The Janus face of Antibiotics:

Life Savers & Microbiota Disrupters

BIOCODEX
Microbiota Institute

THE JANUS FACE OF ANTIBIOTICS:
LIFE SAVERS & MICROBIOTA DISRUPTERS

A page turns: with the advent of antibiotics in the 20th century, this type of therapy, despite its undoubted usefulness in fighting infections, now raises serious concerns for health, notably with microbiota dysbiosis and antibiotic resistance.

Though a more rational use of antibiotics has long been overdue, we must not lose sight of the fact that over the course of the last 80 years their widespread use has saved many millions of lives. They have served as our principal weapon in the fight against bacterial infections. **Alongside vaccinations, they have added around 20 years to the average life**[1].

"18 out of 1,000 people take antibiotics every day[5]."

FROM THE ANTIBIOTIC ERA TO THE MICROBIOTA ERA

Unfortunately, antibiotics eliminate not only pathogenic bacteria, but commensal ones too[2]. **The intestinal microbiota is affected, and likewise all the other human microbiota (cutaneous, lung, urogenital...)** that protect against pathogen overgrowth.
While it remains difficult to define a healthy microbiota with any precision or to provide an adequate description of dysbiosis, science is beginning to understand the ways in which antibiotics affect the functioning of these ecosystems and likewise the consequences of such changes for health over the short and long term[3] (See Figure 1).

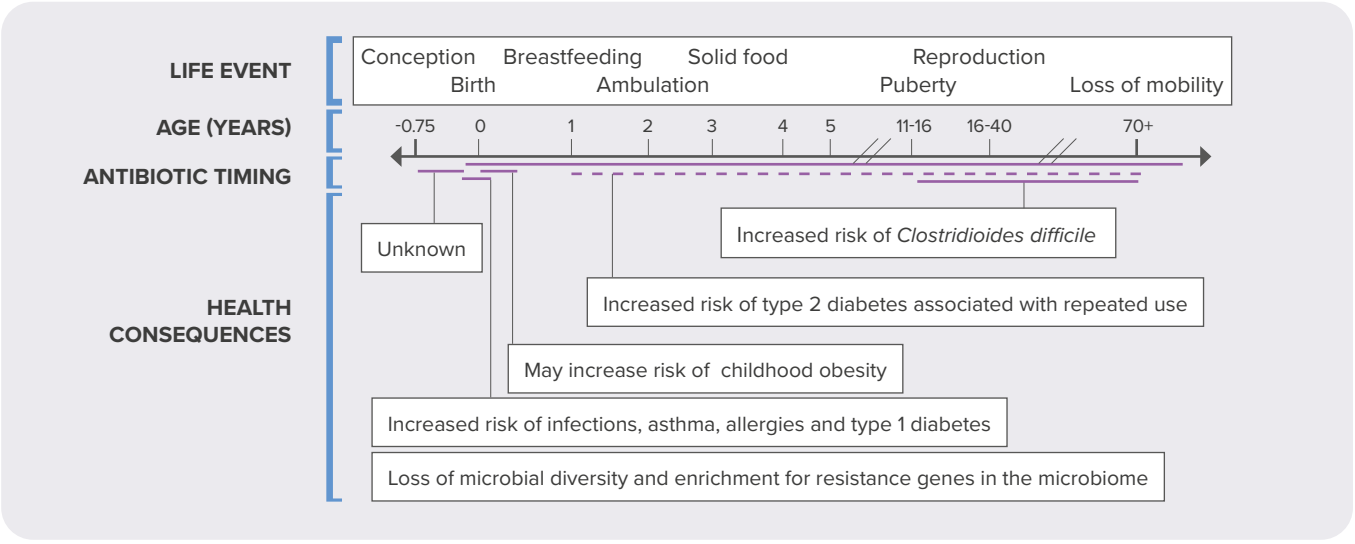
DYSBIOSIS

"Dysbiosis" is not a homogenous phenomenon: it varies according to the state of health of each individual. It is commonly defined as a compositional and functional alteration in the microbiota, driven by a set of environmental and host-related factors that perturb the microbial ecosystem[4].

ANTIMICROBIAL RESISTANCE, A GLOBAL PUBLIC HEALTH PROBLEM

Because of the widespread overuse and misuse of antibiotics in humans and animals, bacteria causing both benign and life-threatening infections are becoming increasingly resistant to them. In 2015, **antibiotic-resistant pathogens were estimated to be causing over 50,000 deaths each year in Europe and the United States**[3]. *"Antibiotic resistance is one of the biggest threats to global health, food security and development today"* states the WHO.

FIGURE 1. Health consequences linked to antibiotic-induced dysbiosis of the microbiota (source: adapted from Langdon *et al.*, 2016[3])



Purple lines indicate that a single dose of antibiotics within the time period has been linked to a health consequence; a dotted purple line indicates that multiple doses of antibiotics within the time period are required for a link to be observed.

1. WHO https://www.euro.who.int/en/media-centre/sections/press-releases/2012/11/self-prescription-of-antibiotics-boosts-superbugs-epidemic-in-the-european-region/antibiotic-resistance.
2. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science.* 2016;352(6285):544-545. **3.** Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med.* 2016;8(1):39. **4.** Levy M, Kolodziejczyk AA, Thaiss CA, *et al.* Dysbiosis and the immune system. *Nat Rev Immunol.* 2017;17(4):219-232. **5.** World Health Organization. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation. Geneva; 2018.

