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Antibiotics in Early Life: Dysbiosis and Damage Done

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Abstract: *Antibiotic are the most common type of medication prescribed to children, including infants, in western world. Antibiotics alter the gut microbial composition. Since the gut microbiota plays crucial role in immunity, metabolism and endocrinology the effects of antibiotics on the microbiota may lead to further health complications. Antibiotic in childhood have been linked with disease including asthma, juvenile, arthritis, type 1diabets, chronic disease and mental illness. In COVID-19 probiotics plays a therapeutic role for GI, IBD, colitis, and even in viral infection. So, we assume that the inclusion of studies to investigate gut microbiome and subsequent therapies such as probiotic might help decrease the inflammatory response of viral pathogenesis and respiratory symptoms by strengthening the host immune system, amelioration of gut microbiome, and improvement of gut barrier function. Focused on four types of dysbiosis loss of keystone taxa, loss of diversity. Establishment of large and diverse baseline healthy infant microbiome development is essential to advancing diagnosis interpretation and eventual treatment pediatric dysbiosis. In this review we present an overview of effects of antibiotics on microbiome in children and correlate them to long lasting complications.*

Objectives:

- *To review on antibiotics are alter the gut microbial composition in children, adult.*
- *To review on gut microbiota plays crucial roles in immunity, metabolism and endocrinology, the effects of antibiotics on microbiota may lead to further health..*

Keywords: Infants, gut microbiota, metabolism, endocrinology, diabetes, inflammatory response, pediatric dysbiosis, microbiome

I. INTRODUCTION

Since the discovery of Penicillin in 1928, antibiotics have brought about a revolution in medicine, saving lives of many patients who would have previously died from infection. There is no doubt that antibiotics have proved extremely efficient against a wide range of bacterial species. It is therefore not surprising that antibiotic are the most commonly prescribed medication to infants and children in the Western world. In fact, antibiotic are administered to over 10% of European children yearly. In the USA, antibiotics account for 25% of all the prescriptions written to pediatric population, with the most common types being amoxicillin, azithromycin and amoxicillin. However, numerous pieces of evidence have begun to indicate that there may also be a price for such frequent antibiotic use. With the development of microbiome research and recognition of the essential roles of microbiota in overall health, concern has been raised regarding the effects of antibiotics on the healthy microbial components residing within our bodies. It has indeed been shown that antibiotic treatment dramatically alters both adult infant microbiome compositions. While the types and duration of the antibiotic treatment may modulate the specific microbial alteration, it has been demonstrated that even brief antibiotic treatment can have long- term effects on microbiota composition. Such changes in microbiota are termed dysbiosis, a microbial imbalance that is correlated with impaired health. Dysbiosis has been associated with many disease states including autoimmune disease, metabolic disease, malnutrition and others. The microbiota has been shown to play role in modulating the immune systems, in hormone secretion and responses and in metabolism. Therefore alteration to microbiota composition caused by antibiotics are likely to have additional health consequence, specifically associated with weight gain and metabolic imbalance, as well as susceptibility to disease. Indeed, early childhood antibiotic exposure is associated with increased risk for excessive weight gain, asthma, allergies and autoimmune disease, such as inflammatory bowel diseases (IBD). As the microbiota have also shown in models of germ- free animals to play a role

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in development of brain structure, and potentially function, concern have also been raised regarding possible effects of antibiotics in child brain development.

The hygiene hypothesis propose that exposure to environmental microorganism and parasites is important for healthy development and maintenance of the immune system. With the increased hygiene levels in Western countries in decreased, potentially diverting normal differentiation of immune cells and consequently raising rates of allergies, asthma and autoimmune disease. As antibiotics are a factor that reduce exposureto microorganism and disrupts the body's natural microbiota, this hypothesis may help explain the observed effects of antibiotic on the immune system.

1.1 What are Antibiotics?

Antibiotics are medicines that help stop infection caused by bacteria. They do this by killing the bacteria or by keeping they form copying themselves or reproducing. The wordantibiotic means "against life". Any drug that kills germs in your body is technically an antibiotic. But most people use the term when they're talking about medicine that is meanto kill bacteria. Before scientists first discovered antibiotic in the 1920s, many people died from minor bacterial infections, like strep throat. Surgery was riskier, too. But afterantibiotic became available in the 1940s, life expectancy increased, surgery was got safer,and people could survive what used to be deadly infections. (1)

1.2 History of Antibiotics

In the past, infectious disease was a normal part of life. In 1900, 30.4% of all deaths occurred in children less than the age of 5. The leading causes of death were pneumonia,tuberculosis, and diarrhoea, accounting for one third of all deaths. From 1918-1919, morepeople died from an influenza pandemic than collectively in combat in World War I, World War II, the Korean War, and the Vietnam War. However, in 1928, medicine was revolutionized. Bacteriology professor, Sir Alexander Fleming, discovered the first true antibiotic, penicillin. Since their first use to treat infections in the 1940s, antibiotics havebecome one of the most impactful discoveries in medicine, attributable for the saving of millions of lives on a global scale. In 1945, just around the time World War II was ending,the average life expectancy staggered around 50 years. However, by 1990, with the widespread use of antibiotics to treat infectious diseases, the average life expectancy riseto around 70 years. The number of deaths in children under five sunk from 30.4% in 1900to 1.4% in 1997. But with all good things, overuse can lead to detriment. Currently, almost every antibiotic ever developed is subject to bacterial resistance, rendering the effect of the drugs useless, and potentially harmful, making infectious disease a potential threat tosociety once again.

For example, nearly 2 million people in the United States are infected with antibiotic- resistant bacteria, and almost 23,000 perish due to these infections. Based on the level of increased antibiotic resistance, a new wave of "next-generation" antibiotics are being created, with modified side chain structures to introduce new properties and potentially restore the effectiveness of certain classes of antibiotics, however, due to the incredibly adaptive nature of bacterial populations, perhaps the modern age of antibiotics as we know it is coming to an end. (2)

1.3 Mechanism of Antibiotic Action

Antibiotics differ in their tissue distribution, rate of elimination, and effects in a living organism. However, the main distinction between antibiotics lies primarily in their differing mechanisms of action. Examples include inhibition of cell wall synthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis, inhibition of metabolic pathways, and interference with cell membrane integrity. Classification of antibiotics by mechanism along with examples of common drugs in each class is shown in in precedingthe study. (2)

Sr. No.	Targeted inhibition/interference	Examples of Antibiotics
1	Cell Wall Synthesis	ß-lactam drugs (Penicillins, Cephalosporins), Vancomycin, Bacitracin
2	Protein Synthesis	Chloramphenicol, Tetracyclines, Macrolides,Lincosamides
3	Cell Membrane	Polymxin B, Amphotericin, Nucleic Acid,Fluoroquinolones (Ciproflaxin), Rifamycin
4	Metabolic Pathways	Sulfonamides

Table 1: Classification of antibiotics by mechanism (2)

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1.4 What is Antibiotic Overuse?

Antibiotic overuse is when antibiotics are used when they're not needed. Antibiotics are one of the great advances in medicine. But overprescribing them has led to resistant bacteria. Some germ that were once very responsive to antibiotics have become more andmore resistant. This can cause more serious infections, such pneumococcal infections, sinus infections, skin infections, and tuberculosis. (3)

Antibiotics before birth and in early life can affect long-term health

Half of Australian infants have received at least one course of antibiotics by their firstbirthday. This is one of the highest rate of antibiotic use in the world.

Although antibiotics are effective and potentially life-saving for bacterial infections in children, they are often prescribed for viral infections, for which they are ineffective.

Unnecessary antibiotics expose individual children to potential side effects, including diarrhoea, vomiting, rashes and allergic reactions.

The overuse of antibiotics also increases the risk of bacterial resistance in the wider community. This is when commonly used antibiotics become ineffective against some bacteria, making it difficult, or even impossible, to treat some infections.

Researchers are also beginning to realise there may be additional long-term health harms from antibiotic exposure in early life and before birth, including an increased risk of infection, obesity and asthma.

At the moment, most bacteria that cause childhood infections in Australia respond well to antibiotics. But this is likely to change, unless we use antibiotics more carefully. (4)

Dysbiosis and IBS: A Small History Lesson

Evidence of the human microbiome was first discovered by an Austrian paediatrician named Theodor Escherich. He actually discovered a type of bacteria (later named *Escherichia coli*) in the intestines of both healthy children and children affected by diarrheal disease. After this initial discovery of what seemed to be harmless bacteria, other scientists began to describe other microorganisms that seemed to exist in many otherareas in and on the human body. For example; the skin, nose, mouth, gastro tract etc.

Over time, the concept of what we now know as the 'human microbiome' was developedin the first decade of the twenty first century.

While each of us has a unique gut microbiota, it always full fills the same physiologicalfunctions, with direct impact on our health. Some of the functions are:

- Helps the body digest certain foods that the stomach and small intestine cannotdigest.
- Production of some vitamins (B and K).
- Plays an important role in the immune system, performing the barrier effect.

