meta-Analysis". Hospital Medicine Orlando Fla 351.

41. Obaitan I, Dwyer R, Lipworth AD, Kupper TS, Camargo CA Jr, et al (2016) Failure of antibiotics in cellulitis trials: a systematic review and meta-analysis. Am J Emerg Med 34(8): 1645-1652.

42. Lipsky BA, Napolitano LM, Moran GJ, Vo L, Nicholson S, et al (2014) Economic outcomes of inappropriate initial antibiotic treatment for complicated skin and soft tissue infections: a multicenter prospective observational study. DiagnMicrobiol Infect Dis 79(2): 266-272.

43. Bruun T, Oppegaard O, Kittang BR, Mylvaganam H, Langeland N, et al (2016) Etiology of Cellulitis and Clinical Prediction of Streptococcal Disease: A Prospective Study. Open Forum Infect Dis 3(1): ofv181.

44. Karppelin M, Siljander T, Haapala AM, Aittoniemi J, Huttunen R, et al (2015) Evidence of streptococcal origin of acute non-necrotising cellulitis: a serological study. Eur J Clin Microbiol Infect Dis 34(4): 669-672.

45. Jenkins TC, Knepper BC, Jason Moore S, Saveli CC, Pawlowski SW, et al (2014) Comparison of the microbiology and antibiotic treatment among diabetic and nondiabetic patients hospitalized for cellulitis or cutaneous abscess. J Hosp Med 9(12): 788-94.

46. Saeed K, Marsh P, Ahmad N (2014) Cryptic resistance in Staphylococcus aureus: a risk for the treatment of skin infection? Curr Opin Infect Dis 27(2): 130-6.

47. NethMap 2016: Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands MARAN 2016: Monitoring of Antimicrobial Resistance of Antibiotic Usage in Animals in the Netherlands in 2015 [Internet]. National Institute for Public Health and the Environment 2016.

48. Kilburn SA, Featherstone P, Higgins B, Brindle R (2010) Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev 6:CD004299.

49. Madaras-Kelly KJ, Remington RE, Oliphant CM, Sloan KL, Bearden DT (2008) Efficacy of oral beta-lactam versus non-beta-lactam treatment of uncomplicated cellulitis. Am J Med 121(5): 419-25.

50. Deak D, Outterson K, Powers JH, Kesselheim AS (2016) Progress in the Fight against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration-Approved Antibiotics, 2010-2015. Ann Intern Med 165(5): 363-72.

51. Castillo DJ, Rifkin RF, Cowan DA, Marnie Potgieter (2019) " The Healthy Human Blood Microbiome: Fact or Fiction?"; Cell. Infect. Microbiol.

52. Yamaguchi M, Terao Y, Mori-Yamaguchi Y, Domon H, Sakaue Y, et al (2013) Streptococcus pneumoniae invades erythrocytes and utilizes them to evade human innate immunity. Plos one 8: e77282.

53. Yamaguchi H, Yamada M, Uruma T, Kanamori M, Goto H, et al. (2004) Prevalence of viable Chlamydia pneumoniae in peripheral blood mononuclear cells of healthy blood donors. Transfusion 44(7): 1072-1078.

54. Gresham HD, Lowrance JH, Caver TE, Wilson BS, Cheung AL (2000) Survival of Staphylococcus aureus inside neutrophils contributes to infection. J. Immunol 164(7): 3713-3722.

55. Thwaites GE, Gant V (2011) Are bloodstream leukocytes Trojan Horses for the metastasis of Staphylococcus aureus? Nat. Rev. Microbiol 9(3): 215-222.

56. Lelouvier B, Servant F, Païssé S, Brunet AC, Benyahya S, et al (2016) Changes in blood microbiota profiles associated with liver fibrosis in obese patients: a pilot analysis. Hepatology 64(6): 2015-2027.

57. Horzempa J, O'dee DM, Stolz DM, Franks JM, Clay D, et al (2011) Invasion of erythrocytes by Francisella tularensis. J. Infect. Dis 204(1): 51-59.