SUMMARY

FROM DIARRHEA TO CHRONIC DISEASES:
THE WELL-DOCUMENTED CONSEQUENCES OF ANTIBIOTIC-RELATED GUT MICROBIOTA DYSBIOSIS

Antibiotic treatment may sometimes take place without any obvious short-term side effects. Nevertheless, the dysbiosis triggers diarrhea for up to 35% of patients; in the long term, antibiotic-induced microbiota alterations may represent a risk factor for allergic, autoimmune or metabolic diseases.

Antibiotics are a powerful tool in the fight against bacterial infections. However, research has also documented detrimental effects on the trillions of commensal bacteria that live in the intestinal tract. This resultant dysbiosis renders the gut microbiota less able to fulfil its protective functions. In the short term, dysbiosis leaves the door open for opportunistic pathogens and the selection of multi-resistant bacteria. In the long term, **the gut microbiota, despite having a certain degree of resilience, can sometimes fail to fully restore itself**[1,2]; this is understood to pave the wave to a range of diseases. Recent research has shown that antibiotics may alter the bacterial diversity and abundance of the normal microbiome and that this impact may be prolonged (typically 8-12 weeks after antibiotics have been discontinued)[3,4].

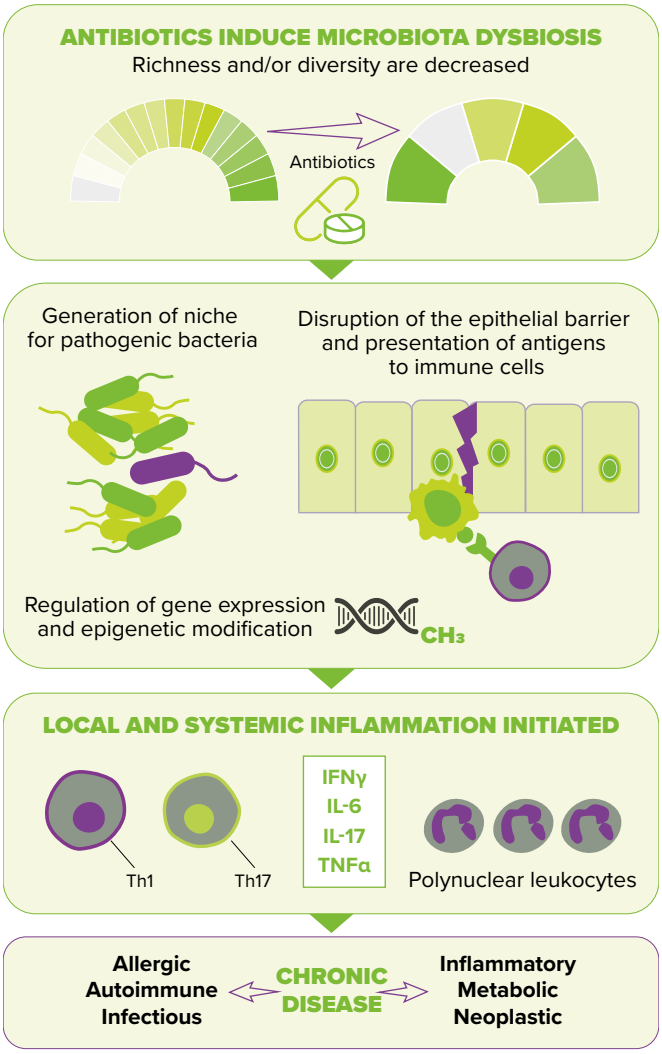
Diarrhea occurs in up to 35% of patients who receive antibiotics[3,5,6].

DIARRHEA, THE MOST COMMON ADVERSE EFFECT OF ANTIBIOTICS

As the main short-term consequence, some patients treated with antibiotics experience a change in their intestinal transit, most often resulting in diarrhea.

The incidence of antibiotic-associated diarrhea (AAD) depends on several factors (age, setting, type of antibiotic, etc.) and may range between 5 and 35% of patients taking antibiotics[3,5,6]. Among children this percentage can reach up to 80%[3]. Most of the time, the diarrhea is purely functional, caused by the antibiotic-induced dysbiosis. It is usually of mild intensity and is self-limiting, lasting 1-5 days. Antibiotics displaying a broader spectrum of antimicrobial activity like

FIGURE 2. Downstream effects of antibiotic-induced gut dysbiosis. (source : adapted from Queen *et al.*, 2020[10])



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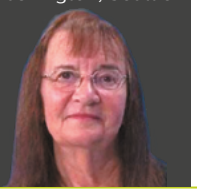


EXPERT OPINION

Antibiotics disrupt the protective intestinal microbiota, which can lead to unintended consequences including antibiotic-associated diarrhea (in up to 35% of patients) and the development of antibiotic resistant strains of pathogens that are of global concern in regards to increased healthcare costs and mortality.

1. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A.* 2011;108 Suppl 1(Suppl 1):4554-4561. **2.** Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. *Front Microbiol.* 2016;6:1543. **3.** McFarland LV, Ozen M, Dinleyici EC *et al.* Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections. *World J Gastroenterol.* 2016;22(11):3078-3104. **4.** Kabbani TA, Pallav K, Dowd SE *et al.* Prospective randomized controlled study on the effects of *Saccharomyces boulardii* CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. *Gut Microbes.* 2017;8(1):17-32.

clindamycin, cephalosporins, and ampicillin/amoxicillin are associated with higher rates of diarrhea[6].