A healthy and balanced gut microbiota is key to ensuring proper digestivefunctioning. (5)

Sr. No.	Age of exposure toabx	Age at evaluation	Study description	Type of abx	Effects
1	Abx treatment between 4-6 weeks of life.	Bacterial analysis was performed between theages 6-12 weeks.	The effects of abx treatment on intestinal bacterial population.	In food-amoxicillin, metronidazole and bismuth	Different in microbial abundance anddiversity
2	Abx treatment from E12-14 until weaning	Bacterial analysis was performed at 6 weeks of age.	Abx during late pregnancy and neonates and the effect on bacterial population, immunity and behavior. Abx in early stages and metabolism.	In water-cefoperazone low- dose penicillin	Lasting effects on microbiota, altered cytokine expression, effects on brain neurochemistry and behavior.

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3	Abx treatment from weaning to 10 weeks of age.	Up to 50 days from Antibiotic exposure.	Abx during early stages and metabolism.	Variety of abx, low doses	Altered microbiota composition, SCFA metabolism Increased adiposity, and increased metabolic hormone levels.
4	Abx treatment at weaning or 1week before birth until 30weeks.	Up to 30 weeks from antibiotic exposure.	Abx during early life and metabolism changes.	Low-dose penicillin	Altered microbiota composition, resulting in metabolic alteration and changes in ileal expression of genes involved in immunity
5	Abx treatment 1 week before birth until 32weeks.	From birth to 32 weeks.	Microbiome perturbation using abx treatment, insulin resistance and NAFLD.	Low- d osepenicillin	Alteration in microbial communities, increased adiposity, insulin resistance and liver disease related to high- fatdiet.
6	Three abx course: between10- 15, days 28-31 and 37-40. Days 28-31 and 37-40.	Up to 6month	Pulsed abx treatment during earlylife and the effect. On metabolite and the effecton metabolite.	Amoxicillin and tylosin	Delayed microbiota adaptation to diet, altered metabolic potential, altered hepatic gene expression.
7	Abx exposure throw neonatal period, and another group from 7week old.	26 days after first sensitization.	Abx at different time periods andthe effects on immunity and allergic asthma	Streptomycin and Vancomycin	Reduced diversity and altered microbiota, effects on the immune system, and increased susceptibility to allergy in response to vancomycin.

Table 2: Summary of studies demonstrating the effects of different antibiotics onmicrobiota (6)

The Infant and Child Microbiome

The infant microbiome differs from that of adults, and is rather dynamic and less diversein children up to 2 years of age. These dynamics are consistent with the variousencounters with microorganisms occurring in early post-natal life, when the infant acquires his initial microbiome. Distinct compositions are observed in the gut microbiota of infants due to variations in mode of delivery (vaginal vs. Caesarean section) and diet (breastfeeding vs. formula).

In preterm infants (gestational age <36 weeks), maintaining a healthy microbiome composition is of extreme importance, as the phylogenetic diversity is low to begin with,and severe dysbiosis can lead to necrotizing enterocolitis or late-onset sepsis. The preterminfant's microbiome is characterized by reduced Bacteroidaceae abundance during the first months of life and by a higher initial abundance of Lactobacillaceae as compared tofull term infants. Additionally, the initial preterm microbial composition is highly influenced by communities colonizing the hospital setting, and is enriched in *Staphylococcus epidermis, Klebsiella pneumoniae* and *Escherichia coli*. This makes the premature infant microbiota richer in Proteobacteria and more vulnerable to instability and disease. Routine prophylactic antibiotic treatment is given to most preterm infants inan attempt to minimize infections, and possibly further leads to vulnerable microbiota. Therefore, the potential side effects on microbiome composition should be considered, ifpossible, when giving antibiotics at this stage.

Since infancy is a crucial time for microbial establishment, it is necessary to evaluate theinfluence of antibiotics given quite liberally during this period. Antibiotic treatment given to both infants and toddlers has already been shown to

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strongly affect microbiome composition. Further studies are required to determine whether these are transient, or rather, long-term effects and to assess a potential window of time when interventions aremost harmful. It is also important to test whether and how perinatal antibiotics influencethe microbiota later in life. (6)

Methods to study the effects of antibiotics on the microbiome

In an attempt to understand the effects of antibiotics on the microbiome, both human reports and experiments in animal models have been employed. Analysis of the human studies is especially complex as there may be a variety of reasons and medical indications for the antibiotic treatment, and thus, the treated population may initially differ from the untreated (healthy) controls. Therefore, large study groups are needed in order to distinguish the effects of the antibiotics from other confounding factors. Alternatively, animal studies in which healthy animals of the same genotype receiving similar diets aretreated with antibiotics or left as untreated controls, may be able to indicate specific effects of antibiotics on microbiota, minimizing background 'noise.' However, mouse and human microbiota compositions and immunity are not identical, so these studies havelimited relevance to human health. To this end, another technique was developed and relies on gnotobiotic mice initially germ-free mice that receive faecal transplants from human subjects. This allows the human microbial compositions to be studied in a mousemodel. Thus, while no method appears to be perfect for analysing microbial effects, the combination of recent findings from the multiple studies performed using various methods is likely to provide revealing insights.

When specifically assessing effects of antibiotics on the microbiota in children, it is important to consider which ages are sampled, how the microbiome composition is assessed (16S rRNA gene sequencing, real-time PCR (RT-PCR) using specific primers or other methodologies), along with the type and dose of treatment. In most murine models assessed, antibiotics are given early in life at two stages: from the prenatal period (administered to the pregnant dams) up to weaning, and post-weaning. Studies in humansinclude recording outcomes of antibiotics administered at prenatal stages, to infants and in childhood.

It is important to note that most studies in this field have been correlative, linking use ofantibiotics with the various physiological outcomes. While many of the findings seem convincing, more research is needed to prove causality, and determine specific mechanisms of antibiotic-mediated effects. (6)

Antibiotics have both short and long-term effects on the microbiome

Many recent studies have focused on deciphering short and long-term alterations of themicrobiota following antibiotic treatment. While most studies report significant effects, there are some inconsistencies between studies, perhaps due to different dosages, route and length of administration, type of antibiotics and other environmental and genetic variables. In general, the most common effects of antibiotics on the gut microbiota are decreased phylogenetic diversity and richness, increased abundance of Proteobacteria including Enterobacteriaceae, leading to a pro-inflammatory state and enhanced bacterialexpression of antibiotic resistance genes.

Most effects of antibiotics on microbiota composition persist for a period of weeks to several months, although some reports have found significant differences in microbial composition even 2 years after exposure. Such microbiota changes may lead to long-termexpression of antibiotic resistance, and physiological alterations associated, for example, with the function of the immune system or metabolism, lasting even years after the antibiotic exposure.

Normally, antibiotics are administered to eliminate pathogenic bacteria at times ofbacterial infection. However, most types of antibiotics are not entirely specific, and therefore also eliminate a broad range gut microbial inhabitants that are not pathogenic, and are often crucial for health. This explains the decrease in α diversity (richness) after antibiotic treatment seen in several studies. When diversity is low, normal microbial homeostasis is disrupted and the microbiota is more susceptible to intrusions and colonization of pathogens. Accordingly, the decreased diversity due to antibiotics is generally disadvantageous. Similarly, decreased numbers of microbial species are a common characteristic of disease states and are a general indication of a 'weaker' microbiome. Therefore, therapies to regain healthy microbial richness, such as prebioticsand probiotics, may be useful after use of antibiotics.

Of the few studies performed on healthy adult volunteers, one study tested the effects ofclindamycin treatment for 1 week on microbial composition, and found significant differences even 2 years after treatment. These included loss of diversity, alterations in specific taxa abundance and upregulation of antibiotic resistance genes. While *Bacteroides*

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abundance was decreased following antibiotic exposure, as could be predicted based on clindamycin's target range, there was an increase in abundance of highly resistant *Bacteroides* spp. clones, which persisted up to 2 years. While in the caseof *Bacteroides* this may not be deleterious on its own, it may raise concerns regarding spreading resistance horizontally to other species. However, answering this requires larger cohorts and additional studies.

