Impact of Antibiotic Misuse on Human Microbiome and Rise of Opportunistic Infections

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ABSTRACT

Excessive and inappropriate antibiotic use has emerged as a critical factor disrupting human microbiome homeostasis, leading to decreased microbial diversity, overgrowth of opportunistic pathogens, and long-term metabolic, immunological, and neuropsychiatric consequences. Reduced populations of beneficial bacteria such as Lactobacillus and Bifidobacterium compromise short-chain fatty acid production, mucosal barrier integrity, and immune modulation, while facilitating the proliferation of antibiotic-resistant and opportunistic species like Clostridioides difficile and Enterobacteriaceae. These changes elevate systemic inflammation, alter host metabolism, and impact mental health via the microbiome-gut-brain axis. Advanced diagnostic tools, including shotgun metagenomics, 16S rRNA sequencing, metatranscriptomics, resistome, and mobile genetic element analysis, provide precise insights into microbiome disruption, functional impairments, and resistance gene dynamics. To mitigate these effects, rational prescription strategies, antimicrobial stewardship programs, microbiome-targeted interventions such as probiotics and fecal microbiota transplantation (FMT), and public health initiatives including education and policy regulation are essential. Implementing these measures can restore microbial balance, limit the emergence of resistant pathogens, and protect both physical and mental health, highlighting the need for integrated approaches to antibiotic use management.

Keywords: *Microbiome, Antibiotic resistance, Opportunistic infections, Dysbiosis*

1. *INTRODUCTION*

Global antibiotic use is alarmingly high, with an average of about 18 defined daily doses per 1,000 people per day. Only around half of this use involves safer, narrow-spectrum antibiotics, while the rest consists of broader-spectrum drugs that drive antimicrobial resistance. During the COVID-19 pandemic, despite only a small fraction of patients having bacterial infections, most were still prescribed antibiotics, contributing to misuse. Overall, it's estimated that roughly 30% of antibiotic use worldwide is inappropriate, highlighting the urgent need for better stewardship.

1.1. Definition and basic importance of the microbiome:

The human microbiome consists of bacteria, archaea, viruses, and eukaryotic microorganisms that live in and on the human body. These microbial communities inhabit different body sites such as the gastrointestinal tract, skin, respiratory system, and urogenital tract, each adapted to the specific conditions of its environment. Under normal circumstances, these microorganisms form a mutually beneficial relationship with the host and play essential roles in metabolic functions, immune regulation, and protection against pathogens.

1.2. The microbiome's role in maintaining health:

It has been proven that maintaining a balanced microbiome is crucial for preserving body homeostasis, proper immune system development, adequate nutrition, and resistance to opportunistic infections. For example, the gut microbiota contributes significantly to host nutrition by producing short-chain fatty acids (SCFAs) and breaking down complex dietary components. In addition, interactions between the microbiome and the immune system help the body distinguish between beneficial and harmful microbes, making these microbial communities fundamental to immune health.

1.3. Dysbiosis and its disease-related consequences:

Dysbiosis, which is an imbalance in the body's microbiome, can have wide-ranging effects on health. It can reduce the number of beneficial microorganisms and allow harmful species to overgrow, disrupting normal bodily functions. In the gut, this imbalance is associated with gastrointestinal problems such as inflammatory bowel diseases like Crohn's disease and ulcerative colitis, irritable bowel syndrome, and nutrient malabsorption. Dysbiosis may also contribute to chronic inflammation, metabolic disorders, and a weakened immune system, making the body more susceptible to infections. Emerging research suggests that gut microbial imbalance can even affect mental health, influencing mood and behavior. Maintaining a diverse and balanced microbiome is therefore critical for overall health and disease prevention. Lifestyle factors, diet, antibiotics, and stress can all impact this microbial balance. Proper interventions, such as probiotics, prebiotics, and dietary adjustments, may help restore healthy microbiome composition.

The primary aim of this article is to review the effects of antibiotic misuse on the human microbiome and its role in the emergence of opportunistic infections. It seeks to highlight the mechanisms by which dysbiosis occurs and how it contributes to increased susceptibility to pathogenic microbes. Additionally, practical strategies for minimizing microbiome disruption and preventing related infections are discussed.

2. THE IMPACT OF INAPPROPRIATE ANTIBIOTIC USE ON THE MICROBIOME

2.1. Decreased microbial diversity:

Improper and repeated antibiotic use severely disrupts gut microbiome homeostasis, significantly reducing species richness and diversity indices (e.g., Shannon and Simpson indices). This loss of diversity affects not only the abundance of key beneficial bacteria such as Lactobacillus, Bifidobacterium, and Faecalibacterium, but also the population structure and balance between dominant and rare species. Microbe-dependent metabolic pathways, including the production of short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate (which play critical roles in maintaining the mucosal barrier and modulating immune responses), are markedly affected.