THE PARTICULAR CASE OF *C. DIFFICILE* DIARRHEA

In 10 to 20% of cases, diarrhea results from infection with *Clostridioides difficile* (formerly known as *Clostridium difficile*) colonizing the microbiota[6]. This bacterium, which persists in the environment via spores, is a gram-positive, spore-forming, obligate anaerobe. Infection occurs via spores ingestion. Under specific circumstances (e.g., antibiotic-induced dysbiosis), the spores may germinate and vegetative bacterial cells of this opportunistic pathogen may colonize the intestines. In the infective phase, *C. difficile* produces 2 toxins that damage the colonocytes and trigger an inflammatory response with a variety of clinical outlooks, ranging from moderate diarrhea to pseudomembranous colitis, toxic megacolon and/or death.

Nearly 1/3 of AAD cases are due to *C. difficile*[3].

Most recognized common risk factors for *C. difficile* infection (CDI) include age > 65 years, use of proton pump inhibitors, comorbiditites and of course antibiotic use. The latest is the most relevant modifiable risk factor for CDI. The association of antibiotics with CDI has been established in hospitals and more recently in community settings[7], where the risk of infection varies from intermediate for people exposed to penicillins, high for these exposed to fluoroquinolones and highest for those receiving clindamycin. As for tetracyclines, they trigger no increased risk[8]. In a hospital setting, **the highest risk of developing CDI was observed for cephalosporins (from 2nd to 4th generations), clindamycin, carbapenems, trimethoprim/sulphonamides, fluoroquinolones and penicillin combinations**[9].

AN OPEN DOOR TO NON-COMMUNICABLE DISEASES

Disruption of the gut microbiota resulting from antibiotic exposure is also **suspected of increasing the risk of several chronic diseases by elevating inflammatory responses locally and systemically,** thereby leading to a deregulated metabolism and compromised immune homeostasis[10] (Figure 2, page 4). The perinatal period, characterized by the development of the immune system along with the maturation of the gut microbiota, has been shown to be a particularly sensitive time, one during which antibiotic-driven dysbiosis translates into long-lasting health effects, i.e. a higher risk of diseases later in life, including inflammatory bowel diseases (e.g., Crohn's disease), atopic diseases (e.g., asthma) and metabolic disorders (e.g., type 2 diabetes, obesity).

WHEN THE GUT MICROBIOTA BECOMES A RESERVOIR OF ANTIBIOTIC RESISTANCE

When exposed to antibiotics, microbial communities respond in the short term not only by changing their composition, but also by evolving, optimizing and disseminating antibiotic resistant genes. **The human gut microbiota overly exposed to antibiotics is now considered a significant reservoir of resistance genes,** in adults as well as in children[2]. By contributing to the growing difficulty to combat bacterial infections, antibiotic resistance has become a major public health concern.

CLINICAL CASE *by Lynne V. McFarland, PhD*

- 53-year old woman consulted her physician with a 3-day history of respiratory tract symptoms (cough, sore throat and runny nose) with fever and fatigue. No co-morbidities and was otherwise healthy. Her physician prescribed a sputum sample and a 10-day course of oral cefaclor (500 mg, b.i.d). The sputum cultures came back negative for pathogens.
- She was admitted at hospital on the 3rd day of the antibiotics because she developed acute diarrhea (with six watery stools per day and abdominal cramping) and unresolved respiratory symptoms. Laboratory cultures (sputum and stool) were negative for pathogens. She was asked to discontinue her antibiotics, but the diarrhea continued for the next two days.
- Her physician prescribed erythromycin (500 mg, t.i.d.) and a probiotic for one week. Her respiratory symptoms and diarrhea resolved within four days and she was discharged one day later with no complications.

5. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002;346:334-9. **6.** Theriot CM, Young VB. Interactions Between the Gastrointestinal Microbiome and *Clostridium difficile*. *Annu Rev Microbiol.* 2015;69:445-461. **7.** Kuntz JL, Chrischilles EA, Pendergast JF *et al.* Incidence of and risk factors for community-associated *Clostridium difficile* infection: a nested case-control study. *BMC Infect Dis.* 2011;11:194. **8.** Brown KA, Khanafer N, Daneman N *et al.* Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother.* 2013;57(5):2326-2332. **9.** Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother.* 2014;69(4):881-891. **10.** Queen J, Zhang J, Sears CL. Oral antibiotic use and chronic disease: long-term health impact beyond antimicrobial resistance and *Clostridioides difficile*. *Gut Microbes.* 2020;11(4):1092-1103.

UROGENITAL MICROBIOTA: THE SPECTRUM OF **MYCOSIS OR URINARY TRACT INFECTIONS** AFTER EACH ANTIBIOTIC TREATMENT

A vicious circle. Vaginal tract infections such as vulvovaginal candidiasis often appear after antibiotic therapy, and sometimes following the administration of antibiotics commonly used to treat those same infections. The situation is no better for urinary tract infections: antibiotics typically used to treat them have become a risk factor for their occurrence.

Historically, until recent scientific work, urine was regarded as sterile. Compared to other microbiota, this ecosystem has low biomass[1]. While a consensus regarding the precise composition has yet to be reached, around 100 species have been identified from 4 principal phyla (Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes)[2]. And though the role of the urinary microbiota is currently a matter of debate, it is well understood that diminished diversity seems to be a risk factor for urinary tract infections.