Most of the antibiotics used in microbiome studies are broad spectrum antibiotics targeting a wide range of pathogens. These include penicillin's, macrolides and vancomycin. Additional types of antibiotics used in studies include metronidazole and streptomycin. Importantly, not all antibiotics have similar effects on the microbiota. As different types of antibiotics have distinct modes of action, they may ablate specific sub- populations of the microbiota. An example of this is seen when comparing the effects oftwo common antibiotic treatments for *Clostridium difficile (C. difficile)*, metronidazole and oral vancomycin in mice; vancomycin was shown to more markedly disrupt the microbiota, leading to decreased resistance to *C. difficile* infection in the long term, and dense colonization by vancomycin-resistant *Enterococcus, K. pneumoniae* and *E. coli*. Indeed, one of the most worrisome phenomena attributed to chronic use of antibiotics is increased abundance of opportunistic pathogens in the gut, especially *C. difficile*, displacing the healthy microbiota populations and leading to acute dysbiosis. In some cases, this may further cause predisposition to infection by pathogens such as *Salmonella* or *Campylobacter* spp. In addition, C. *difficile* infection can itself eventually lead to antibiotic-associated diarrhoea and colitis, manifesting long-term disease. Another example of diverse effects of different antibiotics on the microbiota canbe found in a murine study comparing effects of vancomycin vs. streptomycin, where only vancomycin had apparent effects on the microbial composition. Altogether, data suggest that different antibiotics disrupt the microbiota in different ways. Perhaps the effects of each specific antibiotic on the microbiota should be taken into account by physicians when deciding which antibiotic to prescribe. (6)

Antibiotics affect the infant and child microbiome

While there are similarities between the compositional effects of antibiotics on adult andinfant microbiota, there are also some differences due to the distinct characteristics of theinfant microbiota. The general trend of decreased microbial diversity due to antibiotic treatment is seen in children as well as in adult. A recent study of 142 Finnish children aged 2–7 years demonstrated that macrolides alter the microbiota composition and its potential metabolic functions. More specifically, use of macrolides decreased Actinobacteria abundance, including the genus *Bifidobacteria*, while increasing the abundance of members of the Bacteroidetes and Proteobacteria phyla (including Enterobacteriaceae), compared to children not receiving antibiotics. These microbial alterations lead to significantly lower expression levels of microbial bile-salt hydrolases,which play an important role in host metabolism and weight gain restraint. Similarly, in a study in which human neonates received broad spectrum antibiotics for the first 4 daysof life, arrested growth of *Bifidobacterium* was seen up to 1 month, overgrowth of Enterococci was observed since the first day and increased growth of Enterobacteriaceaewas seen even 2 months after cessation of treatment. In contrast, penicillin does not have the same effects on children's microbiome composition, as there are no significant taxonomical differences between untreated and penicillin-treated infants.

Several studies in young mice reported direct effects on microbiota composition as well.When sub-therapeutic levels of antibiotics were administered to young mice from the time of weaning, the gut microbial populations from mice receiving antibiotics were more similar to one another than to those of control mice. Specifically, the ratio of Firmicutes to Bacteroides as well as representation of Lachnospiraceae was significantly elevated following antibiotic treatment. Administration of low-dose penicillin (LDP) to mice in late pregnancy and in early postnatal life resulted in changes in the gut microbiota lasting weeks after antibiotic exposure, including lower overall diversity, a dramatic increase in Proteobacteria abundance (from 0.5 to 80%), an increase in the Firmicutes/Bacteroidetes ratio and a decrease in Cyanobacteria and Actinobacteria abundance. A similar side effect was found after cefoperazone treatment; mice had altered bacterial communities even 6 weeks after cessation of treatment.

Given its low species diversity, the preterm infant microbiome is especially sensitive to antibiotics. A 5–7 day course of antibiotic treatment (ampicillin and gentamycin) in premature infants during first week of life increased the relative abundance of *Enterobacter* and lowered bacterial diversity in the second and third weeks of the infants' life. It was shown that antibiotics, including meropenem, ticarcillin-clavulanate and cefotaxime, given to preterm infants greatly reduce species richness and increase expression of antibiotic resistance genes. However, gentamicin and vancomycin had variable effects and did not clearly lower species richness. (7)

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Perinatal antibiotic exposure modulates the infant microbiota

Even perinatal antibiotic exposure is sufficient to modulate the infant microbiota. When mothers received intrapartum antibiotic prophylaxis (IAP) before delivery, their offspringhad a unique microbiome composition, which persisted up to 3 months of age, and included over-representation of *Enterococcus* and *Clostridium* at the expense of *Bacteroides* and *Parabacteroides* genera. Similarly, perinatal antibiotics, including an IAP regimen, alter the premature infant gut microbiota composition, raising levels of Enterobacteriaceae species. Several studies in murine models have also demonstrated that antibiotic exposure from the perinatal stage and up to weaning has a marked effect on the gut microbiota. In mice receiving LDP perinatally and through weaning, a distinct gut microbiota composition was observed at 4 weeks of age including reduced level of *Lactobacillus*, *Candidatus Arthromitus* (segmented filamentous bacteria, SFB) and *Allobaculum* abundance. It is yet to be determined whether the perinatal antibiotic effects are a result of disruption of the maternal microbiota (thereby transferring an alteredmicrobiota to the offspring), or an indirect effect on the offspring (e.g. by affecting the immune system). Nonetheless, these findings highlight the effects of maternal antibioticsduring late pregnancy on the microbiota of the progeny. (6)

Childhood antibiotics modulate the immune system

The effect of antibiotics on the natural microbial communities may consequently modulate the immune function and promote illness associated with dysfunctional immune system. This might be especially true in the case of antibiotics administered in early childhood, a period during which the immune system is developing in coordination with the nascent microbial colonization. Indeed, use of antibiotics during childhood has been correlated with increased risk of allergy, asthma, various infections and IBD.

Allergies are extremely common chronic diseases in which the T-helper 2 (Th2) arm of the adaptive immune response is hyper activated. It has been postulated that microbial dysbiosis can affect the Th2 response and may lead to increased susceptibility to allergies. The microbiota has a crucial role in generating a balanced immune phenotype that involves maturation of the Th1 and Th17 cells response and the development of T regulatory (Treg) cells, which suppress the Th2-phenotype. For example, certain Clostridia species are associated with increased numbers of Treg cells in the mouse colon. The immune maturation process in the respiratory mucosa is also modulated during initial microbial colonization. Programmed death ligand (PD-L1) is necessary to induce the development of Treg cells in the lung, whose presence is inversely related to the allergicresponse to the house dust mite. Within the first 2 weeks of life, in parallel with changes in the bacterial profile, PD-L1 expression peaks in the murine lungs of normal mice but not in germ-free mice. The bacteria possess a variety of mechanisms to modulate the immune system, such as generation of metabolic products, including short chain fatty acids (SCFA), from dietary substrates, which can promote Treg cells.

The correlation between asthma and antibiotic exposure during the perinatal period or infancy was also investigated. A cohort study examined a correlation between infant exposure to antibiotics during the first 6 months of life, and eczema, wheeze and allergic sensitization at 2 years, and demonstrated that direct exposure to antibiotics increased the risk for recurrent and prolonged wheeze, though not allergic sensitization or eczema. In another large cohort study of children born to mothers with asthma, increased risk of asthma was associated with maternal antibiotic use during the third trimester of pregnancy. Correlations between macrolide treatment in children and increased risk for asthma, and a correlation between exposure to three or more courses of antibiotics up to 7 years of age and greater odds of food allergies, including allergies to milk were also demonstrated. Although, in one cohort analysis, antibiotics used to treat respiratory infections in childhood were associated with increased risk of asthma, but the excess riskwas decreased when siblings were analysed. This study emphasizes the necessity to assessadditional associations between the exposure to antibiotics in early life and subsequent childhood allergy such as genetics and environmental factors.

Concurrent with the studies in children showing correlations between early life antibiotictreatment and asthma, exposure of prenatal and neonatal mice, but not adults, to antibiotics resulted in exacerbated asthma following intranasal challenge with ovalbumin. Moreover, a critical period was defined between birth and 3 weeks of age, during which an antibiotic-driven shift in microbiota can alter the immune response and increase susceptibility to allergy. These effects were observed when mice were exposed to vancomycin but not streptomycin. While trying to decipher the underlying mechanisms, it was found that vancomycin may lead to elevation of serum IgE and reduced regulatory T cell populations, in contrast to allergic responses, neonatal exposure to streptomycin but not vancomycin dramatically

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enhanced subsequent development of the Th1/Th17- mediated lung disease, hypersensitivity pneumonitis. This suggests that the distinct effects of individual antibiotics on microbiota composition early in life can differentiallydirect immune development.

In terms of autoimmune disease, a cohort study found increased risk for IBD in childrenreceiving antibiotics. This risk factor was especially high for Crohn's disease (CD) and was strongest in the first 3 months following antibiotic administration, as well as in children receiving ≥7 courses of antibiotics. Mechanistically, a study in mice demonstrated that antibiotic treatment during gestation and early life induced a more rapidonset of IBD due to enhanced effector function of $CD4^+$ T cells. They further showed thatantibiotic treatment in early life resulted in a stress response, with high levels ofcorticosterone, which influence $CD4^+$ T cell function.

In summary, the combined findings in several large birth cohort studies as well as mousestudies present a strong link between childhood antibiotics, altered microbial compositionand an aberrant immune response leading to increased risk for allergies and IBD. Data suggest that early in life, the immune system is skewed toward the Th2 phenotype, which facilitates safer microbial colonization in a way that avoids excessive inflammation or tissue damage. In turn, the colonizing microbiota divert the immune response to its maturebalanced phenotype associated with the Th1/Th17/Treg responses.