The reduction in diversity also diminishes microbial competitive capacity and symbiotic function; beneficial species that normally suppress pathogen growth are depleted, shifting the ecosystem toward instability. This can lead to increased gut permeability, chronic mucosal inflammation, and altered expression of innate immune receptors such as TLRs and NOD-like receptors, ultimately affecting immune responses.

Consequently, disruption of microbiome diversity establishes a foundation for increased susceptibility to pathogens, impaired immune regulation, and altered host metabolism. Restoring the microbiome to its pre-antibiotic balance, especially in individuals with sensitive or compromised microbial ecosystems, may take weeks to months and, in some cases, requires targeted probiotic or dietary interventions.

2.2. Pathogens become opportunistic:

The loss of microbial diversity and key species creates opportunities for opportunistic pathogen expansion. Antibiotic-resistant and opportunistic pathogens, including Enterobacteriaceae, Clostridioides difficile, and Candida spp., can proliferate uncontrollably and override the natural microbial control exerted by beneficial species. This overgrowth elevates inflammatory burden and disrupts the balance of innate and adaptive immunity, reducing the body's ability to manage secondary infections.

These pathogens can also transfer antibiotic resistance genes and genotoxic factors to the microbial community, increasing the risk of multidrug resistance and cellular damage. Their interactions with host immune cells, including dendritic cells and macrophages, can lead to excessive production of inflammatory cytokines (e.g., TNF-α, IL-6), amplifying chronic inflammation and tissue injury.

In the long term, stabilization of an opportunistic-dominated microbiome establishes a cycle of chronic disruption; even after antibiotic cessation, restoring balance is challenging, predisposing the host to chronic gastrointestinal diseases, systemic inflammatory syndromes, and recurrent resistant infections.

2.3. Long-term effects:

Disruptions caused by improper antibiotic use can have long-term impacts on host metabolic and immune health. The loss of beneficial species and proliferation of opportunistic pathogens disturb critical metabolic pathways, including vitamin synthesis, SCFA production, and bile acid metabolism. These disruptions lead to increased gut permeability, systemic inflammation, and altered immune responses.

Beyond gastrointestinal effects, long-term microbiome alterations can predispose individuals to metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Immunologically, there is a tendency toward autoimmune responses, heightened sensitivity to allergens, and impaired regulation of systemic inflammation. This demonstrates that microbiome disruption is not merely a transient change but a foundation for complex chronic diseases.

Therefore, maintaining microbiome homeostasis through targeted antibiotic use, nutritional support, and the use of probiotics and prebiotics is critical. These interventions can help mitigate long-term damage and preserve the capacity of the immune and metabolic systems to respond to environmental challenges.

2.4. Mental side effects:

Excessive or inappropriate antibiotic use can profoundly disrupt gut ecosystem balance and impair the microbiome-gut-brain axis. Loss of beneficial species such as Lactobacillus and Bifidobacterium leads to overgrowth of opportunistic bacteria and reduced production of key microbial metabolites, including short-chain fatty acids (SCFAs), which are crucial for regulating brain-derived neurotrophic factor (BDNF) expression, neuronal function, and neuro-immune signaling pathways. Reduced SCFA levels also increase gut permeability, allowing pro-inflammatory molecules to enter circulation, elevating systemic and central nervous system inflammatory cytokines such as IL-6 and TNF-α, which can dysregulate neural signaling and stress responses.

Beyond indirect microbiome-mediated effects, certain antibiotics can directly interact with the nervous system. Interference with GABA-A and NMDA receptors can provoke neural hyperexcitability, contributing to severe anxiety, hallucinations, psychosis, cognitive impairment, and even suicidal ideation. Concurrently, microbiome-induced disruptions in serotonin and GABA production synergize with systemic inflammation to impair mood regulation and cognitive performance.

In the long term, the psychological effects of improper antibiotic use may persist. Even after cessation, reestablishing microbiome-gut-brain homeostasis may take weeks to months, and persistent reductions in SCFA and BDNF levels can sustain anxiety, depression, and cognitive deficits. Therefore, improper antibiotic use threatens not only physical health but also neurocognitive and mental health, establishing a foundation for long-term behavioral and psychiatric disorders.

3. NEW DIAGNOSTIC METHODS:

3.1. Shotgun Metagenomics:

This technique sequences the entire DNA content of a sample, making it the most precise method for detecting microbiome alterations after antibiotic exposure. Its high taxonomic and genetic resolution allows tracking of diversity loss, depletion of key species, and expansion of resistant pathogens. Its major strength is simultaneous detection of bacteria, viruses, fungi, and resistance genes. Its main limitations include high costs and the need for advanced computational analysis. It is ideal for monitoring severe dysbiosis and long-term microbiome recovery. It also enables tracking horizontal gene transfer and mapping resistance-selection trajectories. In antibiotic studies, it provides the most comprehensive view of both short- and long-term impacts.