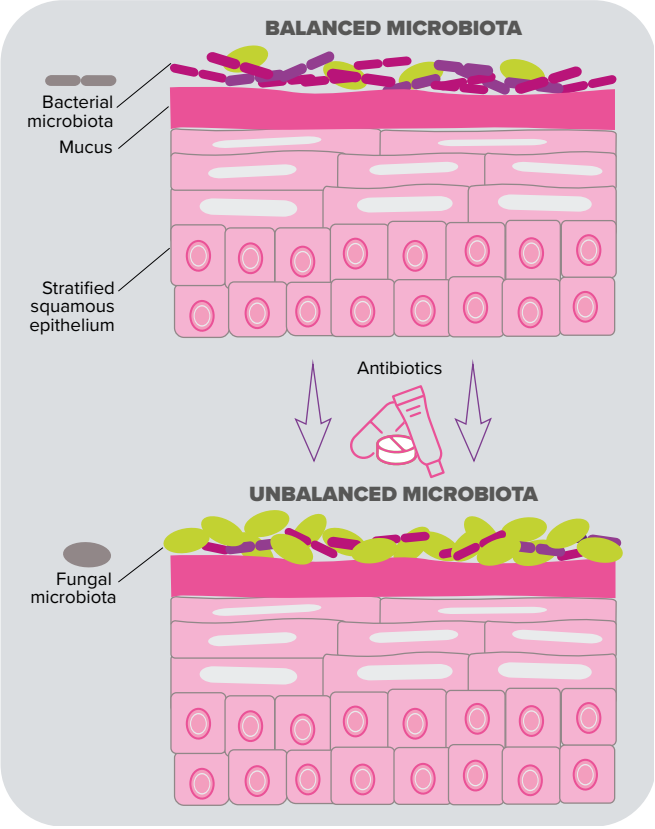
After antibiotic treatment, 10 to 30 % of women develop vulvovaginal candidiasis[5].

Yet, the vaginal microbiota gains on the other hand from having low diversity and being largely dominated by lactobacilli[3]. Despite considerable variability among women, 5 community state types (CST) have been described in the vaginal flora: 4 dominated by one or several species of the *Lactobacillus* genus *(L. crispatus, L. gasseri, L. iners or L. jensenii)* and one polymicrobial[4]. **In both cases, dysbiosis following antibiotic treatment may increase the risk of infection[5].**

A SPECTRUM OF FUNGUS AT EACH ANTIBIOTIC TREATMENT

This is what many women being treated with antibiotics dread: developing post-antibiotic vulvovaginal candidiasis. This anxiety is more than justified: **antibacterial therapy, whether systemic or applied locally to the vagina, is thought to be one of the main factors leading to vulvovaginal candidiasis[5].** This infection may be associated with vaginal microbiota disruption together with *Candida* yeast proliferation

FIGURE 3. Yeast proliferation induced by antibiotics exposure



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EXPERT OPINION

Urinary tract infections are closely linked to imbalances in any one of three microbiota: the urinary microbiota, since urine is not sterile; the vaginal microbiota, with which the urinary microbiota shares many similarities; and the gut microbiota, from where the pathogens involved in urinary tract infections originate (e.g. *E. coli*, which passes from the anus to the vulvar vestibule and then to the bladder).

1. Neugent ML, Hulyalkar NV, Nguyen VH, *et al.* Advances in Understanding the Human Urinary Microbiome and Its Potential Role in Urinary Tract Infection. *mBio*. 2020 Apr 28;11(2):e00218-20. **2.** Morand A, Cornu F, Dufour JC, *et al.* Human Bacterial Repertoire of the Urinary Tract: a Potential Paradigm Shift. *J Clin Microbiol*. 2019 Feb 27;57(3). pii: e00675-18. **3.** Gupta S, Kakkar V, Bhushan I. *et al.* Crosstalk between Vaginal Microbiome and Female Health: A review. *Microb Pathog*. 2019 Aug 23;136:103696. **4.** Greenbaum S, Greenbaum G, Moran-Gilad J, *et al.* Ecological dynamics of the vaginal microbiome in relation to health and disease. *Am J Obstet Gynecol.* 2019;220(4):324-335. **5.** Shukla A, Sobel JD. Vulvovaginitis Caused by *Candida* Species Following Antibiotic Exposure. *Curr Infect Dis Rep.* 2019 Nov 9;21(11):44.

(*C. albicans* in the majority of cases ; Figure 3 page 6). The most common clinical signs of this infection are vulvar pruritus, a burning sensation accompanied by vaginal pain or irritation that may lead to dyspareunia or dysuria[6].

THE VICIOUS CIRCLE OF BACTERIAL VAGINOSIS

Though the etiology of bacterial vaginosis (BV), the main form of vaginal infection, remains unclear, it is believed that antibiotic-induced dysbiosis could be partly responsible for its development: dominant lactobacilli are supplanted by polymicrobial flora derived from numerous bacterial genera *(Gardnerella, Atopobium, Prevotella,* etc.). A vicious circle could be initiated: though antibiotics can be used to treat BV, they are also, alongside sexual history, vaginal douching, contraceptive use, age, stage in the menstrual cycle, tobacco use, etc., among the numerous risk factors associated with this type of infection[7].