When the dialog between the microbiota and the immune system is destabilized, for example as a consequence of antibiotic usage, either the maintenance of the infantile phenotype increases the risk of allergy, or alternatively, abrogation of the delicatetolerance by unregulated inflammatory processes increases the risk for autoimmune diseases, especially those involving primary sites of the microbiota, such as IBD. (8)

Childhood antibiotics affect weight gain

Several studies have investigated a link between childhood antibiotics and weight gain. This may not be surprising, since antibiotics have been used in the agricultural industry as a growth promoter for over 60 years, even though the precise mechanisms underlyingthis effect are as yet unknown. Interestingly, there were some differences between effects in males and females following antibiotic administration. Whereas an increase in fat massas well as a decrease in bone area and mineral content was observed specifically in males, in females there was a significant rise in bone mineral density following treatment. The effects on total and fat mass were even more severe when antibiotics were given Perinat ally and up to weaning, as opposed to post-weaning. The increased body mass phenotypeis transferrable to germ-free mice by microbiota from LDP-exposed mice, demonstratingthat the altered microbial compositions caused by the antibiotics play a causal metabolic role. In yet another study, increased adiposity, insulin resistance and liver disease relatedto high-fat diet were observed in mice receiving long-term LDP treatment from 2 weeksof age. These changes correlated with microbial alterations. Finally, a mouse study attempting to mimic childhood antibiotics by pulsed antibiotic treatments starting from weaning showed a strong correlation between varying antibiotic regimes and body mass,bone growth and slower microbiota adaptation to changes in diet.

Recently, a study in pre-school children found that use of macrolides in early life correlates with increased weight gain. This weight gain was also associated with microbial taxonomical changes including in the abundance of Clostridium, Akkermansiaand Enterococcus. Even exposure of the foetus to antibiotics, administered to the motherduring pregnancy, may result in long-term effects on growth. For instance, it was demonstrated that when pregnant women received antibiotics during the second and thirdtrimester of pregnancy, their offspring had an 84% increased risk for childhood obesity, up to 7 years of age.

The mechanisms underlying the causative role of the microbiota composition on the hostmetabolic function are not clear yet, but several pieces of evidence link the initial microbiota alterations due to antibiotic treatments with long-lasting metabolic effects: early life antibiotic administration in mice was associated with changes in microbial copies of key genes involved in the metabolism of carbohydrates to SCFAs, and increased colonic SCFA levels. Due to this overproduction in early life, the ecosystem might not beable to recover. Also, early life LDP, in a microbial dependent manner, reduced the expression of transcription factors and cytokines important for Th1 and Th17 cell differentiation and function in the intestinal mucosa. This might be the result of the significant reduction in the abundance the bacteria *Lactobacillus*, *Allobaculum*, *Rikenellaceae* and *C. Arthromitus* in response to LDP, all with known effects on the immune functions. It is possible therefore that alteringintestinal immune programming has a long-lasting effect on the

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immune resistance, and inflammatory conditions are known to be associated with metabolic syndromes. (6)

Antibiotics and neurodevelopment

There is now strong evidence, in humans and rodents, supporting the influence of the gutmicrobiota on central nervous system development, brain function, and mood/behavior. Studies in germ-free animals demonstrate that the absence of intestinal bacteria results in changes in brain neurochemistry, decreased anxiety and altered social behaviors, hyperactivity of the hypothalamus–pituitary–adrenal axis and an immature phenotype inmicroglia. While many of these disruptions in central nervous system (CNS) function canbe replicated in animal models exposed to high-dose antibiotic cocktails, there have been few studies examining the potential effects of clinical antibiotic use on neurocognitive outcomes. However, a recent study identified an association between antibiotic treatment in the first year of life and inferior cognitive, behavioral and emotional outcomes throughout childhood. Examining 526 children, investigators demonstrated greater behavioral difficulties at 3.5 years and 7 years, and a greater number of ADHD and depressive symptoms at the age of 11 in those exposed to antibiotics. Furthermore, a causal relationship between early life antibiotic treatment and changes in neurodevelopment has been suggested in a mouse model demonstrating that LDP in late pregnancy, and the early postnatal period in mice lead to increased anxiety-like and impaired social behaviors, together with increased aggression in early adulthood.

These behavioral changes had neural correlates, with increased expression of cytokines and arginine vasopressin receptor 1B in the frontal cortex, as well as modification of blood–brain barrier integrity. Arginine vasopressin receptor 1B has previously been associated with aggressive behavior (Wersin). Together, these studies raise concerns andidentify the need for further investigations regarding the side effects of early life antibiotic treatment on the development of neurodevelopmental and mood disorders.(6)

Antibiotic resistance

The increasing number of antibiotic prescriptions is considered to be the main factors causing the antibiotic resistance crisis. Various observations reveal that exposure to antibiotics leads to elevated and long-term expression of microbial antibiotic resistance genes, as well as increased abundance of resistant bacterial strains. Selective pressure aswell as the innate immune alterations triggered by antibiotic exposure may be exploited by antibiotic-resistant bacterial pathogens, enabling them to thrive following antibiotic treatment.

The expression of antibiotic resistance genes and species has been termed the resistome. Characterization of the gut resistome of 22 healthy infants and children aged 0–19 years demonstrated that infants and children harbored genes conferring resistance to 14 out of the 18 antibiotics tested. The healthy childhood resistome was highly diverse, and the resistance genes appear very early in life. Moreover, even healthy preterm infants have been found to harbour a diverse resistome

A longitudinal study found that children receiving antibiotics in the first 3 years of life contained microbiota expressing higher levels of antibiotic resistance genes as compared to controls, with a peak in their abundance after antibiotic treatment, followed by a sharp decline. However, antibiotic resistance genes on microbial mobile elements tended to persist longer after antibiotic withdrawal. This study also found that some children harbored antibiotic resistance genes prior to any antibiotic treatment. Similarly, in a studytesting microbiota in dental plaques in children, although previous amoxicillin usage increased the numbers and proportions of resistant bacteria, resistance to amoxicillin wasfound both in children receiving amoxicillin during the previous 3 months and in those not exposed to antibiotics.

Altogether these studies demonstrate that a side effect of antibiotic treatment is the increase in abundance of antibiotic resistance genes and consequently increase their potential for horizontal spreading in the healthy community. (6)

Microbiome Development

Although the GI tract of a healthy infant is generally considered to be sterile before birth,recent work suggests that initial colonization may take place in-utero. Hours after birth, microorganisms from the mother's vaginal, faecal, and/or skin microbiome and the environment are important colonizers of the infant gut, with actual contributions depending on mode of delivery. Several other factors including prematurity, infant diet (breast milk or formula), hygiene, and use of antibiotics will ultimately impact the composition of the infant gut microbiome. Despite a seemingly chaotic

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colonization with large swings in composition over time, gut microbiome development is governed by Darwinian dynamics: microbes best adapted for the changing conditions of the gut will be most likely to survive.

As illustrated in Figure 1, we can also see compositional changes in response to diet andhost development throughout the first year of life. In the United States, the infant gut is initially colonized with Proteobacteria and Firmicutes, followed by a gradual increase inActinobacteria (potentially due to the introduction of breast milk). By 6 months of age, Bacteroidetes dominate while Proteobacteria and Actinobacteria gradually decline, which may be attributed to the abundance of carbohydrates in solid foods that coincides with weaning. By the end of the first year of life, the infant gut is dominated by bacteria fromthe phyla Bacteroides and Firmicutes (Figure 1). The healthy infant gut continues with dramatic compositional changes throughout the first 2 years of life before becoming indistinguishable from an adult gut microbiome at age three. (9)