3.2. 16S rRNA sequencing:

This method targets the 16S rRNA gene to characterize bacterial compositional shifts after antibiotic use. Its strengths include low cost, fast processing, and suitability for large-scale population studies. Although it lacks species-level precision and cannot detect resistance genes, it remains the primary tool for ecological profiling of the microbiome. It reveals alpha-diversity loss, community rearrangements, and expansion of opportunistic taxa. It is suitable for tracking microbiome recovery over weeks or months. Its major weakness is the absence of functional or genetic information. Despite these limitations, it remains highly effective for establishing baseline microbial damage caused by antibiotics.

3.3. Metatranscriptomics:

This technique measures active microbial RNA to uncover functional changes in the microbiome after antibiotic exposure. Its strengths include detecting active resistance genes, disrupted metabolic pathways, and microbial stress responses. It uniquely differentiates between live, active, and inactive taxa, which no other technique can do. Its weaknesses involve high sensitivity, the need for fresh samples, and complex bioinformatics. It reveals how antibiotics suppress essential pathways such as SCFA production and immune-modulating functions. It is highly valuable for assessing rapid functional impacts and predicting long-term consequences of microbial disruption. This approach bridges the gap between genetic potential and actual physiological outcomes.

3.4. Resistome Analysis:

This technique examines the complete set of antibiotic-resistance genes within the microbiome. Its major strength is identifying selective pressures, expansion of resistance genes, and mapping horizontal gene transfer networks. It highlights which microbial compositions have the highest potential to harbor and amplify resistance. Its limitation is that it does not directly indicate gene activity unless paired with complementary tools such as metatranscriptomics. It is highly useful for predicting resistant pathogen emergence and assessing long-term risks of antibiotic use. Resistome profiling enables evaluation of ARG density, diversity, and persistence over time. It is one of the most essential tools for studying the evolutionary consequences of antibiotics.

3.5. Mobile Genetic Elements Analysis:

This technique focuses on identifying plasmids, transposons, and bacteriophages that drive the transfer of resistance genes after antibiotic exposure. Its key strength is mapping horizontal gene-transfer dynamics and pinpointing critical hotspots of resistance spread. It reveals how antibiotics increase MGE activity and enable gene flow between harmless commensals and pathogenic bacteria. Its limitations include difficulty resolving repetitive sequences and the need for high sequencing depth. It is essential for predicting superbug emergence and assessing cross-species resistance transmission risks. MGE analysis uncovers rapid evolutionary shifts triggered by antibiotic pressure. This technique is crucial for studies centered on resistance persistence and dissemination.

4. HARM REDUCTION STRATEGIES:

4.1. Rational Prescription and Stewardship:

Reducing harm from inappropriate antibiotic use begins with optimizing prescription practices. Antimicrobial stewardship programs in healthcare settings monitor prescriptions, restrict broad-spectrum antibiotics, implement rapid diagnostic tests, and provide targeted clinician training to ensure shorter, precise, and goal-oriented treatments. These programs not only reduce selective pressure on the microbiome but also prevent the accumulation of resistance genes in the native flora and minimize the need for repeated courses. Integration of machine learning algorithms into electronic prescribing systems can further reduce diagnostic and therapeutic errors, guiding clinicians toward the most appropriate antibiotic choice based on pathogen type and individual patient factors.

4.2. Microbiome Interventions, Probiotics and FMT:

Probiotics can partially restore the gut ecosystem by replenishing beneficial species and producing immunomodulatory metabolites; however, their efficacy depends on strain, dosage, and patient condition, and in some cases may delay full microbiome recovery. In contrast, fecal microbiota transplantation (FMT) is a far more potent approach, capable of restoring microbial diversity and even reducing accumulated resistance genes. FMT transfers a complete, functional microbial community, reactivates disrupted metabolic pathways, repairs the intestinal epithelial barrier, and enhances the competitive fitness of beneficial microorganisms against opportunistic pathogens. This intervention has shown particularly remarkable results in patients with prolonged antibiotic exposure or colonization by multidrug-resistant organisms.

4.3. Public Health Policies and Education:

Effective harm reduction also relies on large-scale public health interventions that limit inappropriate antibiotic use across the population. National guidelines, restrictions on over-the-counter sales, veterinary surveillance, and structured screening programs can collectively reduce population-level selective pressure. Alongside these measures, public education plays a critical role: informing individuals about the dangers of self-medication, the importance of completing prescribed courses, and differentiating viral from bacterial infections directly enhances policy effectiveness. Such educational campaigns not only modify consumer behavior but also decrease unnecessary healthcare visits for antibiotics, ultimately preventing microbiome disruption and curbing the spread of resistance.

CONCLUSION:

Inappropriate antibiotic use disrupts microbiome balance, reducing beneficial bacteria and promoting opportunistic pathogen growth, with long-term gastrointestinal, metabolic, immune, and neuropsychiatric consequences. Microbiome restoration requires precise antibiotic prescription, stewardship programs, and targeted interventions such as probiotics and fecal microbiota transplantation. Public health policies and education play a critical role in reducing unnecessary use and preventing resistance spread. Combining these strategies can protect host health and mitigate the adverse effects of antibiotic misuse.

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