URINARY MICROBIOTA: A TEXTBOOK CASE OF ANTIBIOTIC RESISTANCE

Urinary tract infections (UTI) affect millions of men (a 3% annual incidence rate in the US) and women (10%) every year[8]. Recurrent UTIs contribute greatly to this incidence: notwithstanding their receiving appropriate antibiotic therapy, more than 30% of women will experience a subsequent infection within the following 12 months[8]. UTIs are becoming increasingly difficult to treat because of the rapid spread of drug resistance among Gram-Negative organisms, notably UPEC (uropathogenic *Escherichia coli*) which cause approximately 80% of UTIs[8]. **Paradoxically, broad-spectrum antibiotics used to treat both community-acquired and hospital-associated UTIs have become a risk factor for their occurrence[8].** Mechanisms involving both gut and vaginal microbiota are suspected: in the gut, the ultimate reservoir for UPEC, antibiotic exposure increases inflammation and promotes the proliferation of *E. coli*; in the vagina, they diminish colonization by *Lactobacillus* species that suppress vaginal UPEC invasion and subsequent bacterial ascension from the vagina into the urinary tract. This is the reason why, experts nowadays recommend that they should be used with caution and that microbiota-sparing treatments should be developed[8].

URINARY TRACT INFECTIONS: WHAT TO PRESCRIBE?

According to the 2017 update of the German clinical guidelines on managing uncomplicated urinary tract infections in adult patients[9]:

- *"For the treatment of acute uncomplicated cystitis (AUC), fosfomycin-trometamol, nitrofurantoin, nitroxoline, pivmecillinam, and trimethoprim (depending on the local rate of resistance) are all equally recommended. Cotrimoxazole, fluoroquinolones, and cephalosporins are not recommended as antibiotics of first choice, due to concerns over the possibility of an unfavorable impact on the microbiome.*
- *For AUC with mild to moderate symptoms, instead of antibiotics, symptomatic treatment alone may be considered depending on the patient's preference after discussing possible adverse events and outcomes.*
- ***Primarily non-antibiotic options are recommended for prophylaxis of recurrent urinary tract infections."***

CLINICAL CASE *by Dr. Jean-Marc Bohbot, MD, PhD*

- 18-year-old Solène consults for recurrent vulvo-vaginal candidiasis. For about 3 months, she suffers from recurrent candidiasis (2 episodes per month) with abundant white leucorrhea and intense vulvo-vaginal pruritus. These episodes have a very negative impact on her daily life, not to mention her sex life.
- A vaginal sample confirmed the presence of *Candida albicans* with an intermediate vaginal microbiota (Nugent score 6). Solène has a regular partner who experiences no symptoms. She is not diabetic. The candidiasis appeared a few weeks after starting a daily antibiotic treatment (cyclines) for acne. These antibiotics promote vaginal dysbiosis and facilitate the development of fungi.
- After consultation with the dermatologist, oral cyclines were replaced by a local treatment; the candidiasis disappeared within 2 weeks.

In cases of acne, the use of antibiotics should be limited or should be accompanied by probiotic cures to preserve the balance of the vaginal microbiota.

6. Gonçalves B, Ferreira C, Alves CT, *et al.* Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Crit Rev Microbiol.* 2016 Nov;42(6):905-27. **7.** Coudray MS, Madhivanan P. Bacterial vaginosis-A brief synopsis of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2019 Dec 24;245:143-148. **8.** Klein RD, Hultgren SJ. Urinary tract infections: microbial pathogenesis, host-pathogen interactions and new treatment strategies. *Nat Rev Microbiol.* 2020;18(4):211-226. **9.** Kranz J, Schmidt S, Lebert C, *et al.* The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention. *Urol Int.* 2018;100(3):271-278.

ANTIBIOTICS, **A DOUBLE-EDGED SWORD** WHEN MANAGING SKIN DISEASE

The effects of antibiotics on the skin microbiota have been studied mainly in the context of acne treatment. They may lead to several adverse outcomes including microbiota disruption, bacterial resistance and a risk of further infections hitting the skin or other body sites.

Long regarded mainly as a source of infection, the human skin microbiota is nowadays commonly accepted as an important driver of health and well-being[1]. **By promoting immune responses and defense,** it plays a key role in tissue repair and barrier functions by inhibiting colonization or infection by opportunistic pathogens[2].

TO EACH SKIN SITE, ITS OWN MICROBIOTA

The skin microbiota harbors millions of bacteria, as well as fungi and viruses in lower relative abundances. *Corynebacterium, Cutibacterium* (formerly known as *Propionibacterium*), *Staphylococcus, Micrococcus, Actinomyces, Streptococcus* and *Prevotella* are the most common genera of bacteria encountered on the human skin[3]. However, **the relative abundance of bacterial taxa greatly depends on the local microenvironment of the particular piece of skin being considered,** and especially on its physiological characteristics, i.e., whether it is sebaceous, moist or dry. Hence lipophilic *Cutibacterium* species dominate sebaceous sites while *Staphylococcus* and *Corynebacterium* species are particularly abundant in moist areas[4].

FROM PHYSIOLOGY TO PATHOLOGY, THE AMBIVALENT ROLE OF *C. ACNES*

The aerotolerant anaerobe *C. acnes* is one of the most abundant bacterial species in the skin microbiota. It has been implicated in acne, a chronic inflammatory disorder of the skin with complex pathogenesis[5].
In contrast with previous thinking, recent studies indicate that *C. acnes* hyperproliferation is not the only factor implicated in the development of acne[6]. In fact, **a loss of balance between the different *C. acnes* strains, together with a dysbiosis of the skin microbiota will trigger acne[6].** Moreover, interactions between *S. epidermidis* and *C. acnes* are of critical importance in the regulation of skin homeostasis: *S. epidermidis* inhibits *C. acnes* growth and skin inflammation. In turn, *C. acnes*, by secreting propionic acid which participates, among other things, in maintaining the pilosebaceous follicle acidic pH, inhibits the development of *S. epidermidis*. *Malassezia*, the most abundant skin fungus is also thought to play a role in refractory acne by recruiting immune cells, though its involvement needs to be further explored[6].