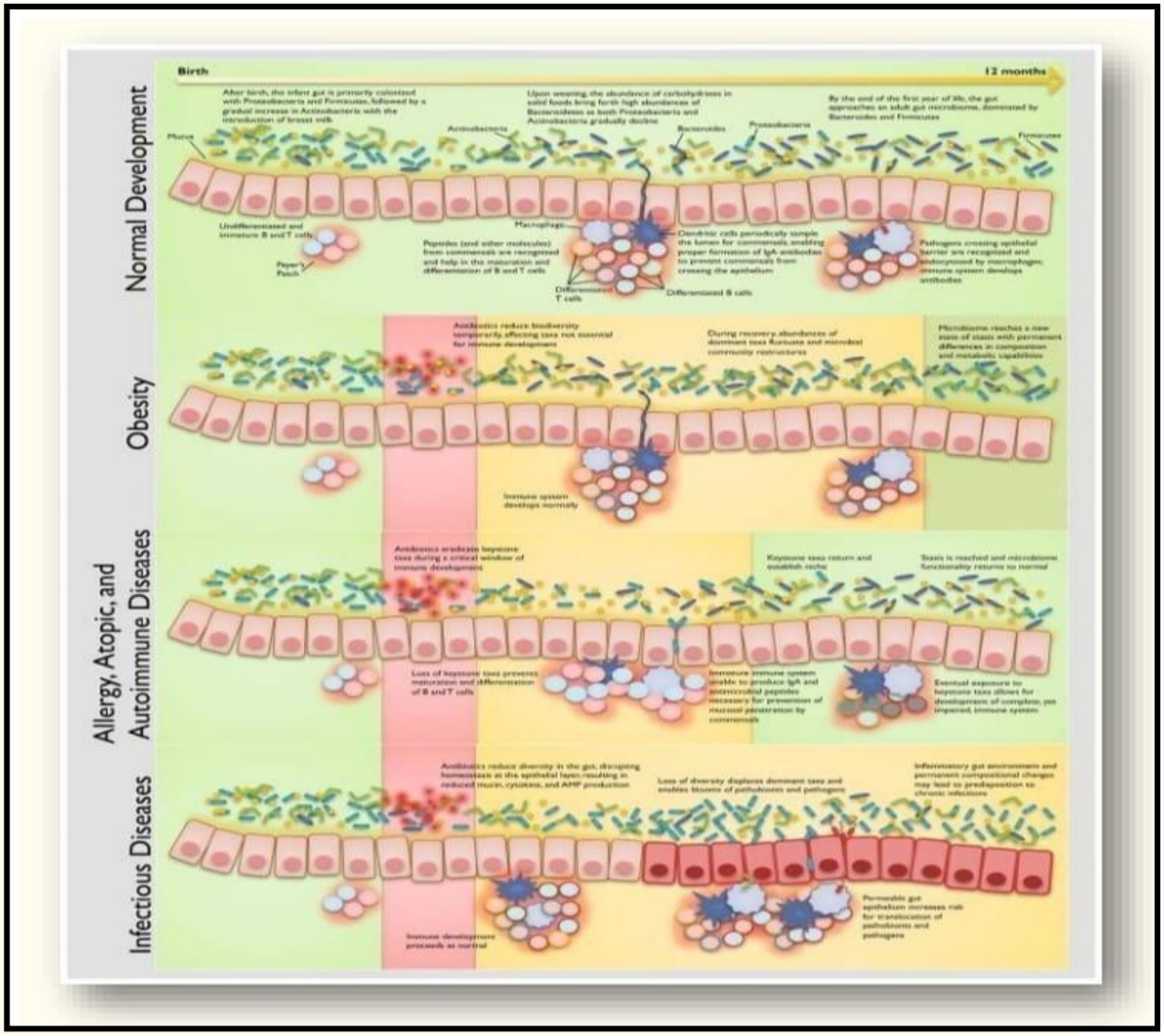

Figure 1: Framework for Host-Microbiome Development in Health, Dysbiosis, and Disease(9)

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Effects of Antibiotics upon Gut Microbiome

The effect of antibiotic drugs to the human microbiome is complex and bi-directional. Except for direct effect, antibiotics can also indirectly affect human microbiota. The gut microbiota dysbiosis following exposure to antimicrobial agents may cause the dysregulation of immune responses .Indeed, it was demonstrated with in vitro and ex vivo studies how a short-term treatment with broad-spectrum antibiotics deeply affected both cellular and humoral immune response some antibiotics have been reported to display immunomodulatory effect in addition to their antimicrobial activity.

Enteropathogenic bacteria such as *Shigella spp., Salmonella spp.*, and *C. difficile*. The antibiotics-induced synthesis of AMPs is the cornerstone mechanism of the indirect action of this group of drugs on the human microbiome. By the same token, antibiotics' influence on intestinal bacterial diversity and long-term abuse has been identified as an independent risk factor for metabolic disorder, such as atherosclerosis-driven events.

Antimicrobial agents induce autophagy and the inhibition of the immune response. In this context, antibiotics may alleviate the progression of the autoimmune and neuro inflammatory diseases. Studies show that antibiotics may influence the pathogenesis of neurodegenerative diseases, such as multiple sclerosis and Amyotrophic between microglia and pain, and that gut bacteria modification by antibiotics has a positive effecton this phenotype.

Another pathway of the indirect effect of antibiotics on the human microbiome is the regulation of radical nitric oxide (NO) synthesis by the activation of the inducible nitric oxide synthase. NO increases mucosal blood flow and mucus thickness and prevents microbial infections. However, the impact of NO on the gut microbiota remains elusive.Studies indicate that the NO plays a vital role in host defense against bacterial infections.

Immune cells play a significant role in the maintenance of tissue homeostasis by exhibiting the plasticity of their phenotypes, such as M1 or M2 for macrophages or N1 and N2 for neutrophils. Microbiota-derived metabolites, short-chain fatty acids (SCFAs), bacterial lipopolysaccharides (LPS), and antimicrobial peptides wield anti-inflammatory or pro-inflammatory effects by acting on immune cells. Demonstrated that the anti- inflammatory action of erythromycin is mediated through the upregulation of the secreted homeostatic protein DEL-1. Through this study, it was shown that erythromycin regulates neutrophil function in the tissues, such as lungs or the periodontium, in a DEL-1- dependent manner. (10)

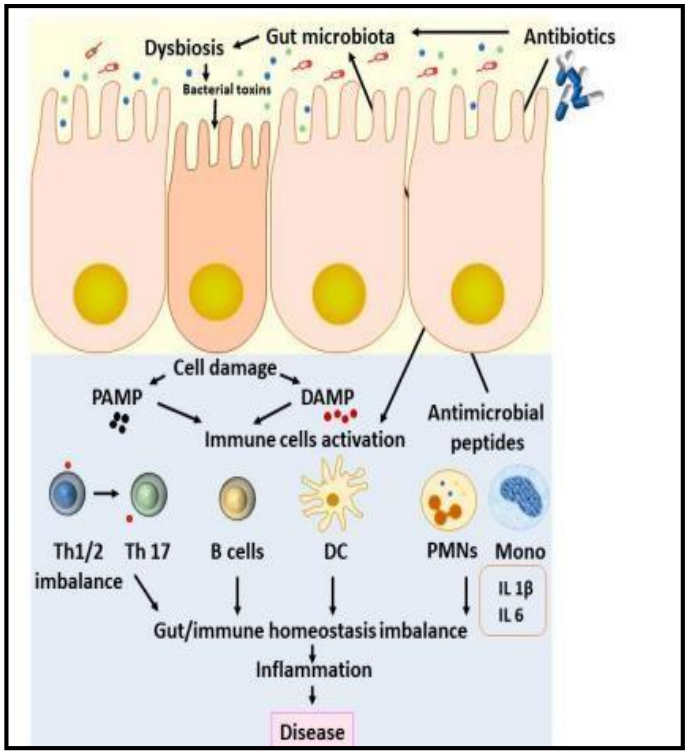

Figure 2: Effect of antibiotic upon gut microbiome (10)

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A high-fat diet (HFD) exhibited impaired neutrophil migration to the intestinal mucosaand reduced the gene expression of the CXCL-1 chemokine and CXCR-2 receptor in theileum. In this context, it was previously shown that the depletion of neutrophil migration is also correlated with the proliferation of tumour cells and tumour-cell DNA damage in an interleukin-17-dependant manner. Moreover, a high-fat diet induced neutrophil activation by enhancing neutrophil elastase activity. The high levels of active neutrophil elastase are associated with a low microbiome diversity and the downregulation of microbiome characteristics. In addition, neutrophil extracellular traps (NETs), as cornerstone mechanisms of neutrophil action, are involved in several disease exacerbations. Dicker et al. report that NETs are associated with disease severity in patients with Chronic Obstructive Pulmonary disease (COPD), a loss of microbiota diversity ($p = 0.009$), and the dominance of Haemophilus species' operational taxonomicunits ($p = 0.01$). Besides this, it was previously reported than neutrophil ageing is regulated by the microbiome. This mechanism is driven by the microbiota via the TLR receptor and myeloid differentiation factor 88-mediated signalling pathways. (8)

The role of gut bacteria

We have vast numbers of bacteria in our gut, as well as viruses, fungi and other organisms. This microbial community is collectively known as the microbiome. Our microbiome is essential for normal health and development and has been linked to an ever-growing listof health outcomes such as mental health, immunity, obesity, heart disease and cancer.

An infant's first major contact with bacteria and other microbes occurs at birth. Babies born vaginally acquire their initial microbiome from the birth canal and gut. Those delivered by caesarean section are more likely to acquire bugs from their mother's skin and the hospital.

Antibiotics during pregnancy can alter the mother's microbiome and therefore themicrobial profile her baby acquires. Antibiotics kill off not only the bacteria causing theinfection, but also bacteria of the microbiome, including those that are beneficial. The resulting imbalance of the microbiome is known as dysbiosis. The baby's early microbiome, acquired from the mother at delivery, "educates" the infant's developing immune system in the first weeks and months of life. Antibiotics in pregnancy can alter the mother's and therefore the baby's microbiome, affecting early immune responses. This may increase the risk of infection in childhood. In a recent Danish study, a mother's exposure to antibiotics in pregnancy was associated with increased risk her child would develop a severe infection in the first six years of life.

The increase in risk was greatest among children whose mothers were prescribed more antibiotics and who received them closer to delivery. There was also some evidence the risk was higher in those delivering vaginally. This suggests antibiotics affect the mother'smicrobiome, with downstream effects for the offspring. Other genetic and environmental factors shared between mother and child are also likely to Plays a role. (4)

Figure 3: Obesity in animals (9)

Obesity

Antibiotics are widely used in meat production as a growth promoter. An estimated 80% of all antibiotic use is in animals. Much of their effect is via the livestock's microbiome, which has a major role in metabolism and energy harvesting.