ACNE TREATMENT, AN IMPORTANT SOURCE OF ANTIBIOTIC RESISTANCE

Despite being used routinely to treat acne, **topical and oral antibiotics have proved to be problematic in several ways.**

ANTIBIOTICS IN ATOPIC DERMATITIS: FRIEND OR FOE?

In atopic dermatitis (AD), patients display skin microbiota dysbiosis characterized by an overgrowth of *Staphylococcus aureus*, which is thought to play a decisive role in the manifestation of AD[14]. Though antibiotic treatments have not demonstrated any efficacy in managing AD[15] and though they are liable to induce bacterial resistance and result in a deleterious impact on skin commensals[14,16], they are nevertheless commonly used.

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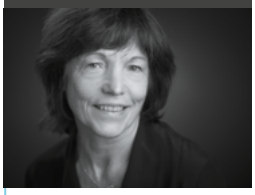

EXPERT OPINION

Antibiotics kill sensitive skin bacteria *(Cutibacterium acnes)*, while concurrently leading to "holes" in the microbiota, which resistant bacteria will fill. This results in cutaneous dysbiosis and the overexpression of multidrug-resistant bacteria. 60% of patients treated for acne have macrolide-resistant *C. acnes* strains, and 90% of *Staphylococcus epidermidis* strains are also resistant to macrolides. The use of antibiotics can also have consequences in orthopedic surgery, where many macrolide-resistant strains of *C. acnes* are similarly observed. During an operation (a hip prosthesis, for example), there is a risk of causing an abscess. This will be all the more difficult to treat, as this bacterium secretes biofilms that adhere to the prosthesis. It is therefore essential, if promoting the selection of resistant bacteria is to be avoided, that the use of topical antibiotics be limited as far as possible (a maximum course of 8 days).

1. Egert M, Simmering R, Riedel CU. The Association of the Skin Microbiota With Health, Immunity, and Disease. *Clin Pharmacol Ther.* 2017;102(1):62-69. **2**. Flowers L, Grice EA. The Skin Microbiota: Balancing Risk and Reward. *Cell Host Microbe*. 2020;28(2):190-200. **3**. Ederveen THA, Smits JPH, Boekhorst J, *et al.* Skin microbiota in health and disease: From sequencing to biology. *J Dermatol.* 2020;47(10):1110-1118. **4.** Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol.* 2018;16(3):143-155. **5.** Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. *Lancet Infect Dis*. 2016;16(3):e23-e33. **6.** Dréno B, Dagnelie MA, Khammari A, *et al.* The Skin Microbiome: A New Actor in Inflammatory Acne. *Am J Clin Dermatol*. 2020 Sep 10. **7.** Park SY, Kim HS, Lee SH, *et al.* Characterization and Analysis of the Skin Microbiota in Acne: Impact of Systemic Antibiotics. *J Clin Med*. 2020;9(1):168. **8.** Karadag AS, Aslan Kayıran M, Wu CY, *et al.* Antibiotic resistance in acne: changes, consequences and concerns. *J Eur Acad Dermatol Venereol.* 2020;10.1111/jdv.16686. **9.** Xu H, Li H. Acne, the Skin Microbiome, and Antibiotic Treatment. *Am J Clin Dermatol*. 2019;20(3):335-344.

A first concern expressed by experts is the disruption to the skin microbiota, although precise data on the subject remain scarce. In this vein, a recent longitudinal study compared the cheek microbiota of 20 acne patients before and after six weeks of oral doxycycline therapy. Interestingly, antibiotic exposure was associated with an increase in bacterial diversity; according to the authors, this could be due to a diminished colonization by *C. acnes*, which would liberate space to allow the growth of other bacteria[7].

Dermatologists prescribe more antibiotics than any other specialists. Two thirds of these prescriptions are for acne[8].

However, the most significant concern over the use of antibiotics for acne treatment relates to bacterial resistance. First observed in the 1970s, it has been a major worry in dermatology since the 1980s[8]. *C. acnes* resistance is by far the most documented: the latest data point to resistance rates reaching over 50% for erythromycin in some countries, 82-100% for azithromycin and 90% for clindamycin. As for tetracyclines, although still largely effective against the majority of *C. acnes* strains, their resistance rates are rising, ranging from 2% to 30% in different geographic regions[9].

And antibiotic resistance is not limited to *C. acnes*: while topical antibiotics used by acne patients (especially as monotherapy) have been shown to **increase the emergence of resistant skin bacteria such as *S. epidermidis*, oral antibiotics have been associated with the increased emergence of antibiotic-resistant oropharyngeal *S. pyogenes***[8,10]. **In addition, increased rates of upper respiratory tract infection and pharyngitis** have been reported as being associated with the antibiotic treatment of acne[11,12].

Strategies from the Global Alliance to Improve Outcomes in Acne to reduce antibiotic resistance in *Cutibacterium acnes* and other bacteria[5]

FIRST-LINE THERAPY

- Combine topical retinoid with antimicrobial (oral or tropical)

If addition of antibiotic is needed:

- Limit to short periods; discontinue when only slight or no further improvement
- Oral antibiotics should ideally be used for 3 months
- Coprescribe benzyl peroxide-containing product or use as washout
- Do not use as monotherapy
- Avoid concurrent use of oral and topical antibiotics
- Do not switch antibiotics without adequate justification

MAINTENANCE THERAPY

- Use topical retinoids, with benzoyl peroxide added if needed
- Avoid antibiotics

From Walsh *et al.*, 2016[5]

A CALL FOR A LIMITED USE OF ANTIBIOTICS IN ACNE

The potential consequences of antibiotic resistance triggered by acne treatment are numerous: failure of the acne treatment itself *(see clinical case),* infection by opportunistic pathogens (locally or systemically), and the dissemination of resistance among the population[8]. Despite this, the levels of antibiotic prescriptions for acne remain high and for longer durations than recommended in the guidelines[13]. Against this background of mounting concerns, **experts are calling for a more limited use of antibiotics in the treatment of acne**[13]. In particular, a strategy has been proposed in this regard by the Global Alliance to Improve Outcomes in Acne *(see box above)*.

CLINICAL CASE *by Prof. Brigitte Dréno, MD, PhD*

- A teenager consulted his dermatologist for facial acne (forehead, chin, and cheeks). He received a topical erythromycin-based treatment.
- 4 to 5 weeks after starting treatment, a new proliferation of papules and pustules appeared on his face. He went back to his doctor, who prescribed oral erythromycin.
- 1 month later, the patient returned to see his doctor because his acne had extended to his neck (profuse impetigo). The doctor took a sample from one of the pustules for a culture test.
- The culture test came back positive for *Staphylococcus*, and the antibiogram indicated a resistance to macrolides. The doctor prescribed benzoyl peroxide, which gave remission within 10 days.

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ENT MICROBIOTA: WHEN ANTIBIOTICS CHALLENGE OUR **FIRST LINE OF DEFENSE**

By disrupting the microbiota in the ears, nose and throat (ENT), antibiotics may leave the door open to opportunistic pathogens implicated in ear and respiratory infections. Their effects could be particularly counterproductive in cases of acute otitis media.

What is commonly referred to as the "ears, nose and throat (ENT) microbiota" is in fact comprised not of one but rather of several microbiota. Antibiotics are likely to act individually on these different microbiota, ranging over the oral cavity through to the pharynx, including inside the sinuses and even the middle ear. This chapter is mainly devoted to the effects of antibiotics on the Upper Respiratory Tract (URT) microbiota, which is an excellent textbook case: **the URT microbiota appears to be one of the safeguards of auricular health, yet it is threatened by antibiotics prescribed for this purpose, notably in cases of acute otitis media.**

"Within 7 days of antibiotics being administered for URT infections, the incidence of acute otitis media has been shown to increase by a factor of 2.6." Pr. Teissier, MD, PhD

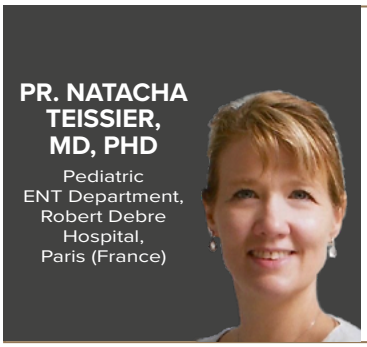
THE URT MICROBIOTA, AN ALLY OF AURICULAR HEALTH?

The URT microbiota is colonized directly after birth by a variety of commensals *(Dolosigranulum Corynebacterium, Staphylococcus, Moraxella, Streptococcus)*. Mounting evidence suggests that a higher relative abundance of commensal species *(Dolosigranulum spp.* and *Corynebacterium spp.)* as well as a greater diversity in the nasopharyngeal microbiota[1] are associated with a lower incidence of URT colonization by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*[2,3], three otopathogens implicated in acute otitis media (AOM) .

ANTIBIOTIC TREATMENT: MUCH RISK FOR LITTLE BENEFIT

Exposure to antibiotics impacts the URT microbiota by decreasing the abundance of protective species and by increasing the abundance of Gram-negative bacteria *(Burkholderia spp., Enterobacteriaceae, Comamonadaceae, Bradyrhizobiaceae)*[4,5], as well as *S. pneumoniae, H. influenzae* and *M. catarrhalis*[5]. As a result of acquiring antimicrobial resistance, these bacteria, which could not otherwise successfully compete in this niche, are given the opportunity to multiply during treatment to an extent that they may become pathogenic[6].

Furthermore, antibiotics are considered unlikely to confer any benefit in most cases of pediatric AOM (the primary reason for prescribing antibiotics to children[7]) and other URT infections (sore throats or common colds)[7,8], **due to the frequently non-bacterial nature of these conditions: from 60% to 90% of children with a AOM recover without antibiotics**[9,10]. Finally, antibiotics lead to gut microbiota dysbiosis that can translate into side effects such as antibiotic-associated diarrhea[3,11] (see page 4: gut microbiota).



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EXPERT OPINION

In flora hitherto unexposed to antibiotic treatment, there is a harmonious balance between the various commensal bacteria. Disrupting this balance with antibiotics can promote the proliferation of certain bacteria, likely to become pathogenic. In particular, the repeated intake of antibiotics promotes the selection of multidrug-resistant bacteria that can no longer be kept in check by the commensal flora, which leads to the more frequent occurrence of infectious complications. It therefore seems essential to preserve the native flora and its natural balance by limiting the use of antibiotics to situations where they are strictly necessary.