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Antibiotics may also play a similar role in promoting growth in humans. There is some evidence antibiotic exposure in pregnancy is associated with increased birth weight and obesity in early life. But large studies are needed to account for the other important factorsthat may also contribute. (4)

The association between antibiotics in early childhood and obesity is clearer. Antibiotic exposure within the first year of life is associated with a 10-15% increased risk of obesity,although the importance of the type and timing of antibiotics is less well understood. (9)

Asthma

Childhood asthma has increased in parallel with antibiotic use, leading researchers to investigate a link. Observational studies have shown an association between antibiotic use in pregnancy or infancy and later risk of asthma. This supports the concept of antibiotic-induced dysbiosis (imbalance of bacteria) and the effect on the immune system.

A large population-based Swedish study, however, found the link between asthma and antibiotics was largely attributable to a number of other factors, including respiratory infections contributing to asthma and unrecognised symptoms of asthma being inappropriately treated with antibiotics.

But other studies have found these factors don't completely explain away the link between antibiotic use and asthma. A better understanding of the role of the microbiome in the development of asthma will help clarify the contribution of antibiotics. The science is unclearabout the link between antibiotics and asthma. (4)

Figure 4: Asthma pump (4)

Systemic and Topical Antibiotics Induce Cutaneous Dysbiosis

Antibiotics and isotretinoin have long been the main treatments for acne. Isotretinoin has been shown to normalize aberrant TLR-2-mediated innate immune responses towards *C. acnes* and this immunomodulatory effect may be involved in the anti-inflammatory response to isotretinoin. However, systemic isotretinoin results in qualitative and quantitative changes in the highly diverse microbiome of the gut and in that of the skin, with marked increases in *S. aureus*. Topical antibiotics induce a 'selective pressure' on the bacteria of the skin microbiome, leading to the selection of resistant *C. acnes, Streptococcus* and *Staphylococcus* strains. The induction of antimicrobial resistance anddysbiosis thus provides a strong argument for limited use of both systemic and topical antibiotics as long term and monotherapy regimens in acne.

As regards alternative treatments to isotretinoin and antibiotics, a study in 2019 indicated that the antiseptic benzoyl peroxide (BPO), an over-the-counter acne treatment with bactericidal, anti-inflammatory, and comedolytic properties, did not affect microbial diversity. However, these data need to be confirmed as a smaller-sized study—including only five preadolescent females with acne treated with BPO—found that microflora diversity decreased after treatment. According to a very recent Cochrane review, there may be little to no difference between treatment with long-term BPO and that in terms of self-reported treatment success in mild-to-moderate acne management.

Thus, we advocate the use of BPO alone, or in association with a cleanser (pH ~ 5) and a moisturizing cream as adjunct treatments, to restore the skin barrier and microbiome. Indeed, intensive washing damages the skin barrier, leads to loss of AMPs and results in impaired innate immunity. Moreover, the pH of the skin is around 5.5. Using cleansers with a higher pH (~ 8) increases activity, leading to skin barrier dysfunction and alters the skin and the microbiota (Fig. 5). In

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particular, Prakash et al. demonstrated that skin pH in patients with mild-to-moderate acne vulgaris in the absence of treatment was significantly higher than that in age- and sex-matched controls. Indeed, the bactericidal activity of antimicrobial peptides is optimal at pH 5.5, and the population size and activity of C. acnes and S. aureus have been shown to increase as skin pH rises. (11)

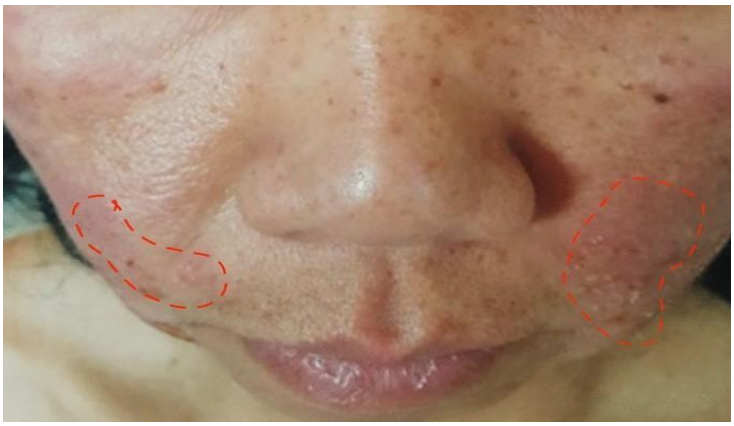

Figure 5: Acne lesions (11)

Role of probiotics in different diseases

Probiotics are live microorganisms or components of dead bacteria that are safe and free of vectors, which, when administered in specific doses, can confer health benefits by inducing resistance against antibiotics, xenobiotics, and pathogenicity or toxicity factors by strengthening immunity through the route of the gut. Strains of diverse microbiota likewise, Bifidobacterium, Enterococcus, Lactobacillus, Saccharomyces boulardii, and Escherichiacoli Nissle 1917, Lactococcus, Leuconostoc Pediococcus, and Streptococcus are widely used as probiotics for the amelioration of GIT associated disorders including acute, nosocomial and antibiotic-associated diarrhea, Clostridium difficile–associated diarrhea, inflammatory bowel disorders in adults, and allergic disorders like atopic dermatitis and allergic rhinitis in infants. Interestingly, probiotics' role is not limited to the disorders mentioned above; instead, its functional importance is emerging.

The researchers show more great interest in identifying the vast therapeutic benefits that probiotics can achieve for treating different diseases. There is a growing field of research towards the possible use of probiotics as co-adjuvants in treating metabolic disorders such as type 2 diabetes, obesity, metabolic syndrome, and non-alcoholic fatty liver disease. However, probiotics' mechanisms of action have not been studied well in different disease conditions and are still in infancy but hold great promise as probiotics' actions are diverse and heterogeneous.

Respiratory tract infections (RTI) are the most prevalent diseases globally, in children, elderly, and immuno compromised individuals. Various studies have revealed the use of probiotics in the treatment of RTI by decreasing the incidence and severity of the diseases. Respiratory conditions including chronic lung disorder; asthma, bacterial infections; tuberculosis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and viral infection such as influenza are all associated with intestinal manifestations and alterations in the composition of gut microbiota, suggesting the correlation between lungs and gut. The use of probiotics has been studied preclinical and is found to be beneficial in asthma models. The administration of Lactobacillus casei or L. rhamnosus and Bifidobacterium Bifidum were found to decrease the viral titters and alleviate the symptoms in respiratory influenzas virus infection. Similarly, nasal administration of Lactobacillus rhamnosus provided protection against respiratory syncytial virus infection in mice models.

Hence, probiotic treatment might have beneficial effects by reducing disease-induced inflammation and fortifying mucosal immunity, thereby controlling the spread of viral infections. (12)

Probiotics-novel approach to boost immunity in viral infections Considering the ineffectiveness or side effects of the available therapies in treating COVID-19, additional supplements with a proven record of amelioration of inflammation may be considered. One such therapy includes the supplementation of probiotics might be helpful as of its effectiveness in previous viral diseases such as in influenzas through boosting immunity. In addition, probiotic ameliorate

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pathogenicity by modulating monocyte chemoattractant protein-1 (MCP-1), which is SARS-2 virus linked mediator and subsequent amelioration of inflammation. Similarly, probiotics may act as a modulator of dysbiosis caused by viral infection, which seems to have promising effects in COVID-19 as well, especially in the attenuation of GIT symptoms. Probiotics may lessen the extent of disease severity by balancing the gut microbiome, which might have valuable outcomes due to its role in the gut–lung axis communication, and vitamin A regulation, which is directly linked with the immune system.

More recently, Barcik and his co-worker associated gut microbiota dysbiosis with dysregulation of microbiota-related immunological processes and subsequent onset of various respiratory disease. Consequently, microbiome analysis must be included in clinics as a diagnostic test as previous viral infections have caused dysbiosis. Probiotic use might be helpful in SARS-CoV-2 specifically as its effect on GIT, lungs, and kidneys have been documented, which has a strong association with microbiome. Gut microbiome analysis and evaluation in COVID-19 individuals, as well as the addition of probiotics in various food items in patients' daily diets, might be useful because of its proven record of anti-inflammatory and antiviral properties in multiple trials and studies, which some are listed. (12)

Urinary Tract Infections in seniors

One of the most frequent reasons seniors are prescribed antibiotics is urinary tract infection (UTI). We know, however, that many of these UTIs are misdiagnosed. A urinary tract infection is caused by bacteria that involves any part of the urinary system including the urethra, bladder, ureters and kidneys.

What are the specific symptoms of a UTI?

- A burning feeling, discomfort or pain with urination.
- Pain in the lower abdomen or back.
- Increase in frequency (needing to "go" more often than usual).
- Repeated strong urges to urinate.
- Blood in the urine.

These symptoms may or may not be accompanied by fever.

- Other symptoms

Such as confusion or a sudden change in behavior?

UTI is less likely without the specific symptoms listed above.

Non-specific symptoms such as confusion, a sudden change in behavior, fatigue or a fall may be caused by other factors, including:

1. Dehydration
2. Inadequate nutrition
3. Poor sleep
4. Depression
5. Constipation

It is important to consider a range of possible causes, to prevent missing the real diagnosis. (13).