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ANTIBIOTIC RESISTANCE:
THE LUNG MICROBIOTA PAYS A HEAVY PRICE

Broad-spectrum antibiotics used for treating lung infections are regarded as one of the principal contributors to the overall burden of antibiotic resistance.

Historically, the lungs of healthy individuals were **considered sterile;** the description of the LRT microbiota (Lower Respiratory Tract, from larynx to alveoli of the lungs[1]) is a recent achievement[2,3]. Along with viral and fungal communities, **six bacterial phyla** dominate a healthy lung microbiota: Firmicutes, Bacteroidetes, Fusobacteria, Proteobacteria, Acidobacteria, and Actinobacteria[1,2,4].

"In Western populations, the treatment of lung infections is a primary driver of antibiotic resistance[4]."

A LOSS OF DIVERSITY IN THE LUNG MICROBIOTA

Microbial dysbiosis is observed in a range of respiratory disorders, including lung infection, asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF)[5,6]. But **only few studies have explored the direct effects of antibiotics on lung microbiota.** Recent investigation has shown that azithromycin treatment decreased bacterial diversity in patients with persistent uncontrolled asthma[1]; however clinical benefits are still controversial[1,7,8]. In COPD patients, azithromycin treatment lowered alpha diversity[1]; in those suffering from CF, antibiotics appear to be the primary drivers of decreased airway microbiota diversity[5].

THE GUT-LUNG AXIS

Respiratory diseases, chronic lung disorders and microbial infections are often accompanied by intestinal symptoms[12]. Indeed, the intestinal ecosystem undergoes change during the course of several lung diseases[12]. While the underling mechanism remains unclear, reciprocal influence between the gut and the lungs could, in part, explain why antibiotic-induced dysbiosis of the gut microbiota in early-life may be a risk factor for subsequent allergic rhinitis and asthma[1,12].

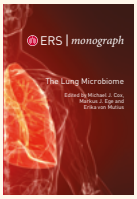
THE PLAGUE OF BROAD-SPECTRUM ANTIBIOTICS

While the misuse of antibiotics is known to lead to the emergence and selection of resistant bacteria, **antibiotic prophylaxis, without a microbial diagnosis, is still widely used to treat lung infections[4].** Of the 12 antibiotic-resistant 'priority pathogens' listed by the WHO, 4 affect lungs: *Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus influenzae* and *Streptococcus aureus*[4,9]. There is agreement among the scientific community as a key route to minimize antimicrobial resistance that the disease management of lung infections needs to be improved[4,10,11].

Promoting research, raising awareness

The Global Alliance Against Respiratory Diseases (GARD), launched by the WHO in 2006 to help combat chronic respiratory diseases, asserts: ***"Physicians worldwide now face situations in which infected patients cannot be treated adequately because the responsible bacterium is totally resistant to available antibiotics[11]."***

At the European level, the ERS (European Respiratory Society) is involved in promoting scientific research, providing access to resources and raising awareness among the public and political decision makers. "*Science, education and advocacy are at the core of everything we do.*" Its latest monograph, 'The lung microbiome'[13], reviews the different components of the respiratory microbiome, examines how diseases (asthma, COPD, cancer...) emerge and discusses new developments and therapies.



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KEY POINTS

WHAT TO TAKE AWAY?

Commonly hailed as one of the most important advances of the 20th century, antibiotics have saved millions of lives. They also had, however, a deleterious impact on microbiota:

- **antibiotic-induced dysbiosis,** which is associated with both short- and long-term health consequences;
- **host-specific pool of antimicrobial resistance genes and organisms** developing as a result of the misuse or overuse of antibiotics.

This points to the need for antibiotics to be handled with care, and that a more rational use of antibiotics be adopted.

Antibiotic-induced dysbiosis can affect every human microbiota:

gut microbiota: diarrhea, its main short-term side effect, occurs in up to 35% of patients receiving antibiotics[1,2,3];

urogenital microbiota: following antibiotic treatment, between 10 and 30 % of women go on to develop vulvovaginal candidiasis[4];

cutaneous microbiota: 60% of patients treated for acne have macrolide-resistant *Cutibacterium acnes* strains;

ears-nose-throat microbiota: antibiotics administered for upper respiratory tract infections increase by a factor of 2.6 the incidence of acute otitis media;

lung microbiota: broad-spectrum antibiotics used for treating lung infections are regarded as one of the principal contributors to the overall burden of antibiotic resistance.

WHAT TO DO?

To prevent dysbiosis:

- adopting **a more diverse diet, high in fiber:** diet has a considerable influence on the composition of the intestinal microbiota[5];
- using **probiotics**[6]: when administered in adequate amounts these live microorganisms (yeasts or bacteria) confer a definite health benefit on the host[7];
- using **prebiotics:** substrates that are selectively utilized by host microorganisms and which thereby confer health benefits[8].

To promote the reconstruction and the functionality of a dysbiotic microbiota:

- **using probiotics**[6] (yeasts or bacteria) may be helpful;
- **considering fecal microbiota transplantation** to treat recurrent *Clostridioides difficile* infection only[9].

To combat antimicrobial resistance:

- **explore phage therapy**[10]: phages, the natural predators of bacteria, were used to treat bacterial infections before the advent of antibiotics;
- **investigate CRISPR-Cas9**[11]: these "molecular scissors" could be used to implement corrections to genes;
- **consider nanomaterial-based therapies**[12]: the physical properties of certain nanomaterials endow them with the capability to target biofilms.

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