Association of antibiotics and chronic disease

For all chronic disease states, individuals were significantly more likely to have taken antibiotics in the last year compared to healthy individuals. Furthermore, antibiotic use in the year last was significantly associated with microbiota composition as assessed by a weight.

Sr. No.	No. of Samples	Type
1	300	Stool
2	300	Stool
3	300	Stool
4	300	Stool
5	100	Stool
6	18	Stool

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7	18	Stool
8	13	Stool
9	13	Stool
10	15	Stool
11	24	Stool
12	43	Stool

Table 3: Diseases and sample number

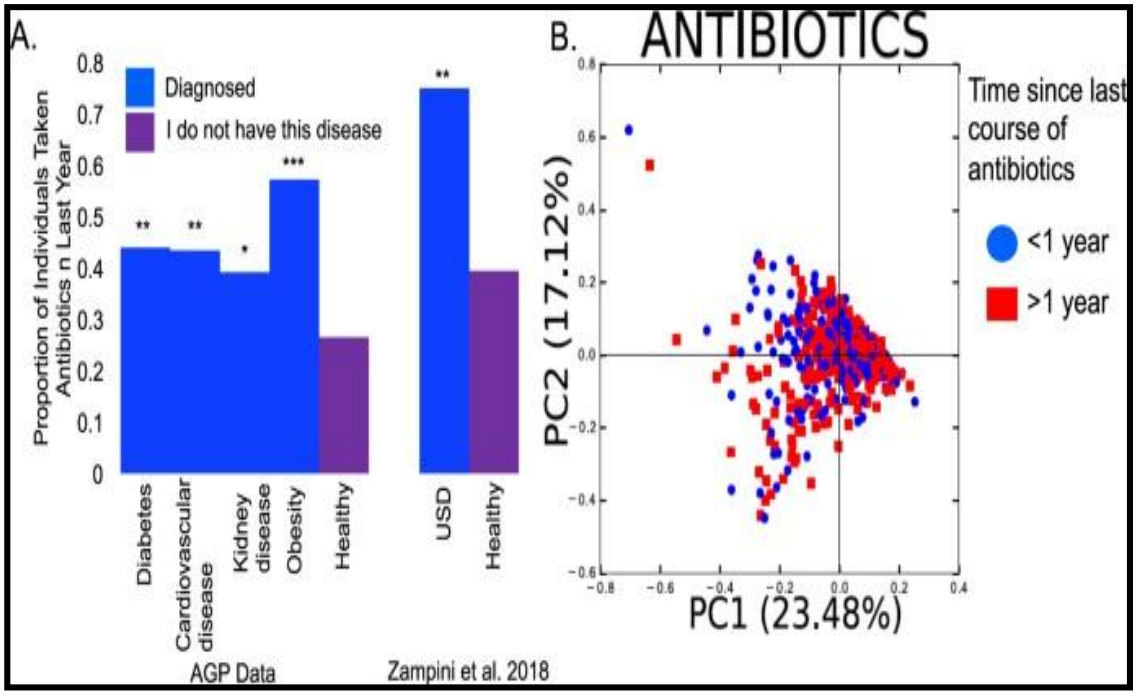

Figure 6: Effect of antibiotics on chronic disease

The effect of antibiotics on chronic disease and the microbiota. (**A**) Antibiotic use within the 2018 year for individuals with or without chronic disease. For diabetes, cardiovascular disease, kidney disease, obesity, and their healthy counterparts, antibiotic history was derived from the subset of AGP samples randomly selected for this study (N = 300 for each group except kidney disease which had 100 samples). Only one study on the microbiome of USD patients included metadata associated with antibiotic use (N = 43 healthy individuals and 24 individuals with USD). Proportions of antibiotic use were compared between chronic disease states and healthy populations with a relative risk ratio followed by a post-hoc Fisher's exact test, which was Holm's corrected for multiple comparisons. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ compared to the healthy population.

PCoA plot based on a weighted UniFrac analysis the microbiome composition from the AGP data. Community composition based on antibiotic use was compared by PERMANOVA with 999 permutations. **p = 0.006**. (14)

Nature of dysbiosis in chronic disease

The differential abundance of OTUs between healthy and disease populations was used to determine if each of the disease states were associated with a depletion or enrichment of microbial diversity compared to healthy controls, with the number of OTUs enriched or depleted in disease quantified for each pairwise comparison in figures. The average fold difference in OTUs enriched in healthy cohorts vs. disease cohorts reveals that for each disease state, there was significantly more OTUs enriched in healthy cohorts than disease cohorts, indicative of a loss of microbial diversity in the gut.

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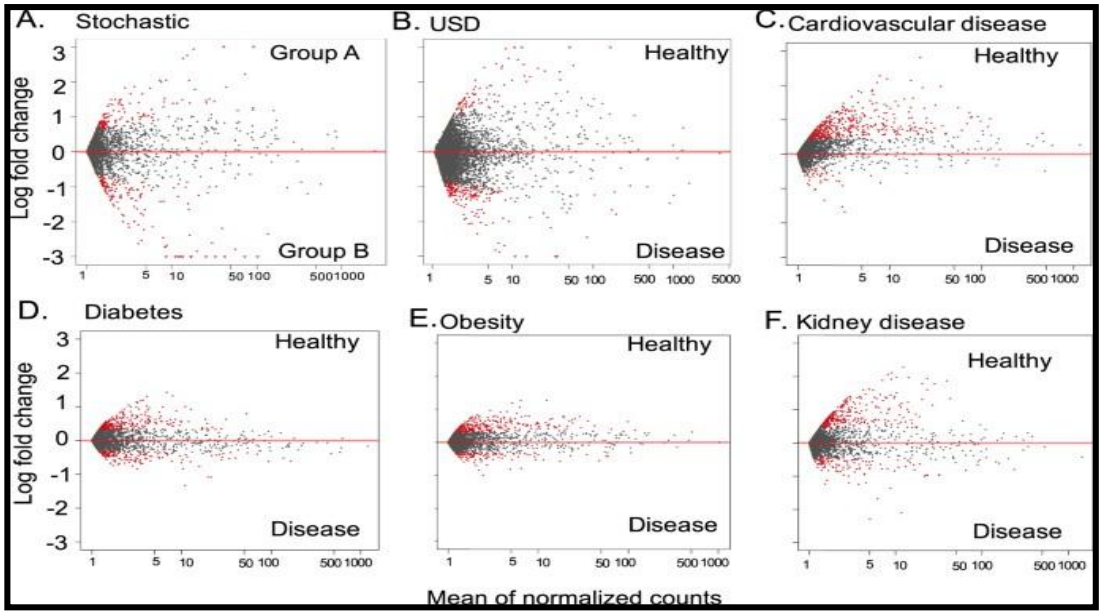

Figure 7: Mean of Normalised count

An example of differential abundance analysis for each of the disease states. Each dot represents an OTU. Grey dots are OTUs that do not exhibit significant differential abundance, while red dots are differentially abundant OTUs. (**A**) Stochastic metadata; (**B**)USD; (**C**) Cardiovascular disease; (**D**) Diabetes; (**E**) Obesity; (**F**) Kidney disease.(14)

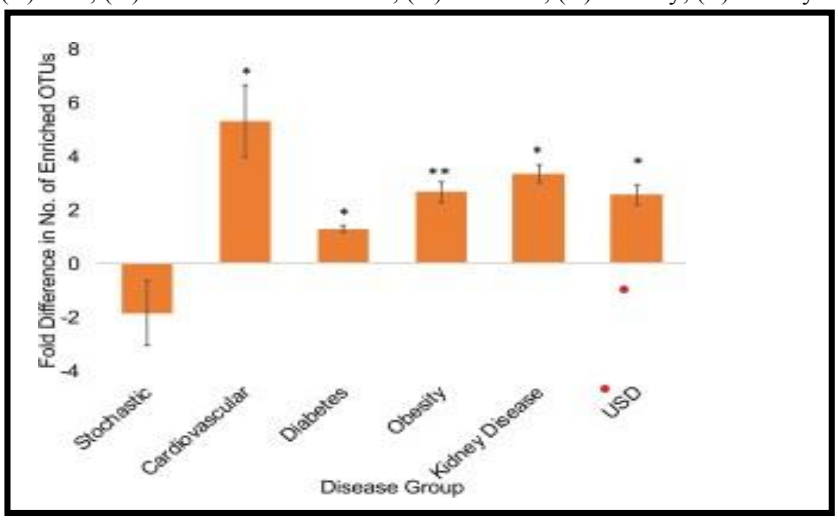

Figure 8: Average fold difference in the no. of OUTs

Average fold difference in the number of OTUs enriched in either the healthy group/stochastic group 1 or in the disease group/stochastic group 2. Positive values reflectgreater enrichment in healthy group/stochastic group 1, whereas negative values reflect greater enrichment in disease group/stochastic group 2. Significance was determined witha one-sample t-test against an expected value of 1. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. (14)

Strength of dysbiotic taxa and commonalities across chronic disease states

The proportion of independent healthy x disease comparisons in which a particular genushad at least one OTU that was differentially abundant was plotted on a heat map. The heatmap reveals that the most common dysbiotic genera were the *Coprococcus, Prevotella*, and *Bacteroides* for OTUs enriched in the healthy cohorts. For OTUs enriched in disease cohorts, the *Bacteroides, Ruminococcus*, and *Blautia* genera were most common. Hierarchal clustering reveals statistically significant similarities between diabetes and kidney disease when considering potential health protective bacteria lost. When considering potential pathogenic bacteria acquired, obesity and USD exhibit a statisticallysignificant cluster, which also clusters with cardiovascular disease. Diabetes again clustered with kidney disease with statistical significance. Additionally, from the heat maps, it is apparent that each of the diseases is associated with a loss of diverse

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genera more so than the gain of microbial genera, largely corroborating analyses based on antibiotic use and the number of dysbiotic OTUs. (14)

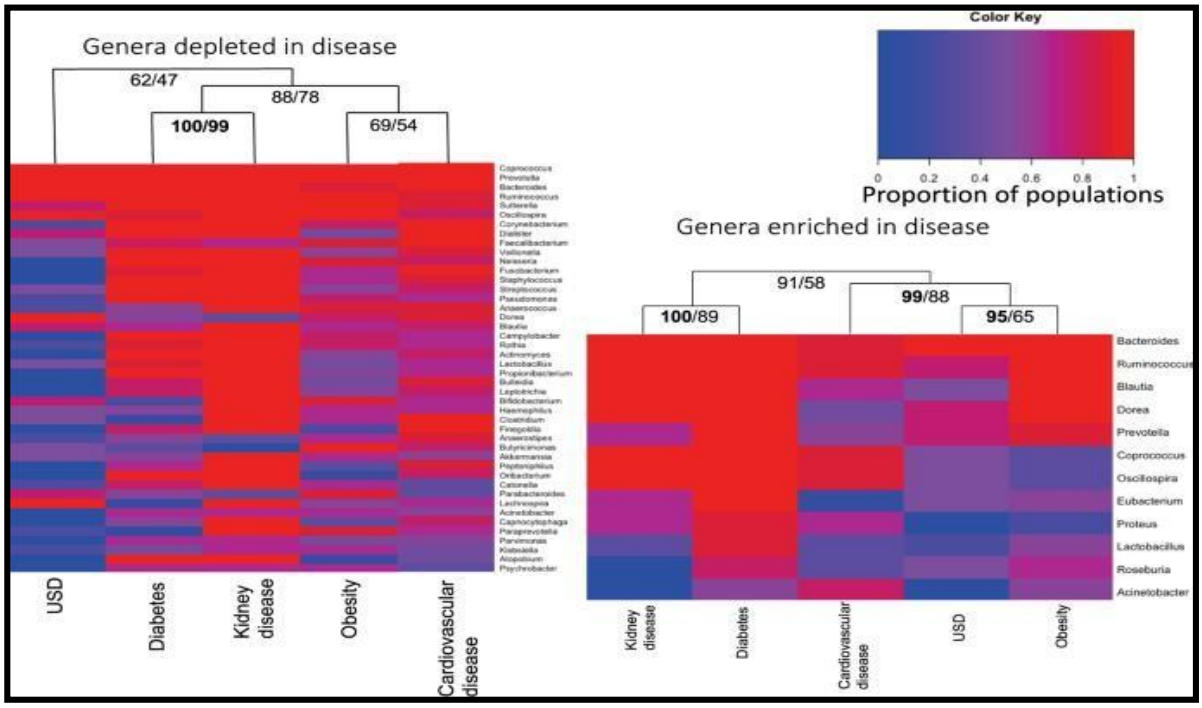

Figure 9: Dysbiotic genera for each disease

Heat maps showing the most common dysbiotic genera for each disease. Genera were counted for each independent population comparison had at least one dysbiotic OTU associated with it. The proportion of populations each genera showed up in is plotted. (**A**)Genera depleted in the disease populations (potential probiotic bacteria lost); (**B**) Genera enriched in disease populations (potential pathogenic bacteria). Hierarchal cluster analysis shows clustering of disease states with the approximately unbiased alpha levels (AU) and bootstrap probability (BP) provided for each cluster (AU/BP). AU values > 95are considered significant and are bolded. (14)

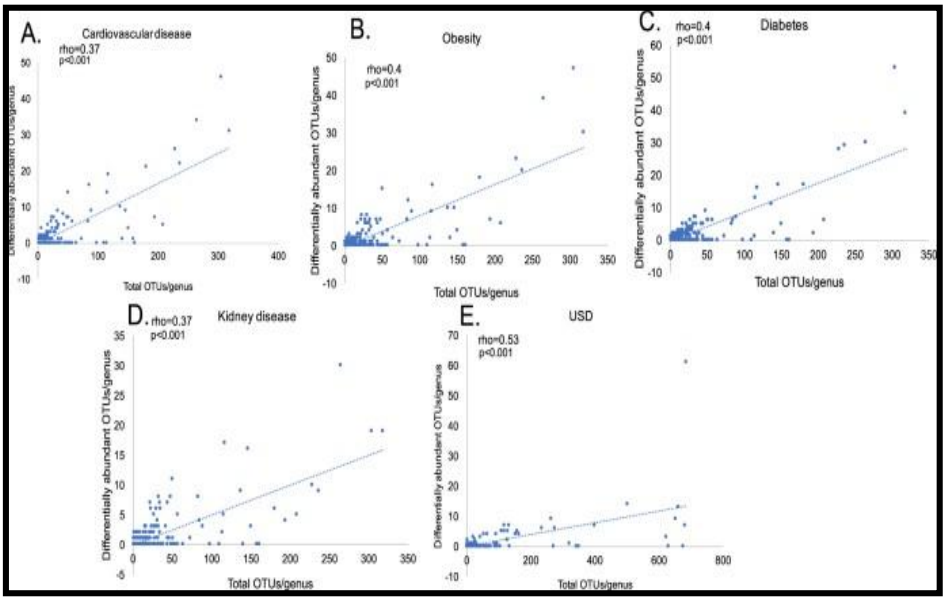

Figure 10: Mean of Normal count

Total genus diversity vs. dysbiotic OTUs per genus. Correlations were calculated with a Spearman's rank order correlation (r). (**A**) Cardiovascular disease; (**B**) Obesity; (**C**) Diabetes; (**D**) Kidney disease; (**E**) USD.

Table 2 Microbial genera that were identified as dysbiotic more than expected based on the number of unique OTUs

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identified per genus. (14)

Impact of genus diversity on dysbiotic OTUs

When the total number of OTUs identified in each genus is plotted against the number ofdysbiotic OTUs identified in each genus, there is a significant correlation between the two factors, reflecting the fact that dysbiosis is driven in part by the number of constituentOTUs in each genus (Fig. 510). However, the number of genera determined to be dysbiotic more than expected given genus level diversity ranged from one (USD) to 14 (kidney disease).

Of these, the *Bacteroides* genus was more likely to be dysbiotic for all diseases and *Corynebacterium* for all but USD. The *Anaerococcus* genus was more likely to be dysbiotic than expected for three of the five disease states (Table 3).

Side effects of antibiotic

All medications have side effects, including antibiotics. Antibiotics are medications that treat infections by killing bacteria or other organisms or slowing their growth.An antibiotic side effect occurs as an unwanted reaction that occurs in addition to the desirable therapeutic action of the antibiotic you are taking. Side effects of antibiotics canrange from mild allergic reactions to severe and debilitating adverse events. When used appropriately, most antibiotics are relatively safe with few side effects (15).

Common side effects with antibiotics include:

- Mild skin rash or other allergic reactions
- Soft stools, short-term diarrhoea
- Upset stomach, nausea
- Loss of appetite
- Fungal (yeast) vaginal infections or oral thrush

More severe antibiotic side effects include:

- Severe allergic reaction that results in difficulty breathing, facial swelling (lips, tongue, throat, face)
- Severe watery or bloody diarrhoea; Clostridium difficile infection
- Stomach cramps
- Yeast infections in the mouth or vagina (white discharge and severe itching in the vagina or mouth sores or white patches in your mouth or on your tongue).(16)

Anaphylactic reactions due to antibiotics may include:

- Shortness of breath
- Wheezing
- Severe nausea/vomiting
- Light headedness, dizziness
- Fast heart rate
- Swelling of the face, lips or tongue
- Shock (19).

II. CONCLUSION

- Antimicrobial resistance poses an immense threat to global health. There is a considerable amount of evidence from animal models regarding the involvement of disrupted intestinal microbiota under antibiotic treatment.
- It seems apparent that antibiotics in general, and specifically those administered during early childhood, have major effects on the microbiota composition. While there are discrepancies between different types and dosage of antibiotics, there are also some common effects.
- The most common effects include a dramatic decrease in overall species diversity, a significant increase in the abundance of Proteobacteria and higher Firmicutes/Bacteroidetes ratios.
- Antibiotics, as well as the related altered microbial profiles, have been correlated with metabolic and immune deficiencies, leading to increased risk for weight gain, allergies and IBD. Therefore, antibiotics administered

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during late pregnancy and in infancy should be critically and carefully assessed while keeping in mind that appropriate antibiotic treatment save lives every day.

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